11th INTERNATIONAL CONFERENCE ON TYPHOID & OTHER INVASIVE SALMONELLOSES

March 26-28, 2019 | Hanoi, Vietnam

SABIN VACCINE INSTITUTE

COALITION AGAINST TYPHOID

FROM GLOBAL ACTION TO LOCAL IMPACT

The Coalition against Typhoid, a program of the Sabin Vaccine Institute, welcomes you to the 11th International Conference on Typhoid and Other Invasive Salmonelloses. Typhoid continues to cause an estimated 11 million cases and more than 116,000 deaths annually, largely affecting children in low-income communities in Asia and Sub-Saharan Africa. However, recent strides in global policy have paved the way for accelerated progress.

Since we last convened two years ago, the World Health Organization prequalified and subsequently recommended the use of typhoid conjugate vaccines, taking the first steps toward protecting children as young as six months of age through routine immunization. Gavi, the Vaccine Alliance, then made a commitment of $85 million to support the introduction of these vaccines. Already, countries have submitted applications for Gavi support and two have begun to use this life-saving intervention in response to drug-resistant outbreaks.

As we come together here in Hanoi under the theme of "Global Action for Local Impact," we aim to translate these recent advancements at the global level into real impact in typhoid prevention and control in communities at the local level. Over the next three days, through 98 oral presentations and 187 posters, researchers, health care professionals, policy makers and advocates will share their practical knowledge and expertise, covering topics from burden of disease to genomics and everything in between. For the first time, attendees will have a choice of concurrent abstract sessions and pre-registered lunchtime workshops to give an opportunity for in-depth updates in various areas of focus. Truly something for everyone!

We are thrilled that this year's conference will host a record-breaking number of participants, with over 450 registered attendees from more than 40 countries. This would not have been possible without the contributions of our Scientific Committee and Abstract Review Panel, as well as the generous support of the Bill & Melinda Gates Foundation and our sponsors. We would also like to extend our gratitude to the government of Vietnam for their assistance and hospitality in organizing this important event in their beautiful country. Finally, we thank each of you for attending and bringing your expertise to our gathering. Throughout this conference, we hope you will use this opportunity to update yourself, to network and to be inspired by your colleagues from all over the world.

We look forward to a conference filled with impactful discussion and actionable strategies. As importantly, we hope to create lasting partnerships that will generate the energy we need as we move from global action to local impact.

Sincerely,

Denise Garrett, M.D., M.Sc.
Vice President, Typhoid Programs
Director, Coalition against Typhoid
Sabin Vaccine Institute

Amy Finan
Chief Executive Officer
Sabin Vaccine Institute

Scientific Committee	Affiliation
Jason Andrews	Stanford University
Adwoa Bentsi-Enchill	World Health Organization
Zulfiqar Bhutta	Aga Khan University
Thomas Cherian	MM Global Health Consulting
John Crump	University of Otago
Dang Duc Anh	National Institute of Hygiene and Epidemiology, Vietnam
Nicholas (Nick) Feasey	Liverpool School of Tropical Medicine
Denise Garrett	Sabin Vaccine Institute
Bruce Gellin	Sabin Vaccine Institute
Melita Gordon	University of Liverpool
Jacob John	Christian Medical College, Vellore
Ashley Latimer	PATH
Florian Marks	International Vaccine Institute
Eric Mintz	Centers for Disease Control and Prevention
Kathleen Neuzil	University of Maryland School of Medicine
Jeffrey (Jeff) Stanaway	Institute of Health Metrics and Evaluation
Duncan Steele	Bill & Melinda Gates Foundation

Abstract Review Panel	Affiliation
Stephen Baker	University of Oxford
Isaac Bogoch	University of Toronto
Dagna Constenla	Johns Hopkins University
Kashmira Date	Centers for Disease Control and Prevention
Bruce Gellin	Sabin Vaccine Institute
Brad Gessner	Agence de Médecine Préventive
Melita Gordon	University of Liverpool
Jan Jacobs	Institute of Tropical Medicine, Antwerp
Gangandeep Kang	Christian Medical College, Vellore
Sam Kariuki	Kenya Medical Research Institute
Karen Kotloff	University of Maryland School of Medicine
Ashley Latimer	PATH
Laura Martin	GSK Vaccines Institute for Global Health
Eric Mintz	Centers for Disease Control and Prevention
Kim Mulholland	Murdoch Children's Research Institute
Kathleen Neuzil	University of Maryland School of Medicine
Ellis Owusu-Dabo	Kwame Nkrumah University of Science and Technology
Virginia (Ginny) Pitzer	Yale School of Public Health
Firdausi Qadri	icddr,b
Farah Qamar	Aga Khan University
Sushant Sahastrabuddhe	International Vaccine Institute
Ken Simiyu	University of Maryland School of Medicine
Jeffrey (Jeff) Stanaway	Institute of Health Metrics and Evaluation

TABLE OF CONTENTS

THE WORLD'S 1st WHO PRE-QUALIFIED TYPHOID CONJUGATE VACCINE

Typbar TCV®

WORLD'S 1ST & ONLY WHO PRE-QUALIFIED TYPHOID CONJUGATE VACCINE

THE TYPBAR TCV® ADVANTAGE

A single dose of 25g/0.5mL ViTT conjugate vaccine elicits an immune response of 97.7%, with four-fold seroconversion

Offers high-avidity (especially IgG having high bactericidal activity) that persists up to 5 years

Co-administration of Typbar TCV® with MMR vaccine exhibits no serological interference

In a human challenge study at Oxford University, Typbar TCV® showed 87.1% efficacy

Offers a flexible dose of vaccination along with good safety and immunogenicity

GLOBAL EFFECTIVENESS STUDY - VACCINE TRIAL KICKS OFF

Clinical trials of the new Typbar TCV® are being conducted to further evaluate vaccine efficacy and impact of a typhoid conjugate in reducing typhoid burden in endemic countries.

THE ROTAVAC® ADVANTAGE

- Three oral doses of 0.5mL dose of ROTAVAC® (nHRV) elicits comparable efficacy and immune response to other rotavirus vaccines
- Ready to use (no reconstitution required) with a low dose volume of 0.5ml mitigating spit-ups and assuring complete delivery of vaccine (multi-dose 5ml and 10ml presentations available)
- Proven short and long-term efficacy till the 2nd year of life
- Low cold chain foot print: 254%-2, 554% lower cold chain volume when compared to existing rotavirus vaccines

ROTAVAC®

5-SWEET DROPS

VACCINE EFFECTIVENESS STUDY: Several multisite vaccine impact and intussusception studies in over 100,000 participants are ongoing with findings expected in 2019/20.

MEDIA

nature

In its Yearbook, Nature Magazine declared Typbar TCV® as one of the treatments that made headlines in 2018.

GLOBAL CITIZEN

THE 10 BIGGEST GLOBAL HEALTH WINS OF 2018: The development of a New Rotavirus Vaccine was approved

Bharat Biotech announced that the WHO had approved the development of a new rotavirus vaccine, ROTAVAC® - which costs only $1 per dose.

The New York Times

THEY SWALLOWED TYPHOID BACTERIA - ON PURPOSE

More than 100 residents of Oxford, England, took part in a trial of a new typhoid vaccine.

Typbar TCV® is the only effective vaccine that is also safe for infants, and is already used widely in India.

INDIAN & GLOBAL PARTNERSHIPS

Bill & Melinda Gates foundation | Bharat Biotech Lead Innovation | Gavi The Vaccine Alliance | TyVAC Typhoid Vaccine Acceleration Consortium | University of Maryland | Stanford University

University of Oxford | The India Trust International | CDC | NICED

Bharat Biotech International Ltd. Genome Valley Shameerpet Hyderabad - 500 078 Telangana India T: +91 40 2348 0560 / 67

www.bharatbiotech.com

Now is the time for countries to decide, introduce, and control typhoid.

Introduce typhoid conjugate vaccines (TCVs) to protect children, families, and communities from typhoid. The World Health Organization has recommended and prequalified a TCV, and Gavi, the Vaccine Alliance support is available.

Get the **materials, data**, and **messages** you need at www.takeontyphoid.org. Whether you are a decision-maker, scientist, researcher, advocate, or government official, **you** can be a ***Take on Typhoid*** champion.

Now is the time to take action!

The Typhoid Vaccine Acceleration Consortium (TyVAC) is **available to support countries** with TCV introduction. TyVAC can help review country burden data, generate health economic evidence, develop advocacy materials, assist with the Gavi application, and provide technical guidance for TCV introduction.

Contact TyVAC@path.org to take on typhoid in your country.

TyVAC Typhoid Vaccine Acceleration Consortium
CENTER FOR VACCINE DEVELOPMENT • OXFORD VACCINE GROUP • PATH

AGENDA

TUESDAY, MARCH 26

8:30-8:50 Opening Session — Grand Ballroom

Welcome Remarks
Amy Finan, Sabin Vaccine Institute

Welcome Remarks and Housekeeping Items
Denise Garrett, Sabin Vaccine Institute

Opening Keynote Address
Kathleen Neuzil, University of Maryland School of Medicine

8:50-9:50 Come Together: Building a Multisector Toolkit — Grand Ballroom

PLENARY SESSION MODERATED BY:
Eric Mintz, Centers for Disease Control and Prevention &
Jason Andrews, Stanford University

Where Are We With Diagnosing Typhoid Fever?
Stephen Baker, University of Oxford

Low-Cost PCR-based Microbial Quantification Methods for Water Quality Control in the Developing World
Michael Hoffmann, California Institute of Technology

Integrating WASH/Hygiene Behaviour Change Interventions into Routine Immunization Programme to Maximise Benefits: WaterAid's Experiences from Pilot to Scale
Om Prasad Gautam, WaterAid

Typhoid Conjugate Vaccine Development: The Last Mile?
Sushant Sahastrabuddhe, International Vaccine Institute

9:50-10:15 Coffee Break — Foyer/Fansipan Ballroom

10:15-11:45 Concurrent Oral Abstract Sessions 1 & 2

Carry That Weight: Burden of Disease — Grand Ballroom

SESSION MODERATED BY:
Dennis Chao, Institute for Disease Modeling &
Robert F. Breiman, Emory University

Tenacious Endemic Typhoid Fever in Samoa: Is Short-Cycle (Chronic Carriers) or Long-Cycle (Water-Borne) Transmission Mainly Maintaining Endemicity?
Myron (Mike) Levine, University of Maryland School of Medicine

We Can Work It Out: Vaccine Development — Truc Bach

SESSION MODERATED BY:
Krishna Ella, Bharat Biotech International Limited &
Laura Martin, GSK Vaccines Institute for Global Health

Age-Associated Heterogeneity of Ty21a-Induced T Cell Responses to HLA-E Restricted *Salmonella* Typhi Antigen Presentation
Marcelo B. Sztein, University of Maryland School of Medicine

Illness, Severity, and Outcomes among Enteric Fever Cases – Data from the Surveillance for Enteric Fever in Asia Project (SEAP)
Caitlin Barkume, Sabin Vaccine Institute

Preclinical Development of a Trivalent Typhoid-Nontyphoidal *Salmonella* Glycoconjugate Vaccine for sub-Saharan Africa
Scott Baliban, University of Maryland School of Medicine

The Burden of Culture-Confirmed Enteric Fever in an Urban Slum – An Ongoing Community-Based Longitudinal Cohort in Delhi, India (Tier 1 SEFI site)
Bireshwar Sinha, Society for Applied Studies

Development of a MAPS-Based Typhoid and Paratyphoid A Vaccine
Richard (Rick) Malley, Boston Children's Hospital

Spatial and Temporal Patterns of Typhoid and Paratyphoid Outbreaks: A Worldwide Systematic Review, 1990-2016
Vittal Mogasale, International Vaccine Institute

The Non-Specific Immunological Impact of Human Oral Vaccination with Live-Attenuated *Salmonella* Typhi
Shaun Pennington, Liverpool School of Tropical Medicine

Mortality Attributed to Ileal Perforations: Prospective Data from a Multi-Centers Enteric Fever Surveillance Project in Pakistan
Saqib Qazi, Aga Khan University Hospital

T Cell Mediated Immunity Elicited in Volunteers Following Immunization with the Live Oral *Salmonella* Paratyphi A Attenuated Vaccine Strain CVD 1902
Rezwanul Wahid, University of Maryland School of Medicine

The Global Burden of Nontyphoidal *Salmonella* Invasive Disease: A Systematic Analysis for the Global Burden of Disease Study 2017
Andrea Parisi, The Australian National University

The Immunogenicity and Safety of ZyVac-TCV, a Typhoid Conjugate Vaccine in Healthy Indian Subjects: Results of First Comparative Clinical Trial
Pavankumar Daultani, Cadila Healthcare Limited

11:45-13:15 Lunch & Posters

JW Café/Fansipan Ballroom

13:15-15:15 Environmental Surveillance for *Salmonella* and Antimicrobial Resistance (AMR) Genes

Grand Ballroom

SYMPOSIUM SESSION CHAIRED BY:
Gagandeep Kang & Venkata Raghava Mohan, Christian Medical College, Vellore

Approach for Harmonization and Quality Control of Environmental Surveillance Methods for Typhoid
John Scott Meschke, University of Washington

Environmental Surveillance for Typhoid in Kibera, an Informal Settlement in Nairobi, Kenya
Jennifer Verani & Jennifer Murphy, Centers for Disease Control and Prevention

Development and Application of Pilot *Salmonella* Typhi in Environmental Surveillance Program in Kolkata, India Christine L. Moe, Emory University

Environmental Sampling as a Tool for Identification of High Typhoid Risk Settings
Jason Andrews, Stanford University

Environmental Surveillance for *Salmonella* and AMR Genes in Tamil Nadu, India
Sidhartha Giri, Christian Medical College, Vellore

Country Decision Making on Typhoid Conjugate Vaccine (TCV) Introduction: Potential Role of Environmental Surveillance Adwoa Bentsi-Enchill, World Health Organization

15:15-15:45 Coffee Break

Foyer/Fansipan Ballroom

15:45-17:15 Concurrent Oral Abstract Sessions 3 & 4

I Should Have Known Better: Antimicrobial Resistance

Grand Ballroom

SESSION MODERATED BY:
Chris Parry, University of Liverpool &
Hubert Endtz, Fondation Mérieux

Antimicrobial Non-Susceptibility among *Salmonella* Typhi and Paratyphi A Isolates – Preliminary Results from SEAP Project
Muhammad Tahir Yousafzai, Aga Khan University

Trends in Resistance to Fluoroquinolones and ESBLs among *Salmonella* Typhi Isolates from Patients at Outpatient Clinics in Nairobi, 2012-2016
Susan Kavai, Kenya Medical Research Institute

Incidence and Antimicrobial Resistance Profile of *Salmonella* Bacteremia Among Children in sub-Saharan Africa: RTS,S/AS01 *Salmonella* Ancillary Study
Calman MacLennan, University of Oxford

***Salmonella* Typhi in Bangladesh: Exploration of Genomic Diversity and Antimicrobial Resistance**
Arif Mohammad Tanmoy, Erasmus University Medical Center

Molecular Mechanisms of Antimicrobial Resistance and Phylogenetic Relationship of *Salmonella enterica* from Febrile Patients in Yangon, Myanmar
Tin Ohn Myat, University of Medicine 1

Predicting the Impact of Typhoid Conjugate Vaccines on Antimicrobial Resistance
Virginia (Ginny) Pitzer, Yale School of Public Health

Here, There, Everywhere: Environmental Surveillance, Disease Modeling, and Geo-Spatial Analysis

Truc Bach

SESSION MODERATED BY:
Nicholas (Nick) Feasey, Liverpool School of Tropical Medicine & Supriya Kumar, Bill & Melinda Gates Foundation

Clinical and Genomic Data to Understand Transmission Patterns of Typhoid Fever and Inform Targeted Environmental Sampling in Blantyre, Malawi
Jillian Gauld, Institute for Disease Modeling & Lancaster University

Optimisation of Culture and Molecular-Based Methods for Detection of *Salmonella* Typhi from Environmental Reservoirs under Laboratory Conditions
Jonathan Rigby, Liverpool School of Tropical Medicine

Environmental Surveillance for Targeting Typhoid Conjugate Vaccines: Drivers of Cost-Efficiency in sub-National Programs
Brittany Hagedorn, Institute for Disease Modeling

Typhoid Environmental Surveillance Sampling Strategies and Adaptive Sampling Site Allocation Method: A Simulation Study for Wards 58 & 59, Kolkata
Yuke Wang, Emory University

A Bayesian Approach for Estimating Typhoid Fever Incidence from Passive Surveillance Data
Maile Phillips, Yale School of Public Health

Geo-Spatial Reporting of Ceftriaxone Resistant *Salmonella* Typhi Outbreak Investigation in Hyderabad and Spread to Karachi
Abdul Momin Kazi, Aga Khan University

17:15-18:00 Break

18:00-19:30 Evening Welcome Reception

Fansipan Ballroom

REMARKS FROM:
Dang Duc Anh, National Institute of Hygiene and Epidemiology, Vietnam

WEDNESDAY, MARCH 27

8:30-10:30 STRATAA/TyVAC — Grand Ballroom

SYMPOSIUM SESSION CHAIRED BY:
Andrew J. Pollard, University of Oxford & Kathleen Neuzil, University of Maryland School of Medicine

Burden of Enteric Fever in Africa and Asia from Three Urban Centres: A Multicentre, Prospective Epidemiological Study with over 600,000 Person-Years of Observation
James Meiring, University of Oxford

Serial Serological Surveillance for Typhoid in Healthy Community Controls in Nepal, and in Fever Cases and Their Families
Merryn Voysey, University of Oxford

Evaluation of Population-Based Serological Surveillance for the Identification of Typhoid Chronic Carriers Using and Anti-Vi IgG ELISA
Farhana Khanam, icddr,b

Interim Analysis of Safety of Typhoid Conjugate Vaccine across Africa and Asia TyVAC
Melita Gordon, University of Liverpool

Interim Analysis of Immunogenicity of Typhoid Conjugate Vaccine in Africa and Asia TyVAC
Dikshya Pant, Patan Academy of Health Sciences

Efficacy of Typhoid Conjugate Vaccine in Nepal: A Participant-Observer-Blind Phase III Randomized Controlled Trial
Mila Shakya, Oxford University Clinical Research Unit, Nepal

10:30-11:00 Coffee Break — Foyer/Fansipan Ballroom

11:00-12:30 Concurrent Oral Abstract Sessions 5 & 6

Got to Get You into My Life: Introduction of Typhoid Conjugate Vaccines — Grand Ballroom

SESSION MODERATED BY:
Ken Simiyu, University of Maryland School of Medicine & Muhammad Salman, National Institute of Health, Pakistan

Safety of Typhoid Conjugate Vaccine in Bangladeshi Children: Preliminary Results from a Double-Blind Cluster-Randomised Controlled Trial
Firdausi Qadri, icddr,b

Implementation and Coverage of the First Public Sector Introduction of Typhoid Conjugate Vaccine, Navi Mumbai, India
Kashmira Date, Centers for Disease Control and Prevention

Fixing a Hole: iNTS — Truc Bach

SESSION MODERATED BY:
Ellis Owusu-Dabo, Kwame Nkrumah University of Science and Technology & Sam Kariuki, Kenya Medical Research Institute

The Phylogeography and Incidence of Multi-Drug Resistant Invasive Nontyphoidal *Salmonella* in sub-Saharan Africa
Se Eun Park, International Vaccine Institute

Transmission of Invasive Nontyphoidal *Salmonella*: Supporting Evidence for Human-to-Human Transmission from Household Samples in Burkina Faso
Annelies Post, Radboudumc Nijmegen & Institute of Tropical Medicine Antwerp

Evaluation of Vaccine Safety during the First Public Sector Introduction of Typhoid Conjugate Vaccine (TCV), Navi Mumbai, India, 2018 Ashley Tate, CDC Foundation	**Fifteen Years of Surveillance for Invasive Salmonellosis in Bamako, Mali: 2002 to 2017** William Still, University of Maryland School of Medicine
Adverse Events following Immunization with Typbar TCV and Measles Vaccine: Mass Immunization against Typhoid Fever and Measles at KGH Hospital Karachi Anayat Baig, Aga Khan University	**Characterising the Cellular and Humoral Immune Response to Invasive Nontyphoidal *Salmonella* (iNTS) Disease in West African Populations** Sean Elias, University of Oxford
Door to Door Campaign of Typbar TCV: Strategies to Reduce Refusal and Increase Coverage Sultan Karim, Aga Khan University	**Characterization of Invasive Salmonellosis in Hospitalized Children with Acute Febrile Illness: Uganda, 2016-2017** Alison Winstead, Centers for Disease Control and Prevention
Safety and Tolerability of a Novel Typhoid Conjugate Vaccine in African Infants and Children Nginache Nampota, Blantyre Malaria Project	**What Have We Learned from the 10,000 *Salmonella* Genomes Project about the Worldwide Epidemiology, Transmission and Virulence of iNTS?** Blanca Perez Sepulveda, University of Liverpool

12:30-14:00 Lunch & Posters

JW Café/Fansipan Ballroom

14:00-15:10 With a Little Help from My Friends: The Essentials for Using Data for Decision Making and Advocacy

Grand Ballroom

PLENARY SESSION MODERATED BY:
Eileen Quinn, PATH & Hope Johnson, Gavi, the Vaccine Alliance

Gavi Typhoid Program: History of Decision-Making, Current Support and Early Lessons Learned
Adam Soble, Gavi, the Vaccine Alliance

On The Essentials of Using Data for Decision Making and Advocacy
N.A. Gonah, Zimbabwe National Immunisation Technical Advisory Group

Advocating to Save Lives: Learnings From Vaccine Introduction Programs
Anjali Nayyar, Global Health Strategies

Advocating for New Vaccine Introduction in the Mekong Region: Lessons Learnt From Laos, Cambodia, Myanmar, and Vietnam
Huong Minh Vu, PATH

Advocacy for Vaccine in LMICs: Focusing on Typhoid
Samir Saha, Child Health Research Foundation & Dhaka Shishu Hospital

15:10-15:30 Coffee Break

Foyer/Fansipan Ballroom

15:30-17:00 Concurrent Oral Abstract Sessions 7 & 8

Across the Universe: Enteric Fever Surveillance

Grand Ballroom

SESSION MODERATED BY:
John Clemens, icddr,b & Megan Carey, Bill & Melinda Gates Foundation

_S._ Typhi and iNTS Disease in Africa – Implications for Vaccination Programs: Results of the Severe Typhoid in Africa Program and Future Trial Plans
Florian Marks, International Vaccine Institute & University of Cambridge

Age-Stratified Incidence of Enteric Fever and Vaccination Implications in Bangladesh, Nepal and Pakistan: Results of the Surveillance for Enteric Fever in Asia Project
Denise Garrett, Sabin Vaccine Institute

Decline in Typhoid Fever Incidence in Kibera, an Urban Informal Settlement in Nairobi, Kenya
Eric D. Ng'eno, Washington State University

Incidence of Typhoid and Paratyphoid Fevers among Adolescents and Adults in Yangon, Myanmar
Win Thandar Oo, University of Otago

Validity of Reported Antibiotic Use among Suspected Enteric Fever Cases in Nepal, Bangladesh and Pakistan
Krista Vaidya, Dhulikhel Hospital

PathogenWatch: Fast and Interactive Genomic Surveillance of _Salmonella_ Typhi, an Example from a Retrospective Study in the Philippines
Silvia Argimón, Centre for Genomic Pathogen Surveillance

Tell Me Why: Immunology

Truc Bach

SESSION MODERATED BY:
Kim Mulholland, Murdoch Children's Research Institute & Richelle Charles, Massachusetts General Hospital

Long Term Persistence of Antibodies to Typbar-TCV Vaccination
Krishna Mohan, Bharat Biotech International

Host Gene Expression Signatures for Enteric Fever Diagnosis
Christoph Blohmke, University of Oxford

Measurement of Antibody Dependent Neutrophil Phagocytosis and the Respiratory Burst against _Salmonella_ Typhi
Mari Johnson, Oxford Vaccine Group

On the Early Cellular Immune Response during _Salmonella_ Typhi Infection
Marije Verheul, University of Oxford

Anti-Vi IgG and IgA Persistence following Immunisation with Vi Conjugate and Polysaccharide Vaccines
Elizabeth Jones, Oxford Vaccine Group

Stem Cell-Derived Gut Organoids and Macrophages as an _In Vitro_ Model for Studying the Interactions of _S._ Typhi and _S._ Paratyphi A with the Human Host
Emily Lees, University of Cambridge & Wellcome Trust Sanger Institute

THURSDAY, MARCH 28

8:30-10:00 Economic Evaluations of Disease Burden and Vaccination Strategies: New Evidence, Future Methods, and Implications for Vaccination Decision-Making

Grand Ballroom

SYMPOSIUM SESSION CHAIRED BY:
Vittal Mogasale, International Vaccine Institute

Surveillance for Enteric Fever in Asia Project (SEAP) II: Health Facility Cost of Illness Preliminary Results
Nelly Mejia Gonzalez, Centers for Disease Control and Prevention

Severe Typhoid Fever Surveillance in Africa Programme (SETA): Patient Cost of Illness Preliminary Results
Enusa Ramani, International Vaccine Institute

Forecasting Demand for the Typhoid Conjugate Vaccine in Low- and Middle-Income Countries
Clint Pecenka, PATH

Costs of Typhoid Conjugate Vaccine Delivery Strategies in Navi Mumbai, India
Dayoung Song, International Vaccine Institute

Cost-Effectiveness of Typhoid Vaccination Strategies: Evidence Gaps and Recommended Methods
Virginia (Ginny) Pitzer, Yale School of Public Health

10:00-10:30 Coffee Break

Foyer/Fansipan Ballroom

10:30-12:00 Concurrent Oral Abstract Sessions 9 & 10

Don't Let Me Down: From Data to Policy

Grand Ballroom

SESSION MODERATED BY:
Mathuram Santosham, Johns Hopkins University & Tony Marfin, PATH

Utilization of Healthcare Services for Enteric Fever under National Health Insurance Program in Selected Districts of Nepal
Palpasa Kansakar, Health Insurance Board, Nepal

Healthcare-Seeking Patterns for Individuals with Suspected Enteric Fever
Alexander Yu, Stanford University

The Long and Winding Road: Genomics

Truc Bach

SESSION MODERATED BY:
Firdausi Qadri, icddr,b & Gordon F. Dougan, University of Cambridge

Assessment of Population Structure and Antimicrobial Resistance Pattern of *Salmonella* Typhi Isolates using Whole Genome Sequencing Data in Bangladesh
Sadia Isfat Ara Rahman, icddr,b

Integration of Transcriptomic and Genomic Data Reveals Important Aspects of the Early Host Response to *Salmonella* Typhi Infection
Amber Barton, University of Oxford

Typhoid Fever in the U.S. Pediatric Population and the Potential Benefits of New Vaccines
Grace Appiah, Centers for Disease Control and Prevention

Phenotypic and Genotypic Analysis of Ciprofloxacin Treatment on Phylogenetically-Related Invasive *Salmonella* Typhimurium
Sushmita Sridhar, Wellcome Sanger Institute

A Multidisciplinary Approach to Increase Awareness and Strengthen the Case for the Introduction of a Vaccine against Invasive Nontyphoidal *Salmonella*
Gianluca Breghi, Fondazione Achille Sclavo

Comparative Genome and Transcriptome Analysis of Antibody Resistant and Susceptible Invasive African *Salmonella* Typhimurium Isolates
Edna Ondari, Swiss Tropical and Public Health Institute

Comparison of Cost of Illness of Extensively Drug-Resistant (XDR) vs. Non-XDR Typhoid Fever in Pakistan: Policy Implications for Typhoid Vaccine
Ashar Malik, Aga Khan University

DNA-Gyrase/Topoisomerase-IV Mutations and Antibiotic Susceptibility Patterns of *Salmonella* Paratyphi A
Mohammad Saiful Islam Sajib, Child Health Research Foundation

Epidemiology of Typhoid and Paratyphoid: Implications for Vaccine Policy
Senjuti Saha, Child Health Research Foundation

The Role of Genomics in Typhoid Control: Sentinel Traveler Surveillance, In-Host Evolution, and Transmission Dynamics
Zoe Dyson, University of Cambridge, University of Melbourne & Monash University

12:00-13:30 Lunch & Posters

JW Café/Fansipan Ballroom

13:30-15:00 Oral Abstract Session 11

Grand Ballroom

Magical Mystery Tour: The Late Breakers

SESSION MODERATED BY:
Farah Qamar, Aga Khan University & Myron (Mike) Levine, University of Maryland School of Medicine

Assessment of Humoral and Cellular Responses to Vi Polysaccharide Vaccine as a Booster after Vi Conjugate Prime
Thomas Bentley, Oxford Vaccine Group

Extensively Drug Resistant Typhoid Fever in Karachi, Sindh: An Analysis of Lab Based Surveillance Data, 2018
Ishfaque Hussain Memon, FELTP

Emergence of Azithromycin Resistance in Typhoidal *Salmonella* in Dhaka, Bangladesh
Senjuti Saha, Child Health Research Foundation & Stanford University

***Salmonella* Non-Typhi Stool Excretion after Bloodstream Infection in DRC: Proportion and Genetic Similarity between Paired Blood and Stool Isolates**
Marie-France Phoba, National Institute for Biomedical Research

Community-Based Incidence of Typhoid in India
Jacob John, Christian Medical College, Vellore

A Contagious City: 120 Years of Typhoid Control and Eradication in Oxford (1840-1960)
Claas Kirchhelle, University of Oxford

15:00-15:15 Coffee Break

Foyer/Fansipan Ballroom

15:15-16:45 Imagine: Global Action for Local Impact Toward Elimination

Grand Ballroom

PLENARY SESSION MODERATED BY:
Denise Garrett, Sabin Vaccine Institute &
Duncan Steele, Bill & Melinda Gates Foundation

Data Gaps as Obstacles to Elimination
Jeffrey (Jeff) Stanaway, Institute of Health Metrics and Evaluation

Considerations for Typhoid Elimination
John A. Crump, University of Otago

A Timeline for Typhoid Elimination
Stephen Luby, Stanford University

The Role of Vaccination Towards Elimination
Phionah Atuhebwe, World Health Organization Regional Office for Africa

16:45-17:05 Closing Session

Grand Ballroom

Closing Keynote Address
Anita Zaidi, Bill & Melinda Gates Foundation

Meeting Adjournment
Denise Garrett, Sabin Vaccine Institute

PROGRAM

TUESDAY, MARCH 26

8:30 Opening Session

Grand Ballroom

Welcome Remarks
Amy Finan, Sabin Vaccine Institute

Welcome Remarks and Housekeeping Items
Denise Garrett, Sabin Vaccine Institute

Opening Keynote Address
Kathleen Neuzil, University of Maryland School of Medicine

8:50 Come Together: Building a Multisector Toolkit

Grand Ballroom

PLENARY SESSION MODERATED BY
Eric Mintz & Jason Andrews

Enteric fever control and prevention requires coordination and collaboration across many different sectors, including vaccinology, water and sanitation, diagnostics, clinical care, and immunization, not to mention surveillance, modelling, advocacy and more. It has taken all of us to get where we are today, and it will take all of us to move forward for local impact. This session will jump-start the conference by exploring how a multi-pronged, multi-disciplinary approach can leverage all of our combined and varied strengths as we work toward the shared goal of eliminating typhoid and other invasive salmonelloses.

Where Are We With Diagnosing Typhoid?
Stephen Baker, University of Oxford

Low-Cost PCR-Based Microbial Quantification Methods for Water Quality Control in the Developing World
Michael Hoffmann, California Institute of Technology

Integrating WASH/Hygiene Behaviour Change Interventions into Routine Immunization Programme to Maximise Benefits: WaterAid's Experiences from Pilot to Scale
Om Prasad Gautam, WaterAid

Typhoid Conjugate Vaccine Development: The Last Mile?
Sushant Sahastrabuddhe, International Vaccine Institute

9:50-10:15 Coffee Break

Foyer/Fansipan Ballroom

10:15 Carry that Weight: Burden of Disease

Grand Ballroom

CONCURRENT ABSTRACT SESSION 1 MODERATED BY
Dennis Chao & Robert F. Breiman

Tenacious Endemic Typhoid Fever in Samoa: Is Short-Cycle (Chronic Carriers) or Long-Cycle (Water-Borne) Transmission Mainly Maintaining Endemicity?

Myron (Mike) Levine, University of Maryland School of Medicine

Myron Levine[1], Take Naseri[2], Robert Thomsen[2], Michael Sikorski[1], Savitra Rambocus[3], Sachin Desai[1]

[1]Center for Vaccine Development and Global Health, University of Maryland School of Medicine, [2]Samoa Ministry of Health, [3]Micribiological Diagnostic Unit, University of Melbourne

BACKGROUND

Typhoid fever has been tenaciously endemic in Samoa at a moderate incidence rate, since the 1960s, despite improvements in water and sanitation infrastructure serving much of the population and low young-child mortality. There are two main populated islands, Upolu (78% of population; N=152,472) and Savaii (22%; N=43,507). Blood culture-confirmed cases of typhoid were reviewed for the period 2009-2018 to gain insights on the epidemiology of typhoid fever in this setting.

METHODS

Blood culture availability has been consistent on Upolu (except for occasional 1-3 week stockouts of media) since 2009 but has been inconsistent on Savaii. Blood culture data were reviewed to determine the occurrence of typhoid on Upolu by age, month of the year, and village of residence to gain insights on transmission, identify high-risk groups, and establish targets for use of typhoid vaccine.

RESULTS

Samoa has rainfall throughout the year, albeit less from June through September. Periodic cyclones hit Samoa, sometimes inundating downtown Apia (capital). Confirmed typhoid appears throughout the year on Upolu, with no evidence of seasonality. Data from 2015-2018 (through September 30, 2018) were reviewed to ascertain the distribution of all 309 cases by decennial age groups. Thus, 22% of all cases occurred among children <10 years old; 25% of cases were 10-19 year olds, 22% were 20-29 year olds, 17% were 30-39 year olds, and 9% were 40-49 year olds. Cumulatively, ~95% of all cases of typhoid occur among persons <50 years of age. Most cases on Upolu occur either within the capital or along the coastal road from Apia westward. These are also the most populous areas. While most household have access to water, a notable fraction of piped water is untreated; ~80% of households in high typhoid-endemic areas use concrete septic tanks.

CONCLUSIONS

Intensive epidemiological studies will be needed to decipher the modes of transmission of typhoid in Samoa. Nevertheless, vaccines may be able to diminish the susceptibility of the at-risk population. Mass vaccination with high coverage among all Samoans <50 years of age (who account for ~95% of all cases) should drastically diminish the typhoid burden.

Illness, Severity, and Outcomes among Enteric Fever Cases: Data from the Surveillance for Enteric Fever in Asia Project (SEAP)

Caitlin Barkume, Sabin Vaccine Institute

Ashley Tate[1], **Caitlin Barkume**[2], Denise Garrett[2], Samir Saha[3], Jason Andrews[4], Farah Qamar[5], Stephen Luby[4], Kashmira Date[6]

[1]CDC Foundation, [2]Sabin Vaccine Institute, [3]Child Health Research Foundation, [4]Stanford University, [5]Aga Khan University, [6]Centers for Disease Control and Prevention

BACKGROUND

Enteric fever, caused by *Salmonella* Typhi and *Salmonella* Paratyphi, can lead to severe illness including prolonged hospital stays and clinical complications. The Surveillance for Enteric Fever in Asia Project (SEAP), a prospective, population-based surveillance study, aims to characterize the burden of enteric fever, including severity of illness and outcomes, in selected settings in Bangladesh, Nepal, and Pakistan.

METHODS

We analyzed clinical data from blood culture confirmed enteric fever cases enrolled at SEAP site hospitals (outpatient and inpatient) from September 2016 – October 2018 to assess severity of illness and outcomes of infection. We examined age, time to seek care, hospitalization, length of hospital stay, and complications of enteric fever at the enrollment visit to assess indicators of severe illness.

RESULTS

Among 3,286 blood culture confirmed enteric fever cases enrolled at SEAP hospitals in the three countries, 1,200 (37%) were hospitalized (Nepal 110/400 (28%), Bangladesh 682/1993 (34%), Pakistan 408/893 (46%)). The median duration of fever prior to seeking care was 5 days in Nepal, 7 days in Bangladesh, and 6 days in Pakistan. Significantly more typhoid cases were hospitalized compared with paratyphoid cases in Pakistan (48% vs. 26%, p<0.0001). At least one complication was verified by chart review at the enrollment visit among 32 (29%), 19 (3%), and 28 (7%) hospitalized cases in Nepal, Bangladesh, and Pakistan, respectively; complications were most

common among children 5 – 15 years old. The most commonly identified complications were hepatitis (21%) and pulmonary complications (14%). Complications were over twice as common among patients with typhoid compared with paratyphoid (7% vs 3%). The majority of cases with a complication were discharged after a median hospital stay of 7 days versus 5 days for those with no complications identified. Approximately 12% of all blood culture confirmed cases reported symptoms within a 6-week follow-up period, for which 66% sought additional healthcare.

CONCLUSIONS

A high proportion of hospitalizations and complications were noted among blood culture confirmed typhoid cases at SEAP sites. This highlights the need for implementing enteric fever prevention and control measures in these settings, including the new typhoid conjugate vaccine.

The Burden of Culture-Confirmed Enteric Fever in an Urban Slum: An Ongoing Community-Based Longitudinal Cohort in Delhi, India (Tier 1 SEFI site)

Bireshwar Sinha, Society for Applied Sciences

Bireshwar Sinha[1], Alok Arya[1], Nidhi Goyal[1], Ananya Thupaki-Sreepurna[1], Ankita Dutta[2], Deepak More[1], Chandra Mohan Kumar[2], Temsunaro Rongsen-Chandola[1]

[1]Society for Applied Studies, [2]Abdul Hameed Centenary Hospital, New Delhi

BACKGROUND

The community-based active surveillance component of the Surveillance of Enteric Fever in India (SEFI) study was initiated in 2017 in 4 sites in India i.e. Vellore, Pune, Delhi, Kolkata with the primary objective to estimate the overall and age-specific burden of culture-confirmed typhoid fever in the community among children aged <15 years. Here we describe some preliminary findings from the Delhi site.

METHODS

A prospective cohort of 6000 children (6m-15y) is followed-up in a resource-poor-urban-setting of Delhi for febrile illnesses with a mandatory weekly-contact for a period of 2 years. Children with fever are contacted daily and those with 3-consecutive-days of reported fever are evaluated in a study-clinic by a physician; blood cultures are sent if fever present in last 12 hours or on clinical suspicion. Data collection is web-based through tablets.

RESULTS

6183 children were screened and 6000 were enrolled. Of them, 48% were female; 62 (1.1%) received typhoid vaccination. Till 31st August 2018, 3922 person-years of follow-up was completed, of which 27%, 41%, and 32 % are contributed by children aged 6m-<5y, 5y-<10y and ≥10y, respectively. There were 4291 fever episodes with the highest incidence in the 6m-<5y age-group i.e. 1782 episodes; incidence rate 164 (95%CI 156 to 172)/100 person-years. The median duration of the fever was 2 days (IQR 1 to 3). 1244 episodes of suspected typhoid fever (≥3 consecutive days of fever) were reported; highest incidence in 6m-<5y age-group; 48 (95%CI 44 to 52) /100 person-years. A total of 19 cases were culture-positive for enteric fever of which 15 are *S.Typhi* and 4 are *Paratyphi*; all presented with fever, one had diarrhea as an additional symptom; one was hospitalized; all recovered without any sequelae. The overall incidence rate of enteric fever was 484.5 (95%CI 291.7 to 756.5) /100000 person-years; highest in the 5 to <10 years age-group 552.5 (95%CI 252.6 to 1084.1)/100000 person-years. On Anti-microbial-susceptibility-testing, 5 and 13 of the 19 cases were resistant to ciprofloxacin and pefloxacin, respectively.

CONCLUSIONS

The preliminary data show high-burden of enteric fever; completion of two-years of follow-up will help to better capture the seasonality; age-specific incidence across the different regions.

Spatial and Temporal Patterns of Typhoid and Paratyphoid Outbreaks: A Worldwide Systematic Review, 1990-2016

Vittal Mogasale, International Vaccine Institute

Vittal Mogasale[1], Samuel Kim[2], Kang Sung Lee[1], Jean-Louis Excler[1], Sushant Sahastrabuddhe[1], Florian Marks[1], Jerome H. Kim[1]

[1]International Vaccine Institute, [2]Imperial College London, London, United Kingdom

BACKGROUND

An analysis of global spatial and temporal distribution of enteric fever outbreaks and their risk factors is useful in enhancing the evidence on enteric fever disease burden. The number, size and location of enteric fever outbreaks worldwide are important factors to consider in estimating the disease burden.

METHODS

We conducted a systematic review of enteric fever outbreak data using multiple databases from January 1st 1990 to December 31st 2016 and classified them by time, place, diagnostic methods and drug susceptibility to develop spatial maps.

RESULTS

There were 136,238 cases in 279 identified outbreaks. The size of outbreak ranged from one to 30,000. Fifty-three percent of outbreaks occurred in Asia, 14% in Africa and 13% in Oceania, and the rest in other regions. Fourty-six percent of outbreaks specified confirmation by blood culture, and 82 outbreaks reported drug susceptibility, of which 54% were multi-drug resistant. Paratyphoid outbreaks were less common compared to typhoid (22 *vs.* 255), although more prevalent in Asia than Africa. Risk factors were multi-factorial with contaminated water being the main factor.

CONCLUSIONS

Enteric fever outbreak burden remains high in endemic LMICs and, despite its limitations, outbreak data provides valuable contemporary evidence in prioritising resources and public health policies and actions. This review highlights geographical locations where urgent attention is needed for enteric fever control and calls for global action.

Mortality Attributed to Ileal Perforations: Prospective Data from a Multi-Centers Enteric Fever Surveillance Project in Pakistan

Saqib Qazi, Aga Khan University Hospital

Noureen Abdul Malik[1], Tahir Yousafzai[1], Nasir Saddal[2], **Saqib Qazi**[3], Caitlin Barkume[4], Denise Garrett[4], Farah Qamar[3], Neelam Sadrudin[3]

[1]Aga Khan University, [2]National Institute of Child Health, [3]Aga Khan University Hospital, [4]Sabin Vaccine Institute

BACKGROUND

Surveillance of enteric fever in Asia project (SEAP) is a prospective study design to estimate burden of enteric fever in Pakistan, Nepal and Bangladesh. Data on clinical manifestation, severity of illness, anti-microbial resistance pattern and cost of illness are obtained. Here we report the data of patients with ileal perforations from Pakistan who were enrolled in the study and died during or post-operatively.

METHODS

Surgical data was collected from Aga Khan University hospital (AKUH), Jinnah Post Graduate Medical Center (JPMC), Kharadar General Hospital (KGH) and National Institute of Child Health (NICH) Karachi. Cases of ileal perforation with or without blood/tissue culture proven S.Typhi were eligible to enroll. Ileal perforations due to trauma or any other etiology were excluded. A trained research nurse and assistant under the supervision of a surgeon screened and enrolled the participants. Data was recorded using a structured electronic questionnaire in tablets.

RESULTS

During January 2016 to October 2018, a total of 84 cases of ileal perforation were enrolled from AKUH, KGH and NICH. All cases underwent surgery and 100% recovered at KGH (n=1) and AKUH (n=12). Out of 71 patients with perforations from NICH, 9 died (9/71;13%) due to post-surgical complications. The average length of hospital stay ranged from 03 day to 52 days in these three hospitals. At JPMC the surveillance was initiated on 01 April 2018 and total 78 cases of ileal perforations were enrolled until October 2018. Out of 78, 06 (8%) patients died post operatively. The length of hospital stay ranged from 01 to 27 days at JPMC. At NICH, the age of children who died ranged from 6 months to 12 years and at JPMC, it ranged between 20-50 yrs. Mostly, the patients who died belonged to the remote areas of interior Sindh rather than Karachi city. The most common post-operative complications were hemodynamic instability, wound infection and pulmonary complications.

CONCLUSIONS

Ileal perforation due to suspected enteric fever is not un-common in Pakistan. Patients with ileal perforation are at high risk of mortality due to post-operative complications. Introduction of typhoid vaccine in national program, availability of safe drinking water and environmental sanitation are recommended.

The Global Burden of Nontyphoidal *Salmonella* Invasive Disease: A Systematic Analysis for the Global Burden of Disease Study 2017

Andrea Parisi, The Australian National University

Jeffrey D. Stanaway[1], **Andrea Parisi**[2], Kaushik Sarkar[3], John A. Crump[4]

[1]University of Washington, [2]The Australian National University, [3]Malaria No More, [4]University of Otago

BACKGROUND

Nontyphoidal *Salmonella* invasive disease (iNTS) is a major cause of global morbidity and mortality with malnourished children, those with recent malaria, and HIV-infected adults being at particular risk of disease.

METHODS

To provide complete estimates of iNTS disease burden, we conducted a systematic review of scientific databases and grey literature and estimated iNTS incidence and mortality by year, age, sex, and geographical location using DisMod-MR, a Bayesian meta-regression tool. We estimated case fatality by age, HIV-status, and socio-demographic development. In addition, we calculated HIV attributable fraction and estimated health gap metrics including disability adjusted life years (DALYs).

RESULTS

We estimated that there were 534.6 (95% uncertainty interval [UI] 409.0 – 705.0) thousand cases of iNTS disease in 2017 with the highest incidence rates in sub-Saharan Africa and in children under age of 5 years. There were 77.5 thousand (95% UI 46.4–122.8) deaths of which 24.3 thousand (95% UI 16.9–32.9) were attributable to HIV in 2017. The remaining 59.1 (95% UI 33.3–98.1) thousand deaths non-attributable to HIV accounted for 4.26 million (95% UI 2.38–7.38) DALYs in 2017. Mean all-age case fatality was 14.5% (95% UI 9.18–21.1), with higher estimates among children and elderly, HIV-infected, and in areas of low socio-demographic development.

CONCLUSIONS

We present the first iNTS disease estimates as part of the Global Burden of Diseases Study (GBD) summarizing data from 1990 to 2017. Given the high disease burden particularly in children, elderly, and HIV-infected, it is crucial to investigate sources and transmission pathways of iNTS disease to implement effective preventive and control measures.

10:15 We Can Work It Out: Vaccine Development

Truc Bach

CONCURRENT ORAL ABSTRACT SESSION 2 MODERATED BY
Krishna Ella & Laura Martin

Age-Associated Heterogeneity of Ty21a-Induced T Cell Responses to HLA-E Restricted *Salmonella* Typhi Antigen Presentation

Marcelo B. Sztein, University of Maryland School of Medicine

Mark E. Rudolph, Monica A. McArthur, Laurence S. Magder, Robin S. Barnes, Wilbur H. Chen, **Marcelo B. Sztein**

University of Maryland, Baltimore

BACKGROUND

Human-restricted Salmonella enterica serovar Typhi (*S.* Typhi) is the causative agent of typhoid fever—a life-threatening disease of great global health significance, particularly in the developing world. Ty21a is an oral live-attenuated vaccine that protects against the development of typhoid disease in part by inducing robust T cell responses, among which multifunctional CD8+cytotoxic T lymphocytes (CTL) play an important role. Following Ty21a vaccination, a significant component of adult CTL have shown to be targeted to *S.* Typhi antigen presented by the conserved major histocompatibility complex (MHC) class Ib molecule, human leukocyte antigen-E (HLA-E). *S.* Typhi challenge studies have shown that baseline, multifunctional HLA-E responsive T cells are associated with protection from, and delayed onset of, typhoid disease. However, despite the overwhelming burden of typhoid fever in school-aged children, and due to limited availability of pediatric samples, incomplete information is available regarding these important HLA-E-restricted responses in children, even though studies have shown that younger children may be less likely to develop robust cell mediated immune (CMI) responses than adults following vaccination.

METHODS

To address this gap, we have studied this phenomenon in depth by using mass cytometry to analyze pediatric and adult T cell responses to HLA-E-restricted *S.* Typhi antigen presentation, before and after Ty21a vaccination.

RESULTS

Herein, we show variable responses in all age strata following vaccination among T effector memory (T_{EM}) and T effector memory CD45RA+(T_{EMRA}) cells based on conventional gating analysis. However, by utilizing the dimensionality reduction tool tSNE (t-distributed Stochastic Neighbor Embedding), we are able to identify diverse, highly multifunctional gut-homing-T_{EM} and T_{EMRA} clusters of cells which are more abundant in adult and older pediatric participants than in younger children.

CONCLUSIONS

These findings highlight a potential age-associated maturation of otherwise conserved HLA-E restricted T cell responses. Such insights, coupled with the marked importance of multifunctional T cell responses to combat infection, may better inform future pediatric vaccination strategies against *S.* Typhi and other infectious diseases.

Preclinical Development of a Trivalent Typhoid-Nontyphoidal *Salmonella* Glycoconjugate Vaccine for sub-Saharan Africa

Scott Baliban, University of Maryland School of Medicine

Raphael Simon[1], **Scott Baliban**[1], Andrew Lees[2], Sharon Tennant[1], Krishna Mohan[3], Krishna Ella[3], Myron Levine[1]

[1]University of Maryland, Baltimore, [2]Fina Biosolutions, [3]Bharat Biotech

BACKGROUND

Typhoid fever and invasive nontyphoidal *Salmonella* (iNTS) infections with serovars Enteritidis (SE) and Typhimurium (STm) and monophasic variant I 4,[5],12:i:- are major pediatric health problems in sub-Saharan Africa. Typhoid has high complication rates, and iNTS infections have high case fatality rates; moreover, emerging antimicrobial resistance is diminishing treatment options. Typbar-TCV™ (Vi conjugated to tetanus toxoid, Bharat Biotech, India), licensed in India and pre-qualified by the World Health Organization, elicits durable immunity when administered to infants, but no iNTS vaccines are licensed or imminent. We have developed monovalent SE and STm glycoconjugate vaccines based on coupling lipopolysaccharide-derived core-O polysaccharide (COPS) to phase 1 flagellin protein (FliC) from the homologous serovar. We assessed here the immunogenicity and induction of functional antibodies in rabbits immunized with a trivalent formulation of iNTS COPS:FliC conjugates with Typbar-TCV™.

METHODS

New Zealand White rabbits were immunized (n=5/group) three times at two week intervals with buffer alone, monovalent SE COPS:FliC, bivalent iNTS COPS:FliC or the trivalent typhoid-iNTS conjugate formulation. Sera taken prior to immunization and after the final dose were assessed for IgG titers to the vaccine antigens by ELISA, COPS epitope specificity by adsorption and western blot analyses, functional antibacterial activity by serum bactericidal assay (SBA) and enhancement of opsonophagocytic uptake (OPA) into macrophages, and protective function after passive transfer into mice with subsequent iNTS challenge.

RESULTS

Rabbits immunized with the trivalent typhoid-iNTS glycoconjugate vaccine generated high geometric mean titers (GMT) and full seroconversion of serum IgG antibody to all three polysaccharide antigens. Equivalent anti-COPS responses were obtained in monovalent and multivalent formulations. Furthermore, anti-COPS IgG antibodies were directed primarily against serogroup-specific OPS epitopes. Responses to SE and STm FliC were lower relative to anti-COPS titers. Importantly, post-vaccination rabbit sera mediated functional SBA and OPA activity *in-vitro*, and protected mice (88-100% efficacy) after passive transfer against fatal challenge with virulent SE or STm Malian blood isolates.

CONCLUSIONS

A trivalent typhoid/iNTS glycoconjugate vaccine formulation comprised of SE and STm COPS:FliC conjugates and Typbar-TCV™ has been developed and is being advanced to clinical trials, with anticipated use to prevent pediatric invasive *Salmonella* infections in sub-Saharan Africa.

Development of a MAPS-Based Typhoid and Paratyphoid A Vaccine

Richard (Rick) Malley, Boston Children's Hospital

Yingjie Lu, Fan Zhang, Fan Zhang, Nicole Ma, Katherine Lucas, Olivia Ledue, **Richard Malley**

Boston Children's Hospital

BACKGROUND

The Multiple Antigen Presenting System (MAPS) is a promising alternative to traditional conjugation. This novel technology uses the affinity pair biotin-rhizavidin to generate a complex of polysaccharide and proteins. MAPS is a highly efficient way of generating antibody against polysaccharide. MAPS-based vaccines induce very robust, boostable and CD4+ T cell-dependent anti-polysaccharide antibody responses, as well as functional antibody and Th1/Th17cell response to carrier proteins, which may provide additional benefits over conventional conjugate technology.

METHODS

With support from the Bill and Melinda Gates Foundation, we have been developing individual as well as a combination of Vi- and paratyphi A O polysaccharide (OSP)-MAPS vaccines. Different potential carrier proteins (including CRM197, rEPA of Pseudomonas and a pneumococcal fusion protein AFF1) were evaluated; different doses of polysaccharides and their impact on immunogenicity of the individual and combination vaccines in several animal models (including mice, rabbits and guinea pigs) were studied. We compared the immune responses to individual vs. combination vaccines with respect to antibody responses and killing activity of sera. We have also evaluated the duration of antibody persistence as well as affinity maturation of antibodies using thiocyanate.

RESULTS

All Vi-MAPS vaccines showed excellent immunogenicity in mice, guinea pigs and rabbits. The presence of Vi-specific memory B cells present was confirmed by adoptive transfer into Rag mice. There was no evidence of interference when Vi- and paratyphi A OSP-MAPS were combined. Antibody responses for Vi after primary immunization with MAPS or conjugate reached peak at 2 weeks and dropped quickly to 50% of original activity in 2-6 weeks; the Vi antibody response boosted after second immunization. OSP antibody responses remained high up to 24 weeks after primary immunization and boosted 2-4 fold after a second immunization. Avidity analysis of antibody showed affinity maturation for both Vi and OSP MAPS.

CONCLUSIONS

Our preclinical results with a combination Vi- and OSP-MAPS vaccine strongly support the feasibility of this approach. The presence of memory B cells and affinity maturation suggest that the responses to this vaccine reflects CD4+ T cell-mediated IgG responses. Our approach has promise for Salmonella typhi and paratyphi, and also for other important salmonella and shigella species.

The Non-Specific Immunological Impact of Human Oral Vaccination with Live-Attenuated *Salmonella* Typhi

Shaun Pennington, Liverpool School of Tropical Medicine

Shaun Pennington[1], Daniela Ferreira[1], Eva Caamano-Gutierrez[1], Angela Wright[1], Stephen Gordon[1,2], Melita Gordon[2,3]

[1]Liverpool School of Tropical Medicine, [2]Malawi College of Medicine, [3]University of Liverpool

BACKGROUND

Epidemiological and immunological evidence suggests that some vaccines can reduce all-cause mortality through non-specific changes made to innate immune cells. We describe the non-specific immunological impact of oral vaccination with live-attenuated *Salmonella* Typhi strain Ty21a.

METHODS

We vaccinated healthy adults with Ty21a and assessed immunity in vaccinated volunteers (n=17) and controls (n=13). Peripheral blood samples were acquired at baseline (0 days), 14 days, 3 months and 6 months following vaccination. We assessed rested monocyte phenotype and also assessed cytokine production among monocytes, TCRγδ, MAIT cells, $CD4^+$ T cells, $CD8^+$ T cells and $CD20^+$ B cells, following *in vitro* stimulation with vaccine as well as unrelated antigens by flow cytometry.

RESULTS

Following vaccination with Ty21a, the expression of TLR-4, CD11b, CD16 and CD303 was upregulated on monocytes for at least 3 months and the expression of TLR-5, CD11c and CD64 was upregulated on monocytes

for at least 14 days. Linear discriminant analysis of principal components suggested that cytokine responses to vaccine-antigens as well as unrelated non-vaccine-antigens were altered amongst vaccinated volunteers over the 6 month study period.

CONCLUSIONS

Monocytes typically only persist in circulation for a single day. It is, therefore, reasonable to hypothesise that the relatively long-lived phenotypic changes which we have observed are a result of changes which have occurred at the progenitor level. It is unclear whether the altered cytokine responses which we observed are the result of altered antigen-presentation occurring *in vitro*, or whether these changes reflect fundamental changes among the adaptive immune cell population *in vivo*. Regardless, the changes which we have observed suggest that vaccination with live-attenuated *Salmonella* Typhi may enhance immune responses to subsequently encountered pathogens.

T Cell Mediated Immunity Elicited in Volunteers Following Immunization with the Live Oral *Salmonella* Paratyphi A Attenuated Vaccine Strain CVD 1902

Rezwanul Wahid, University of Maryland School of Medicine

Rezwanul Wahid, Karen Kotloff, Myron Levine, Marcelo Sztein

Center for Vaccine Development, University of Maryland School of Medicine

BACKGROUND

Salmonella Paratyphi A (PA) infection is responsible for a considerable proportion of enteric fever cases and no licensed vaccines are available for prevention of this important disease. T cell mediated immune (CMI) responses are considered to be an important component of the protective immunity against typhoidal *Salmonella*-infections. A candidate live oral PA vaccine (strain CVD 1902) was evaluated in a Phase 1 clinical trial to measure PA-responsive CMI responses in immunized volunteers.

METHODS

PBMC samples were collected from volunteers (n=12) before and 28 days after oral immunization with a single dose of 10^9 (n=6) or 10^{10} (n=6) CFU of CVD 1902 and placebo controls (n=4). T effector/memory (T_{EM}) mediated PA-responsive cell "functions" (e.g., expression/production of CD107a, interferon(IFN)-g, interleukin(IL)-2 and tumor necrosis factor(TNF)-a) were measured following ex-vivo stimulation of PBMC with PA-infected autologous Epstein-Barr virus (EBV)-B cell targets using multichromatic flow cytometry assay.

RESULTS

Post-vaccination increases in PA-responsive CD69+CD8+ T_{EM} cells expressing CD107a or producing IFN-g, IL2 and/or TNF-a in vaccinees (pooled, n=12), were higher than those observed in placebo controls (n=4). These increases in two or more functions (CD8+ responders) were observed in 58% (7/12) of the vaccinees. Vaccine elicited PA-responsive CMI responses in CD8+ responders (n=7), were predominantly mediated by multifunctional cells and were comprised of similar proportions of 2+, 3+ and 4+ multifunctional subsets. An equal proportion of those cells also co-expressed, or not, the gut-homing marker integrin a4b7. Similarly, CD69+CD4+ T_{EM}-mediated responses were elicited in 50% (6/12) vaccinees showing post-vaccination increases in two or more functions (CD4+ responders). Altogether, 8 out of 12 (67%) volunteers were responders for CD8-and/or CD4-mediated vaccine responses. No responders were observed in the placebo controls (0/4). Moreover, a positive correlation was observed with vaccine elicited PA-responsive IFN-g+ ($p<0.02$) CD8+ and CD4+ T_{EM} cells.

CONCLUSIONS

Immunization with a single dose of CVD 1902 elicited CMI responses mediated by PA-responsive CD8+ and CD4+ T_{EM} multifunctional cells. These results supports further evaluation of CVD 1902 as a potential vaccine candidate against paratyphoid A fever including the immunogenicity elicited by two doses administered at different intervals.

The Immunogenicity and Safety of ZyVac-TCV, a Typhoid Conjugate Vaccine in Healthy Indian Subjects: Results of First Comparative Clinical Trial

Pavankumar Daultani, Cadila Healthcare Limited

Pavankumar Daultani, Pradip Patel, Ravindra Mittal, Jayesh Sanmukhani, Kapil Maithal

Cadila Healthcare Limited, Ahmedabad, Gujarat, India

BACKGROUND

Several new generation typhoid conjugate vaccines (TCVs) have been developed to overcome limitations of the conventional polysaccharide vaccines. This study was conducted to compare the immunogenicity and safety of ZyVac-TCV, a typhoid Vi polysaccharide-tetanus toxoid conjugate vaccine (Vi-TT) developed by M/s. Cadila Healthcare Ltd. with the commercially available Vi-TT, Typbar-TCV of M/s. Bharat Biotech International Ltd. This was the first study comparing TCVs of two different manufacturers.

METHODS

This randomized, single-blind, non-inferiority study was conducted at 8 tertiary care/multispecialty hospitals across India during Jun-Dec 2016 and 240 healthy subjects of 6 months to 45 years were enrolled. Pediatric subjects (<18 years) were enrolled after completion of day 21 safety follow-up of adult subjects. Participants received a single-dose of allocated study vaccine at the baseline and were then followed up for 6 weeks. Blood samples were collected before vaccination and 6 weeks post-vaccination to evaluate anti-Vi IgG antibody titre. The immunogenicity variables included seroconversion (≥4-fold rise in antibody titre) and geometric mean titre (GMT) of antibodies, while safety variable included adverse events (AEs) reported during the study.

RESULTS

A total of 117/119 subjects (Adults-58, Pediatric-59) in ZyVac-TCV group and 119/121 subjects (Adult-60, Pediatric-59) in Typbar-TCV group completed the study. The seroconversion rate with ZyVac-TCV (overall-94.8%, adult-96.6% & pediatric-93.1%) was non-inferior to Typbar-TCV (overall-91.6%, adult-91.7% & pediatric-91.5%). The GMT of antibodies (in EU/ml) after vaccination with ZyVac-TCV (overall-1121, adult-1411 & pediatric-891.1) and Typbar-TCV (overall-1104, adult-1199 & pediatric-1014) were also comparable (P>0.05). A total of 33.6% and 43.8% subjects in the ZyVac-TCV and Typbar-TCV group respectively reported AEs (P=0.11). The most common AE was pain at site of injection followed by fever while other AEs were reported with lesser frequency. All except one AE in Typbar-TCV group were mild-to-moderate in intensity.

CONCLUSIONS

ZyVac-TCV was found to be immunogenic and well tolerated in the target population and the immunogenicity and safety profile of ZyVac-TCV was comparable to the marketed comparator vaccine.

11:45-13:15 Lunch & Posters

JW Café/Fansipan Ballroom

POSTER EXHIBITION SPONSORED BY TUBEX®

13:15 Environmental Surveillance For Salmonella And Antimicrobial Resistance (AMR) Genes

Grand Ballroom

SYMPOSIUM SESSION CHAIRED BY
Gagandeep Kang & Venkata Raghava Mohan

Typhoid fever continues to be a burden on health care resources in low-income and middle-income countries of Asia and Africa, where vaccines would most likely be introduced. The emergence of antimicrobial resistant bacteria, and antimicrobial resistance genes in the aquatic environment (sewage, waste water) have important implications for human health. This symposium will bring together researchers, who have developed methods for detecting *Salmonella* and AMR genes in the environment, and those who have deployed these methods in Asia and Africa to generate evidence which could be potentially used in decision making for introduction of typhoid vaccines in these countries. The objective of the symposium is to discuss methods for environmental surveillance of *Salmonella* and antimicrobial resistance (AMR) genes, and to share findings from studies in Asia and Africa.

Approach for Harmonization and Quality Control of Environmental Surveillance Methods for Typhoid
John Scott Meschke, University of Washington

Environmental Surveillance for Typhoid in Kibera, an Informal Settlement in Nairobi, Kenya
Jennifer Verani and Jennifer Murphy, Centers for Disease Control and Prevention

Development and Application of Pilot *Salmonella* Typhi in Environmental Surveillance Program in Kolkata, India
Christine L. Moe, Emory University

Environmental Sampling as a Tool for Identification of High Typhoid Risk Settings
Jason Andrews, Stanford University

Environmental Surveillance for *Salmonella* and AMR Genes in Tamil Nadu, India
Sidhartha Giri, Christian Medical College, Vellore

Country Decision Making on Typhoid Conjugate Vaccine (TCV) Introduction: Potential Role of Environmental Surveillance
Adwoa Bentsi-Enchill, World Health Organization

15:15-15:45 Coffee Break

Foyer/Fansipan Ballroom

15:45 I Should Have Known Better: Antimicrobial Resistance

Grand Ballroom

CONCURRENT ORAL ABSTRACT SESSION 3 MODERATED BY
Chris Parry & Hubert Endtz

Antimicrobial Non-Susceptibility Among *Salmonella* Typhi and Paratyphi A Isolates – Preliminary Results from SEAP project

Muhammad Tahir Yousafzai, Aga Khan University

Muhammad Tahir Yousafzai[1], Farah Qamar[1], Denise Garrett[2], Jason Andrews[3], Caitlin Barkume[2], Kashmira Date[5], Steve Luby[3], Samir Saha[6]

[1]Aga Khan University, [3]Sabin Vaccine Institute, [4]Stanford University, [5]Centers for Disease Control and Prevention, [6]Child Health Research Foundation

BACKGROUND

Enteric fever, caused by the organisms *Salmonella* Typhi and Paratyphi A, is among the most common bacteremic illnesses in South Asia. Growing non-susceptibility to antibiotics especially ceftriaxone and fluoroquinolones, severely limit the treatment options. SEAP is a large, multi-center, prospective surveillance capturing data on the burden of enteric fever and the antimicrobial susceptibility of the isolates, in Bangladesh, Nepal, and Pakistan.

METHODS

We analyzed antimicrobial non-susceptibility of Typhi and Paratyphi A, isolated from hospitals (in- and out-patient department) and selected diagnostic centers of SEAP sites, during September 2016 to September 2018. Susceptibility testing were performed using CLSI guideline.

RESULTS

During the study period, 5,326 Typhi and Paratyphi A were isolated from SEAP network; Bangladesh (n=3,325), Nepal (n=1,092), and Pakistan (n=999). The majority of isolates were Typhi (86%) in all three countries. The rate of MDR (non-susceptibility to ampicillin, chloramphenicol and cotrimoxazole) isolates among *Salmonella* Typhi was low in Bangladesh (18%) and Nepal (##%), contrast to Pakistan (69%). Non-susceptibility to fluoroquinolone was high in all three countries (ranged 94% to 97%). In addition, there is an ongoing outbreak of XDR strains (non-susceptibility to third generation cephalosporin and fluoroquinolone, along with MDR); 85% of all currently isolated typhi strains are XDR.

Among Paratyphi A isolates, resistance pattern for flouroquinolones was similar to Typhi (non-susceptibility=97%), but proportion for MDR was low (1%) and none of them were non-susceptible to ceftriaxone. Cases with non-susceptible isolates were more likely to be hospitalized (38% vs. 29%, p<0.0001).

CONCLUSIONS

Our results show low proportion of MDR isolates among Typhi (18%) and Paratyphi A (1%) isolates and high rate of non-susceptibility to fluoroquinolone across the sties in Bangladesh and Nepal. This generate the hope of using first line of drugs. However, evolution of XDR strains in Pakistan is alarming and warrants i) urgent prevention typhoid using TCV and ii) practicing antibiotic stewardship by rational use of third generation cephalosporins in the typhoid endemic area with low prevalence of MDR.

Trends in Resistance to Fluoroquinolones and ESBLs among *Salmonella* Typhi Isolates from Patients at Outpatient Clinics in Nairobi, 2012-2016

Susan Kavai, Kenya Medical Research Institute

Susan Kavai[1], Mourine Kangogo[2], Anne Muigai[2], Sam Kariuki[1]

[1]KEMRI, [2]JKUAT

BACKGROUND

Typhoid fever caused by the bacterium *Salmonella enterica* serovar Typhi (*S.* Typhi) causes an estimated 25 million illnesses and approximately 200,000 deaths annually in developing countries. In addition, *Salmonella* Typhi is increasingly becoming resistant to the currently recommended drugs for treatment of typhoid including fluoroquinolones and extended spectrum β-lactams. There is limited data on surveillance of antimicrobial resistance in S. Typhi as this is not routinely carried out in Kenya. The main objective of this study was to determine the trends in Multi Drug Resistant (MDR) with emphasis on resistance to fluoroquinolones and ESBLs.

METHODS

This study utilized a quasi-experimental design focusing on archived samples collected for a period of 5 years (2012-2016). These isolates were obtained from patients who tested positive for *Salmonella* Typhi. The isolates were revived and subjected to various tests including serology, antibiotic susceptibility testing, in-vitro conjugation and polymerase chain Reaction.

RESULTS

All 287 isolates were confirmed to be S. Typhi through the serology tests. Among the 287 isolates 158 (55.5%) were found to be MDR to all first line classes of antimicrobials used in treatment, such as ampicillin, chloramphenicol

and sulfamethoxazole-trimethoprim. In addition to these, isolates were resistant to at least one of the currently recommended drugs of choice, either a β-lactam or a fluoroquinolone. This study observed resistances at 18.2% and 15.4% to fluoroquinolones and cephalosporins, respectively. Among the 34 isolates that had combined resistance to flouroquinolones and extended spectrum β-lactams, 2(5.8%) transferred resistance to *E. coli* strain J53 (Sodium azide resistant strain) by in-vitro conjugation. PCR tests revealed presence of bla_{TEM}, bla_{INT} and bla_{CTX-M} genes coding for resistance to β-lactams in 27(80%) of the isolates that had combined resistance to β-lactams and fluoroquinolones

CONCLUSIONS

In conclusion this study showed that a large proportion of isolates were at least resistant to one drug used in the test panel. Resistance was mostly observed in nalidixic acid in the flouroquinolones class of drugs and amoxicillin clavulanic acid which is a beta lactamase inhibitor. Heavy presence of the bla genes as well as the PAR genes was observed. This implied that these drugs may not be as effective as before.

Incidence and Antimicrobial Resistance Profile of *Salmonella* Bacteremia Among Children in sub-Saharan Africa: RTS,S/AS01 *Salmonella* Ancillary Study

Calman MacLennan, University of Oxford

Calman MacLennan[1], Ryan Wiegand[2], Nelli Westercamp[2], Samuel Kariuki[3], Simon Kariuki[4], Maxim Agnanji[5]

[1]University of Oxford, [2]Centers for Disease Control and Prevention, [3]KEMRI Nairobi, [4]KEMRI Kisumu, [5]Investigators of the Clinical Trials Partnership Committee

BACKGROUND

Robust up-to-date epidemiological data to support the development and implementation of new interventions including vaccines against iNTS disease are currently lacking. Our aim was to determine incidence and antimicrobial resistance profile of *Salmonella* bacteremia in children under five years of age across sub-Saharan Africa using data from the phase 3 RTS,S/AS01 malaria vaccine trial (NCT20866619).

METHODS

Children aged 6-12 weeks (n=6537) and 5-17 months (n=8922) from 11 sites were recruited and randomized to receive RTS,S/AS01 or comparator vaccines. They were followed up for a median of 38 and 48 months respectively between 2009 and 2014. Blood cultures were performed for all children with fever leading to hospital admission. *Salmonella* isolates were characterized by serotyping, antimicrobial sensitivity testing and whole genome sequencing.

RESULTS

260 microbiologically-confirmed cases of *Salmonella* bacteremia were detected during 50,280 person years of observation (PYO), with an overall incidence of 517 cases/100,000 PYO (95%CI 456-584). Incidence of bacteremia due to *Salmonella* Typhi (n=32, 12.3% of bacteremias) was 63.6 (95%CI 43.5-89.9), and that for nontyphoidal *Salmonella* (NTS; n=225, 86.5% of bacteremias) was 448 (95%CI 391-510) cases/100,000 PYO. 89.3% (n=201) of the 225 cases of iNTS disease were due to two serovars of *Salmonella*, *S.* Typhimurium (n=136, 60.4%) and *S.* Enteritidis (n=65, 28.9%). Incidence of *Salmonella* bacteremia varied from 0 in Bagamoyo, Tanzania; Kilifi, Kenya; and Lamberene, Gabon, to 1262 (95%CI 956-1635) in Kintampo, Ghana, and 1714 (95%CI 1369-2119) in Siaya, Kenya. NTS bacteremia, but not typhoid fever, was significantly associated with the number of malaria episodes during the trial, but NTS bacteremia was not reduced by RTS,S/AS01 compared with comparator vaccines (incidence rate ratio=0.83 (95%CI 0.63-1.10). Over 60% of isolates were multidrug resistant with reduced susceptibility to ampicillin (75%), cotrimoxazole (70%) and chloramphenicol (65%). 26% and 10% of isolates had reduced susceptibility to ciprofloxacin and ceftriaxone respectively.

CONCLUSIONS

These findings confirm *Salmonella* as a major and persistent cause of bacteremia among children under five years of age across sub-Saharan Africa, with *S.* Typhimurium, Enteritidis and Typhi as the three commonest serovars, and increasing breadth of antimicrobial resistance. A vaccine able to protect against these serovars could have a major public health impact.

Salmonella Typhi in Bangladesh: Exploration of Genomic Diversity and Antimicrobial Resistance

Arif Mohammad Tanmoy, Erasmus University Medical Center

Arif Mohammad Tanmoy[1], Emilie Westeel[2], Katrien De Bruyne[3], Johan Goris[3], Alex van Belkum[4], Samir Kumar Saha[5], Florence Komurian-Pradel[2], Hubert P Endtz[2]

[1]Erasmus University Medical Center, [2]Fondation Mérieux and Centre International de Recherche en Infectiologie (CIRI), [3]Applied Maths, [4]Data Analytics Unit, bioMérieux, [5]Child Health Research Foundation, Bangladesh Institute of Child Health, Dhaka Shishu Hospital

BACKGROUND

Typhoid fever, caused by *Salmonella enterica* serovar Typhi (*S.* Typhi), is a global public health concern due to increasing antimicrobial resistance (AMR). Characterization of *S.* Typhi genomes for AMR and the evolution of different lineages, especially in endemic countries such as Bangladesh, will inform public health professionals to better design and implement appropriate preventive measures.

METHODS

We studied whole genome sequences (WGS) of 536 *S.* Typhi isolates collected in Bangladesh during 1999-2013, and compared these with data from a recent outbreak in Pakistan, reported by Klemm et al. (2018) and a laboratory surveillance in Nepal by Britto et al. (2018) using core-genome MLST (cgMLST) and whole-genome SNP (wgSNP) analysis. We also compared the antibiotic susceptibility results of the isolates from Bangladesh against their resistance gene analysis.

RESULTS

WGS showed high sensitivity and specificity for prediction of ampicillin, chloramphenicol, cotrimoxazole, and ceftriaxone AMR phenotypes, but needs further improvement for ciprofloxacin (cip) resistance. cgMLST analysis showed almost similar differentiation among isolates like wgSNP analysis, except the former was not contrasting enough to resolute the existence of multiple lineages of H58 (genotype 4.3.1). wgSNP analysis also detected a new local lineage of genotype 4.3.1 named lineage Bd, which recently diverged into a sub-lineage (named Bdq) containing *qnr* genes associated with high-level cip-resistance. While looking at the background mutations for cip-resistance, we identified three different mutations, namely- *gyr*A-D538N, *gyr*A-N529S, and *parE*-A364V, which are not linked to AMR, rather different genotypes, respectively 4.3.1, 2.0 and 3.3. Genotype 4.3.1 was dominant in all three countries but formed country-specific clusters in the wgSNP maximum-likelihood phylogenetic tree. We found a ceftriaxone-resistant isolate with the $bla_{CTX\text{-}M\text{-}15}$ gene, but distinct genotype compared to extensively drug-resistant (XDR) isolates from Pakistan.

CONCLUSIONS

Different genotypes for ceftriaxone-resistance in Bangladesh and Pakistan suggests distinct source and geographical origin of AMR. Multiple independent genetic events leading to ciprofloxacin and ceftriaxone resistance took place in Pakistan, Nepal, and Bangladesh. These independent mutational events may enhance the risk of global spread of these highly resistant *S.* Typhi clones. In light of our findings, it is urgent to accelerate the preventive water, sanitation and hygiene measures and fast-track vaccination programs.

Molecular Mechanisms of Antimicrobial Resistance and Phylogenetic Relationship of *Salmonella* enterica from Febrile Patients in Yangon, Myanmar

Tin Ohn Myat, University of Medicine 1

Tin Ohn Myat[1], Khine Oo[1], Ambarish Biswas[2], Wah Htike[1], David Murdoch[3], John Crump[2], James Ussher[2]

[1]University of Medicine [1], Yangon, [2]University of Otago, Dunedin, [3]University of Otago, Christchurch

BACKGROUND

Data on causes of enteric fever are lacking from Myanmar. We sought to describe patterns and mechanisms of antimicrobial resistance, and to determine phylogenetic relatedness of Myanmar *S. enterica* isolates to each other and to strains from South and Southeast Asia.

METHODS

From 5 October 2015 through 4 October 2016, we collected blood for culture from febrile patients aged ≥12 years attending two hospitals in Yangon, Myanmar. We tested antimicrobial susceptibility and performed whole-genome sequencing to determine molecular mechanisms of antimicrobial resistance. We identified *S. enterica* strain type and analyzed phylogenetic relationships among Myanmar isolates, and for serovar Typhi with isolates from neighboring countries.

RESULTS

From 1,583 blood cultures, we isolated 153 (9.7%) pathogens. Among pathogens, 73 (47.7%) were *S. enterica*, of which 39 (53%) were serovar Typhi and 34 (47%) were serovar Paratyphi A. All *S. enterica* were resistant to fluoroquinolones but were susceptible to other antimicrobial classes. Fluoroquinolone resistance was associated with chromosomal mutations in the quinolone resistance-determining region (QRDR). Sixteen (41%) of 39 *S. enterica* Typhi isolates had a ciprofloxacin MIC of 8 µg/mL and two mutations in *gyr*A and one in *par*C while 22 (56%) had a ciprofloxacin MIC of 0.5-1 µg/mL and one mutation in *gyr*A. All *S. enterica* Paratyphi A had a ciprofloxacin MIC of 0.5-1 µg/mL and one mutation in *gyr*A and one in *par*C. Phylogenetic analysis showed that all *S. enterica* Typhi isolates belonged to 4.3.1 (formerly H58) subclade and formed two clusters. Cluster one consisted of isolates with three QRDR mutations and was most closely related to an Indian strain isolated in 2012. Cluster two included remaining *S. enterica* Typhi and was most closely related to two previous Myanmar isolates and more distantly to two isolates from India from 2012. All Myanmar *S. enterica* Paratyphi A were closely related.

CONCLUSIONS

While susceptible to other antimicrobial classes, *S. enterica* were resistant to fluoroquinolones, mediated by QRDR mutations. Two clusters of *S. enterica* Typhi subclade 4.3.1, phylogenetically related to strains from a neighboring country, are circulating in Yangon. Our findings form the basis for future surveillance and epidemiological studies of enteric fever in Myanmar.

Predicting the Impact of Typhoid Conjugate Vaccines on Antimicrobial Resistance

Virginia (Ginny) Pitzer, Yale School of Public Health

Samantha Kaufhold, Reza Yaesoubi, **Virginia Pitzer**

Yale School of Public Health

BACKGROUND

Empiric prescribing of antimicrobials in typhoid-endemic settings has increased selective pressure on the development of antimicrobial-resistant *Salmonella enterica* serovar Typhi. The introduction of typhoid conjugate vaccines (TCVs) in these settings may relieve this selective pressure, thereby reducing resistant infections and improving health outcomes.

METHODS

A deterministic transmission dynamic model was developed to simulate the impact of TCVs on the number and proportion of antimicrobial-resistant typhoid infections and chronic carriers. One-way sensitivity analyses were performed to ascertain particularly

impactful model parameters influencing the proportion of antimicrobial-resistant infections and the proportion of cases averted over ten years.

RESULTS

The model simulations suggested that increasing vaccination coverage would decrease the total number of antimicrobial-resistant typhoid infections, but not affect the proportion of cases that were antimicrobial resistant. In the base-case scenario with 80% vaccination coverage, 35% of all typhoid infections were antimicrobial resistant and 44% of the total cases were averted over ten years by vaccination. Vaccination also decreased both the total number and proportion of chronic carriers of antimicrobial-resistant infections. The prevalence of chronic carriers, recovery rates from infection, and relative fitness of resistant strains were identified as crucially important parameters.

CONCLUSIONS

Model predictions for the proportion of antimicrobial resistant infections and number of cases averted depended strongly on the relative fitness of the resistant strain(s), prevalence of chronic carriers, and rates of recovery without treatment. Further elucidation of these parameter values in real-world typhoid-endemic settings will improve model predictions and assist in targeting future vaccination campaigns and treatment strategies.

15:45 Here, There, Everywhere: Environmental Surveillance, Disease Modeling, And Geo-Spatial Analysis

Truc Bach

CONCURRENT ORAL ABSTRACT SESSION 4 MODERATED BY
Nicholas (Nick) Feasey & Supriya Kumar

Clinical and Genomic Data to Understand Transmission Patterns of Typhoid Fever and Inform Targeted Environmental Sampling in Blantyre, Malawi

Jillian Gauld, Institute for Disease Modeling & Lancaster University

Jillian Gauld[1,2], Peter J. Diggle[2], Alex M. Wailan[3], Franziska Olgemoeller[4], Nicholas R. Thomson[3], Jonathan M. Read[2], Nicholas A. Feasey[5]

[1]Institute for Disease Modeling, [2]Lancaster University, [3]Wellcome Sanger Institute, [4]Malawi-Liverpool-Wellcome Trust Clinical Research Programme, [5]Liverpool School of Tropical Medicine

BACKGROUND

There was a sharp increase in cases of typhoid fever in Blantyre, Malawi beginning in 2011. The majority of these cases have been identified as multi-drug resistant, and transmission continues today. Despite ongoing transmission, the key environmental niches and dominant transmission routes remain unknown, posing a challenge for targeting water, sanitation and hygiene (WASH) interventions and environmental surveillance for effective exposure monitoring. Integrating spatial distributions and genetic relatedness of clinical isolates of *Salmonella* Typhi may offer insight into the mechanisms of transmission occurring.

METHODS

Beginning in 2015, 341 *S.* Typhi isolates from cases presenting to Queen's Hospital, Blantyre were whole-genome sequenced, and households were geo-located. Variable regions of the sequences (i.e. highly recombinant and prophage regions) were excluded, leaving 400 informative single nucleotide polymorphisms (SNPs) across isolates. Resulting pairwise SNP distances were converted into informative variables for statistical modeling using multidimensional scaling.

RESULTS

Genetic patterns of *S.* Typhi isolates across Blantyre showed a heterogeneous distribution of genotypes, with spatial correlation occurring among isolates of cases living up to 2 kilometers apart. Risk factor analyses have identified cooking and cleaning with river water as a potential exposure pathway for *S.* Typhi in Blantyre, therefore we evaluated the ability of river catchment to explain the spatial patterns using a linear model with a spatial random effect, implemented in R statistical software. Results from the analysis indicate that the spatial genetic patterns seen across the city are influenced by three primary components: river catchment, close neighbors (living a maximum of 200 meters apart), and household units.

CONCLUSIONS

Classical field epidemiology has highlighted multiple water, sanitation and hygiene factors as being key drivers in the current Typhoid epidemic. Integration of these findings with spatial and genomic data highlight the potential role of river catchment areas in the transmission of *S.* Typhi in Blantyre. These findings will inform targeted environmental surveillance, to confirm key environmental exposures and monitor changes over time. Results from this study highlight the need to integrate complex data to understand the transmission of typhoid fever, which can be used to support the deployment of control measures such as pairing vaccines with targeted WASH interventions.

Optimisation of Culture and Molecular-Based Methods for Detection of *Salmonella* Typhi from Environmental Reservoirs under Laboratory Conditions

Jonathan Rigby, Liverpool School of Tropical Medicine

Jonathan Rigby[1], Nicholas Feasey[1], Satheesh Nair[2], Nicola Elviss[2]

[1]Liverpool School of Tropical Medicine, [2]Public Health England

BACKGROUND

Transmission of *Salmonella* Typhi is associated with inadequate WASH infrastructure. Whilst easy to culture from patients with typhoid fever, recovery from environmental niches have proved to be challenging, especially by culture. We have attempted to improve culture and molecular-based methods for the environmental detection of *S.* Typhi.

METHODS

Preliminary work tested media and techniques to select and isolate *S.* Typhi from Water, Food and Environmental samples. The primary method involved inoculating a primary broth; sub-culture in a secondary broth and a spread plate with chromogenic agar. The pathways involved Selenite Cysteine sub-cultured into both Bile and Iron Bile broths, and inversely, bile broths into Selenite Cysteine. Both primary and secondary broths were enumerated with the Miles and Misra Method. Mixed culture challenges, using five broths made of control strains were tested blindly and screened by PCR. Spiked river and pond waters; six, four and two months old, were concentrated with a filter. We optimised and multiplexed the q-PCR primer sets of the enteric fever PCR developed by PHE and streamlined it by removing the *S.* Paratyphi primers, then converted them into High Resolution Melt PCR using the EVAGreen intercalating dye.

RESULTS

Salmonella spp. grew strongly with all media whilst *E. coli* was significantly reduced by these pathways. From mixed culture, one correctly screened as negative. *S.* Typhi was isolated from remaining samples. Difficulties occurred when isolating from other *Salmonella* spp. and fungal colonies. *Salmonella spp.* was isolated successfully from the two-month-old water samples but not older. Slow growing contaminants shared blue colouration, however had distinctive morphologies. Multiplexed q-PCR effectively screened mixed cultures. High Resolution Melt gave average melt temperatures of: 82.7°C: *ttr*, 79.3°C: *tvi*B, 82.6°C: staG, 79.5°C: *sse*J.

CONCLUSIONS

Long-term water samples and mixed culture showed recovery of *S.* Typhi and field testing will allow better evaluation of efficacy. The q-PCR successfully screened samples when multiplexed, however further validation is required to determine sensitivity and specificity. The high-resolution melt PCR appears to have potential, however, *ttr* and *sta*G share similar melting points. Removing *ttr* may be beneficial as *Salmonella* spp. should already have been selected.

Environmental Surveillance for Targeting Typhoid Conjugate Vaccines: Drivers of Cost-Efficiency in Sub-National Programs

Brittany Hagedorn, Institute for Disease Modeling

Brittany Hagedorn[1], Jillian S. Gauld[1], Nicholas A. Feasey[2], Hao Hu[1]

[1]Institute for Disease Modeling, [2]Liverpool School of Tropical Medicine

BACKGROUND

Since the WHO prequalification of the Typhoid conjugate vaccine in January 2018, there has been motivation to introduce the vaccine across typhoid endemic countries as part of routine immunization, and implement catch-up campaigns for areas of the highest burden. Introducing vaccine in high incidence settings has been previously demonstrated to be cost-effective. However, with limited case reporting at the sub-national level, it is difficult for policy makers identify these high-risk areas within country. In this study, we evaluate the cost-efficiency of environmental surveillance as a tool for targeting catch-up vaccination campaigns.

METHODS

We conducted a simulation study with an integrated cost model. Using an individual-based mathematical model, we simulate potential heterogeneity in typhoid incidence across a country by dividing the simulation into transmission locales, which can be assigned to be either endemic, with incidence patterns of typhoid fever fit to hospital surveillance data from Blantyre, Malawi, or a low transmission setting. The cost model was built from a programmatic perspective, which was used to compare cost-effectiveness between combinations of environmental surveillance intensity, sensitivity, and heterogeneity in the underlying disease burden. We tested vaccination strategies that limit response only to locations that report positive environmental samples, and strategies that trigger national catch-up campaigns after any local detection.

RESULTS

Environmental surveillance-based catch-up campaigns are cost-effective for both national and sub-national response decisions, when compared to either a do-nothing or routine immunization strategy. Though dependent on the surveillance coverage and sensitivity, national and sub-national responses had average costs per capita of $4.84 ($2.92,$5.24) and $4.05 (2.95, $5.03), respectively. National strategies result in a greater burden reduction, but sub-national strategies were more cost-effective. The incremental portion of the population covered by environmental surveillance was a significant driver of disease burden for both national and sub-national strategies ($p < .001$). These results were consistent across assumptions of underlying heterogeneity of disease burden.

CONCLUSIONS

We found that environmental surveillance responsive catch-up vaccination campaigns are beneficial for reducing disease burden and are more cost-effective than routine strategies. This is particularly true when considering sub-national vaccination strategies, as long as the surveillance catchment area is adequate to obtain a representative sample.

Typhoid Environmental Surveillance Sampling Strategies and Adaptive Sampling Site Allocation Method: A Simulation Study for Wards 58 & 59, Kolkata

Yuke Wang, Emory University

Yuke Wang[1], Christine Moe[1], Ashutosh Wadhwa[2], Wolfgang Mairinger[1], Peter Teunis[1]

[1]Center of Global Safe WASH, Emory University, [2]Centers for Disease Control and Prevention

BACKGROUND

Detection of pathogens circulating in sewage can be used to monitor disease transmission in communities. Environmental surveillance (ES) of infectious organisms (e.g. poliovirus) has been used to complement clinical surveillance, in particular for tracking asymptomatic shedding. Although WHO published guidelines for ES for poliovirus in 2003, there is no systematic method to allocate sampling sites for ES. We developed an adaptive sampling sites allocation method for ES of typhoid in Kolkata that optimizes selection of sampling sites by dynamically updating site locations based on their performance.

METHODS

The simulation model included information about shedding dynamics of *S.* Typhi and *S.* Paratyphi A at different incidence rates and pathogen flow in the sewage network in specific geospatial areas. Three types of sampling locations (pumping station, individual household toilets, pooled samples from multiple adjacent household toilets) were compared in different scenarios to determine the best sampling strategy. An initial set of ES sites was chosen at random, followed by periodic updates, characterizing relocated sites by their influence on the performance. Information loss (i.e. the number of positive results lost for the entire ES system) by removing a site can be evaluated to determine which site(s) should be relocated. Any logistic settings (the initial number of sites, numbers of sites relocated per update, the time between updates) can thus be optimized to rapidly achieve an ES system with sensitivity as high as possible.

RESULTS

Three types of sampling locations were compared for 8 scenarios with different disease incidence, pathogen decay and loss in the environment, and sensitivity of pathogen detection. A decision tree for sampling location selection was created. The model allowed systematic study of the performance of the adaptive site allocation method in settings of high or low disease incidence. For example, with appropriate parameters and settings, the sensitivity of ES increased dramatically, from 50% to 80%, within 20 updates, and the adaptive sampling site allocation method consistently outperformed simulations with fixed site locations for most of the scenarios.

CONCLUSIONS

Optimum sampling locations for typhoid ES can be predicted systematically, and the adaptive sampling site allocation method can enhance the sensitivity of ES for typhoid.

A Bayesian Approach for Estimating Typhoid Fever Incidence from Passive Surveillance Data

Maile Phillips, Yale School of Public Health

Maile Phillips[1], Merryn Voysey[2], James Meiring[3], Andrew Pollard[3], Virginia Pitzer[1]

[1]Yale School of Public Health, [2]Oxford Vaccine Group, Department of Paediatrics, University of Oxford, and the National Institute for Health Research Oxford Biomedical Research Centre; Nuffield Department of Primary Care Health Sciences, University of Oxford, [3]Oxford Vaccine Group, Department of Paediatrics, University of Oxford, and the National Institute for Health Research Oxford Biomedical Research Centre

BACKGROUND

Typhoid fever is a major cause of morbidity and mortality in developing countries, with an estimated 12-21 million cases per year. Decisions about typhoid prevention and control are based on current estimates of typhoid incidence and their uncertainty, which can be difficult to measure. Limits of using facility-based estimates alone—the lack of specific clinical diagnostic criteria, poorly sensitive and specific diagnostic tests, and scarcity of accurate or full data—contribute to difficulties in calculating population-level incidence of typhoid.

METHODS

Using data from the Strategic Alliance across Africa & Asia (STRATAA) programme, we integrated information from a demographic census, healthcare utilization survey, facility-based passive surveillance, and serological surveillance from sites in Nepal, Bangladesh and Malawi. We then developed a Bayesian framework that adjusts the count of blood-culture-positive reported cases of typhoid for each of four phases: healthcare-seeking, blood culture collection, blood culture detection, and reporting of laboratory-confirmed cases. We estimated the proportion of "true" typhoid cases occurring in the population under surveillance captured at each phase by combining information from the observed cases from STRATAA datasets and estimates from prior studies. The Bayesian approach allows each phase of the reporting process to be synthesized with its associated uncertainties to estimate the true incidence of typhoid fever.

RESULTS

The observed incidence of typhoid fever cases in Nepal, Bangladesh, and Malawi was 66.2, 143.1, and 61.1 cases per 100,000 person-years over the study period, respectively. By applying our model, we were able to use multiple datasets to estimate the upward-adjusted

incidence of typhoid fever in each site (results forthcoming). The ratio between observed and adjusted incidence rates varied by age and across the three sites. Adjusted incidence rates were within the limits of the incidence rate of typhoid infection determined by the serological data.

CONCLUSIONS

Passive surveillance of blood culture-confirmed typhoid fever results is a considerable underestimation of the true incidence of typhoid in the population. Our model provides an approach for estimating typhoid incidence while accounting for different sources of information on the reporting process. Estimates of population-based incidence from this model can inform decision-making for typhoid prevention and control.

Geo-Spatial Reporting of Ceftriaxone Resistant *Salmonella* Typhi Outbreak Investigation in Hyderabad and Spread to Karachi

Abdul Momin Kazi, Aga Khan University

Abdul Momin Kazi, Ayub Khan, Tahir Yousufzai, Sultan Karim, Farah Qamar

Aga Khan University

BACKGROUND

It is estimated that around 21 million cases and 222,000 typhoid-related deaths occur worldwide annually. In November 2016, the first case of ceftriaxone resistant Salmonella typhi was reported from Hyderabad. An outbreak investigation was conducted to identify the determinants, burden and spatial distribution of the outbreak using GIS mapping geospatial analysis. Simultaneously spread of cases in Karachi from Hyderabad were also identified.

METHODS

An age-matched case-control (1:4) study was conducted from 1st December 2016 to 15th September 2017. Google Map® layer was integrated into the Esri ArcGIS version 10.5 to identify famous points and localities in Hyderabad, using geospatial mapping technique. A paper-based map of Hyderabad sewerage line network was also acquired from Hyderabad water board which was scanned and georeferenced in the ArcGIS software. Color coding of positive and negative cases, as well as water positive cases, were also conducted. Using similar strategy XDR cases in Karachi were also mapped.

RESULTS

Geospatial analysis of the cases revealed a clustering of the cases around sewage lines both in Qasimabad and Latifabad indicating mixing of sewage water with municipal water supply. Microbiological analysis of household water samples from the drinking source also indicated E-Coli contamination supporting our hypothesis of broken sewerage lines and mixing of sewerage water with the drinking water; this was confirmed by molecular detection of S. Typhi DNA by PCR. Clustering of cases in few localities of Karachi was also identified.

CONCLUSIONS

Data collected through mobile phone/tablet helped in generating geospatial maps and incorporation of information with Google maps and paper-based maps. This helped in identifying the specific distribution of the outbreak and in the prediction of water born origin of bacteria that was causing infection. The geospatial data of Karachi also reinforced the evidence of spread and further analyses are required to understand the pattern of spread and work on a geospatial prediction model. This study highlights the importance of using digital technology in a resource-constrained settings to improve routine immunization coverage among Pakistani children and worldwide.

17:15-18:00 Break

18:00-19:30 Evening Welcome Reception

Fansipan Ballroom

REMARKS FROM:
Dang Duc Anh, National Institute of Hygiene and Epidemiology, Vietnam

WEDNESDAY, MARCH 27

8:30 STRATAA/TyVAC

Grand Ballroom

SYMPOSIUM SESSION CHAIRED BY
Andrew J. Pollard & Kathleen Neuzil

The Global Burden of Disease study estimates nearly 11 million cases and more than 116,000 deaths annually due to typhoid worldwide. The Strategic Typhoid alliance across Africa and Asia (STRATAA) is a multi-component, multi-site, study designed to answer some of the key questions around typhoid epidemiology and provide the evidence to drive vaccine introduction. The Typhoid Vaccine Acceleration Consortium (TyVAC) capitalized on the STRATAA data to conduct field impact studies at sites in Africa and Asia. TyVAC is a partnership between the Center for Vaccine Development at the University of Maryland, the Oxford Vaccine group at the University of Oxford and PATH, an international non-profit, which aims to accelerate the introduction of new typhoid conjugate vaccines (TCVs) as part of an integrated approach to reducing the burden of morbidity and mortality from typhoid in countries eligible for support from Gavi, the Vaccine Alliance.

This symposium will disseminate data from the past two years of research activity from STRATAA. The unique design of the study combines passive surveillance for febrile illness with serological surveillance for chronic carriage and seroconversion episodes. The studies are nested within a demographic census population, which enables a detailed description of disease burden, anti-microbial resistance patterns, and serological responses.

The World Health Organization Strategic Advisory Group of Experts used STRATAA data in decision-making for typhoid vaccine recommendations. TyVAC has partnered with STRATAA on the first efficacy, safety, and immunogenicity trials conducted with the new TCVs. We will discuss TyVAC's progress, including new data on typhoid burden, vaccine implementation, and early TCV safety and immunogenicity data from the vaccine effectiveness studies.

The symposium combines data from STRATAA and TyVAC to add to the growing body of epidemiological and TCV effectiveness data from Africa and Asia, which will inform key stakeholders and countries on vaccine introduction.

Burden of Enteric Fever in Africa and Asia from Three Urban Centres: A Multicentre, Prospective Epidemiological Study with Over 600,000 Person-Years of Observation
James Meiring, University of Oxford

Serial Serological Surveillance for Typhoid in Healthy Community Controls in Nepal, and in Fever Cases and Their Families
Merryn Voysey, University of Oxford

Evaluation of Population-Based Serological Surveillance for the Identification of Typhoid Chronic Carriers Using and Anti-Vi IgG ELISA
Farhana Khanam, icddr,b

Interim Analysis of Safety of Typhoid Conjugate Vaccine across Africa and Asia TyVAC
Melita Gordon, University of Liverpool

Interim Analysis of Immunogenicity of Typhoid Conjugate Vaccine in Africa and Asia TyVAC
Dikshya Pant, Patan Academy of Health Sciences

Efficacy of Typhoid Conjugate Vaccine in Nepal: A Participant-Observer-Blind Phase III Randomized Controlled Trial
Mila Shakya, Oxford University Clinical Research Unit, Nepal

10:30-11:00 Coffee Break

11:00 Got To Get You Into My Life: Introduction Of Typhoid Conjugate Vaccines

Grand Ballroom

CONCURRENT ABSTRACT SESSION 5 MODERATED BY
Ken Simiyu & Muhammad Salman

Safety of Typhoid Conjugate Vaccine in Bangladeshi Children: Preliminary Results from a Double-Blind Cluster-Randomised Controlled Trial

Firdausi Qadri, icddr,b

Firdausi Qadri[1], Katherine Theiss-Nyland[2], Xinxue Liu[2], Farhana Khanam[1], Andrew Pollard[2], John Clemens[1], TyVAC study team[1]

[1]icddr,b, [2]Oxford Vaccine Group, Department of Paediatrics, University of Oxford, UK

BACKGROUND

Typhoid fever, caused by Salmonella enterica serovar Typhi, remains a major public health problem in low and middle-income countries. In 2018, the WHO prequalified a new typhoid conjugate vaccine (Vi-TCV) which showed a vaccine efficacy of 55-87% in a human challenge model. Limited safety data show that Vi-TCV is safe in infants, young children and adults in trials in India, and adults in the human challenge model in the UK. In this study, we aim to evaluate the safety and efficacy of Vi-TCV in a large field setting at Dhaka, Bangladesh.

METHODS

This study is a participant- and observer-blinded, cluster-randomised controlled trial with a pilot safety phase. In the main study, participants aged 9 months to <16 years in 150 geographical clusters were randomised to receive Vi-TCV or Japanese encephalitis (JE) vaccine and will be followed up for 2 years to assess the effectiveness of the trial vaccine. A subset of participants were selected on a 1:1 basis (Vi-TCV vs JE) from all 150 clusters to actively collect adverse events following immunisation (AEFI) 7 days after vaccination by telephone or in person. All participants were able to access a trial doctor to report any adverse events within the first week after vaccination. All serious adverse events (SAEs) observed by the investigators, members of the study team, or reported by the parent/guardian, were recorded and reported.

RESULTS

We have successfully vaccinated 41,344 participants in the main vaccination campaign. A subset of 4,807 participants was followed up to collect AEFI data. Among all 4,807 participants, 4% of children were reported as unwell in the 7 days after vaccination.17 SAEs from 17 participants were reported, none of which related to study vaccines. The most common events were diarrhoea and dehydration.

CONCLUSIONS

The blinded preliminary data show that both vaccines were safe and well tolerated. The safety data will be cleaned and locked once the 6-month follow-up is completed. An unblinded interim analysis will be carried out on the updated data, and the unblinded results will be presented.

Implementation and Coverage of the First Public Sector Introduction of Typhoid Conjugate Vaccine, Navi Mumbai, India

Kashmira Date, Centers for Disease Control and Prevention

Kashmira Date[1], Stephen Luby[2], Pauline Harvey[3], Rahul Shimpi[3], Arun Katkar[3], Benjamin Nygren[1], Anagha Loharikar[1], Pankaj Bhatnagar[3]

[1]Centers for Disease Control and Prevention, [2]Stanford University, [3]World Health Organization (WHO) - India

BACKGROUND

Typhoid fever poses a significant public health problem in India. In 2016, India had an estimated 6.6 million cases and 66,000 deaths, 56 percent of which were among children <15 years old. In 2018, the first typhoid conjugate vaccine (TCV) was prequalified by the World Health Organization (WHO). In an effort to protect children from typhoid, the Navi Mumbai Municipal Corporation (NMMC) took a landmark decision to be the first in the world to introduce TCV into its immunization program. During July–August 2018, the first phase of the TCV campaign, targeting children 9 months to <15 years old in 11 urban primary health center (UPHC) areas, was conducted by NMMC with support from multiple governmental and non-governmental partners and the private sector.

METHODS

We describe decision-making, planning, implementation and lessons learned from the first public sector vaccination campaign. During September–October 2018, we conducted a community-based household survey using a structured questionnaire based on the most recent revised WHO Coverage Survey Guidelines.

RESULTS

In preparation for the campaign, workshops and trainings were conducted for medical officers, pediatricians, and UPHC staff. Social mobilization activities including

distribution of pamphlets and information booklets, and media briefings. The campaign was implemented using existing NMMC immunization program resources through fixed posts. Overall, 1,210 vaccination booths (hospitals, clinics, schools, and other designated locations) were set up for a 10-day campaign and 3 days were used for mop-up rounds. According to NMMC reports, 113,420 children were vaccinated (administrative coverage=70%). A total of 1,368 households in 57 primary sampling units (PSUs), based on the polio microplan, were selected for the coverage survey. Among 956 eligible children (528 households), 719 (75%) received vaccine during the campaign (recall and vaccination card); 53 (6%) reported receiving TCV previously through the private sector. Data analysis is ongoing and final results included weighted coverage estimates will be presented.

CONCLUSIONS

The first public sector TCV campaign was successfully implemented by NMMC with technical support from partners. The campaign was well accepted with high coverage achieved in most targeted areas. Evaluations are ongoing to understand vaccine effectiveness and impact.

Evaluation of Vaccine Safety during the First Public Sector Introduction of Typhoid Conjugate Vaccine (TCV), Navi Mumbai, India, 2018

Ashley Tate, CDC Foundation

Ashley Tate[1], Stephen Luby[2], Kashmira Date[3], Pankaj Bhatnagar[4], Vineet Goyal[4], Vijay Yewale[5], Arun Katkar[4], Jane Gidudu[3]

[1]CDC Foundation, [2]Stanford University, [3]Centers for Disease Control and Prevention, [4]WHO India, [5]Dr. Yewale Multispeciality Hospital for Children

BACKGROUND

In 2018, the World Health Organization prequalified the first typhoid conjugate vaccine (TCV) (Typbar-TCV). No safety concerns were identified in the pre and post-licensure studies and post-marketing surveillance, though the sample sizes were small. During July – August 2018, The Navi Mumbai Municipal Corporation (NMMC) launched the first public sector TCV introduction in the world. Following the Global Advisory Committee on Vaccine Safety recommendations to include robust safety evaluations in large-scale TCV implementations, we systematically evaluated adverse events to characterize the safety profile of TCV.

METHODS

We collected data using the following methods: 1) telephone interviews among a randomly selected subset (5%) of vaccine recipients at 48 hours and 7 days following TCV using a standard questionnaire, 2) chart abstraction for adverse events of special interest (AESI) using the Brighton Collaboration criteria for diagnostic certainty followed by ascertainment of vaccination status in five hospitals in Navi Mumbai (AESI included anaphylaxis, Guillain-Barré syndrome, meningitis, encephalitis, myelitis, acute disseminated encephalomyelitis, seizures, thrombocytopenia, and sudden death), and 3) reports from the NMMC adverse event following Immunization (AEFI) surveillance system within 30 days of vaccination.

RESULTS

According to administrative reports, 113,420 children aged 9 months to <15 years old received TCV during the campaign. Among 5,605 interviews completed at 48 hours, 33% reported one or more adverse event; pain at the injection site (26%, n=1452), local injection site swelling (8%, n=419), and fever (7%, n=416) were most commonly reported. At 7 days, among 4,728 interviews completed, the most commonly reported events included fever (4%, n=200), pain (1%, n=52) and headache (1%, n=42). The most common AESI identified in hospitals were thrombocytopenia (n=43) and seizures (n=18), though these were more than 6 times more commonly identified among unvaccinated patients. A total of 225 (0.2%) events were reported through the NMMC AEFI surveillance system using the national guidelines, including 213 (0.19%) mild, 3 (0.003%) severe, and 9 (0.008%) serious. None of the severe or serious events were attributed to vaccination.

CONCLUSIONS

This large scale introduction provides further evidence of an excellent safety profile of TCV when administered to children 9 months to < 15 years of age.

Adverse Events Following Immunization with Typbar TCV and Measles Vaccine: Mass Immunization against Typhoid Fever and Measles at KGH Hospital Karachi

Anayat Baig, Aga Khan University

Anayat Baig, Amber Junejo, Hina Memon, Farah Qamar, Tahir Yousafzai, Sultan Karim

Aga Khan University

BACKGROUND

Pakistan is facing the largest outbreak of extensive drug resistant typhoid reported since November 2016. The outbreak was tracked primarily from Hyderabad and affected children less than 10 years of age. Some sporadic cases have now been reported from few towns of Karachi. The aim of this study was to ascertain the adverse effects following immunization (AEFI) for parallel immunization of Typhoid Conjugate Vaccine (TCV) with Measles Vaccine.

METHODS

The Aga Khan University in collaboration with Government of Sindh, acquired the WHO pre-qualified Typhoid conjugate vaccine (TCV) to commence a mass immunization campaign in Hyderabad in response to the outbreak. Meanwhile, measles supplementary immunization activity (SIA) was started across the country and we administered TCV alongside measles vaccine in Karachi. In order to determine the adverse events following immunization (AEFI), we followed 325 children aged 9- 60 months who received measles along with TCV during 15th - 27th October, 2018. Vaccination cards with a

hotline phone number were provided to the parents and counseling was done to contact on the given number in case of any adverse effects such as local reaction, fever, diarrhea, vomiting, seizures or any other illness. Follow-up was done on 7th and 14th day post immunization. A trained research staff interviewed the caregivers using the standard AEFI questionnaire.

RESULTS

The preliminary analysis so far shows that out of 325 enrollments, 150 children had completed their 7th day follow-up visits. No serious adverse event had occurred and no anaphylaxis reported. However, 42/150 (28%) respondents have reported mild AEFI events, out of which 30/42 (71%) reported mild fever, 3/42 (7.1%) stated diarrhea, 1/42 (2.3%) reported pain at injection site, 3/42 (7.1%) reported lethargy, 4/42 (9.4%) reported flu and very rare cases 1/42 (2.3%) of constipation were reported.

CONCLUSIONS

Typbar-TCV vaccine was found to be safe for administering alongside measles vaccine in campaign setting. Mild fever was found to be most frequent AEFI with very rare events of diarrhea and no other serious AEFI or SAE has occurred.

Door to Door Campaign of Typbar TCV: Strategies to Reduce Refusal and Increase Coverage

Sultan Karim, Aga Khan University

Sultan Karim, Farah Qamar, Tahir Yousafzai, Hina Memon, Anayat Baig, Amber Kashif, Numan Hussain

Aga Khan University

BACKGROUND

Vaccination campaign in low socio-economic countries and countries with less literacy rate is highly challenging to conduct, AKU is running a campaign of Typhoid conjugate vaccine in Hyderabad Pakistan. Our aim of the study was to control the outbreak of XDR typhoid in the vicinities of Latifabad and Qasimabad Talukas of Hyderabad city of Sindh during the high season for spread of typhoid. Various strategies were implied to increase the uptake of vaccination and reduce the refusals.

METHODS

Door-to-door vaccination targeting age group 6 months to 10 years in two sub-districts (Latifabad and Qasimabad) of Hyderabad was initiated. Multi- prong strategy was used to address the refusals. Multiple training sessions were conducted with the lady health workers and community mobilizers regarding the vaccination campaign, vaccine, reasons of the campaign and potential benefit to the vaccines. Involvement of government implied lady health workers (LHW) from the respective communities, recruitment of social mobilizers from the same ethnicity and same community, support letters from the district health office, visibility of the temporary immunization camps using banners printed in local language, distribution of hand bills about the typhoid vaccination camp during the polio supplementary immunization activities (SIA), and display of employment cards of the vaccination teams/community mobilizers significantly increased the vaccine acceptance. Vaccination cards without the logo of the institution especially health department of Sindh, endorsement from the local community leaders, religious clerks, unions, lady health workers and false rumours on social media resulted in vaccine refusals

RESULTS

Until now 130k HH visited and 110k vaccine doses have been successfully administered. After the administration of refusal mitigation strategies our coverage has increased from 40% to 79%.

CONCLUSIONS

Door-to-door vaccination is extremely challenging in a country like Pakistan. Incorporating various strategies including the active involvement of local stakeholders and increasing the visibility has significantly improved the vaccine uptake.

Safety and Tolerability of a Novel Typhoid Conjugate Vaccine in African Infants and Children

Nginache Nampota, Blantyre Malaria Project

Nginache Nampota[1], Lameck Khonde[1], Victoria Mapemba[1], Osward Nyirenda[1], James Meiring[2], Melita Gordon[3], Kathleen Neuzil[4], Matthew Laurens[4]

[1]Blantyre Malaria Project, [2]Oxford Vaccine Group, University of Oxford, [3]Malawi-Liverpool-Wellcome Trust Clinical Research Programme/University of Liverpool, [4]University of Maryland School of Medicine

BACKGROUND

Recent World Health Organization recommendations for use of an efficacious typhoid conjugate vaccine for *Salmonella enterica* serovar Typhi (*S.* Typhi), the causative organism of typhoid fever, provide hope that global control is possible. Safety and tolerability data, including co-administration with routine measles-rubella vaccination, are needed by stakeholders and health officials to inform decision-making. Here we present the first reactogenicity data from children in Africa vaccinated with a typhoid conjugate vaccine.

METHODS

The Typhoid Vaccine Acceleration Consortium conducted a phase 3 randomized, blinded, controlled clinical efficacy trial of typhoid Vi-capsular conjugate vaccine in Malawian children ages 9 months to 12 years. Participants were randomized in a 1:1 ratio to receive either typhoid Vi-capsular conjugate vaccine or meningococcal serogroup A conjugate vaccine. A subset of 600 children (200 in each age group: 9-11 months, 1-5 years, and 6-12 years) were included in a safety and immunogenicity sub-study where we actively collected solicited and unsolicited adverse events in person at 3 and 7 days after vaccination. The 200 children aged 9-11 months received typhoid Vi-capsular conjugate vaccine co-administered with measles-rubella vaccine at a different anatomic site. We documented all non-serious unsolicited adverse events until 28 days after vaccination and serious adverse events for six months after vaccination.

RESULTS

As of an interim data lock on June 29, 2018, 471 participants were enrolled in the sub-study and vaccinated. Parent and participant recall of adverse events on the day of vaccination included fever (3.4%), mild or moderate irritability (1.5%), and malaise (1.1%). Injection site reactions included pain/tenderness (1.1%), swelling (0.2%), and myalgia (0.6%). Fewer solicited reactogenicity events were recorded at 3 and 7 days after vaccination, with fever the most common (1.9% on day 7).

CONCLUSIONS

The typhoid conjugate vaccine and meningococcal serogroup A conjugate vaccine were associated with few solicited reactogenicity events after vaccination. The vaccinations were well-tolerated and no safety signal was detected. Additional safety and tolerability data for the entire sub-study cohort will be available for presentation at the meeting.

11:00 Fixing A Hole: iNTS

Truc Bach

CONCURRENT ORAL ABSTRACT SESSION 6 MODERATED BY
Ellis Owusu-Dabo & Sam Kariuki

The Phylogeography and Incidence of Multi-Drug Resistant Invasive Nontyphoidal *Salmonella* in sub-Saharan Africa

Se Eun Park, International Vaccine Institute

Se Eun Park[1], Duy Thanh Pham[2], Gi Deok Pak[1], Ursula Panzner[1], Ligia Maria Cruz Espinoza[1], Vera von Kalckreuth[1], Florian Marks[1], Stephen Baker[2]

[1]International Vaccine Institute, [2]Oxford University Clinical Research Unit, 764 Vo Van Kiet, Quan 5, Ho Chi Minh City

BACKGROUND

Invasive nontyphoidal *Salmonella* (iNTS) is one of the leading causes of bloodstream infections in sub-Saharan Africa. The disease burden is further exacerbated due to the emergence of multidrug resistance in various iNTS serovars. We conducted a comprehensive genomic investigation into the genotype, multidrug resistance distribution and phylogenetic relatedness of all common iNTS serovars in ten sub-Saharan African countries. Incidence of multidrug resistant iNTS disease is also estimated.

METHODS

166 iNTS isolates from a population-based multicenter surveillance in ten African countries were whole genome sequenced and subjected to bioinformatics and phylogenetic analyses for the identification of multilocus sequence type, antimicrobial resistant gene and plasmid, and phylogenetic reconstruction. Major iNTS serovars collected were phylogenetically mapped in context of the global context to investigate the likelihood of common ancestors and transmissions.

RESULTS

Salmonella Typhimurium-ST313 (60%, 99/166) was the most predominant cause of iNTS disease in Africa, followed by Enteritidis-ST11 (17%, 28/166) and Dublin-ST10 (11%, 18/166). Typhimurium-ST313 and Enteritidis-ST11 appeared to be pervasive in both West and Southeastern Africa while Dublin-ST10 was exclusively found in West Africa. Multidrug resistance was predominantly found in Typhimurium-ST313 (95%, 95/99) and Enteritidis-ST11 (25%, 7/28). Overall, incidence of multidrug resistant (MDR) iNTS disease exceeded 100/100,000-person years of observation (PYO) especially in children under 15 years old in Western African countries: Burkina Faso (NiokoII, 274/100,000 PYO, 95% confidence interval [CI], 185-406; and Polesgo, 255/100,000 PYO, 95% CI, 138-470), Ghana (Asante Akim North, 414/100,000, 95% CI, 333-515), and Guinea-Bissau (Bandim, 105/100,000, 95% CI, 69-161). The virulence-resistance plasmid pSLT is consistently found in ST313; whereas novel virulence-resistance IncI1 plasmid was found in MDR ST11. We found evidence of inter-country transmission of ST313 lineage II between Ghana and its neighboring countries (Mali, Burkina Faso and Nigeria), while multiple lineages of ST11 were identified with evidence of endemic circulation in Madagascar, South Africa, Ghana (Global epidemic clade) and inter-country transmission between West African countries (West Africa and Global epidemic clades).

CONCLUSIONS

Significant burden of MDR iNTS disease is identified in sub-Saharan countries. Various MDR iNTS serovars are continually spreading in sub-Saharan Africa. Routine surveillance, antimicrobial stewardship and development of multivalent vaccine for iNTS disease are urgently needed.

Transmission of Invasive Nontyphoidal *Salmonella*: Supporting Evidence for Human-to-Human Transmission from Household Samples in Burkina Faso

Annelies Post, Radboudumc Nijmegen & Institute of Tropical Medicine, Antwerp

Annelies Post[1,2], Seydou Nakanabo Diallo[2], Issa Guiraud[2], Palpouguini Lompo[2], Marc Christian Tahita[2], Halidou Tinto[2], Wesley Mattheus[3], Jan Jacobs[2]

[1]Radboudumc Nijmegen, [2] Institute of Tropical Medicine Antwerp, [3]Clinical Research Unit of Nanoro, [4]Sciensano

BACKGROUND

Salmonella Typhimurium and *Salmonella* Enteritidis (NTS) are major causes of bloodstream infections in children in sub-Saharan Africa. This study assessed evidence for their zoonotic versus human transmission.

METHODS

Index patients were children with blood culture confirmed *Salmonella* infection identified during a microbiological surveillance study carried out in Nanoro, rural Burkina Faso, between May 2013 and August 2014. After consent, households of index patients were visited. Water for consumption, stool from household members and stool from livestock (pooled samples per species) were collected and cultured for *Salmonella*. *Salmonella* isolates with identical serotype obtained from index patient and a second source in the same household were defined as "paired isolates" and assessed for genetic relatedness through multilocus variable number tandem-repeat analysis (MLVA).

RESULTS

Twenty-nine households were visited for 30 out of 42 (71.4%) eligible index patients (one household comprised two index cases). Most index cases had *Salmonella* Typhimurium (n=26), followed by *Salmonella* Enteritidis (n=5) and *Salmonella* Freetown (n=1). Median delay between blood culture sampling and household visits was 13 days (range 6–26 days). *Salmonella* was recovered from 16/186 (8.6%) livestock samples (13 different serotypes) and 18/290 (6.2%) household members (9 different serotypes). None of the water samples yielded *Salmonella*. In three households representing four index patients with *Salmonella* Typhimurium, *Salmonella* Typhimurium was recovered from a corresponding household member (n=3). MLVA types were identical in two paired isolates and similar in the third (consisting of two index patients and one household member). *Salmonella* Typhimurium was not detected in any of the animals, and *Salmonella* Enteritidis was not detected in any household samples. Other serotypes shared by human carriers or by human carriers and livestock in the same household were *Salmonella* Derby, Drac, Tennessee and Muenster.

CONCLUSIONS

The current study further supports evidence toward a human-to-human transmission of invasive *Salmonella* Typhimurium.

Fifteen Years of Surveillance for Invasive Salmonellosis in Bamako, Mali: 2002 to 2017

William Still, University of Maryland School of Medicine

William Still, Milagritos Tapia, Sharon Tennant, Mamadou Sylla, Aliou Touré, Samba Sow, Karen Kotloff

University of Maryland, Baltimore, Center for Vaccine Development and Global Health

BACKGROUND

Enteric fever caused by *Salmonella* spp. is a significant cause of childhood morbidity and mortality worldwide. Disease burden is highest in low-resource settings where surveillance programs are rare. Herein we report 15 years of surveillance for pathogens causing serious invasive bacterial infections at a bacteriology laboratory that we established at l'Hôpital Gabriel Touré, the national pediatric hospital in Bamako, Mali.

METHODS

Between June 2002 and December 2017, Bamako children aged <16 years who were hospitalized with fever and/or suspected invasive bacterial infection were invited to submit a blood culture. Samples of normally sterile body fluid obtained during routine clinical care were also cultured.

RESULTS

Non-typhoidal *Salmonella* was identified in 460 (1.8%) of 26,168 enrolled inpatients and in 12.8% of those with pathogens isolated, making it the third most prevalent bacterial pathogen. Typhimurium was the most common non-typhoidal *Salmonella* serovar, accounting for 35.2% of all serovars (n = 162), followed by Enteritidis (32.4%, n = 149), Dublin (12.4%, n = 57), and I:4,[5],12:i:- (6.5%, n = 30). The mean age of children with a culture positive for non-typhoidal *Salmonella* was 2.7 years (standard deviation = 3.1 years). Overall case-fatality was 18.9% (13.0% for Typhimurium, 24.8% for Enteritidis). An additional 100 children (0.4%) had a positive culture for *S.* Typhi, and 8 (0.0003%) had a positive culture for *S.* Paratyphi C. Annual incidence of non-typhoidal *Salmonella* per 100,000 children under 5 years decreased from a peak of 14.4 cases in 2011 (95% CI: 10.1, 18.6) to 2.0 cases in 2017 (95% CI: 0.7, 3.3), but case-fatality remained high (33%). Incidence of *S.* Typhi and *S.* Paratyphi C also decreased, with negligible isolation (<2% of pathogens) since 2008 and 3.4% overall case-fatality.

CONCLUSIONS

Although incidence decreased, non-typhoidal *Salmonella* remains a major cause of serious invasive bacterial infection and mortality among hospitalized children in Bamako, while *S.* Typhi and *S.* Paratyphi C are uncommon. Because 86.3% of non-typhoidal *Salmonella* belonged to only four serovars, vaccination against these serovars may reduce the burden and mortality of bacterial infections.

Characterising the Cellular and Humoral Immune Response to Invasive Nontyphoidal *Salmonella* (iNTS) Disease in West African Populations

Sean Elias, University of Oxford

Sean Elias[1], Calman MacLennan[1], Justin Im[2], Se Eun Park[2], Japhet Senyo[3], Michael Owusu[3]

[1]Jenner Institute, University of Oxford, [2]IVI, [3]KCCR, KNUST

BACKGROUND

NTS are major causes of invasive disease among young children and HIV-infected individuals in Sub-Saharan Africa commonly manifesting as bacteraemia. Little is known about immunity to iNTS disease across different West African populations. Previous studies suggest acquisition of antibody to NTS antigens are important for protection. We have characterised the cellular and humoral immune responses of individuals with iNTS disease compared with age-matched controls in Ghana and Burkina Faso.

METHODS

Febrile adults and children in Ghana and Burkina Faso were enrolled following diagnosis of iNTS disease and followed for a year as part of the Severe Typhoid in Africa (SETA) study. The humoral response was characterised by ELISA to O-antigen and flagellin from *Salmonella* Typhimurium and Enteritidis. The cellular response was assessed by flow cytometry of whole blood stimulated with *Salmonella* Typhimurium.

RESULTS

IgG and IgM to all iNTS antigens tested were ubiquitously present among cases and controls, while IgA was absent in some infants. iNTS IgG and IgA median antibody levels were higher in cases compared with controls, and up to 1-3 logs higher for some individual cases. iNTS IgA correlated strongly with iNTS IgG and IgM. However, iNTS IgG and IgM only correlated for *S.* Typhimurium O-antigen. T cell responses among cases were characteristically driven by $CD4^+$ T cells producing multiple cytokines, including IFN-γ, IL-2, IL-4, IL-17 and TNF-. Controls displayed variable responses, usually characterised by monofunctional $CD4^+$ and $CD8^+$ T cell populations.

CONCLUSIONS

Antibody to iNTS antigens are universally present in west Africans, with acute iNTS disease appearing to drive increased specific IgG and IgA in parallel. Cellular immune responses to iNTS disease are characterised by multifunctional $CD4^+$ T cells, while responses are variable and typically monofunctional in controls. Further studies are required to understand the precise role of these cellular and humoral responses in preventing and clearing iNTS infection.

Characterization of Invasive Salmonellosis in Hospitalized Children with Acute Febrile Illness—Uganda, 2016–2017

Alison Winstead, Centers for Disease Control and Prevention

Alison Winstead[1], Arthur Mpimbaza[2], Mohammed Lamorde[3], Molly Freeman[1], Eric Mintz[1], Kiersten Kugeler[1], Grace Appiah[1]

[1]Centers for Disease Control and Prevention, [2]Makerere University College of Health Sciences, [3]Infectious Diseases Institute (IDI)

BACKGROUND

Typhoid fever, paratyphoid fever, and invasive non-typhoidal *Salmonella* cause an estimated 30.4 million illnesses and >1 million deaths annually worldwide. In a systematic review, *Salmonella enterica* was found to cause 29% of community-acquired bacterial bloodstream infections in Africa (58.4% of which were non-typhoidal *Salmonella*). However, data from sub-Saharan Africa are scarce because of limited laboratory capacity. To characterize invasive salmonellosis in hospitalized Ugandan children, we evaluated data from six hospitals participating in the Uganda Acute Febrile Illness (AFI) Project.

METHODS

The Uganda AFI Project recommends a blood culture for any febrile child ≤14 years old admitted to a hospital surveillance site with a negative test for malaria. We evaluated demographic information, blood culture results, and antimicrobial susceptibility results from all six participating hospitals from July 1, 2016 to November 16, 2017.

RESULTS

Over a combined total of 2,146 days across all sites, blood cultures were performed and results were available for 4,257 (19%) of 22,533 hospitalized children. Overall, 3,894 (91%) yielded no growth, 220 (5%) yielded a likely contaminant, and 143 (3%) yielded a pathogen. *Salmonella* was the most commonly detected pathogen, found in 57 (38%) positive samples. Of 49 isolates available for further testing at the Centers for Disease Control and Prevention, 43% were identified as *Salmonella* Enteritidis, 29% as *Salmonella* Typhi, 27% as *Salmonella* Typhimurium, and 2% as *Salmonella* I 4,5,12:i:-. Among patients with *Salmonella* bacteremia, the median age was 36 months (range: 2 days to 12 years), 70% were male, and 3 (6%) died. The median length of stay for patients with *Salmonella* bacteremia was 6 days, compared to 3 days for those without *Salmonella* bacteremia (P<.0001). 61% of *Salmonella* isolates were multidrug resistant (MDR), indicating resistance to ampicillin, chloramphenicol, and trimethoprim-sulfamethoxazole. 29% were resistant to nalidixic acid and intermediate to ciprofloxacin, including 93% of *Salmonella* Typhi isolates. None were resistant to ceftriaxone.

CONCLUSIONS

Salmonella appears to be a primary cause of bacterial bloodstream infections in Ugandan children. The majority (71%) of *Salmonella* bloodstream infections were caused by non-typhoidal serotypes. A majority of *Salmonella* isolates were multidrug resistance, which has important implications for treatment.

What Have We Learned from the 10,000 *Salmonella* Genomes Project about the Worldwide Epidemiology, Transmission and Virulence of iNTS?

Blanca Perez Sepulveda, University of Liverpool

Blanca Perez Sepulveda[1], Caisey Pulford[1], Alex Predeus[1], Nicholas Feasey[2], Ross Low[3], Neil Hall[3], Jay C. D. Hinton[1]

[1]University of Liverpool, [2]Liverpool School of Tropical Medicine, [3]Earlham Institute

BACKGROUND

Non-typhoidal *Salmonella* (NTS) are typically associated with enterocolitis and linked to the industrialisation of food production. In recent years, NTS has been associated with invasive disease (iNTS disease), causing an estimated 680,000 deaths each year worldwide, the majority of which occur in sub-Saharan Africa (Ao *et al.*, 2015). In addition to the high prevalence of immunosuppressive illness which predisposes individuals to iNTS disease in sub-Saharan Africa, new clades of *S.* Typhimurium and *S.* Enteritidis have been identified. These clades are characterised by genomic degradation, altered prophage repertoires and novel multidrug resistant plasmids. To understand how these clades are contributing to the burden and severity of iNTS disease, it is crucial to expand the genome-based surveillance of Salmonellae from Africa and other parts of the world, including isolates associated with invasive disease, gastroenteritis and both animals and the environment.

METHODS

We initiated collaborations with researchers from several developing countries, assembling a diverse collection of clinical and environmental *Salmonella* isolates with associated metadata. These isolates were collected in barcoded tubes and sequenced at the Earlham Institute, using a novel optimised DNA extraction method and Illumina HiSeq technology.

RESULTS

The "**10,000 *Salmonella* genomes**" project established a worldwide research collaboration to generate information relevant to the epidemiology, drug resistance and virulence factors of Salmonellae using a whole-genome sequencing approach. The project assembled a diverse collection of **10,301 clinical and environmental isolates within one year**. Genome sequences are now available for *Salmonella* isolates from 51 countries/territories dating from 1959 to 2017. The African and Latin-American datasets represent ~80% of the collection, and are providing important information concerning the evolution of iNTS-associated *Salmonella*. Detailed analysis of the accessory genomes of these strains are in progress for the identification genes associated with drug resistance and virulence.

CONCLUSIONS

The "10,000 *Salmonella* genomes" project represents a worldwide research collaboration that collected and sequenced 10,301 NTS isolates. We are using a collaborative open-access philosophy to maximise the value for the worldwide *Salmonella*-research community, and our latest findings will be presented. It is hoped that the resulting genome sequence data will contribute to public health control strategies in developing countries.

12:30-14:00 Lunch & Posters — **JW Café/Fansipan Ballroom**

POSTER EXHIBITION SPONSORED BY TUBEX®

14:00 With a Little Help from My Friends: The Essentials for Using Data for Decision Making and Advocacy

Grand Ballroom

PLENARY SESSION MODERATED BY
Eileen Quinn & Hope Johnson

Everybody can be an advocate, and it will take all of our voices to take on typhoid. The most effective advocates are often those who work day in and day out on research projects, or those implementing infectious disease control measures in hospitals or in their communities; people who have seen the effects of enteric fevers up close and can speak to the importance of prevention and control. But how do we take that leap, moving from our day-to-day roles to helping raise awareness in our communities? This session brings together advocates from the global, regional, national and local levels, sharing their stories and tactics of how to use data to inform decision making and advocacy.

Gavi Typhoid Program: History of Decision-Making, Current Support and Early Lessons Learned
Adam Soble, Gavi, the Vaccine Alliance

On The Essentials of Using Data for Decision Making and Advocacy
N.A. Gonah, Zimbabwe National Immunisation Technical Advisory Group

Advocating to Save Lives: Learnings From Vaccine Introduction Programs
Anjali Nayyar, Global Health Strategies

Advocating for New Vaccine Introduction in the Mekong Region: Lessons Learnt From Laos, Cambodia, Myanmar, and Vietnam
Huong Minh Vu, PATH

Advocacy for Vaccine in LMICs: Focusing on Typhoid
Samir Saha, Child Health Research Foundation & Dhaka Shishu Hospital

15:10-15:30 Coffee Break

Foyer/Fansipan Ballroom

15:30 Across The Universe: Enteric Fever Surveillance

Grand Ballroom

CONCURRENT ORAL ABSTRACT SESSION 7 MODERATED BY
John Clemens & Megan Carey

S. Typhi and iNTS Disease in Africa – Implications for Vaccination Programs: Results of the Severe Typhoid in Africa Program and Future Trial Plans

Florian Marks, International Vaccine Institute & University of Cambridge

Florian Marks[1,2], Justin Im[1], Mekonnen Teferi[3], Abdramane Bassiahi Soura[4], Ellis Owusu-Dabo[5], Iruka Okeke[6], Octavie Lunguya[7], Raphael Rakotozandrindrainy[8]

[1]International Vaccine Institute, [2]University of Cambridge, [3]Armauer Hanssen Research Institute, [4]University of Ouagadougou, [5]Kwame Nkrumah University of Science and Technology, [6]University of Ibadan, [7]Institut National de Recherche Biomédicale, [8]University of Antananarivo

BACKGROUND

Available incidence data for invasive *Salmonella* disease in sub-Saharan Africa are limited. Standardized, multi-country data are required for better understanding the nature and burden of disease in Africa, particularly focusing on disease severity to identify areas for future deployment of vaccines. Here, we report the results of the Severe Typhoid in Africa (SETA) program as well as plans for future clinical trials in support of vaccine introduction decision-making.

METHODS

We instituted the Severe Typhoid in Africa (SETA) program and conducted surveillance for invasive *Salmonella* infection disease particularly focusing on disease severity and mortality in the Democratic Republic of the Congo, Nigeria, Madagascar, Ethiopia, Ghana and Burkina Faso from 2015 to 2019. Census data and healthcare records were used to define study catchment areas and populations; surveillance procedures were standardized across sites.

RESULTS

From February 2016 to September 2018, 12,767 blood cultures were performed. Among these 11% (1,385/12,767) yielded bacterial growth. 35.5% (491/1,385) were *Salmonella* species (*S.* Typhi=213, iNTS=269, *S.* Paratyphi=9). Of note is the high number of iNTS cases in the Democratic Republic of Congo with 88.5% (238/269) of all iNTS serovars. The nine *S.* Paratyphi originated from Nigeria. The study team further identified 206 intestinal perforations, indicative of severe typhoid fever; among these, 15% (31/206) succumbed to the disease.

CONCLUSIONS

TF and iNTS-disease are major causes of invasive bacterial febrile disease in the sampled locations, most commonly affecting children in both low and high population density settings. The data collected to date have important implications for future vaccination schemes and Gavi introductions. In addition to above data, we will present information on planned clinical trials, a cluster-randomized typhoid conjugate vaccine trial in Kumasi, Ghana and a mass vaccination campaign with vaccine effectiveness assessment in Kisantu, Democratic Republic of the Congo. This planned work complements the ongoing trials executed through the Typhoid Vaccine Acceleration Consortium (TyVAC).

Age-Stratified Incidence of Enteric Fever and Vaccination Implications in Bangladesh, Nepal and Pakistan: Results of the Surveillance for Enteric Fever in Asia Project

Denise Garrett, Sabin Vaccine Institute

Denise Garrett[1], Jason R. Andrews[2], Caitlin Barkume[1], Farah Naz Qamar[3], Samir K. Saha[4], Ashley Tate[5], Kashmira Date[5], Stephen P. Luby[2]

[1]Sabin Vaccine Institute, [2]Infectious Diseases and Geographic Medicine, Stanford University, [3]Department of Pediatrics and Child Health, Aga Khan University, [4]Child Health Research Foundation, Department of Microbiology, Dhaka Shishu (Children) Hospital, [5]Global Immunization Division, Centers for Disease Control and Prevention

BACKGROUND

Enteric fever is a potentially fatal illness caused from infection by the water and foodborne organisms *Salmonella* Typhi or Paratyphi. The Surveillance for Enteric fever in Asia Project (SEAP) is a multi-center, prospective surveillance study designed to characterize the burden, including incidence, of enteric fever in three countries in South Asia.

METHODS

We recruited patients at hospitals in Bangladesh, Nepal, and Pakistan with ≥3 days of fever and residing within a pre-determined catchment area (outpatients) or with a clinical suspicion of enteric fever (inpatients) between September 2016 – 2018. We performed blood cultures for all enrolled patients using automated blood culture systems. Cases were defined as individuals with a positive blood culture for *Salmonella* Typhi or Paratyphi. We also recruited cases identified at the laboratory not captured through surveillance, and additional cases from nearby hospitals and diagnostic centers. We conducted community surveys concomitantly to estimate the proportion of individuals with febrile illness who sought care at surveillance sites. We calculated crude incidence per year by site, and adjusted rates accounting for healthcare seeking behavior, eligible patients missed at the hospital, and culture sensitivity. For this analysis, patients >25 years and residing outside the catchment area were excluded.

RESULTS

This analysis includes 25,481 recruited patients ≤25 years and living in the catchment area, of which 17,191 (67%) were advised a blood culture and eligible; 13,804 (80%) eligible patients were enrolled. Of enrolled participants, 1,948 cases were captured through hospital surveillance (culture positivity rate: 16%) and 1,528 additional cases were captured through laboratory surveillance. Of the 3,476 cases, 2994 (86%) were positive for Typhi and 482 (14%) were positive for Paratyphi. 2028 (58%) cases were male and the median age was 5 years (IQR 3-9 years). In Bangladesh, Nepal, and Pakistan, the crude rates for enteric fever were 220, 95, and 20 cases per 100,000; adjusted rates were 5,731, 919, and 416 cases per 100,000.

CONCLUSIONS

There is a continued high burden of enteric fever in South Asia, the majority of which is due to *S.* Typhi. These findings underscore the urgency of scaling up prevention strategies, including new typhoid conjugate vaccines.

Decline in Typhoid Fever Incidence in Kibera, an Urban Informal Settlement in Nairobi, Kenya

Eric D. Ng'eno, Washington State University

Eric D. Ng'eno*[1], Margaret Lind*[2], Alice Ouma[3], Samuel Kiplangat[3], Newton Wamola[3], Allan Audi[3], Typhoid Project Investigators Group, Kibera[3], Jennifer R. Verani[4]

[1]Washington State University, Global Health Program, [2]University of Washington, [3]Kenya Medical Research Institute, Center for Global Health Research, Kisumu, [4]Division of Global Health Protection, U.S. Centers for Disease Control and Prevention, Nairobi, Kenya

BACKGROUND

Typhoid fever epidemiology is dynamic. Disease can be epidemic or endemic, and the burden is sensitive to interventions such as typhoid vaccines or improvements in access to clean water and sanitation. We describe trends in typhoid fever incidence over an 11-year period in Kibera, a densely populated urban informal settlement in Nairobi, Kenya, where a very high burden of typhoid fever was previously described.

METHODS

We used data from 2007 to 2017 from the Population-Based Infectious Disease Surveillance (PBIDS) system. PBIDS participants, a population of ~25,000 Kibera residents, receive free health care at a centrally located clinic and are regularly surveyed at their households (initially every 2 weeks, since 2015 every 6 months). PBIDS clinic patients meeting case definitions for acute febrile illness or pneumonia undergo blood culture. *Salmonella* is isolated using standard microbiologic techniques after incubation in an automated machine, with typing by *Salmonella* antisera and/or genomic sequencing. We estimated annual and age-specific incidence of *Salmonella enterica* serovar Typhi bacteremia using Poisson regression and person-time denominators derived from household data.

RESULTS

We observed significant annual risk reduction in typhoid fever incidence over the study period (relative risk [RR] 0.866, 95% confidence interval [95%CI] 0.826 – 0.906; p-value <0.001). Highest incidences were observed in 2012 (189 per 100,000 person-years) and 2011 (153 per 100,000). Incidence fell to 60.1 per 100,000 in 2013, and then continued to decline further, reaching a low of 18 per 100,000 in 2017. Individuals aged 2-4 years had the highest incidence (215 per 100,000 person-years), followed by 5-9 years (203 per 100,000 person-years), while those aged >50 had the lowest incidence (25.6 per 100,000 person-years). Individuals <10 years old had a significantly higher risk of disease than those 10 and older (RR 2.82, 95%CI 2.20 – 3.62; p-value <0.001). The shape of the time trend did not differ significantly by age-group.

CONCLUSIONS

Our results indicate that typhoid fever has been declining within Kibera, although the incidence remains high in children. Future analyses should focus on identifying environmental and behavioral drivers of the reduction and explore the potential value of typhoid vaccination within this population.

Incidence of Typhoid and Paratyphoid Fevers among Adolescents and Adults in Yangon, Myanmar

Win Thandar Oo, University of Otago

Win Thandar Oo[1], Tin Ohn Myat[1], David R Murdoch[1], Hla Hla Win[2], James E Ussher[1], John A Crump[1], Wah Win Htike[2], Min Zaw Oo[2]

[1]University of Otago, [2]University of Medicine [1], Yangon

BACKGROUND

Accurate estimates of typhoid disease burden are needed to guide policy decisions, including on vaccine use. Data on the incidence of enteric fever in Myanmar are scarce. We estimated typhoid and paratyphoid fever incidence among adolescents and adults in Yangon, Myanmar, by combining sentinel hospital surveillance with a healthcare utilization survey.

METHODS

We conducted a population-based household health care utilization survey in the Yangon Region 12 March through 5 April 2018. Multipliers derived from this survey were then applied to hospital-based surveillance of *Salmonella* Typhi and Paratyphi A bloodstream infections from 5 October 2015 through 4 October 2016 at Yangon General Hospital (YGH) to estimate the incidence of typhoid and paratyphoid fevers among person ≥12 years of age. Healthcare seeking questions asked separately about usual health care seeking behavior in the event of fever <3 days and ³3 days duration, as well as actual healthcare-seeking behavior of individual household members experiencing fever in the past 3 months.

RESULTS

A total of 336 households representing 1,598 persons were enrolled in the health care utilization survey and multipliers were derived based on responses to questions about health care seeking in the event of febrile illness. Of 671 Yangon residents enrolled over a 1 year period at YGH, we identified 33 (4.9%) with *Salmonella* Typhi and 9 (1.3%) with *Salmonella* Paratyphi A bloodstream infection. After applying multipliers, we estimated the 2015-16 annual incidence of enteric fever among adolescents and adults in the of Yangon Region as 498 per 100,000 population, with typhoid incidence in this age group 391 per 100,000 persons and paratyphoid incidence 107 per 100,000 persons. The difference in proportion of 'usually healthcare seeking' against 'actual healthcare seeking' behavior of the community using YGH as healthcare facility in case of fever was not statistically significant (p = 0.84).

CONCLUSIONS

Typhoid and paratyphoid fever incidence is high among adolescents and adults in Yangon, Myanmar, warranting increased attention on prevention and control, including consideration of typhoid conjugate vaccine use as well as non-vaccine control measures. Research is needed to understand incidence among infants and children, and on sources and modes of transmission.

Validity of Reported Antibiotic Use among Suspected Enteric Fever Cases in Nepal, Bangladesh and Pakistan

Krista Vaidya, Dhulikhel Hospital

Krista Vaidya[1], Kristen Aiemjoy[2], Farah N. Qamar[3], Samir K. Saha[4], Caitlin Barkume[5], Denise Garrett[5], Stephen P. Luby[2], Jason R. Andrews[2]

[1]Dhulikhel Hospital, Kathmandu University Hospital, [2]Division of Infectious Diseases and Geographic Medicine, Stanford University, [3]Department of Pediatrics & Child Health, Aga Khan University, [4]Child Health Research Foundation, Department of Microbiology, Dhaka Shishu (Children) Hospital, [5]Sabin Vaccine Institute

BACKGROUND

Enteric fever is a major cause of morbidity and mortality globally. Culture is the mainstay of diagnosis, but antibiotic use prior to seeking care can reduce the sensitivity of culture for enteric fever, with implications for both clinical care and surveillance. Prior antibiotic use is typically measured via self or caregiver report and may be vulnerable to measurement error.

METHODS

The Surveillance of Enteric Fever in Asia Project (SEAP) is a prospective study of enteric fever incidence in Nepal, Bangladesh and Pakistan, which enrolls individuals with fever > 3 days. Among a random sequential subset of SEAP study participants, we assessed reported antibiotic use and collected a urine sample to test for the presence of antibiotics using a biological assay, whereby the *in vitro* inhibition of growth of pan-susceptible bacteria (*Kocuria rhizophila*) by the participant's urine indicates presence of antibiotics. We calculated the sensitivity and specificity of reported antibiotic use against antibiotics detected in the urine using binomial logit models with a sandwich estimator to adjust standard errors for clustering by study site.

RESULTS

We collected urine samples from 2,600 patients with suspected enteric fever between September, 2016 and September, 2018. Antibiotics were detected in 256/1000 (26.5%) of urine samples collected in Nepal, 337/910 (37.0%) of samples in Bangladesh, and 468/882 (53.1%) of samples in Pakistan. The sensitivity and specificity of reported antibiotic use, compared with the urine assay, were 78.5% (95% CI: 68.6, 86) and 70.6% (95% CI: 57.6, 80.9) in Nepal; 78.5% (95% CI: 71.1, 84.4) and 80.5% (95% CI: 78.7, 82.1) in Bangladesh; and 57.4% (95% CI: 35.6, 76.7) and 67.9% (95% CI: 65.6, 70.1) in Pakistan. There was no significant difference in the sensitivity or specificity of reported antibiotic use by patient age.

CONCLUSIONS

We found substantial pre-hospital antibiotic use among patients with suspected enteric fever in Bangladesh, Nepal and Pakistan. Patient or caregiver self-report was moderately reliable, with substantial heterogeneity between countries. These findings may be useful in interpreting the results of blood cultures for clinical care and surveillance.

PathogenWatch: Fast and Interactive Genomic Surveillance of *Salmonella* Typhi, an Example from a Retrospective Study in the Philippines

Silvia Argimón, Centre for Genomic Pathogen Surveillance

Silvia Argimon[1], Melissa Massim[2], Marietta Lagrada[2], Celia Carlos[2], Kathryn Holt[3], Gordon Dougan[4], Aanensen David[1,5]

[1]Centre for Genomic Pathogen Surveillance, Wellcome Genome Campus, Hinxton, [2]Antimicrobial Resistance Surveillance Reference Laboratory, Research Institute for Tropical Medicine, Alabang, [3]London School of Hygiene and Tropical Medicine, London; and Dept Infectious Diseases, Monash University, Melbourne, [4]Addenbrooke's Hospital, Cambridge University Hospitals NHS Foundation Trust, Cambridge Biomedical Campus, Hills Road, Cambridge, [5]Big Data Institute, Oxford University, Oxford

BACKGROUND

Whole genome sequencing can transform the surveillance and management of typhoid fever, for example by detecting the emergence of strains resistant to multiple antibiotics, or by monitoring in real time the response of a *Salmonella*Typhi population to the new generation of typhoid conjugate vaccine. However, microbial genome data needs to be made broadly and rapidly accessible to the public health sector via tools that facilitate interpretation.

METHODS

We have developed PathogenWatch (https://pathogen.watch/), a web application for genomic surveillance of microbial pathogens that provides rapid genotyphi calls, core single nucleotide polymorphisms (SNPs)-based

clustering and predictions of antimicrobial resistance (AMR) for *S.*Typhi genome assemblies. Users can analyse their own assemblies and contextualize them with the over 3,100 *S.*Typhi genomes available in PathogenWatch. Users can quickly access an individual genome report, as well as explore interactive map, trees and tables, which we exemplify with the genomes of 148 *S.*Typhi isolates from the Philippines collected in 2013 and 2014.

RESULTS

PathogenWatch rapidly revealed that the 148 *S.*Typhi genomes group into four main lineages corresponding to genotyphi clades 3.0 (N=121), 3.2.1 (N=14), 4.1 (N=11) and 3.4 (N=2). By linking geographical location (map) with clustering (tree) PathogenWatch shows that the prevalent 3.0 clade is found throughout the Philippines, while the other three clades have a more regional distribution. The global trees showed strong phylogeographical clustering of the Filipino genomes, which form distinct lineages within major clones circulating in S/SE Asia. The genomic predictions of AMR show that one isolate resistant to beta-lactams ampicillin and ceftriaxone harbours the extended-spectrum beta lactamase gene blaCTX-M-15, while five genomes carry known mutations *gyr*A_D87N (N=3) and *gyr*A_D87G (N=2), in agreement with decreased susceptibility to ciprofloxacin of the isolates. The interactive visualization of AMR predictions on the map and on the tree intuitively shows that the two different mutations in *gyr*A both arose in the context of clade 3.0 but in different years and locations.

CONCLUSIONS

The analyses and genomic data made easily accessible in PathogenWatch can aid the local investigator in surveillance and epidemiological investigations of typhoid fever, regardless of their expertise in bioinformatics.

15:30 Tell Me Why: Immunology

Truc Bach

CONCURRENT ORAL ABSTRACT SESSION 8 MODERATED BY
Kim Mulholland & Richelle Charles

Long Term Persistence of Antibodies to Typbar-TCV Vaccination

Krishna Mohan, Bharat Biotech International

Krishna Mohan
Bharat Biotech International

BACKGROUND

Following previously reported safety and immunogenicity of a Vi-polysaccharide tetanus-toxoid conjugate vaccine (Typbar-TCV™) up to 2-years post primary vaccination, we now present persistence of antibody response up to 5-years. The objective is to investigate the GMTs and sero-conversion levels at different time points in different cohorts with single dose groups and those who have been given a booster post 2 years.

METHODS

We measured geometric mean titers (GMTs), seroconversion rates, and avidity of anti Vi IgG antibodies in a randomized controlled trial (RCT), in individuals aged 2–45 years, where Typbar-TCV™ was compared to Vi-polysaccharide (Typbar™), and, in an open-label trial (OLT) in 6–23 month-old children, where only Typbar-TCV™ was administered. All parameters were compared in subjects, without and with booster given post 2-years.

RESULTS

In both RCT and OLT, the booster dose had the expected effect on GMTs and 4-fold seroconversion, although in unboosted cohorts of Typbar-TCV, persistence of antibodies was observed even after 5 years. The proportion of unboosted Typbar-TCV™ vaccinees with Avidity Index (AI) > 60% in both RCT and OLT persisted even after 5-years, whereas a drastic decline to a sub-baseline level was observed in the unboosted Typbar™ vaccinees after 5-years.

CONCLUSIONS

At the end of 5 years, Typbar-TCV™ demonstrated sustained longevity and persistence of Anti Vi IgG, higher seroconversion rates and high avidity antibodies in all the age groups of boosted and unboosted cohorts, as compared with Typbar™.These results have established that a single dose of Typbar-TCV is effective in imparting long term immunogenicity to subjects of all age groups studied.

Host Gene Expression Signatures for Enteric Fever Diagnosis

Christoph Blohmke, University of Oxford

Christoph Blohmke[1], Julius Mueller[1], Sabina Dongol[2], Steven Baker[2], Andrew Pollard[1], Thomas Darton[3]
[1]University of Oxford, [2]OUCRU, [3]University of Sheffield

BACKGROUND

The lack of accurate diagnostics for enteric fever is a major global health problem. While most tests rely on direct pathogen detection, either by culture, antigen detection or PCR amplification, our objective was to characterise the human gene expression response, and to identify a signature diagnostic of infection.

METHODS

We investigated the modulation of human gene expression in response to challenge with oral *Salmonella* Typhi or *Salmonella* Paratyphi A and compared expression profiles at diagnosis with those generated from samples collected from culture-confirmed and healthy control participants in Kathmandu, Nepal. Utilizing publicly available datasets from 2 malaria, 4 tuberculosis, 4 dengue study cohorts, and further challenge studies we applied a machine learning algorithm (random forest – 100 iterations, 70/30 split) to identify gene signatures that would identify enteric fever (EF) from non-enteric fever (non-EF) cases. Signatures were validated in a further, independent cohort of challenge participants and the endemic infection cohort by high-throughput qPCR.

RESULTS

Comparison of gene expression profiles obtained from challenge participants (n=93) and endemic zone patients (n=31) with confirmed EF demonstrated marked similarity. In gene set enrichment analysis up-regulation of blood transcriptional modules including cell cycle, type I/II interferon, and immune and inflammatory was found, whereas T-cell signatures were down-regulated as identified previously. Applying the machine learning algorithm to the discovery cohort identified 5 genes whose expression reliably discriminated between culture-confirmed EF and non-EF cases. This signature correctly predicted the independent validation cohort with a sensitivity and specificity of 97% and 88%, respectively (AUROC 97%). For classification of specific aetiologies, our algorithm identified a 7-gene signature that could correctly classify 3/5 aetiologies (EF, malaria and controls) with high sensitivities and specificities for each condition (92%/93%, 100%/98%, 96%/91%, respectively). Significant correlation between qPCR expression of identified genes and temperature or CRP values demonstrated the applicability and clinical plausibility of this diagnostic signature.

CONCLUSIONS

Our results demonstrate that advanced analysis applied to host response data is capable of identifying a 5-gene expression signature that accurately identifies individuals with confirmed EF infection. This response signature is common to non-endemic and endemic settings and merits further investigation as a novel diagnostic biomarker.

Measurement of Antibody Dependent Neutrophil Phagocytosis and the Respiratory Burst against *Salmonella* Typhi

Mari Johnson, Oxford Vaccine Group

Mari Johnson, Jennifer Hill, Andrew Pollard

Oxford Vaccine Group

BACKGROUND

Correlates of protection can aid vaccine development by building confidence in new products or the deployment of effective vaccines in different populations. No absolute correlate of protection has been identified for typhoid. Vi polysaccharide (Vi-PS) and Vi conjugate vaccines (Vi-TCV) can only protect through the generation of antibodies, and evidence suggests that the Fc region class, as well as antibody titre, play a role. Functional antibody assays were used to quantify the Fc antibody-mediated response in Vi polysaccharide and conjugate vaccine recipients in a human challenge study, identifying antibody-dependent neutrophil phagocytosis as an important effector function in protection against typhoid. Methods used previously, relied upon fluorescent beads coupled to Vi antigen for measurement of the phagocytic response. To better represent the *in vivo* conditions in which the antibodies would act, we are developing an assay using fluorescently labelled bacteria. In addition, we quantify the respiratory burst in neutrophils following antibody-mediated uptake, a mechanism for bacterial cell death.

METHODS

Typhoid-naïve healthy adult volunteers received either a Vi-PS or Vi-TCV vaccine, donating blood at baseline (D0) and 28 days post vaccination (D28). Isolated serum was used for the development of assay procedures. Live *Salmonella* bacteria were non-specifically stained with an amine-reactive fluorescent dye. Dihydrorhodamine-123 was used for assessment of the respiratory burst.

RESULTS

A significant increase in antibody-dependent phagocytosis was seen between baseline and D28 following vaccination in both bead and bacterial based assays, and this correlated with a significant increase in neutrophil respiratory burst. In the live bacterial assays we also observed considerable phagocytosis induced by serum from Day 0, when Vi antibody titres (as determined by ELISA) are low. This indicates a possible role for antibodies with specificities other than Vi, and we are currently investigating this further.

CONCLUSIONS

Methods incorporating live bacteria can be used to assess the production of important antibody classes in response to future vaccine candidates, and will be applied to samples from human challenge studies. In so doing, we can better understand antibody-mediated mechanisms of protection.

On the Early Cellular Immune Response during *Salmonella* Typhi Infection

Marije Verheul, University of Oxford

Marije Verheul[1], Deborah Cross[1,2], Irina Mohorianu[1,2], Michael Leipold[3], Gerlinde Obermoser[3], Jennifer Hill[1,2], Andrew Pollard[1,2]

[1]The Oxford Vaccine Group, Department of Paediatrics, University of Oxford, [2] NIHR Oxford Biomedical Research Centre, Oxford, [3]The Human Immune Monitoring Center, Institute for Immunity, Transplantation and Infection, Stanford School of Medicine, Stanford, CA

BACKGROUND

Each year, millions of people are infected by *Salmonella* Typhi and are at risk to develop typhoid fever. Natural infection with *S.* Typhi affords little opportunity to investigate the early cellular immune response to

infection as these crucial events occur prior to diagnosis. Consequently there is a gap in our knowledge of the immunological events occurring in the first few days after exposure, the period we expect to be critical for determining whether an exposed individual develops typhoid fever. Using a controlled human typhoid infection model, we investigated a broad spectrum of cellular responses in human volunteers immediately after ingestion of a suspension of *S.* Typhi bacteria.

METHODS

PBMCs were collected at baseline, 1, 2, 4 and 7 days after *S.* Typhi infection and at time of typhoid fever diagnosis. We measured the presence of 37 cellular markers using cytometry time of flight (CyTOF) technology. The antibody staining panel included standard lineage and subset classification markers accompanied by markers of cellular activation and indicators of homing directions. Data were analyzed using both classical gating strategies and clustering approaches.

RESULTS

Both gating and clustering analysis show major changes as soon as one day after exposure, most significantly changes in activation markers such as CD62L on B cells, monocytes and dendritic cells. Initial changes in activation were accompanied by changes in homing markers, which became more pronounced two days after exposure. Most changes persisted for 4 days after exposure. In those who did not develop typhoid fever, most cell types returned to baseline frequencies and marker expression by day 7 post exposure. In contrast, for those who develop typhoid fever almost every activation and homing marker measured was differentially expressed at the time of diagnosis. The preliminary data analysis does not reveal an early change that is associated with the development of typhoid fever.

CONCLUSIONS

Consumption of *S.* Typhi results in significant changes in the composition of the cellular immune system, present in blood within one day of exposure. Further mechanistic investigations into these cellular responses will enrich our knowledge on *S.* Typhi pathogenesis and protective immune responses.

Anti-Vi IgG and IgA Persistence following Immunisation with Vi Conjugate and Polysaccharide Vaccines

Elizabeth Jones, Oxford Vaccine Group

Elizabeth Jones, Thomas Bentley, Celina Jin, Jennifer Hill, Andrew Pollard

Oxford Vaccine Group

BACKGROUND

Antibodies generated in response to Vi vaccines have an important role in protection against typhoid fever. While no threshold titres for protection have been determined, recent work on samples from a human challenge efficacy trial of a Vi conjugate vaccine suggest both IgG and IgA play important roles in protection. Here we used samples from this study to evaluate antibody persistence up to one year after vaccination with either a Vi polysaccharide (Vi-PS) or Vi tetanus-toxoid conjugate (Vi-TT) vaccine.

METHODS

112 typhoid naive and previously unvaccinated adults were randomised to receive Vi-PS, Vi-TT, or a MenACWY control vaccine, and were subsequently challenged by oral ingestion of 10,000 CFU of *Salmonella* Typhi 28 days later. Serum samples from the Vi vaccine recipients were collected immediately prior to vaccination and at one, two, four, seven, and thirteen months after. Anti-Vi IgG titres were quantified using a commercially available kit (VaccZyme Human Anti-*Salmonella* Typhi Vi IgG Enzyme Immunoassay Kit, The Binding Site). A modification of this kit was used to measure anti-Vi IgA titres.

RESULTS

Vaccination with Vi-TT induced significantly higher titres of anti-Vi IgG and IgA compared with use of Vi-PS at one month post-vaccination and this difference remained significant up to seven, and two months respectively. After one year, antibody titres remained significantly increased in both study arms when compared with baseline levels. Although titres in the Vi-TT group decreased significantly at thirteen months when compared with one-month post vaccination titres, this is thought to be as a result of such high titres being generated in the first instance.

CONCLUSIONS

Anti-Vi antibodies generated in response to Vi vaccination of typhoid naïve and previously unvaccinated adults were shown to persist for up to thirteen months post vaccination. These data show that vaccination with Vi-TT produces higher titres of anti-Vi antibodies compared with Vi-PS, which remain at higher levels for longer. Further work is required to delineate the effect of *S.* Typhi exposure on the persistence of Vi-vaccine induced anti-Vi antibodies. It will be important to assess these findings alongside information on antibody function to determine how Vi vaccines can provide long lasting protection.

Stem Cell-Derived Gut Organoids and Macrophages as an *In Vitro* Model for Studying the Interactions of *S.* Typhi and *S.* Paratyphi A with the Human Host

Emily Lees, University of Cambridge & Wellcome Trust Sanger Institute

Emily Lees[1,2], Derek Pickard[3], Jennifer Hill[4], Christine Hale[2], Claire Cormie[2], David Goulding[2], Subhankar Mukhopadhyay[5], Gordon Dougan[3]

[1]University of Cambridge, [2]Wellcome Trust Sanger Institute, [3]Department of Medicine, University of Cambridge, [4]Oxford Vaccine Group, Centre for Clinical Vaccinology and Tropical Medicine, [5]King's College London

BACKGROUND

Salmonella enterica serovars Typhi (*S.*Typhi) and *S.* Paratyphi A are human-restricted enteric pathogens, responsible for a significant global disease burden. The intestinal 'organoid' system (iHO), wherein 3-D structures representative of the gut epithelium can be produced

from induced pluripotent stem cells (hIPSCs) and maintained in culture, provides the opportunity to directly model the epithelial response to these pathogens. hiPSC-derived macrophages can be used to model immune responses following translocation of these pathogens into the bloodstream.

METHODS

hiPSCs were differentiated to iHOs by sequential addition of cytokines to their culture medium, and ensuing placement into Matrigel-based pro-intestinal culture system. hiPSCs were also differentiated to embryoid bodies and macrophages via culture with specific cytokines. Organoids were microinjected and macrophages stimulated with *S.* Typhi (Quailes strain), S. Paratyphi A (NVGH308) or *S.* Typhimurium (SL1344), and underwent modified gentamicin protection assays. Intracellular colony forming unit (CFU) counts were compared between pathogens. Samples were fixed for transmission electron microscopy (T_{EM}).

RESULTS

S. Typhi and *S.* Paratyphi A both appeared to interact with and invade the intestinal epithelium, with significantly more *S.* Paratyphi A and SL1344 being recovered from within cells following inoculation ($p<0.0001$). TEM demonstrated that *S.* Paratyphi A expressed pili when interacting with the epithelium, which is a novel finding. *S.* Typhi and *S.* Paratyphi A were both able to survive and replicate within macrophages, with maximum CFUs being recovered in cells stimulated with SL1344, followed by *S.* Paratyphi A and *S.* Typhi ($p<0.0001$).

CONCLUSIONS

This is the first demonstration that *S.* Typhi and *S.* Paratyphi are able to interact with and invade the intestinal epithelium in the organoid model. This opens up opportunities for detailed investigation of the host response to these pathogens, both in the gut and in immune cells. We await RNA-sequencing data from infected organoids and macrophages. As demonstrated by our imaging studies, there is still much to learn about how these pathogens behave during infection too; for example, bacterial transcriptomics could help identify novel vaccine targets. We will expand on this work by looking at clinically relevant serovars of *S.* Typhi, such as members of the H58 clade.

THURSDAY, MARCH 28

8:30 Economic Evaluations Of Disease Burden And Vaccination Strategies: New Evidence, Future Methods, And Implications For Vaccination Decision-Making

Grand Ballroom

SYMPOSIUM SESSION CHAIRED BY
Vittal Mogasale

The symposium objectives are to: (i) report preliminary results from ongoing economic evaluations of typhoid and paratyphoid disease burden and typhoid vaccination strategies, (ii) share methodological lessons learned from ongoing evaluations and planned methods for future economic evaluations, and (iii) highlight how available and future economic evidence can contribute to typhoid vaccination decision-making.

The symposium will provide a summary of results and methods from typhoid economic evaluations across research projects in multiple countries, highlighting what is new versus the existing economic evidence base and where gaps remain. Presentations will explain for a non-economist audience the "so what" implications of differences in economic evaluation methods for interpreting and using economic evaluation results in typhoid vaccination decision-making.

Surveillance for Enteric Fever in Asia Project (SEAP) II: Health Facility Cost of Illness Preliminary Results
Nelly Mejia Gonzalez, Centers for Disease Control and Prevention

Severe Typhoid Fever Surveillance in Africa Programme (SETA): Patient Cost of Illness Preliminary Results
Enusa Ramani, International Vaccine Institute

Forecasting Demand for the Typhoid Conjugate Vaccine in Low- and Middle-Income Countries
Clint Pecenka, PATH

Costs of Typhoid Conjugate Vaccine Delivery Strategies in Navi Mumbai, India
Dayoung Song, International Vaccine Institute

Cost-Effectiveness of Typhoid Vaccination Strategies: Evidence Gaps and Recommended Methods
Virginia (Ginny) Pitzer, Yale School of Public Health

10:00-10:30 Coffee Break

Foyer/Fansipan Ballroom

10:30 Don't Let Me Down: From Data To Policy

Grand Ballroom

CONCURRENT ABSTRACT SESSION 9 MODERATED BY
Mathuram Santosham & Tony Marfin

Utilization of Healthcare Services for Enteric Fever under National Health Insurance Program in Selected Districts of Nepal

Palpasa Kansakar, Health Insurance Board, Nepal

Palpasa Kansakar[1], Madan Kumar Upadhyay[2], Nijan Upadhyay[1], Prajwal Shrestha[1], Bhagwan Regmi[1], Suresh Singh Tinkari[1], Purushottam Sapkota[1], Palpasa Kansakar[1]

[1]Health Insurance Board, [2]Health Insurance Board, KTM

BACKGROUND

Enteric fever is one of the major causes for outpatient consultations and inpatient admissions in Nepal. Fever patients in Nepal have a trend of visiting standalone pharmacies and indulge in self-management of fever, which could result in high morbidity and mortality in the absence of proper treatment. In Nepal, with the inception of National Health Insurance Program (NHIP) in 2016, healthcare utilization has been increasing.

METHODS

A retrospective cross sectional study was conducted to assess healthcare utilization for enteric fever among ensures of NHIP in 15 districts located across Nepal. Demographic data and healthcare benefits utilized by ensures diagnosed of enteric fever during one year period from August 2017 to July 2018 were analyzed using Insurance Management Information System (IMIS).

RESULTS

Overall, 12.5 % of population of the selected 15 districts were enrolled in NHIP with the lowest enrollment (1.57%) in Baitadi and highest enrollment (37.16%) in Chitwan district. Among ensures, 3162 (0.5%) utilized healthcare benefit for treatment of enteric fever at any facilities enlisted in NHIP. Among them, 18% received treatment at Primary Health Care Center, 42% at ≤25 bed/ district level facility and 40% at >25 bed facilities. Majority of these patients were between ages of 20–40 years and female (60%). Treatment received as outpatient was 73%, emergency visits 13%, while 13% received inpatient care and 1% were referral cases. Out of 3162 hospital visits, highest (16%) was reported in Bhaktapur district which is located adjacent to capital Kathmandu. Average length of hospital stay was 3.25 days for inpatients. Maximum number of visits were reported during April to July. Culture and susceptibility testing facilities were utilised only through >25 bed facilities. Cost associated with treatment was higher among >25 bed, urban based facilities compared to primary health care and rural based settings.

CONCLUSIONS

Enteric fever was reported in all 15 districts assessed. Healthcare utilization varied greatly across different sites. In urban setting, service utilization from >25 bed facilities was higher. Majority of ensures getting treated at ≤25 bed facilities based on clinical judgment where culture facilities are unavailable calls for strengthening diagnostic services for optimum identification and management of enteric fever.

Healthcare-Seeking Patterns for Individuals with Suspected Enteric Fever

Alexander Yu, Stanford University

Alexander Yu[1], Rajani Shakya[2], Caryn Bern[3], Bikram Adhikari[2], Dipesh Tamrakar[2], Krista Vaidya[2], Rajeev Shrestha[2], Jason Andrews[1]

[1]Stanford University, [2]Dhulikhel Hospital, Kathmandu University Hospital, [3]University of California, San Francisco

BACKGROUND

We used a hybrid approach, combining population-based, age-structured health care utilization data with facility-based typhoid surveillance, to produce age-adjusted burden estimates in an urban and peri-urban setting in Nepal.

METHODS

We conducted healthcare utilization surveys in the catchment areas of Kathmandu Medical College Hospital (urban Kathmandu) and Dhulikhel Hospital (peri-urban areas of Kavrepalanchok district), where prospective typhoid surveillance has been ongoing since September 2016. Clusters were selected randomly within catchment areas, comprised of the wards of a majority of typhoid cases in the year prior to initiation of surveillance. Data on healthcare seeking behavior, socioeconomic status and symptom severity were collected for each household member with an episode of fever ≥ 3 days in the previous 8 weeks.

RESULTS

From January 2017 to October 2018, we enrolled 24,515 households, representing 81,369 individuals (47,198 in Kathmandu, 34,171 in Kavrepalanchok) with a median age of 27 years (IQR 18-40). Household period prevalence of fever ≥ 3 days was lower in Kathmandu (5.7% vs 15.4%, p<0.01). Children <5 had the highest period prevalence (13.9%) while adults 22-45 had the lowest (2.1%) . The period prevalence of fever was lower in the rainy season compared to drier winter months (4.9% vs 6.4%, p<0.01). Higher SES and education was associated with lower fever prevalence. The majority with fever sought medical care (87.7%), most commonly from pharmacies and

medical shops. Only a small proportion presented to the surveillance facility (6.2% in Kathmandu, 12.6% in Kavre). Fever lasted a median 4 days (IQR 3-7) and kept participants from activities for a median 3 days (IQR 1-5) Those taken to a facility had a longer mean duration of fever (5.8 vs 4.7 days, p<0.001) and had spent more time in bed on the worst day of illness (13.1 vs 11.7 hrs, p<0.001).

CONCLUSIONS

More than 85% of individuals with suspected enteric fever sought medical care, most frequently at medical shops. Although our surveillance facilities are major medical centers, only a small proportion of those with febrile illness presented to them, highlighting the importance of adjusting for healthcare utilization to produce accurate estimates of disease burden.

Typhoid Fever in the U.S. Pediatric Population and the Potential Benefits of New Vaccines

Grace Appiah, Centers for Disease Control and Prevention

Alison Winstead[1], Gordana Derado[1], Michael Hughes[2], Amelia Bhatnagar[1], **Grace Appiah**[1], Felicita Medalla[1], Jarred McAteer[1]

[1]Centers for Disease Control and Prevention, [2]Atlanta Research and Education Foundation, Inc.

BACKGROUND

In the United States, approximately 300 typhoid fever cases are reported to CDC annually through the National Typhoid and Paratyphoid Fever Surveillance (NTPFS) system. Most are acquired during international travel. CDC recommends pre-travel vaccination of at-risk children with one of two currently available vaccines: oral (≥6 years) or injectable (≥2 years). Since 2016, an outbreak caused by extensively drug-resistant (XDR) Salmonella enterica serotype Typhi has been reported in Pakistan. XDR isolates are multi-drug resistant (MDR) — resistant to ampicillin, chloramphenicol, and trimethoprim-sulfamethoxazole — and resistant to ciprofloxacin and ceftriaxone. In light of this recent outbreak and increasing availability of new protein-conjugate typhoid vaccines that could be administered to children ≥6 months old, we characterized clinical, epidemiologic, and antimicrobial resistance data of pediatric typhoid fever cases reported to CDC.

METHODS

We reviewed laboratory-confirmed Typhi infections reported to NTPFS and antimicrobial resistance data in the National Antimicrobial Resistance Monitoring System (NARMS) from 1999—2015. We reviewed NARMS and NTPFS data from 2016—2018 for XDR Typhi cases.

RESULTS

From 1999—2015, 2,007 pediatric (<18 years) cases of typhoid fever were reported; 83% had traveled internationally within 30 days of illness onset (most frequently to South Asia [79%]), 81% (1559/1921) were hospitalized (median duration 6 days; range 0—77 days), and none died. Eight hundred and six (40%) were <6 years old; 214 (11%) were 6 months—2 years old. While 88% (1435/1627) of pediatric cases were vaccine-eligible (≥2 years old with travel to a country at-risk for typhoid), only 6% (56/994) were known to be vaccinated. Of 2,003 pediatric isolates tested for antimicrobial susceptibility, 1,216 (61%) had decreased susceptibility or resistance to ciprofloxacin, of which 272 (22%) were also MDR. None were resistant to ceftriaxone or azithromycin. MDR isolates were more likely in children [16% (320/2003)] than adults [9% (272/3001); p<0.05)]. From 2016—2018, XDR Typhi infections were identified in five children, all recently in Pakistan.

CONCLUSIONS

Among children with typhoid fever from 1999—2015, only 6% of currently vaccine-eligible patients were known to be vaccinated. Promotion of pre-travel vaccination using current vaccines and introduction of an effective vaccine for children ≥6 months could reduce the burden of typhoid disease in the United States.

A Multidisciplinary Approach to Increase Awareness and Strengthen the Case for the Introduction of a Vaccine against Invasive Nontyphoidal *Salmonella*

Gianluca Breghi, Fondazione Achille Sclavo

Gianluca Breghi, Diletta Magini, Tiziana Spadafina

Fondazione Achille Sclavo

BACKGROUND

Non-typhoidal *Salmonella* (NTS) is a leading cause of bacteremia in sub-Saharan Africa especially among under 5 children and immunocompromised individuals. *Salmonella* serovars Typhimurium and Enteritidis are the most widely associated with invasive disease across Africa. Despite a substantial burden of disease (case fatality rate of about 20% and increasing antibiotic resistance), a difficult diagnosis contributes to make the invasive non-typhoidal salmonellosis a major neglected tropical disease that has received little attention as a target for intervention by global health policy institutions and funding agencies. There are no specific recommendations for disease treatment, and the increasing prevalence of multidrug-resistant isolates strengths the need to accelerate availability of affordable vaccines against invasive non-typhoidal *Salmonella* (iNTS) that are already being developed by research groups.

METHODS

A coordinated advocacy and scientific leadership group composed by experts from public and private institutions has been created under the S-AFRIVAC project (co-financed by an Italian grant launched by the Tuscany Regional Government) to increase awareness of iNTS disease highlighting its profile as a neglected tropical disease, and support planning of an effective vaccination program for Africa.

RESULTS

The project advanced the development and introduction of a sustainable iNTS vaccine based on the innovative technology platform called Generalized Modules for Membrane Antigens (GMMA) developed by GSK Vaccines Institute for Global Health:

- Supporting pre-clinical characterization of the vaccine (immunogenicity and efficacy studies, toxicology study);
- Improving understanding of iNTS epidemiology;
- Modelling disease transmission, cost of illness and vaccine program costs;
- Estimating the cost-effectiveness of introducing the iNTS-GMMA vaccine in sub-Saharan Africa.

CONCLUSIONS

The S-AFRIVAC project allowed to progress the iNTS-GMMA vaccine development from pre-clinical to clinical phase, standardize serological assays for immunogenicity analysis and reduce the knowledge gaps in disease epidemiology. Furthermore, the cost-effectiveness of introducing the iNTS-GMMA vaccine in sub-Saharan Africa has been assessed providing also suggestions on the most affordable immunization strategy. These data are necessary to generate interest among global public health institutions and stakeholders to develop an effective advocacy strategy to tackle the burden of iNTS disease in the endemic countries.

Comparison of Cost of Illness of Extensively Drug-Resistant (XDR) vs. Non-XDR Typhoid Fever in Pakistan: Policy Implications for Typhoid Vaccine

Ashar Malik, Aga Khan University

Muhammad Tahir Yousafzai[1], Farah Qamar[2], **Ashar Malik**[1], Caitlin Barkume[2], Denise Garrett[2], Alice Lee[2], Kashmira Date[3], Ashley Tate[3]

[1]Aga Khan University, [2]Sabin Vaccine Institute, [3]Centers for Disease Control and Preventions

BACKGROUND

Surveillance for Enteric fever in Asia Project (SEAP) is a large, multi-center, prospective surveillance study designed to estimate the disease and economic burden of enteric fever in Bangladesh, Nepal, and Pakistan. The emergence of extensively drug-resistant (XDR) typhoid fever (resistant to cotrimoxazole, ampicillin, chloramphenicol, and ceftriaxone antibiotics) during a recent outbreak in Pakistan has had a serious impact on the health system, given the limited and expensive options for treatment. This analysis compares the cost of illness of blood culture-confirmed XDR vs. non-XDR typhoid fever cases from SEAP in Pakistan.

METHODS

Data were collected from hospitalized patients with blood culture-confirmed cases of *Salmonella* (S.) Typhi enrolled in SEAP in Pakistan from September 2016 to July 2018, including a private sector (Aga Khan University Hospital, AKU) and a charity-based hospital (Kharadar General Hospital, KGH). Patient costs of illness were collected by phone survey with the patient/caregiver 2-3 days after testing or hospital discharge. Data included direct medical and non-medical costs and productivity losses from illness onset until the survey. Other data collected were antimicrobial sensitivity of isolates and duration of hospital stay.

RESULTS

September 2016-July 2018, 260 patients were hospitalized with blood cultures positive for *S.* Typhi, 193 at AKU and 67 at KGH; 41% of *S.* Typhi isolates were resistant to ceftriaxone, a marker for XDR. Median length of inpatient stay was 4 days for XDR and 2 days for non-XDR patients. In 2016 US dollars, the reported median direct medical expenses were $573 for XDR and $157 for non-XDR at AKU, and $94 for XDR and $42 for non-XDR at KGH; direct non-medical expenses were $10 for XDR and $8 for non-XDR at AKU, and $4 for XDR and $3 for non-XDR at KGH. The median number of days of work, sick leave, and school lost were 20 for XDR and 14 for non-XDR at AKU, and 15 for XDR and 12 for non-XDR at KGH.

CONCLUSIONS

The economic burden is much higher for XDR compared with non-XDR typhoid fever patients from SEAP due to higher costs for inpatient care, highlighting the serious impact of XDR typhoid on Pakistan's health care system.

Epidemiology of Typhoid and Paratyphoid: Implications for Vaccine Policy

Senjuti Saha, Child Health Research Foundation

Senjuti Saha[1], Md Islam[1], Mohammad Sajib[1], Maksuda Islam[1], Stephen Luby[2], Jason Andrews[2], Samir Saha[1]

[1]Child Health Research Foundation, [2]Stanford University

BACKGROUND

Typhoid and paratyphoid remain the most common bloodstream infections in many resource-poor settings. The World Health Organization recommends typhoid conjugate vaccines (TCVs) in settings with high burden and prequalified the first TCV. Countries are now facing important decisions regarding vaccine target groups and introduction strategies that require contemporary and locally relevant epidemiological data. However, questions regarding typhoid and paratyphoid epidemiology persist, specifically severity in young children.

METHODS

We conducted enteric fever surveillance in Bangladesh from 2004 through 2016 in the inpatient departments of two pediatric hospitals and outpatient departments of one paediatric hospital and one private consultation clinic. Blood cultures were advised at the discretion of the treating physician and patients with a positive blood culture for *Salmonella* Typhi or Paratyphi A were enrolled. We used hospitalization and duration of hospitalization as proxies for severity in children <12 years.

RESULTS

We identified 7,072 typhoid and 1,810 paratyphoid culture-confirmed cases. There was no increasing trend in proportion of paratyphoid over the 13 years. The median age of typhoid cases was 60 months and 15% of cases occurred in children <24 months. The median age of paratyphoid cases was significantly higher at 90 months (p <0.001) and 9.4% of cases were <24 months. The proportion of children (<12 years) hospitalized with typhoid (32%) and paratyphoid (21%) decreased with age, however, there was no significant difference in duration of hospitalization between age groups. Children with typhoid were hospitalized for longer than those with paratyphoid.

CONCLUSIONS

With 8,882 cases, our findings demonstrate that typhoid and paratyphoid are common in young children. Although case fatality is low, emergence of widespread antimicrobial resistance is threatening effective treatment and if the right intervention strategies are not put in place soon, increases in mortality rates in the near future may occur. Fifteen percent of cases occur in children under two years of age with equivalent disease severity as seen in older children. Early immunization with TCVs could avert substantial morbidity. Efforts to reduce exposure to contaminated water and food, as well as developing vaccines against paratyphoid, are important steps for prevention and control of enteric fever.

10:30 The Long And Winding Road: Genomics

Truc Bach

CONCURRENT ORAL ABSTRACT SESSION 10 MODERATED BY
Firdausi Qadri & Gordon F. Dougan

Assessment of Population Structure and Antimicrobial Resistance Pattern of *Salmonella* Typhi Isolates using Whole Genome Sequencing Data in Bangladesh

Sadia Isfat Ara Rahman, icddr,b

Sadia Isfat Ara Rahman[1], Zoe Dyson[2], Elizabeth Klemm[2], Farhana Khanam[1], Gordon Dougan[2], Firdausi Qadri[1]

[1]International Centre for Diarrhoeal Disease Research, Bangladesh (icddr,b), [2]Department of Medicine, University of Cambridge

BACKGROUND

Multi-drug resistant typhoid fever remains an enormous public health threat in low and middle-income countries. The effort to discriminate among individual isolates becomes more complicated due to limited genetic variation of the *S.* Typhi genome. We have utilized the high-throughput SNP-based whole genome sequence data to investigate the genetic diversity and antimicrobial resistance patterns in Bangladeshi *S.* Typhi strains isolated from typhoid fever patients from 1998-2016.

METHODS

Whole genome sequence data from 816 Typhi strains were used to infer a maximum likelihood phylogeny including 202 novel Bangladesh strains from this study as well as 614 others from previous studies by Wong *et al.* 2016 and Tanmoy *et al.* 2018. For worldwide context, 1,560 additional sequences from over 30 counties were included in order to better understand both global and regional *S.*Typhi strain circulation patterns.

RESULTS

Whole genome sequencing of 816 isolates revealed 17 distinct genotypes where majority of the isolates (477/816, 58.5%) belonged to genotype 4.3.1. 137 strains from a newly defined H58 lineage reported in Tanmoy et al. 2018 as "lineage Bd" were observed. Most of the H58 isolates with acquired AMR genes *catA1*, *dfrA*, *sul1*, bla_{TEM-1}, *strAB*, and *sul2* without any evidence of the IncHI1 plasmid suggesting that these have been acquired via the chromosomal translocation of a MDR Tn2670-like complex transposable element. Decreased fluoroquinolone susceptibility was also observed due to nonsynonymous point mutations in the in quinolone resistance determining regions (QRDR) of genes *gyrA*, and *parC*, of which *gyrA-S83F* was most frequently observed. Besides the H58 isolates, the appearance of genotype 2.3.3, genotype 3.2.2 and genotype 3.3.0 were increased in recent years, the majority of which possessed at least one QRDR mutation. In comparison to global isolates, most of the Bangladeshi isolates closely clustered with isolates from neighboring India.

CONCLUSIONS

Whole genome sequence data of *S.* Typhi strains from Bangladesh isolated over 18 years, showed the recent emergence of genotypes 3.2.2, 2.3.3, 3.3.0 in Bangladesh. Many of these strains harbored QRDR mutations associated with reduced susceptibility to fluoroquinolones highlighting the importance of molecular WGS based surveillance to monitor their ongoing evolution and transmission between different countries.

Integration of Transcriptomic and Genomic Data Reveals Important Aspects of the Early Host Response to *Salmonella* Typhi Infection

Amber Barton, University of Oxford

Amber Barton[1], Daniel O'Connor[2,3], Jennifer Hill[2,3], Christoph Blohmke[2,3], Andrew Pollard[2,3]

[1]University of Oxford, [2]Department of Paediatrics, Oxford Vaccine Group, University of Oxford, [3]NIHR Oxford Biomedical Research Centre, Oxford, UK

BACKGROUND

Because studying *Salmonella* Typhi infection prior of clinical presentation with enteric fever is difficult in field settings, little is known about host-pathogen interactions during the incubation period. Stool shedding, early plasma cytokine responses and *S.* Typhi DNAaemia have been detected in volunteers who ingested a suspension of *S.* Typhi but did not develop disease, suggesting that despite infection, these volunteers may rapidly raise a protective innate response. Here we have applied functional genomics to investigate the nature of the early host response in human volunteers challenged with *S.* Typhi.

METHODS

70 unvaccinated volunteers were challenged with *S.* Typhi Quailes strain suspended in sodium bicarbonate solution. RNA was extracted from a subset of peripheral blood samples prior to challenge then 12 and 24 hours post-challenge. Gene expression was quantified by Illumina HT-12v4 bead-arrays and genotypes were determined using a Human OmniExpress-24 v1.0 BeadChip (716,503 probes). Differential expression analysis was carried out using the limma package and expression quantitative trait loci (eQTL) mapping using MatrixEQTL.

RESULTS

Linear modelling was used to assess differential expression between baseline (n = 37), 12 hours (n = 58) and 24 hours (n = 41) post-challenge. Changes in differentially expressed genes were significantly correlated between participants who did not develop enteric fever compared with those who were diagnosed following challenge (Pearson's r=0.9; p-value < 10^{-15}). However, fold changes in gene expression were greater in participants who remained healthy (p-value = 4 x 10^{-4}). To further investigate differences in response we carried out a preliminary eQTL analysis on genes most differentially expressed 12 hours post-challenge between the two outcome groups (52 genes with p-value < 0.001) and identified cis-eQTLs correlated with changes in *HLA-C* (p-value = 3 x 10^{-5}) and *BTN3A3* expression (p-value = 1 x 10^{-4}).

CONCLUSIONS

Our results reveal that host genetic factors may impact early antigen presentation in response to oral challenge with *S.* Typhi, ultimately affecting whether infection develops into typhoid fever. In the future the potentially protective nature of a robust response within the first 24 hours of exposure could be exploited through rational design of vaccines and adjuvants to modulate early responses.

Phenotypic and Genotypic Analysis of Ciprofloxacin Treatment on Phylogenetically-Related Invasive *Salmonella* Typhimurium

Sushmita Sridhar, Wellcome Sanger Institute

Sushmita Sridhar[1], Derek Pickard[2], Sandra Van Puyvelde[1,3], Josefin Bartholdson Scott[2], Sally Forrest[2], Stephen Baker[2,4,5], Gordon Dougan[2]

[1]Wellcome Sanger Institute, [2]Department of Medicine, University of Cambridge, [3]Department of Biomedical Sciences, Institute of Tropical Medicine, [4]The Hospital for Tropical Diseases, Wellcome Trust Major Overseas Program, Oxford University Clinical Research Unit, [5]Centre for Tropical Medicine and Global Health, Nuffield Department of Clinical Medicine, Oxford University

BACKGROUND

Invasive non-typhoidal *Salmonella* is a significant cause of bacterial infection globally, for which there is no vaccine. The ST313 lineage of *Salmonella* Typhimurium is responsible for much of the burden of salmonellosis in sub-Saharan Africa, and in recent years, there has been a drastic rise in multidrug resistance within this lineage. In particular, there has been a trend of increasing fluoroquinolone resistance, the first line drug against typhoid and other invasive *Salmonella*. In this study, we seek to understand the effects of ciprofloxacin, a fluoroquinolone, on bacterial transcription, morphology, and survival.

METHODS

We used a combination of RNA-seq and high-throughput fluorescent imaging to compare *Salmonella* Typhimurium isolates in the presence and absence of ciprofloxacin. Specifically, we exposed batch cultures of bacteria to their minimum inhibitory concentration for varying lengths of time and then performed RNA-seq and imaging. Upon identifying genes upregulated in the treatment condition, we have chosen a subset of genes for further analysis, including further imaging, RT-PCR, and additional RNA-seq.

RESULTS

We found firstly that *S.* Typhimurium can survive and replicate under high concentrations of ciprofloxacin. Secondly, we found that many of the genes upregulated at an early timepoint under ciprofloxacin treatment are associated with DNA damage and the stress response, consistent with previous findings. These RNA-seq data were corroborated by microscopy, which showed that treated bacteria were elongated and had stalled cell division, and that this elongation was further exaggerated at later time points. However, at eight hours post-treatment, many of the upregulated genes in the treatment condition were in metabolic and biosynthetic pathways rather than in acute stress response.

CONCLUSIONS

While this is an ongoing study, we have found that ciprofloxacin treatment has broad-reaching effects on *Salmonella* Typhimurium ST313 strains, uregulating a range of genes involved in pathways from stress response to metabolism, several of which we will analyse in further detail. Some of these transcriptional changes can be identified visually and validated by microscopy.

Importantly, this study highlights the power of combining RNA-seq and microscopy to understand and investigate *Salmonella* Typhimurium genotypic and phenotypic responses to ciprofloxacin.

Comparative Genome and Transcriptome Analysis of Antibody Resistant and Susceptible Invasive African *Salmonella* Typhimurium Isolates

Edna Ondari, Swiss Tropical and Public Health Institute

Edna Ondari[1], Elizabeth Klemm[2], Chisomo Msefula[3], Jennifer Heath[4], Moataz abd el Ghany[5], Lars Barquist[6], Robert Kingsley[7], Calman MacLennan[8]

[1]Swiss Tropical and Public Health Institute (current adress: KEMRI-CGHR), [2]Wellcome Trust Sanger Institute, [3]Department of Microbiology, College of Medicine, University of Malawi, [4]School of Immunity and Infection, College of Medicine and Dental Sciences, University of Birmingham, [5]The Westmead Institute for Medical Research and Marie Bashir Institute for Infectious Diseases and Biosecurity, University of Sydney, [6]Institute for Molecular Infection Biology, University of Würzburg, [7]Quadram Institute Bioscience, Colney, Norwich Research Park, Norwich, [8]Jenner Institute, Nuffield Department of Medicine, University of Oxford

BACKGROUND

Invasive nontyphoidal *Salmonella* infections are estimated to cause 3.4 million illnesses and over 680,000 deaths annually, with approximately 57% of these fatalities occurring in sub-Saharan Africa. Children and HIV-infected adults are at greatest risk of life-threatening illness. Widespread multiple drug resistance among circulating strains has facilitated the emergence and spread of the *S.* Typhimurium ST313 pathovar, which is now dominant among *Salmonella*e causing invasive human disease in Africa. Against this backdrop, candidate vaccines eliciting protective antibody responses provide a promising avenue for disease control. Circulation of antibody resistant strains could compromise a vaccination strategy.

The objective of the study was to identify the basis for complement resistance among invasive *S.* Typhimurium strains from Africa.

METHODS

Full genome sequences and transcriptomes of *S.* Typhimurium ST313 strains with differential susceptibility to antibody-dependent complement-mediated serum bactericidal activity were compared and contrasted. Sequence variations (gene polymorphisms and larger genomic rearrangements) were identified in a subset of six strains, and specific variants functionally characterized using RNA-seq transcriptomics, high-throughput transposon mutagenesis (TraDIS) and targeted gene deletion.

RESULTS

Transcriptional responses to serum exposure, distinguished between resistant and sensitive isolates. Genes associated with polysaccharide synthesis significantly accounted for these differences, particularly LPS and *wca* (colanic acid) locus genes. Fold induction of *wca* genes was higher in susceptible strains, however, and disruption of the *wca* locus did not diminish viability in serum. Conversely, up-regulation of *fepE*, regulator of very long-chain lipopolysaccharide was greater in resistant strains. In contrast, we found no common genotype among strains of either resistant (with net growth in serum) or susceptible phenotype in any of the isolates characterized. There was also no observed impact of polymorphisms or larger chromosomal modifications on serum sensitivity.

CONCLUSIONS

These results support evidence of modes of resistance to humoral immunity in ST313 that may be independent of genetic background.

DNA-Gyrase/Topoisomerase-IV Mutations and Antibiotic Susceptibility Patterns of *Salmonella* Paratyphi A

Mohammad Saiful Islam Sajib, Child Health Research Foundation

Mohammad Saiful Islam Sajib[1], Senjuti Saha[1], Arif Mohammad Tanmoy[2], Maksuda Islam[1], Samir Kumar Saha[1]

[1]Child Health Research Foundation, [2]Erasmus Medical Center

BACKGROUND

Salmonella enteica serovar Paratyphi A, the etiologic agent of paratyphoid fever, can lead to severe morbidity if treatment is inappropriate. With increasing reports of ciprofloxacin and multidrug resistance (MDR; resistance to ampicillin, chloramphenicol and cotrimoxazole), newer antibiotics like ceftriaxone and azithromycin are often prescribed. Antimicrobial activity of *S.* Paratyphi A is not well understood thus empirical treatment of Paratyphi A is often based on the susceptibility profile of *S.* Typhi. Here we examined the susceptibility patterns and respective gene mutations of *S.* Paratyphi A in Bangladesh.

METHODS

From 1999 to 2016, we conducted an enteric fever surveillance in two largest pediatric hospitals and one private consultation clinic in Dhaka, Bangladesh. Blood cultures were advised at the discretion of the treating physicians; cases of culture-confirmed paratyphoid were included. Identification was done via serum agglutination method. Antimicrobial susceptibility was determined following CLSI guidelines (2017). A total of 640 strains were available for further molecular analysis. Polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) was used for the detection of *gyrA-83, 87, gyrB-464, parC-57, 80 and parE-420* mutations.

RESULTS

During the 15-year surveillance, a total of 2,141 *S.* Paratyphi A were isolated. No MDR strain was detected; 0.3% (71/2121) was resistant to ampicillin, 0.03% (7/2103) to chloramphenicol and 0.1% (71/2129) to cotrimoxazole. Resistance against ceftriaxone was absent (0/1807). Decreased ciprofloxacin susceptibility (DCS) was seen in 98% (628/640) isolates (MIC50 = 0.5µg/mL, MIC90 = 1µg/mL). In total, 98% (628/640) strains had *gyrA-83/87*

mutations, 94% (599/640) had *gyrB-464* and 91% (585/640) had *parC-57* mutations. Unlike commonly seen for *S.* Typhi, no Paratyphi A isolate had *parE-420* or *gyrA-83+87* mutation. Average ciprofloxacin MIC of strains with *gyrA-83* and *parC-57* mutations was 1.7 µg/mL.

CONCLUSIONS

This is one of the first comprehensive studies reporting antimicrobial susceptibility pattern of *Salmonella* Paratyphi A. Presence of gyrase and topoisomerase mutations support the wide prevalence of DCS. Due to the absence of MDR, paratyphoid cases should not be grouped with typhoid and can be treated with first-generation antibiotics in Bangladesh. This will curb use of newer antibiotics thus restrict emergence of resistance.

The Role of Genomics in Typhoid Control: Sentinel Traveler Surveillance, In-Host Evolution, and Transmission Dynamics

Zoe Dyson, University of Cambridge, University of Melbourne & Monash University

Zoe Dyson[1,2,3], Balaji Veeraraghavan[4], Firdausi Qadri[5], Timothy Dallman[6], Andrew Pollard[7,8], Gordon Dougan[1], Kathryn Holt[2,3,9]

[1]Department of Medicine, School of Clinical Medicine, University of Cambridge, Cambridge, United Kingdom, [2]Department of Biochemistry and Molecular Biology, Bio[21] Institute, University of Melbourne, Melbourne, Australia, [3]Department of Infectious Diseases, Clinical School, Monash University, [4]Department of Clinical Microbiology, Christian Medical College, Vellore, [5]International Centre for Diarrhoeal Disease and Research, Bangladesh, [6]Bacteriology Reference Department, National Infection Service, Public Health England, London, United Kingdom, [7]Oxford Vaccine Group, Department of Paediatrics, University of Oxford, Oxford, United Kingdom, [8]National Institute for Health Research, Oxford Biomedical Research Centre, Oxford, United Kingdom, [9]Department of Pathogen Molecular Biology, Faculty of Infectious and Tropical Diseases, London School of Hygiene and Tropical Medicine, London, United Kingdom

BACKGROUND

Pathogen whole genome sequencing (WGS) is increasingly used for genomic surveillance and transmission modelling for typhoid. However, most routine WGS sequencing of typhoid agents is conducted in non-endemic countries, and it is unclear whether the evolutionary rate of typhoid pathogens is sufficient to resolve transmission chains in outbreak scenarios. Here we investigated whether *Salmonella* Typhi cultured from travelers returning from typhoid endemic areas are representative of the pathogen population at the destination of travel, and directly measured the evolutionary rate of the pathogen during *in vivo* infection in the human challenge model.

METHODS

WGS was used to identify base substitutions, type *S.* Typhi into lineages (genotypes), to infer a core genome maximum likelihood phylogeny, and to detect molecular determinants of antimicrobial resistance (AMR). AMR and genotype profiles of travel-associated isolates collected by public health laboratories in the United Kingdom and Australia were compared with those collected locally in India, Bangladesh, Samoa, and Papua New Guinea. Genomes from isolates obtained from blood and stool cultures of human challenge participants were compared with the complete genome of the inoculating strain to identify mutations arising *in vivo*.

RESULTS

For all four endemic countries examined, travel-associated isolates were intermingled in the phylogeny with those collected locally across similar sampling periods, and were significantly positively correlated in terms of both the genotypes present (Pearson correlation, 0.94, $p=1.1x10^{-15}$) and AMR determinants (Pearson correlation 0.96, $p=2.22x10^{-07}$). Of 203 post-challenge S. Typhi isolates, n=7 (~1 in 30) harboured *de novo* DNA base substitution mutations compared with the inoculating strain, yielding an estimate of in-host evolution of $4.39x10^{-7}$ [95% CI, $1.92x10^{-7}$ - $9.49x10^{-7}$] substitutions/site/genome/year, in line with substitution rates estimated from Bayesian phylogenomic analyses of WGS data on natural infections.

CONCLUSIONS

Genomic surveillance is highly informative for typhoid control strategies, revealing transmission dynamics, AMR mechanisms, regional strain circulation patterns, and resolving point source outbreaks, although the substitution rate of *S.* Typhi is too low to resolve individual transmission events during outbreaks. Similarity between travel-associated and locally isolated *S.* Typhi demonstrates the utility of the former as a source of routine sentinel surveillance for regions where local genomic surveillance is not yet available.

12:00-13:30 Lunch and Posters — **JW Café/Fansipan Ballroom**

POSTER EXHIBITION SPONSORED BY TUBEX®

13:30

Magical Mystery Tour: The Late Breakers

Grand Ballroom

ORAL ABSTRACT SESSION 11 MODERATED BY
Farah Qamar & Myron (Mike) Levine

Assessment of Humoral and Cellular Responses to Vi Polysaccharide Vaccine as a Booster after Vi Conjugate Prime

Thomas Bentley, Oxford Vaccine Group

Thomas Bentley, Elizabeth Jones, Celina Jin, Jennifer Hill, Maria Moore, Andrew Pollard

Oxford Vaccine Group

BACKGROUND

The Vi tetanus-toxoid conjugate (Vi-TT) vaccine has been shown in recent human challenge efficacy trials (VAST) to confer protection against typhoid fever. Here we set out to assess the humoral and cellular response in a novel subset of participants who received Vi-polysaccharide (Vi-PS) vaccine as a booster vaccination 18 months after receiving the Vi-TT vaccine.

METHODS

10 participants from the VAST study received a dose of the Vi-PS vaccine 18 months after receiving Vi-TT. Serum and PBMC samples were collected immediately prior to vaccination and 7 days and 28 days after vaccination. Anti-Vi IgG titres were quantified using a commercially available ELISA kit (VaccZyme Human Anti-*Salmonella* Typhi Vi IgG Enzyme Immunoassay Kit, The Binding Site). A modification of this kit was used to measure anti-Vi IgA titres. ELISpot was used to assess memory B cell and plasma cell responses.

RESULTS

Vi-PS vaccine induced a significant increase in anti-Vi IgG and IgA over 28 days, with the most prominent increases being in individuals where antibody titres generated in response to Vi-TT had waned (4 out of 10). The analysis revealed no significant increase in plasma cell frequency at any time point. However, as plasma cells are responsible for the production of antibody, these results suggest that a transient plasma cell response occurred which was not captured by the limited time points tested. Vi-PS boost did not induce a significant increase in activated memory B cells, which corroborates observations from Vi-PS primed individuals (unpublished).

CONCLUSIONS

A Vi-PS boost induces a significant increase in both anti-Vi IgG and IgA titre in adults previously vaccinated with the Vi-TT vaccine. There is a more prominent response in adults with lower antibody titres, which indicates that vaccination amongst those whose antibody has waned beyond 18 months may boost immunity and potentially protection. Vi-PS vaccination does not induce activation of anti-Vi IgG and IgA memory B cells, as expected with a PS vaccine.

Extensively Drug Resistant Typhoid Fever in Karachi, Sindh: An Analysis of Lab Based Surveillance Data, 2018

Ishfaque Hussain Memon, FELTP

Ishfaque Hussain Memon, Anam Vighio, Sayyad Masroor Zia, Muhammad Asif Syed, Mirza Amir Baig

FELTP

BACKGROUND

In November 2016, an outbreak of extensively drug-resistant typhoid fever (XDR-TF) was reported in Sindh, Pakistan. A laboratory-based surveillance system was established to collect information on drug susceptibility of *Salmonella typhi* isolates. This surveillance data was analyzed with objective to find out the extent, pattern and time trend of XDR-TF

METHODS

A total of 25 surveillance sites were identified for the surveillance system in Karachi. The reporting was erratic at first but 13 sites reported data regularly between 1st January to 31st December 2018. Data from 2017 was excluded because of poor data quality and completeness. An isolate resistant to five classes of antibiotics (ampicillin, chloramphenicol, trimethoprim-sulfamethoxazole, ciprofloxacin and third-generation cephalosporin) was considered as a case of XDR-TF. Descriptive analysis, attack rates (AR) and patterns of XDR-TF were computed. Statistical analysis was performed using the Cochran-Armitage trend test for the comparison of proportions; $p< 0.05$ was considered statistically significant.

RESULTS

A total of 6, 253 drug susceptibility test results were reported in 2018, out of which 3,739 (60%) were identified as XDR-TF. The XDR-TF cases were predominantly males (n=2264, AR 22/100,000). Overall attack rate was 19 per 100,000 population and the most affected age group was 3-4 years (n=779, AR 58/100,000) with the highest attack rates seen in children under 15 years of age. XDR-TF cases in each week ranged from 1–153 with a peak observed in week 32. Off 18 towns of Karachi, Gulshan-e-Iqbal town was the most severely affected (n=285, AR 27/100,000). The proportion of XDR-TF cases among the typhoid isolates increased from 17% in January to 63% in December 2018 (R^2=0.772: X^2 = 20.4, P < 0.0001).

CONCLUSIONS

The burden of XDR-TF increased with time and more cases were observed in the summer season. Children under 10 years had higher attack rates as compared to other age groups, which needs further research for evaluation of risk factors. In collaboration with Government of Sindh typhoid vaccination campaigns were conducted targeted at high risk areas and age groups. Continuous monitoring of resistance patterns of Salmonella *typhi* strain was also recommended.

Emergence of Azithromycin Resistance in Typhoidal *Salmonella* in Dhaka, Bangladesh

Senjuti Saha, Child Health Research Foundation & Stanford University

Yogesh Hooda[1], **Senjuti Saha**[2, 3], Mohammad Sajib[2], Stephen Luby[3], Jason Andrews[3], Samir Saha[2]

[1]University of Toronto, [2]Child Health Research Foundation, [3]Stanford University

BACKGROUND

With the rise in fluoroquinolone-resistant *Salmonella* Typhi and the recent emergence of ceftriaxone-resistance, azithromycin has become the last oral drug available against typhoid for which resistance is rare. Its increasing use places selective pressure for the emergence and spread of azithromycin-resistant isolates. However, little is known about azithromycin resistance in *Salmonella*, and no data are available on its molecular mechanism.

METHODS

We conducted enteric fever surveillance in the two largest pediatric hospitals of Bangladesh from 2009-2016. All typhoidal *Salmonella* strains were screened for azithromycin resistance using disc diffusion; resistance was confirmed using E-tests. Whole genome sequencing was conducted on all resistant strains, and the results were compared to genomes of sensitive strains to identify candidate resistance-conferring mutations. To test the role of specific mutation(s) present in azithromycin-resistant strains, we cloned selected genes from azithromycin-resistant and sensitive strains, expressed them from a plasmid in *E. coli*, and tested their azithromycin susceptibility.

RESULTS

We isolated 1,120 *Salmonella* Typhi and Paratyphi A strains; among these, 13 strains (12 Typhi, 1 Paratyphi) collected between 2013 and 2016 were confirmed as azithromycin-resistant (MIC range: 32-64 µg/ml). Whole genome SNP tree showed that the 12 Typhi resistant strains clustered together within the 4.3.1 sub-clade (H58). We found a non-synonymous single-point mutation exclusively in these 12 strains in the gene encoding the inner membrane permease AcrB, known to export macrolides out of bacterial cells. The mutation changed the conserved amino acid arginine (R) at position 717 to a glutamine (Q). When we expressed AcrB R717Q in an *E. coli* Δ*acrB* strain, we observed an 8-fold increase in MIC in comparison to wildtype AcrB present in sensitive strains. A mutation at R717 (R717L) was also detected in the single azithromycin-resistant Paratyphi A strain we had isolated. AcrB R717L led to a 5-fold increase in MIC when introduced in *E. coli* Δ*acrB*.

CONCLUSIONS

This report confirms 12 azithromycin-resistant *Salmonella* Typhi strains and one Paratyphi A strain. The molecular basis of this resistance is a mutation in the AcrB protein at position 717. With increase in azithromycin use, strains with R717 mutations may spread and lead to treatment failures.

Salmonella Non-Typhi Stool Excretion after Bloodstream Infection in DRC: Proportion and Genetic Similarity between Paired Blood and Stool Isolates

Marie-France Phoba, National Institute of Biomedical Research

Marie-France Phoba[1], Barbara Barbé[2], Wesley Matheus[3], Sandra Van Puyvelde[2], Stijn Deborggraeve[2], Octavie Lunguya[1], Jan Jacobs[2]

[1]National Institute for Biomedical Research, [2]Institute of Tropical Medicine, [3]Sciensano

BACKGROUND

Non-typhi *Salmonella* (NTS) are a major cause of bloodstream infections in sub-Saharan Africa. Although originally considered zoonotic, there is increasing evidence of humans being the reservoir and the source of transmission. We assessed the proportion of children excreting NTS in the stool after BSI and assessed pairs of blood and stool NTS isolates for genetic similarity.

METHODS

Between November 2013 - April 2017, blood cultures were sampled in children (29 days - 14 years) suspected of BSI at Kisantu Hospital, Democratic Republic of the Congo. In a subset of children with blood culture proven NTS, stool cultures for *Salmonella* were performed. Stool cultures of non-febrile children admitted to the hospital were used as a control group. Pairs of blood-stool isolates (*i.e.* identical serotypes recovered in the same patient) were assessed for genetic similarity by multiple-locus variable-number of tandem repeats analysis (MLVA) and Illumina Whole Genome Sequencing (WGS).

RESULTS

Of 1092 children with blood culture confirmed NTS (Typhimurium 57.0%; Enteritidis 36.3%), 28% (n = 306, Typhimurium 66.0%, Enteritidis 28.8%) had a stool sample processed. The proportion of children with *Salmonella* grown from stool samples was 34.3% (105/306, comprising Typhimurium 70.5% and Enteritidis 25.7%). Controls showed grown stool cultures in 2.0% of children (36/1822; Typhimurium 72.2%, Enteritidis 27.8%). In 86/105 (81.9%) children with blood and stool NTS, identical serotypes (paired isolates) were found, comprising Typhimurium (66/86, 76.7%) and Enteritidis (20/86, 23.3%). The median delay between blood and stool sampling among paired isolates was 2 days (range -7 – 43 days). MLVA types were identical or similar in 61/66 (92.4%) Typhimurium and 20/20 (100%) Enteritidis pairs; for both serotypes combined genetic similarity between pairs was 94.2% (81/86). WGS sequencing (done on 32 Typhimurium and 11 Enteritidis pairs) confirmed high genetic similarity within 93.0% (40/43) pairs with nearly perfect concordance between MLVA and WGS.

CONCLUSIONS

A considerable proportion of children with NTS bloodstream infection showed stool excretion of genetically identical or similar NTS isolates. These observations contribute to the understanding of the pathogenesis of invasive NTS infections and add to the hypothesis of human intestinal carriers as potential reservoir of NTS.

Community-Based Incidence of Typhoid in India

Jacob John, Christian Medical College, Vellore

Jacob John

Christian Medical College, Vellore

BACKGROUND

Typhoid vaccines have not been introduced in India despite WHO recommendations due in part to the uncertainty about the epidemiology of typhoid. This uncertainty stems from hospital-based studies that suggest a decline in morbidity and mortality and a heterogenous distribution. The perceived decline may however be a result of rampant antimicrobial use in the community masking the burden in blood culture-based hospital studies. We report preliminary incidence rates from four community pediatric cohorts that are part of the Surveillance for Enteric Fever in India (SEFI).

METHODS

The SEFI network established closed cohorts of 6000 children between 6 months and 15 years in each of four Indian sites. This included three urban (Vellore, Delhi, Kolkata) and one rural site (Pune). Active weekly surveillance for fever was undertaken and blood cultures performed on children with fever lasting 3 or more consecutive days using standardized protocols.

RESULTS

In the 24,969 child-years of observation from study inception to 15th December 2018, we observed 1.54 (1.53 -1.56) episodes of fever per child year and 460.6 (383.6-552.9) episodes of culture-confirmed typhoid per 100,000 child-years. The incidence of typhoid varied across settings with the highest incidence at Vellore 805.3 (618-1048.9) per 100,000 child-years to 31.9 (8.0-127.6) per 100,000 in the rural site at Pune, despite the incidence of fever being similar. The incidence of typhoid was similar across the different age-groups (0.5-4 years, 5-9 and 10-14 years).

CONCLUSIONS

SEFI was established to estimate the incidence of typhoid fever in the community. Community based surveillance reveals that, in contrast to the reported trends from tertiary care facilities, typhoid transmission and bacteriologically confirmed typhoid continues unabated in urban settings in India. The emergence of drug resistance may lead to higher morbidity and complications if the underlying disease transmission remains unaddressed. The low incidence at the rural site and the varying incidence across time periods within each site suggest that despite heterogeneity, all settings remain at risk of substantial disease transmission in settings of poor environmental sanitation, which may be exacerbated by as yet unknown factors affecting transmission.

A Contagious City – 120 Years of Typhoid Control and Eradication in Oxford (1840-1960)

Claas Kirchhelle, University of Oxford

Claas Kirchhelle, Samantha Vanderslott

University of Oxford

BACKGROUND

Despite its status as an overlooked disease, typhoid has long been a prominent subject of study by clinicians, epidemiologists, and microbiologists. For ca. 150 years, researchers have compiled detailed records on what they believed to be typhoid incidence and effective clinical and public health interventions. This long history of data collection means that typhoid is a promising topic for interdisciplinary medical humanities and sciences research on disease prevention and incidence.

METHODS

We examined British attempts to control typhoid via sanitary interventions in Oxford between the 1840s and 1960s. For this purpose, we conducted a qualitative examination of governmental sources, local and national media reports, and contemporary experts' personal papers to assess how varying perceptions of typhoid and conflicts of interest inspired different types of sanitary intervention. We next used historical mortality data and ARCGIS-based spatial analyses of disease incidence in different parts of the city to quantify and evaluate individual sanitary measures' impact on typhoid prevalence.

RESULTS

Our long-term analysis of typhoid interventions in Oxford highlights the importance of multipronged approaches to typhoid control. Our quantitative evaluation of historical data shows how the improvement of water supplies maximised the efficacy of new vaccine-, and chemotherapy-based interventions in the early 20th century. However, our qualitative study of contemporary discourse and decision-making reveals the limits of top-down interventions in the face of local resistance. The availability of finance and cheap credit to efficiently mobilise resources for integrated control efforts at the municipal level emerges as one of the most decisive factors for effective typhoid control. There are significant parallels between the historical challenges of typhoid intervention in Oxford and the current context of rapid urbanisation and strong income disparities in many endemic low- and middle income settings.

CONCLUSIONS

Our study highlights the significant potential of interdisciplinary research to better understand the long-term efficacy of various typhoid control measures in different socio-economic and spatial settings. The long-term historical-epidemiological study of typhoid interventions in Oxford reveals the limits of top-down public health intervention, the importance of finance, and the efficacy of interlayered approaches to typhoid control.

15:00-15:15 Coffee Break

Foyer/Fansipan Ballroom

15:15 Imagine: Global Actions For Local Impact Toward Elimination

Grand Ballroom

PLENARY SESSION MODERATED BY
Denise Garrett & Duncan Steele

Whew – three days of deep dives into the data surrounding enteric fever prevention and control. So what's next? Where do we go from here? This session will round out the 11th International Conference on Typhoid and Other Invasive Salmonelloses by focusing on next steps as we turn our collective attention from global action to local impact, ensuring recent victories on the global stage lead to measurable impact for communities. We will discuss data gaps that need to be filled and what steps must be taken to advance us along the path to elimination. We will forecast what elimination could look like and focus in on how TCV implementation could get us there.

Data Gaps as Obstacles to Elimination
Jeffrey (Jeff) Stanaway, Institute of Health Metrics and Evaluation

Considerations for Typhoid Elimination
John A. Crump, University of Otago

A Timeline for Typhoid Elimination
Stephen Luby, Stanford University

The Role of Vaccination towards Elimination
Phionah Atuhebwe, World Health Organization Regional Office for Africa

16:45 Closing Session

Grand Ballroom

Closing Keynote Address
Anita Zaidi, Bill & Melinda Gates Foundation

Meeting Adjournment
Denise Garrett, Sabin Vaccine Institute

SPEAKER & MODERATOR BIOS

Jason Andrews

Stanford University

Jason Andrews, MD, SM, DTM&H is an Assistant Professor in the Division of Infectious Diseases and Geographic Medicine at Stanford University. He is also serving as the Nepal site Principal Investigator for the Surveillance for Enteric Fever in Asia Project (SEAP). Jason is a graduate of Yale School of Medicine and received his Master of Science from Harvard School of Public Health.

Grace Appiah

Centers for Disease Control and Prevention

Dr. Grace Appiah is a medical epidemiologist at the Centers for Disease Control and Prevention (CDC), where she works on foodborne and waterborne disease prevention in developing countries. She graduated from the University of Virginia School of Medicine in 2008 and completed her residency in pediatrics at St. Christopher's Hospital for Children in 2011. She completed a fellowship in pediatric infectious diseases at Children's National Medical Center and earned a Masters in Clinical and Translational Research from the George Washington University School of Medicine and Health Sciences in 2014. She is board certified in pediatrics and pediatric infectious diseases. She joined CDC in 2014 as an Epidemic Intelligence Service Officer.

Silvia Argimón

Centre for Genomic Pathogen Surveillance

Silvia Argimón is a genomic epidemiologist at the Centre for Genomic Pathogen Surveillance, Wellcome Sanger Institute, UK, where she analyses population level pathogen genome sequences in the context of global surveillance and antimicrobial resistance (AMR), and informs the development of transitional tools for pathogen surveillance in public health. She has participated in the implementation of whole-genome sequencing for surveillance of AMR in the Philippines, and is currently extending her experience to other low and middle income countries. She holds a PhD from the University of Aberdeen, UK, and an undergraduate degree in Biology from the University of Buenos Aires, Argentina. Her research background is in opportunistic pathogens of humans, both bacterial and fungal.

Phionah Atuhebwe

World Health Organization Regional Office for Africa

Dr. Atuhebwe is a Medical Doctor, Public Health Specialist and Vaccinologist recognized as one of Africa's biggest contributors to the continent's immunization programmes. She leads the World Health Organization's work in the African Region on introduction of new vaccines including outbreak situations. Her most recent achievement has been the hands-on support in Zimbabwe for the first ever use of a Typhoid vaccine in response to an outbreak in Africa.

Prior to this, Dr. Atuhebwe worked with PATH as the Regional Technical Advisor for Africa and Asia leading work on introduction of new vaccines including work on the Typhoid Vaccine Acceleration Consortium (TyVAC), HPV and Malaria vaccines.

Dr. Atuhebwe's extensive knowledge and experience combined with her ability to share inter-country experiences make her a much sought after speaker for low and middle-income country experience spanning from decision making, funding applications, implementation and evaluation of new vaccine introductions. She also is a member of various global and regional vaccine platforms.

Dr. Atuhebwe holds a Bachelor of Medicine and Bachelor of Surgery from Mbarara University in Uganda and a Masters' Degree in International Public Health from The University of Leeds, UK.

Anayat Baig

Aga Khan University

Anayat Baig is currently working as research associate at the Aga Khan University Hospital Karachi's department of pediatrics and child health. Based in Hyderabad Pakistan, Mr. Baig works at the typhoid outbreak investigation and control project which is primarily a control intervention against the XDR typhoid outbreak in the city. Baig is also a columnist, blogger and a web-TV anchor where he works mainly on the socio-economic perspective of health, particularly in context of social class and gender. His research interests revolve around the correlations of social class, gender and health.

Stephen Baker

University of Oxford

Stephen Baker is a Professor of Molecular Microbiology at the University of Oxford. He is located at the Wellcome Africa/ Asia programme in Ho Chi Minh City, Vietnam where he is head of the enteric infections group. He has 20 years experience in working on enteric fever and specialises in genome approaches to study disease dynamics, AMR and epidemiology.

Scott Baliban

University of Maryland School of Medicine

Dr. Baliban received his Ph.D. from Drexel University in 2014. While training in the laboratory of Dr. Michele Kutzler, Dr. Baliban focused on the pre-clinical development of *Clostridium difficile* DNA vaccines and mouse models to study the interplay between advanced age and susceptibility to *C. difficile*. After completing these studies, Dr. Baliban took a postdoctoral fellowship in the laboratory of Dr. Raphael Simon at the Center for Vaccine Development and Global Health located at the University of Maryland, School of Medicine. Here, Dr. Baliban explores the functional complexity of protective immune responses to carbohydrate-based vaccines for invasive bacterial infections. He specializes in optimization and down-selection of candidates by assessing immunogenicity and protective efficacy in different animal models. Dr. Baliban is also interested in pediatric immunology and understanding the basis for enhancing polysaccharide-specific immunity in this age group.

Caitlin Barkume

Sabin Vaccine Institute

Caitlin Barkume, MS is a Manager on the Typhoid Programs at the Sabin Vaccine Institute, where she manages the Surveillance for Enteric Fever in Asia Project (SEAP). Prior to working at Sabin, Caitlin obtained her Masters of Science in Public Health Microbiology and Emerging Infectious Disease from George Washington University.

Amber Barton

University of Oxford

Amber is a final year DPhil Candidate from the Oxford Vaccine Group, researching human immune responses in the early stages of typhoidal *Salmonella* infection. Outside of OVG she has also completed research placements in Bangkok and Okinawa, worked as a children's science show presenter in Oxford, and received four awards for innovation.

Thomas Bentley

University of Oxford

Tom Bentley is a third year medical student at Trinity College, University of Oxford. Alongside his studies, Tom has spent time with the Oxford Vaccine Group (OVG) working on the VAST (Vaccines against *Salmonella Typhoid*) study. Tom is interested in the field of Tropical Medicine, particularly vaccine development and HIV/ AIDS. Tom is doing an intercalated degree in infection and immunity and is currently writing his dissertation on the potential of CRISPR-Cas9 to be used in novel therapeutics.

Adwoa Bentsi-Enchill

World Health Organization

Dr. Adwoa Bentsi-Enchill is an epidemiologist in the Department of Immunization, Vaccines and Biologicals of the World Health Organization, Geneva where she is the focal point on activities related to typhoid and other invasive salmonelloses. In this area, Adwoa has led WHO's activities leading to the recent revision of the global policy on typhoid vaccines and specifically recommendations for typhoid conjugate vaccine use in endemic countries, as well as WHO surveillance standards. Her previous work in WHO has included immunization safety and implementation research. She has over 17 years of experience in international health including collaboration with key global stakeholders as well as technical support to immunization and other public health programmes in several countries across WHO's six regions. Prior to joining WHO, Dr. Bentsi-Enchill worked as an epidemiologist in Health Canada (now Public Health Agency of Canada) from 1994 to 2000 and gained significant experience in public health programmes, field epidemiology, and immunization.

Christoph Blohmke

University of Oxford

Christoph Blohmke received a BSc in Molecular Biotechnology (University of Lübeck), a MSc in Medical Biochemistry (University of Amsterdam), and a PhD in Experimental Medicine (University of British Columbia) where he investigated the mechanism underlying the hyperinflammatory immune response of Cystic Fibrosis lung epithelial cells. After completing his PhD studies, he took a post-doctorate position working on the enteric fever human challenge model at the Oxford Vaccine Group (OVG), University of Oxford. There, as a Marie Curie Research Fellow, he developed and led several of the systems biology projects within the enteric fever programme. These focused on investigating host responses to challenge with S. Typhi and Paratyphi, disease pathogenesis, correlates of protection following vaccination and diagnostic biomarker discovery. Christoph recently accepted a role in data science at GSK Vaccines where he develops data-driven approaches and advanced analytics solutions for clinical and pre-clinical vaccines R&D.

Gianluca Breghi

Fondazione Achille Sclavo

Gianluca Breghi is Managing Director of the Fondazione Achille Sclavo and COO of the Sclavo Vaccines Association, based in Italy. Gianluca has been working in Life Sciences for over 30 years holding several management and consulting positions in the biotech and pharmaceutical field, especially in vaccines and small molecules with: Parke-Davis, Warner Wellcome, Chiron Vaccines, Intercell, Novartis, GSK and others, being in charge of national and international business, policy and strategy. He held the position of Deputy Provost at the Sant'Anna School of Advanced Studies in Pisa, Italian excellence research and academic institution. Gianluca holds a Bachelor's degree in Economics as well as MBA from Emory University, USA.

His professional life has led him to conjugate his business background with research and innovation activities in Life Sciences, with a global outlook to viable product development and implementation strategies in infectious, neglected and orphan diseases. During his professional life he interacted with international health authorities, institutions and charities acquiring a comprehensive vision of the ghlobal vaccine field, both for products heading to the market as well as for projects on orphan/neglected diseases, with particular emphasis to their epidemiological and economic components.

In the last years he engaged in projects accelerating availability of vaccines for developing countries, like typhoid conjugate and invasive non-typhoidal salmonella. He was also the Coordinator of the 5th Master in Vaccinology and Pharmaceutical Clinical Development offered to MDs from Low-Middle-Income Countries by UNSI in cooperation with Fondazione Sclavo.

Robert F. Breiman

Emory University

Dr. Robert F. Breiman is the Director of the Emory Global Health Institute and Professor of Global Health, Environmental Health, and Infectious Diseases at Emory's Rollins School of Public Health and School of Medicine. He is the Executive Director and Principal Investigator for the Child Health and Mortality Prevention Surveillance (CHAMPS) network, which works to characterize specific cause of child death for use in preventing childhood mortality in sub-Saharan Africa and south Asia. Dr Breiman is a member of the National Academy of Medicine and Fellow of the Infectious Diseases Society of America (IDSA), as well as the American Society of Tropical Medicine and Hygiene.

Megan Carey

Bill & Melinda Gates Foundation

Megan Carey is an epidemiologist who is currently working as a Program Officer focused on enteric vaccines for the Bill and Melinda Gates Foundation. She completed her M.S.P.H degree in Global Disease Epidemiology and Control at Johns Hopkins Bloomberg School of Public Health, as well as a certificate in Vaccine Science. She has received training in clinical and biological aspects of infectious diseases, epidemiological methods, biostatistics, surveillance, health behavior change, disease control programs, immunology, vaccine science and policy, and effectiveness evaluations of public health programs. She joined the Enteric & Diarrheal Diseases team two years ago, and manages a large portfolio of grants in the enteric vaccines area, with a primary focus on rotavirus and typhoid. These grants have included preclinical and early clinical vaccine development (typhoid conjugate vaccines), late-stage development (RV3-BB), cost-effectiveness analyses of vaccines, and vaccine impact studies. She has also managed grants aimed at assessing epidemiology and characterizing clinical aspects of diseases of interest, as well as grants supporting environmental surveillance and understanding transmission dynamics of disease.

Before joining the Enteric & Diarrheal Disease team, Megan worked with the Vaccine Delivery, Polio, and Malaria teams at the Gates Foundation. Prior to joining the Gates Foundation, Megan worked at the Engelberg Center for Health Care Reform at the Brookings Institute, and worked in financial services management consulting. She completed a post-baccalaureate premedical program at Georgetown University, and studied International Relations and Government as an undergraduate at Harvard College.

Megan is a dual Irish and American citizen. She enjoys yoga, travel, reading, and running.

Dennis Chao

Institute for Disease Modeling

Dennis Chao is a Senior Research Scientist at the Institute for Disease Modeling. He has developed disease transmission models of influenza, dengue, and cholera to evaluate the effectiveness of interventions. His current projects include modeling the impact of mass cholera vaccination, analyzing the seasonality of diarrheal disease, and improving the diagnosis of disease using patient symptoms and local epidemiology.

Richelle Charles

Massachusetts General Hospital

Dr. Richelle Charles is an Assistant Professor of Medicine at Harvard Medical School and on faculty in the Division of Infectious Diseases at Massachusetts General Hospital. She has experience working in multicenter collaborative efforts with investigators at various institutions such as the International Centre for Diarrhoeal Disease Research, Bangladesh (icddr,b), Partners In Health, Stanford University, and MGH-Harvard that has been focused on broadening our understanding of host-pathogen and immune responses during human infection by *Vibrio cholerae* (the cause of cholera) and *Salmonella enterica* serovar Typhi and Paratyphi A (the primary causes of enteric fever). Her primary research focus is on 1) application of high-throughput proteomic and genomic platform technologies to identify immunogenic antigens for vaccine and diagnostic development for these infections, 2) development of diagnostics for S. Typhi and Paratyphi A infection, and 3) characterization of immune responses during human infection and vaccination with enteric infections.

John Clemens

icddr,b

Prof John David Clemens is Executive Director, icddr,b. Prof Clemens is an infectious disease epidemiologist with 29 years of experience designing, conducting, and analyzing large, population-based epidemiologic studies and vaccine field trials in developing countries, including Tanzania, Mozambique, Bangladesh, India, Pakistan, China, Indonesia, Vietnam, and Chile. His work on bacterial enteric pathogens has included studies on salmonellosis, shigellosis, cholera, and ETEC. Several of these studies have entailed use of GIS, genotyping of pathogens, modeling, as well as conventional cohort and case-control designs to evaluate candidate risk factors.

A graduate of Stanford (B.S.) and Yale (M.D.) Universities, Dr. Clemens is U.S.-Board Certified in Internal Medicine, and received his post-doctoral research training in clinical epidemiology at Yale. From 1983-88, he served as a research scientist at the International Centre for Diarrhoeal Disease Research, Bangladesh, where he led the first efficacy trial of an oral vaccine against cholera, and where he conducted additional research on measles vaccine. After returning to the U.S., he served as Chief of the Epidemiology Section of the Center for Vaccine Development of the University of Maryland, and then as Chief of the Epidemiology Branch of the National Institute of Child Health and Human Development , U.S. National Institutes of Health (NIH). While at NIH he was the Director of the first WHO Collaborating Centre for Vaccine Evaluation in Developing Countries. In 1999 he became the first Director-General of the IVI. While at IVI he led the team that developed a killed oral cholera vaccine that achieved licensure in India in 2009 and WHO prequalification in 2010. In 2011 he moved to UCLA to become the Founding Director of a new Center for Global Infectious Diseases. Since 2013, Dr Clemens is the Executive Director of the International Centre for Diarrheal Disease Research (icddr,b) that conducts, research, training and program-based activities to develop and share knowledge for global lifesaving solutions.

Dr. Clemens is the author of over 300 peer-reviewed publications and the recipient of the 2010 Sabin Gold Medal and the 2018 Prince Mahidol Award for Public Health.

John A. Crump

University of Otago

John Crump is McKinlay Professor of Global Health and Co-Director, Otago Global Health Institute, and Adjunct Professor of Medicine, Pathology, and Global Health at Duke University. He graduated from the University of Otago Medical School in 1993 and trained as both an internist in infectious diseases and as a pathologist in medical microbiology, training at Christchurch Hospital, New Zealand; the Royal Free Hospital, London; the Canberra Hospital, Australia; Duke University Medical Center; and with the US Centers for Disease Control and Prevention. He is a Fellow of the Royal Australasian College of Physicians, a Fellow of the Royal College of Pathologists of Australasia, a Fellow of the Royal College of Physicians of the United Kingdom, and a diplomate of the London School of Hygiene and Tropical Medicine. His main interests are in the prevention, diagnosis, and treatment of infectious diseases in developing countries, with particular focus on febrile illness; invasive bacterial diseases especially the salmonelloses; bacterial zoonoses; and enteric infections.

Dang Duc Anh

National Institute of Hygiene and Epidemiology, Vietnam

Professor Dang Duc Anh has been director of NIHE since 2015. He graduated from Sofia University, Bulgaria in 1988, obtained Master Degree of Medical Biology from the University of Amsterdam in 1995, and a PhD in 2001 the from National Institute of Hygiene and Epidemiology Vietnam. He has 30-years experience in microbiological and epidemiological research of emerging and re-emerging infectious diseases such as avian influenza H5N1, cholera and dengue fever. He is also interested in and has dedicated his time to many clinical trial studies.

Kashmira Date

Centers for Disease Control and Prevention

Kashmira Date, MD MPH, is a medical officer and the technical lead for typhoid and cholera vaccines with the Global Immunization Division at the US Centers for Disease Control and Prevention (CDC), Atlanta, USA. Dr. Date has been serving as CDC's primary focal point on typhoid vaccines since 2010, and is the principal investigator and co-investigator on numerous typhoid and cholera vaccine projects. She is the lead for the evaluation of the first public sector introduction of typhoid conjugate vaccine (TCV) in Navi Mumbai, India and a co-PI for the Surveillance for Enteric Fever in Asia Project (SEAP). She is the chair of the oral cholera vaccine working group at the Global Taskforce for Cholera Control and a member of the Gavi typhoid vaccine sub-team. She has won numerous awards, including the Presidential Early Career Awards for Scientists and Engineers (PECASE) under the Obama administration, and has coauthored several important scientific publications. Prior to her current role, Dr. Date completed her Epidemic Intelligence Service (EIS) fellowship at CDC where she led several foodborne and waterborne disease outbreak investigations and program evaluations.

Pavankumar Daultani

Cadila Healthcare Limited

Dr. Pavankumar Daultani, MBBS, MD (Pharmacology) has completed his graduation from MPSMC, Jamnagar and post-graduation from PDUMC, Rajkot. He is currently working as Senior Manager in Medical & Regulatory Affairs Department of Cadila Healthcare Ltd., Ahmedabad, India. His job portfolio mainly includes project management of clinical trial operations for vaccines and drugs, and medical writing (clinical trial protocols, clinical trial reports and manuscript preparation). He has also worked as medical reviewer in Pharmacovigilance Department of the Organization. He has also regularly represented the Organization in various subject expert committee meetings of Indian Regulatory Authority for many clinical trial projects. He has been associated with the organization for more than 5 years. Prior to joining Cadila Healthcare Ltd., he has worked as Manager in Medical Services Department of Troikaa Pharmaceuticals Ltd. His research interest includes clinical research of vaccines and drugs for conditions having potential community interest.

Gordon F. Dougan

University of Cambridge

Professor Dougan, who is a Professor in the Department of Medicine at Cambridge University, is an internationally recognised expert in vaccinology. He was Head of Pathogens at The Wellcome Trust Sanger Institute (WTSI) for over a decade. His personal research team studies enteric pathogens with a strong emphasis on pathogenic mechanisms, genomics and antibiotic resistance. He has a particular interest in using genomics to study the evolution of *Salmonella enterica* serovar Typhi, the cause of typhoid. Before moving to the WTSI he was the founding Director of the Centre for Molecular Microbiology and Infection at Imperial College London and a Professor of Biochemistry. He is a member of EMBO and a Fellow of the Royal Society. He received his B Sc and Ph.D. from the University of Sussex and conducted postdoctoral studies at the University of Washington (Seattle) in the laboratory of Stanley Falkow. He worked in industry developing novel vaccines at an internationally renowned multi-national company. He currently sits on the board of The Hilleman laboratories, a joint venture between Wellcome and Merck. He is a founder of VHSquared and Microbiotica, both spin outs of The Sanger Institute. He is currently an 'Expert in Residence' at The Wellcome Trust, advising them on vaccine strategy and innovations. He has published over 500 research papers (many in high impact journals), edited several books and has sat on the editorial boards of a number of prestigious journals. He also holds adjunct professorships at the Universities of Monash and Melbourne.

Zoe Dyson

University of Cambridge & University of Melbourne

Zoe Dyson has undergraduate degrees in Applied Science (Biotechnology) and Computer Science, as well as a PhD in bacteriophage genomics from La Trobe University in Australia. In 2015 Zoe joined Prof. Kathyn Holt's pathogen genomics research group at the University of Melbourne in Australia as a postdoctoral researcher for the Strategic Typhoid alliance across Africa and Asia (STRATAA) project where she works on pathogen genomic epidemiology of typhoid. She is now seconded to the lab of Prof. Gordon Dougan at the University of Cambridge in the United Kingdom, where she continues to work on pathogen genomics at STRATAA study sites and other typhoid endemic areas.

Sean Elias

University of Oxford

I have been at the Jenner Institute; University of Oxford since 2008 first as an RA and then as a PhD student working on B cells and antibodies responses in malaria vaccine studies.

Since May 2016 I have been working as a Post Doc with Professor Calman MacLennan on the study of invasive nontyphoidal Salmonella (iNTS) disease. The focus of this project is trying to get a better understanding on the immunological basis of susceptibility by studying patients in Ghana and Burkina Faso with confirmed iNTS disease. Our particular focus is on antibody, T cell and innate cell immunology. This work is done in collaboration with the SETA study run by the International Vaccine Institute (IVI).

More recently I have been leading my own small study exploring the use of oral fluid as a non-invasive alternative to blood for measuring antibody responses to nontyphoidal Salmonella. My hope is that this can provide data to support new correlates of protection, susceptibility or carriage, given Salmonella is an orally-ingested pathogen and this is a measure of a relevant mucosal response.

I also have a keen interest in public engagement, in particular the use of board games as teaching tools.

Krishna Ella

Bharat Biotech International Limited

Born into a family of farmers from a small village in Tamil Nadu, India, Dr. Ella pursued his graduation from the University of Agriculture Sciences – Bangalore, post-graduation from the University of Hawaii, followed by Ph. D. from the University of Wisconsin-Madison, there on served as a faculty at the Medical University of South Carolina-Charleston.

After returning to India in 1997, Dr. Ella established Bharat Biotech International Limited, a biotech company specialised in R&D, manufacturing and marketing of vaccines and bio-therapeutics.

With over 100 global patents, more than 1700 employees, with exports to over 100 countries and more than 3.8 billion vaccine doses delivered to date, Bharat Biotech is leading innovation globally.

Bharat Biotech is boastful of having the largest marketing team in India in the biotech space with over 400 executives catering to more than 30000 paediatricians.

Under Indo-US VAP, Bharat Biotech developed Rotavac®, the first vaccine from the developing world in collaboration with BMGF, DBT and DST. Bharat Biotech successfully developed and commercialized World's 1st and only WHO-PQ Typhoid Conjugate Vaccine, Typbar TCV®. Bharat Biotech was the 1st in the world to file patents for *Chikungunya* and *Zika* candidates.

Committed to shaping India's science education and policy, Dr. Ella is a member on various committees. The prominent ones include - current role as Member -Scientific Advisory Committee to Union Cabinet (SAC-C), Member- Governing Body, CSIR and Board Member- TIFAC, CCMB and CFTRI.

Hubert P. Endtz

Fondation Merieux

Hubert Endtz holds the chair in Tropical Bacteriology at Erasmus University in Rotterdam, The Netherlands. Until 2007 he was head of R&D and deputy Chairman of the Department of Medical Microbiology & Infectious Diseases at Erasmus University Medical Centre in Rotterdam. From 2007-2012 was seconded to the International Centre for Diarrheal Disease Research, Bangladesh (ICDDR,B), as Director of the Centre for Food and Waterborne Diseases and the Laboratory Sciences Division. He joined the Merieux Foundation, Lyon, France, in 2013 as Scientific Director. He holds M.D. and PhD degrees from Leiden University Medical School in the Netherlands and his post-graduate training includes work in tropical medicine at the U.S. Naval Medical Research Unit 3 in Cairo and at the Mycology Department at the Institut Pasteur in Paris. His main research interest include diarrheal and respiratory diseases in low-income countries; the pathogenesis of Guillain-Barré syndrome and antecedent infections; and antimicrobial resistance. He is the author of over 200 peer-reviewed scientific publications and 4 book chapters. H-factor 46 (web of Science)

Nicholas (Nick) Feasey

Liverpool School of Tropical Medicine

Nick Feasey lives and works in Malawi, at the Malawi Liverpool Wellcome Trust Clinical Research Programme where he heads the Drug Resistant Infection Group. Nick is a Reader at the Liverpool School of Tropical Medicine and consultant in medical microbiology & clinical infectious diseases. His research focuses on understanding environmental reservoirs and transmission of enteric pathogens, including *Salmonella* Typhi, nontyphoidal Salmonellae and Enterobacteriaceae and the clinical impact of drug resistant infection. He is supported by funding from the BMGF, Wellcome Trust, and MRC.

Patricia I. Fields

Centers for Disease Control and Prevention

Dr. Patricia I. Fields received her PhD in Microbiology from the Pennsylvania State University and was postdoctoral fellow at The Research of Scripps Clinic in La Jolla, California, where she began her work with *Salmonella*. She is currently the Lead for the *Salmonella* Reference Unit in the Enteric Diseases Laboratory Branch and the Associate Director for Laboratory Science in the Division of Foodborne, Waterborne, and Environmental Diseases at the CDC. Her research focuses on development of molecular diagnostic and subtyping methods for *Salmonella*, in particular genetic methods for the determination of serotype; and, she has a particular interest in *Salmonella* pathogenesis and genomics.

Amy Finan

Sabin Vaccine Institute

Amy Finan was appointed as the Chief Executive Officer of the Sabin Vaccine Institute in April 2016. Prior to joining Sabin, Amy served as Senior Vice President responsible for business development at the Biotechnology Innovation Organization (BIO). During her 11-year tenure at BIO, Amy played a critical role in expanding the organization's membership and revenue base and implementing innovative approaches to fundraising, branding, marketing and programming. From 2011 to 2013 and simultaneous with her BIO responsibilities, she also served as President of the Biotechnology Institute. Prior to BIO, Amy worked in the life sciences

community for more than 15 years in government relations, communications and investor relations roles. She studied at the London School of Economics & Political Science and graduated with a bachelor's degree in political science from Trinity College in Washington, D.C.

Denise Garrett

Sabin Vaccine Institute

Denise Garrett, M.D., M.Sc., is the Vice President of Typhoid Programs and the Director of the Coalition against Typhoid Secretariat at Sabin Vaccine Institute. Dr. Garrett also serves as the Principal Investigator for the Surveillance of Enteric Fever in Asia Project (SEAP). Before joining Sabin, Dr. Garrett worked at the Centers for Disease Control and Prevention (CDC) for over 20 years. During her tenure with CDC, Dr. Garrett focused on international health and epidemiologic research, leading several multicenter research studies. She served as an Epidemic Intelligence Service officer and Medical Epidemiologist at the former Hospital Infections Program, the CDC Resident Advisor for the Field Epidemiology Training Program and the National Tuberculosis Program in Brazil, the Lead of the Epidemiology Team/Division of TB Elimination, the Project officer of the Tuberculosis Epidemiologic Studies Consortium, and the CDC Resident Advisor to the President's Malaria Initiative in Angola. Through her career, Dr. Garrett has gained extensive experience collaborating with international governments, multilateral agencies, universities, private sector, non-governmental, and global health organizations to expand infectious disease control and prevention. Dr. Garrett received her medical training in Brazil with special focus on infectious diseases, including typhoid fever.

Jillian Gauld

Institute for Disease Modeling

Jillian Gauld is a postgraduate research scientist at the Institute for Disease Modeling in Bellevue, Washington, and a PhD student with the Centre for Health Informatics, Computing, and Statistics at Lancaster University. Jillian has a Master of Science in Population and Public Health from the University of British Columbia. She received funding from the Canadian Institutes of Health Research for her master's thesis, which focused on the development of contact networks in the hospital setting, and modeling the transmission of respiratory pathogens between healthcare workers. Before her current appointment, she was an environmental health scientist at the BC Centre for Disease Control in Vancouver, Canada.

Jillian's research focuses on statistical and mathematical modeling of typhoid fever. Her projects include model development and intervention impact estimation in endemic locations, as well as areas that have experienced successful control of typhoid fever. Her thesis focuses on using clinical, spatial and genomic data to better understand transmission dynamics of typhoid fever in Blantyre, Malawi, and inform environmental sampling strategies to understand heterogeneity in exposure.

Om Prasad Gautam

WaterAid

Dr Om Prasad Gautam is a public health expert and behaviour change scientist with more than 19 years of work and research experiences in Water, Sanitation & Hygiene (WASH), environmental health, behaviour change, child health, immunization, food hygiene/safety, and diseases surveillance. Dr Om holds PhD from London School of Hygiene and Tropical Medicine-UK and two Master's degree (from Bangladesh and Nepal). Dr Om currently works at WaterAid UK as a Senior WASH Manager – Hygiene and he leads WA's global hygiene behaviour change programme. He previously worked at various international organizations including World Health Organization. Dr Om is a global resource person for hygiene behaviour change, health and WASH related development programme, monitoring and evaluation and has led large scale intervention research for WASH, hygiene behaviour change, food hygiene, integrating hygiene into vaccination programme, and health/ behaviour change interventions. Dr Om published many journal articles, and he acts as an independents reviewers in international journals.

Sidhartha Giri

Christian Medical College, Vellore

Dr. Sidhartha Giri is Associate Professor of Microbiology in the Division of Gastrointestinal Sciences at Christian Medical College (CMC), Vellore, India. He received his MD in Microbiology from Sri Ramachandra Medical College & Research Institute, Chennai, after completing his graduation in medicine (MBBS) from VSS Medical College, India.

Sidhartha worked on mucosal immunity to poliovirus following administration of inactivated polio vaccine (IPV) for his PhD dissertation. His current research interests include viral gastroenteritis in Indian children, evaluation of effectiveness of oral rotavirus vaccines, and environmental surveillance for *Salmonella*, AMR genes, and vaccine polioviruses.

N.A. Gonah

Zimbabwe National Immunisation Technical Advisory Group

Dr. Nhamo Archibald Gonah born 26 January 1963 is a Senior Paediatrician with the Ministry of Health and Child Care Zimbabwe. He has been working as a Paediatrician with the Ministry since 1997.

He has been involved in child health programmes at National Level, namely, Immunisation Programme, Child Survival Strategy, IMNCI (Intergrated Management of Childhood Illness) and Maternal and Child Health Road Map. Dr Gonah is a Core member of the AMR (Anti-Microbial Resistance) Committee. He is a part –time lecturer with the University of Zimbabwe. He is involved in training of undergraduate medical students, post graduate students and clinical officers. He is the current Head of Paediatrics Division at Chitungwiza Central Hospital.

He is Chairperson of ZIMBABWE NITAG (Zimbabwe National Immunisation Technical Advisory Group) since 2014. He is a WHO trained NITAG Consultant for the WHO – AFRO region. He assists countries within the region in establishing and strengthening their NITAGs. He is also Chairperson of Zimbabwe NCC (National Certificate Committee) on Polio Eradication.

He is a member of the Paediatric Association of Zimbabwe (PAZ) and Zimbabwe Medical Association (ZIMA). Dr Gonah is a member of the Global NITAG Network (GNN) and World Medical Association (WMA).

He has been involved in research on the safety and Pharmacokinetics of Nevirapine used in infants as prophylaxis in a breast feeding population. He has been a co-investigator in several published articles on Rotavirus related diarrhoeal diseases and the impact of Rotavirus Vaccine on children under 5 in Zimbabwe.

Dr Gonah is a family man and a father of 4 children. He is an avid golfer and enjoys playing the game to relax his mind and to cope with his very busy schedule.

He is a Christian and a member of Celebration International Ministries (CMI) His main dream is to see the improvised Societies(Countries) in this World prosper economically and to see PEACE AND PROSPERITY prevailing in the lives of all mankind.

Melita Gordon

University of Liverpool

Prof Melita Gordon is a gastroenterologist and clinical scientist with 20 years track-record working on typhoidal and non-typhoidal invasive Salmonella disease in Malawi and UK. She has worked on the clinical epidemiology and clinical pathogenesis, and the immunology and host response of both typhoid and invasive non-typhoidal Salmonella disease, at cellular, molecular and transcriptomic level, working ex vivo and in vitro, on human systemic and gut mucosal tissue. She currently leads a large community-based study of typhoid epidemiology (STRATAA) which underpinned the first and ongoing clinical trial in Africa of a typhoid conjugate vaccine (TyVAC), a double-blind randomized trial of 28,000 children. In addition, she has described the emergence of novel clades of invasive Salmonella Typhimurium, S. Enteritidis and S. Typhi in Africa, investigating their genomic epidemiology and the key role of the emergence of antimicrobial resistance. More recent work has described the transcriptional and functional pathogenetic mechanisms of these novel epidemic Salmonella clades.

She has been awarded the Sir Francis Avery Jones research medal of the British Society of Gastroenterology, and the SAGE first prize for Excellence in Gastroenterology. She is based full-time in Blantyre, Malawi as Professor in the University of Liverpool, and leads a large and active research group that continues to focus on vaccines for typhoid and non-typhoidal invasive Salmonella disease, and to train local and international scientists and clinicians.

Brittany Hagedorn

Institute for Disease Modeling

Brittany Hagedorn is a research scientist for the Institute for Disease Modeling. She collaborates with multiple disease teams to estimate the cost of proposed interventions and to assess their value in comparison to alternative strategies for disease control. Brittany is interested in questions around the value of information in helping policy makers design more cost-effective strategies, particularly as it pertains to the use of disease surveillance data. She also studies the trade-offs between alternative intervention strategies under budgetary constraints and the impacts on donor policies. Prior to joining IDM, Brittany worked with healthcare delivery systems to increase workflow efficiency while also clinical outcomes and managing costs. Brittany is an ASQ-certified Six Sigma Black Belt and holds a B.S. in Systems Engineering and Masters of Business Administration (MBA) from Washington University in St. Louis.

Michael Hoffmann

California Institute of Technology

Michael R. Hoffmann is the John S. and Sherry Chen Professor of Engineering and Applied Science at the California Institute of Technology (Caltech). Hoffmann was educated at Northwestern University (BA) and Brown University (PhD). He spent two years as post-doctoral fellow at the California Institute of Technology (Caltech) and five years as an assistant and associate professor at the University of Minnesota. He continued with his professorial career at Caltech in 1980. Hoffmann has been cited more than 58,000 times on Google Scholar. The Web of Science named him one of the world's most highly cited researchers in engineering. Prof. Hoffmann was awarded an Alexander von Humboldt Prize in 1991, the American Chemical Society Award for Creative Advances in 2001, and the Jack E. McKee Medal presented by the Water Environment Federation for groundwater remediation in 2003. Hoffmann is a Member of the US National Academy of Engineering and the Chinese Academy of Engineering. In 2012, he received a prize from Bill Gates and the Gates Foundation for his research group's work on developing solar-powered biochemical and electrochemical treatment systems for processing human waste onsite as applied to improving sanitation and water quality control in the developing world.

Jacob John

Christian Medical College, Vellore

Jacob John is a Professor in the Department of Community Medicine at the Christian Medical College Vellore. He works on the prevention and control of paediatric infectious diseases focussing on their epidemiology, transmission and the impact of public health interventions. Jacob currently leads a tiered national surveillance system in India to address evidence gaps on typhoid burden in India through primary data generation in community and hospital based surveillance systems.

Previously, he has helped generate epidemiologic evidence to support vaccine policy related to *Haemophilus influenza* B, Pneumococcus and Rotavirus through population-based studies and was involved in the clinical evaluation of an indigenous rotavirus vaccine.

Hope Johnson

Gavi, the Vaccine Alliance

Dr. Hope L. Johnson completed her graduate studies at the Johns Hopkins University Bloomberg School of Public Health where she was previously faculty and co-instructor for a course on Vaccine Policy. Dr. Johnson is an infectious disease epidemiologist by training and has 20 years of experience in public health including public health practice, policy and strategy development and epidemiologic research. Her prior research focused on establishing the evidence base to inform decision-making to accelerate development and implementation of child health interventions and policies with a specific focus on vaccine preventable diseases. Dr. Johnson is currently the Director of Monitoring & Evaluation at the Gavi, The Vaccine Alliance where she is responsible for overseeing the monitoring and evaluation of Gavi's strategy, programmes it supports, policies and initiatives; strategic information; and management of Gavi investments in immunization data and research.

Mari Johnson

Oxford Vaccine Group

Mari graduated in 2017 with a BSc in Cellular and Molecular Medicine from the University of Bristol, with a focus on immunology and infectious disease. The same year she began the Wellcome Trust funded PhD programme in Infection, Immunology and Translational Medicine at Oxford University. During her first year she worked in the department of Biochemistry, developing skills in structural biology and vaccine design. For the next three years she will complete her PhD at the Oxford Vaccine Group where she is focused on developing systems serology methods to understand typhoid vaccine responses in clinical trials.

Elizabeth Jones

Oxford Vaccine Group

Elizabeth Jones is a Senior Research Assistant at Oxford Vaccine group (OVG) where she has worked on the controlled human infection studies since 2015. Elizabeth is interested in studying the immune response to vaccination and enteric fever and has worked extensively on developing a Serum Bactericidal Activity (SBA) assay, as well as looking at other humoral responses to vaccination and infection. Prior to working at OVG, Elizabeth gained a BSc in Medical Science from the University of Birmingham, where her interest in immunology and infectious diseases began after working on a project investigating *Salmonella* Typhimurim and *Nippostrongylus* Brasilensis co-infection.

Gagandeep Kang

Christian Medical College, Vellore

Gagandeep Kang is the Executive Director, Translational Health Science Technology Institute (THSTI), an autonomous institute of the Department of Biotechnology from August 2016. The THSTI has a mission to conduct innovative translational research across disciplines to understand disease biology accelerate development of concepts into products and strategies for public health. Prof. Gagandeep Kang is a physician scientist who is also a Professor of Microbiology at the Division of Gastrointestinal Sciences and the Wellcome Trust Research Laboratory at the Christian Medical College (CMC), Vellore. Focusing on vaccines, enteric infections and nutrition in young children, she combines field epidemiology with intensive laboratory investigations to develop data, insight and tools that have advanced both the science of infectious diseases and policy in India. Over two decades, she built a research program that has conducted key studies to understand enteric infectious diseases in impoverished communities. Working in partnership with non-governmental organizations and the government, she has carried out phase I-III studies of rotaviral vaccines and provided laboratory support for vaccine development in India and for other developing countries. With the Indian Council for Medical Research and the World Health Organization, she has supported the establishment of networks of sentinel hospitals and laboratories that carry out surveillance for rotavirus disease in children and ancillary studies.

She chairs the Immunization Technical Advisory Group for the WHO's South East Asian Region. She is an Independent Director of the Hilleman Laboratories, a partnership established to make affordable vaccines by Merck and the Wellcome Trust.

Palpasa Kansakar

Health Insurance Board, Nepal

Dr Palpasa Kansakar holds a PhD degree in Microbiology and is currently working as a technical expert (Laboratory Services) for the National Social Health Insurance Program, Ministry of Health and Population (MoHP) Nepal. She has over 15 years of experience in diagnostic microbiology, antimicrobial resistance in bacteria and public health sector. She has worked as a clinical Microbiologist at National Public Health Laboratory (from 2002-2006) to provide technical assistance in strengthening laboratory capacity to establish and sustain antimicrobial resistance monitoring program in Nepal. After completion of her PhD degree, she joined WHO- Nepal in 2012 as a Microbiologist to support National Public Health Laboratory/ MoHP, Nepal in implementing WHO collaborative programs for strengthening Blood Safety and Laboratory capacity. She is also actively involved in planning/ mentoring research and as a guest lecturer in Microbiology. Her research interests include laboratory and hospital based surveillance of infectious diseases, use of molecular based assays to study the diversity of bacterial pathogens, antimicrobial resistance and health financing. She has over 15 publications in various international and national journals.

Sultan Karim

Aga Khan University

I have done my Masters in Health Economics and Management from Quaid Azam University of Pakistan which is the best university in the country. Main focus of the study include Public Health, Health economics and management & Economic Evaluations. I have had my preferences of Learning Hospital management, public health research and Economic evaluations. Am currently associated with the Aga Khan University as project Manager TOIC (Typhoid Outbreak Investigation and control) Hyderabad. Prior to this I have experience of over 4 years in Health care research, Monitoring and Evaluation and Project Management. Moreover I was also associated with World Health Organisation polio Eradication program as Zonal Field Manager 3rd party monitoring in Islamabad Pakistan. My future research interest are public health interventions, specifically studies related to vaccines, Surveillance of infectious diseases, outbreak investigation and emergency interventions to control outbreaks.

Sam Kariuki

Kenya Medical Research Institute

Sam Kariuki obtained his PhD in Tropical Medicine from the Liverpool School of Tropical Medicine in 1997. He is currently the Director, Research and Development, Kenya Medical Research Institute. He is a Wellcome Trust Sanger Institute International Fellow and a visiting Professor of Tropical Microbiology, Nuffield Department of Medicine, University of Oxford, and a member of the American Sciety for Microbiology and Fellow of the African Academy of Sciences. He serves as World Health Organization consultant on food safety, antimicrobial resistance and infectious disease surveillance for the East Africa Region, and is a member of the WHO Advisory Group for Integrated Surveillance of Antimicrobial Resistance (AGISAR). As a member of the National Antimicrobial Stewardship Advisory Committee we advise Ministries of Health and Agriculture on policy on Antimicribial stewardship in human and veterinary medicine and implememntation of the National Action Plan to combact AMR.

His research interests are in the Epidemiology and Genomics of enteric bacterial pathogens and antimicrobial resistance, including invasive non-typhoidal salmonellosis (NTS) and typhoid fever, *Vibrio cholerae and Escherichia coli*. He has authored/co-authored over 140 papers in peer-reviewed journals and 3 text books on Antimicrobial Resistance and Food Safety.

Susan Kavai

Kenya Medical Research Institute

Susan Kavai completed her BSc in Medical Microbiology at Jomo Kenyatta University of Agriculture and Technology in Kenya in 2015 and shortly after enrolled for her MSc. Medical Microbiology. The focus of her project part of MSc is Characterization of Antimicrobial Resistance (AMR) in *Salmonella* Typhi which is endemic in most informal settlements in cities in Kenya. Susan is currently working as a Research Assistant in charge of Laboratory Quality Assurance at the Centre for Microbiology Research, KEMRI. Some of her roles include AMR surveillance, Quality Control of all Laboratory procedures, Quality Management Systems, Data entry and Analysis. She plans to enrol for a PhD in 2019.

Abdul Momin Kazi

Aga Khan University

Momin Kazi is a senior instructor research, at the Aga Khan University Hospital. He is a physician (M.B.B.S in Dow Medical College, Pakistan), an epidemiologist (MSc. Vanderbilt University, TN USA) and is currently completing his PhD from the University of British Columbia, BC, Canada. Momin Kazi main research focus is digital/mobile health(mhealth) and health surveillance system measures. Currently Momin Kazi is involved with multiple research studies, with primary focus of using technology as a tool in research studies and public health projects related to maternal and child health. His work also focuses in the field of mobile-health based behavioral interventions in improving vaccination coverage in Pakistan. His current work and interest also includes development and collection of data through cell phones/smart phones from household level with geospatial analysis and development of auto generated programs to disseminate public health messages, through SMS, and voice messages for improving maternal and child health including vaccination coverage. He has published over 30 papers with h-index of 11 focusing on vaccine preventable diseases in lower-middle income countries. His papers have been published in leading journals including the Lancet Infectious Diseases, Lancet Global health, World Health Bulletin and Journal of Medical Internet Research.

Farhana Khanam

icddr,b

Dr Khanam is the Project Coordinator, Mucosal Immunology & Vaccinology Laboratory, Infectious Diseases Division, at icddr,b, Dhaka, Bangladesh. Over the last 11 years she has been involved in carrying out research into diagnostics, vaccines and natural infection in enteric diseases. After completion of her MBBS form Sir Salimullah Medical College, she has obtained her M. Phil in Microbiology. She has excellent laboratory capability in the field of mucosal immunology and understanding the mechanism of correlates of protection. She can use both humoral immunity and cellular responses to understand mechanisms of responses. Farhana has been able to apply her knowledge of infectious disease to vaccine responses. She has been involved in using high throughput proteins generated by genome sequence and microarray experiments and test these for their capacity to work as diagnostic tools or components of future vaccines. She has been working on understanding killing of bacteria by phagocytes in the blood and has obtained evidence of novel methods of protection to invasive enteric pathogens.

The antimicrobial resistance pattern of *Salmonella* Typhi strains that are emerging is something that she is particularly interested in. She is working with local pharmacies to give them knowledge of antimicrobial resistance and use these appropriately. This is an important activity that she plans to expand.

Farhana is involved in many studies of vaccines needed in Bangladesh, including typhoid, cholera and ETEC vaccines. More recently her activity and work on a large typhoid conjugate vaccine in children has expanded her capacity immensely. She has taken a lead in actively vaccinating large number of participants in high risk urban population.

Claas Kirchhelle

University of Oxford

Claas (DPhil, Oxon 2015) is a Junior Research Fellow at Wolfson College and a Research Associate at the University of Oxford's Wellcome Unit for the History of Medicine. His prize-winning dissertation *Pyrrhic Progress – Antibiotics in Western Food Production* (1949-2015) (forthcoming Rutgers University Press 2019) addresses the history of agricultural antibiotic use in the US and UK. As part of the Oxford Martin Programme on Collective Responsibility for Infectious Disease, Claas' current research focusses on the global history of antibiotic use, resistance, and regulation since the 1930s. He is particularly interested in why societies regulate similar risks differently and has published and given numerous talks on the past and current challenges of antibiotic regulation and resistance. Claas is a co-curator of the international exhibition 'Alice in Typhoidland - the past & present of global typhoid' (2020-2022).

Supriya Kumar

Bill & Melinda Gates Foundation

Supriya Kumar is a Program Officer in Global Health at the Bill & Melinda Gates Foundation, and works on the Gut Health and Typhoid portfolios. She manages multiple clinical trials in the gut health portfolio aimed at preventing or reversing growth faltering in infants in Africa and Asia. She is also leading the Foundation's efforts in developing tools for typhoid environmental surveillance. Prior to joining BMGF in 2017, she was a faculty member at the Graduate School of Public Health at the University of Pittsburgh. She collaborated with partners in India and at the CDC on household surveys to assess contact heterogeneities in rural Indian populations. She also used realistic, data-driven computational models of disease transmission to assess the impact of interventions to reduce respiratory infection inequalities in the US. At BMGF, Supriya draws on this experience to manage studies aimed at understanding the transmission of pathogens such as Campylobacter in children, and the incidence of typhoid in India.

Ashley Latimer

PATH

Ashley Latimer, MA is a senior policy and advocacy officer with PATH's Center for Vaccine Innovation and Access. Ashley has more than a decade of experience working on maternal, newborn, and child health and vaccine advocacy and policy change at the global and national level. During her time at PATH, Ashley has supported policy change strategies in more than a dozen countries, led the UN Commission on Lifesaving Commodities Advocacy Working Group, provided capacity building and technical assistance for strategy development, and created advocacy resources, including toolkits and case studies for health commodities and vaccines. Prior to joining PATH, Ashley worked for the Malaria & Child Survival Department at PSI, and for the Center for Development and Population Activities. She holds a master's degree in international development and global health from the University of Denver Josef Korbel School of International Studies, and an undergraduate degree in Economics from the University of Rochester.

Emily Lees

University of Cambridge & Wellcome Trust Sanger Institute

I am currently in the 3rd year of my PhD working at the University of Cambridge / Wellcome Trust Sanger Institute, supervised by Prof Gordon Dougan. My project is investigating the interactions of Salmonellae with the intestinal epithelium, using macrophages and intestinal organoids generated from human induced pluripotent stem cells as a model with which to do this. It has been an exciting opportunity to use organoids generated from human tissue to study human-restricted serovars such as S. Typhi and S. Paratyphi A in vitro at high resolution, using cell invasion assays, imaging and transcriptomics.

My background is in paediatrics, I am currently on hiatus from my clinical training, but will resume this following my PhD in order to be able to specialise in paediatric infectious diseases alongside continuing with research in this field.

Myron (Mike) Levine

University of Maryland School of Medicine

Myron M. Levine is the Bessie & Simon Grollman Distinguished Professor at the University of Maryland School of Medicine, Associate Dean for Global Health, Vaccinology and Infectious Diseases, and the Founder and Former Director of the Center for Vaccine Development (1974-2014). He is clinically trained in pediatrics, pediatric infectious diseases, tropical public health, and epidemiology. He has extensive experience in design and evaluation of vaccines to prevent bacterial enteric infections, and has made substantial contributions in basic vaccinology, bacterial pathogenesis, clinical research, field epidemiology and public health. He has published over 668 peer reviewed journal articles, is an inventor or co-inventor on many issued patents and is Senior Editor of New Generation Vaccines, 4th ed,. A few of his achievement awards include the Albert B. Sabin Gold Medal Award for lifetime achievement, ASM's 2012 Maurice Hilleman/ Merck Award, ASTMH's Donald Mackay Medal, American College of Physicians Award for Outstanding Work in Science, 2017 Maxwell Finland Award for Scientific Achievement, and is a member of the National Academy of Medicine, USA.

Stephen Luby

Stanford University

Stephen Luby, MD is a physician and epidemiologist. He lived in Karachi, Pakistan for 5 years and Dhaka, Bangladesh for 8 years working with local researchers to broaden understanding of exposure pathways and disease burden of infectious diseases, and developing interventions to reduce that burden.In 2012 Dr. Luby joined Stanford University as a Professor of Infectious Diseases and Director of Research for Stanford's Center for Innovation in Global Health. Dr. Luby has mentored 41 scientists from low income countries to publish their initial first-authored manuscript in a peer reviewed international scientific journal; he has authored over 400 scientific articles.

Cal MacLennan

University of Oxford

Cal MacLennan is a Senior Program Officer in Enteric and Diarrheal Diseases at the Bill and Melinda Gates Foundation, with responsibility for bacterial vaccines, particularly vaccines against *Shigella* and *Salmonella*. He is an MRC Senior Clinical Fellow at the Jenner Institute, University of Oxford, where his group is investigating immunity to *Salmonella* and developing a vaccine against gonorrhoea. He directs the BactiVac MRC/GCRF bacterial vaccinology network and is Professor of Vaccine Immunology at the University of Birmingham. From 2004 to 2007, Cal studied invasive *Salmonella* disease as a Wellcome Tropical Research Fellow in Malawi. He was Head of the Exploratory Programme at the Novartis Vaccines Institute for Global Health, in Italy, from 2010 to 2014, where his team was responsible for preclinical development of vaccines against typhoid, *Shigella*, invasive nontyphoidal *Salmonella* disease and meningococcus.

Ashar Malik

Aga Khan University

Ashar Malik is working as full-time faculty at the department of Community Health Sciences, of the Aga Khan University, Karachi, Pakistan. His area of expertise is health economics and outcomes research. He holds M. Sc. degree in Health Economics from University of York, a Post Graduate Diploma in Public Administration and an M.A. in Economics from Peshawar University and currently pursuing a PhD in health economics.

Ashar is involved in teaching of graduate and post graduate level teaching in his area of expertise. His research interest is in the field of economic and impact evaluation sciences, especially policies and programs evaluation. His most recent research is on estimating economic impact of Tobacco in Pakistan, Economic analysis of management of typhoid fever and evaluation of major polices of MDGs in Pakistan. He is active member of international society for Pharmacoeconomics and outcome research, International Health economics Association.

Richard (Rick) Malley

Boston Children's Hospital

Rick Malley, M.D., began his education at the Ecole Active Bilingue in Paris, France, getting his French Baccalaureate in 1982. He received his B.A. from Yale University and his M.D. from Tufts University in 1990. He pursued pediatric training at Boston Children's Hospital, following which he trained in both pediatric infectious diseases and emergency medicine, also at Children's. In 1997, a chance meeting with Dr. Porter Anderson led to his interest in the development of a species-specific pneumococcal vaccine for use in developing countries. Under Dr. Anderson's mentorship, he shifted his research to vaccine development.

Dr. Malley runs a research laboratory at Boston Children's Hospital, with funding from NIH, PATH, the Bill and Melinda Gates Foundation, focusing on *Streptococcus pneumoniae, Staphylococcus aureus, Salmonella* Typhi and Paratyphi, and *Mycobacterium tuberculosis*.

In 2014, with support from the Bill and Melinda Gates Foundation, Dr. Malley and collaborators started a biotechnology company, Affinivax, for the development of novel vaccines. The company is based on the MAPS (for Multiple Antigen Presenting System) technology that enables the creation of highly immunogenic polysaccharide-protein complexes at very high efficiency and low cost of goods. *Streptococcus pneumoniae*, the lead target being developed at Affinivax, is in clinical trials.

Tony Marfin

PATH

Dr. Marfin is PATH's Director of Vaccine Introduction & Impact (VI&I) within the Center for Vaccine Innovation and Access. In addition to managing a group of 25 doctoral- and MPH-level staff, he is the Director for the Japanese encephalitis vaccine programs and the PATH Principal Investigator for TyVAC, a consortium of the University of Maryland, Oxford Vaccine Unit, and PATH to accelerate the uptake of typhoid conjugate vaccine. In addition, as a senior medical officer and an infectious diseases specialist, he provides medical and public health oversight for PATH's conjugated meningococcal, respiratory syncytial virus, whole cell pneumococcal, non-replicating rotavirus, and other childhood vaccines that are in various stages of clinical development.

Florian Marks

International Vaccine Institute

Dr. Florian Marks, MPH, PhD, senior scientist at the International Vaccine Institute (IVI) has over 15 years' experience in conducting epidemiological studies and provision of technical assistance to low-income countries. As the head of the Epidemiology Unit he oversees epidemiological studies of the institute. His duties include the organization, supervision and management of standardized surveillance studies, vaccination campaigns and associated effectiveness studies to generate scientific data for vaccine introduction recommendations and improvement of existing programs. His expertise is the execution of large, multi-center studies such as the Typhoid Fever Surveillance in Africa Program (TSAP) Program that generated incidence data on invasive bacterial bloodstream infections from 13 African sites; a second stage is currently underway focusing on severe typhoid (Severe Typhoid Surveillance in Africa Program (SETA). In Africa, Dr. Marks has been working in Guinea-Bissau, Senegal, Burkina Faso, Ghana, Sudan, Ethiopia, Kenya, Tanzania, Madagascar, South Africa, DR Congo, Malawi and Nigeria. In Asia, he has instituted antimicrobial resistance surveillance in Vietnam, Cambodia and Bangladesh and conducted vaccination programs in North Korea, Nepal, Indonesia and Vietnam.

Laura Martin

GSK Vaccines Institute for Global Health

Dr. Martin's career has focused on filling the translational research void in the development of vaccines for poverty related diseases. Laura joined GSK Vaccines Institute for Global Health (GVGH) in Siena, Italy in 2008 when it was owned by Novartis. She currently heads GVGH's Project Portfolio which addresses diseases that cause nearly 1 million deaths per year. GVGH and collaborators are targeting vaccines for Typhoid and Paratyphoid A fevers, invasive non-typhoidal Salmonella (iNTS), Shigellosis and Group A Streptococcus. These vaccines, in preclinical and early clinical development, are based on classical conjugate and novel GMMA technologies. She has guided the vaccines against Typhi and Paratyphi A from preclinical through early clinical development and subsequent out licensing to Biological E Ltd. for commercialization and WHO prequalification. She is the principle investigator on grants from the Wellcome Trust (Typhi/Paratyphi A vaccine), Bill & Melinda Gates Foundation (4-component Shigella) to demonstrate proof of concept in humans, and supported successful

awards for iNTS. Prior to joining GSK, Laura spent nearly 10 years developing adjuvanted recombinant protein blood-stage malaria vaccines at the NIH (Rockville, MD, USA) and at the Queensland Institute of Medical Research (Brisbane, Australia).

James Meiring

University of Oxford

James is a medical doctor specialising in infectious diseases and microbiology. He is currently studying for a DPhil in typhoid epidemiology with Professor Andrew Pollard at the Oxford Vaccine Group but based largely at the Malawi Liverpool Wellcome Trust Clinical Research Programme in Blantyre, Malawi.

Nelly Mejia Gonzalez

Centers for Disease Control and Prevention

Nelly Mejia, PhD, is a Senior Service Fellow at the Centers for Disease Control (CDC) and Prevention in Atlanta, USA. Originally from Mexico, Dr. Mejia earned her doctorate in policy analysis from the Pardee RAND Graduate School in Santa Monica, CA. For her dissertation, she developed three essays on obesity and dietary habits focusing on empirical analyses of the effects of cash transfers and food environment. Prior to RAND, Dr. Mejia worked for the Mexican Federal Government and UNICEF Mexico conducting economic analysis on social policies. At CDC, Dr. Mejia works at the Global Immunization Division in the Center for Global Health. Among her research projects, she investigates the economic burden of enteric fever in Asia, the program costs of integrating birth registration and immunization referrals in rural Zambia, and the costs of the vaccine preventable disease (VPD) surveillance system in Ethiopia. Dr. Mejia's manuscript "Neighborhood Food Environment, Diet, and Obesity Among LA County Adults" received the Preventing Chronic Disease 2015 Annual Student Paper Contest. Her research interests are health economics, immunization economics, labor markets, and development economics.

Ishfaque Hussain Memon

FELTP

Dr. Ishfaque Hussain Memon is a fellow of field epidemiology laboratory training program (FELTP) of Pakistan, and attached with Regional Disease Surveillance and Response Unit (RDSRU) @ Karachi. He worked as a town surveillance officer in District Korangi and his responsibilities include surveillance and outbreak investigation of communicable diseases. He is a medical doctor, graduate from University of Sindh in year 2000. After graduation he worked as Executive Health Officer in a Health Insurance Company and later Chief Medical Officer in a multinational security company. He has multiple success stories of public health outbreak investigation and management including Chikungunya, Naegleria, Candida Auris. CCHF and others. In addition, he is first author of two research paper were presented in national and international conference

John Scott Meschke

University of Washington

Dr. Meschke is an environmental and occupational health microbiologist, specializing in the fate, transport, detection, and control of pathogens in environmental media (Air, Water, Food, and Surfaces). His current research focuses on development and standardization of environmental surveillance methods for Typhoid and Polio. He is a Professor and Assistant Chair in the Department of Environmental and and Occupational Health Sciences, and an Adjunct Professor in Civil and Environmental Engineering at the University of Washington.

Eric Mintz

Centers for Disease Control and Prevention

Dr. Eric Mintz obtained his medical degree from the State University of New York in 1984, completed an internal medicine residency and chief residency at Harlem Hospital in 1987, and received a Masters in Public Health from Columbia University in 1989. That year he joined the US Centers for Disease Control and Prevention, where he has worked on approaches to

prevent waterborne and foodborne diseases in the Americas, Africa and Asia. Dr. Mintz has authored or co-authored over 180 scientific publications on topics such as epidemic cholera, dysentery (bloody diarrhea), and typhoid fever, and on new technologies to make safe drinking water, safe sanitation and better hygiene, more accessible, affordable, and sustainable in developing countries. He was one of the first CDC staff to respond to the earthquake in Haiti, and has participated in many responses to epidemic cholera, and the Ebola Response in Guinea. Since 199, he has led the Global Epidemiology Team of the Waterborne Diseases Prevention Branch in the National Center for Emerging and Zoonotic Infectious Diseases at CDC.

Christine L. Moe

Emory University

Dr. Moe is the Eugene J. Gangarosa Professor of Safe Water and Sanitation in the Rollins School of Public Health and the Director of the Center for Global Safe Water, Sanitation and Hygiene at Emory University.

Her research focuses primarily on the environmental transmission of infectious agents, in particular, foodborne and waterborne diseases. Her field research in Bangladesh, Bolivia, Cambodia, China, El Salvador, Ethiopia, Ghana, Honduras, India, Kenya, Mozambique, the Philippines, Rwanda, Uganda and the United States includes studies of diarrheal diseases, dry sanitation systems, fecal contamination in low-income urban environments, water quality in distribution systems, water, sanitation and hygiene in healthcare facilities in low-resource settings, and environmental contamination of vegetable crops.

Dr. Moe has a BA in Biology from Swarthmore College and an MS and PhD in Environmental Microbiology and Infectious Disease Epidemiology from the University of North Carolina at Chapel Hill. She completed a post-doctoral fellowship at the Centers for Disease Control and Prevention in the Viral Gastroenteritis Unit. Her primary appointment is in the Hubert Department of Global Health with joint appointments in the Departments of Epidemiology and Environmental Health.

Vittal Mogasale

International Vaccine Institute

Vittal Mogasale, MBBS, MPH., PhD is Head, Policy and Economic Research Department at International Vaccine Institute. He has worked for the control of infectious diseases and immunization programs in several countries for past 20 years. His current work focusses on Health Economics and Policy Research to support evidence based decision making at global, regional and country levels.

Dr. Mogasale has obtained his Medical Degree (1997) from Manipal University, India; International Masters in Public Health from Hebrew University, Israel (2003) and Doctor of Philosophy from University of Queensland, Australia (2010).

Krishna Mohan

Bharat Biotech International

Dr Krishna Mohan is designated as the Executive Director, Bharat Biotech International Ltd and working with the Organization for around 15 years. Bharat Biotech is a 20-year old Organization with strong focus on Novel Vaccines and New Biological Entities although some part of the current revenues come from Biogenerics. His previous work experience is at senior Management positions in Pharmaceutical / Specialty Chemicals Companies having started his career as a Research Scientist.

Dr Krishna Mohan obtained his Ph.D from Indian Institute of Science in Chemical Physics and subsequently carried out Post-doctoral work in USA, UK and Japan, including at the prestigious Cavendish Laboratory, University of Cambridge. He is a Gold Medalist in the Master's Program at IIT, Kharagpur and a recipient of the Graduate Fellowship Award of Rotary Foundation of Rotary International. He was also invited as a Visiting Scientist at the Indian Institute of Science under the Joint Advanced Technology Program. His primary research areas of work have been in the fields of Specialty Chemicals and Pharmaceuticals. He has supervised 9 Ph. D candidates under the External Ph.D registration program of the Osmania University, Hyderabad and the Indian Institute of Science, Bangalore and published around 125 papers in various refereed international journals and 30 Technical Reports along with 20 patents in the field of Speciality chemicals, Pharmaceuticals, and Vaccines / Biologicals. Dr Krishna Mohan gave scientific lectures at several National Laboratories in India, U.S.A., U.K, Sweden and Japan and presented papers at several international conferences in these countries.

Dr. Krishna Mohan has displayed strong leadership skills in the areas of Fundamental Research, Technology Development and Products Commercialization and has an unique combination of Fundamental Research Work leading to Commercial Technology Development. He has demonstrated effective leadership in managing Teams of highly qualified scientists and engineers in different disciplines in bringing new Ideas/Products from the Laboratory to the Market place, thereby, successfully passing the test of innovation.

Dr Krishna Mohan's current work involves developing vaccines for various infectious diseases such as Rotavirus, Japanese Encephalitis, Typhoid, Rabies, Polio, H1N1, etc. He is involved as a Team member in major aspects from Product development to GMP manufacture and carrying out Clinical trials for these vaccines, with several Patents and Publications to his credit.

Venkata Raghava Mohan

Christian Medical College, Vellore

Dr Venkata Raghava Mohan is Professor in the Department of Community Health at CMC. Having finished his Masters degree in Community Medicine at CMC, Vellore he has acquired training in Environmental and Spatial epidemiology during his MPH at Tufts University, USA. His areas of interest include Health Information Systems, Spatial and Environmental epidemiology with focus on enteric infections, child malnutrition and WASH.

He is responsible for the management of the geo-spatial database for rural, urban and tribal communities of over 300,000 residents where the Department of Community Health provides primary and secondary care, and has collected demographic and morbidity data since 1986.

He has been involved in research projects on the use of Geographic Information System in describing traffic-related injuries and detecting the most accident-prone areas of the national and state highways in Vellore district, assessing spatial distribution and clustering of taeniasis cases and low birth weight children in Vellore district, and evaluating village water supply systems to identify the critical control points in the water distribution network. Dr Mohan has also conducted studies on agrochemical and heavy metal exposure among the residents of Vellore.

In collaboration with the division of Gastrointestinal Sciences, he was instrumental in setting the Vellore Health and Demographic Surveillance System for a population of over 150,000 individuals and has spatially mapped the burden, rural-urban differentials in nutritional status of these communities.

Currently, Dr Mohan is an investigator on many large scale multi-centric studies looking at Rotavirus vaccine impact assessment in India, burden of Enteric fever in India, environmental surveillance for polio viruses, salmonella and Antimicrobial Resistance genes in Vellore.

Farzana Muhib

PATH

Farzana Muhib is a senior program officer at PATH's Center for Vaccine Innovation and Access. She is a part of the Health Economics and Outcome Research team and works on a variety of vaccine development and introduction projects providing support on demand forecasting, vaccine impact assessment, and cost of vaccine delivery. Prior to joining PATH, Farzana worked at Results for Development Institute (R4D), where she was responsible for the management of project activities for the aids2031 Costs and Financing Working Group. Before joining R4D, she worked at Johns Hopkins University on the Pneumococcal Vaccine Accelerated Development and Introduction Project (PneumoADIP) as the research project manager in charge of coordinating more than 40 research and surveillance projects. She also served as the PneumoADIP's focal point for the EMRO region and helped to set up surveillance for pneumococcal disease in several countries, including Mongolia and Pakistan. Farzana holds an MPH from the Rollins School of Public Health at Emory University, where she concentrated in international health and epidemiology. She also obtained her MA in law and diplomacy from the Fletcher School of Law and Diplomacy at Tufts University.

Kim Mulholland

Murdoch Children's Research Institute

Kim Mulholland is an Australian paediatrician, trained at Melbourne University and the Royal Children's Hospital, Melbourne. With post-graduate training in immunology, respiratory medicine and tropical medicine he joined the Medical Research Council Laboratories in 1989, where he developed a program of research covering all aspects of the problem of childhood pneumonia. This included studies of the aetiology, clinical signs, and treatment of pneumonia cases, with particular reference to very young infants and malnourished children. These studies guided WHO policy in the field and contributed to the development of the strategy of Integrated Management of Childhood Illness (IMCI), as well as

guiding oxygen and antibiotic management for hospitalized children. His Hib vaccine trials were the first to demonstrate the capacity of conjugate vaccines to prevent bacterial pneumonia, and paved the way for Hib vaccine introduction in Africa. After six years in the Gambia he joined WHO where he oversaw the development of standardized methods for the evaluation of pneumonia vaccines in developing countries. Since leaving WHO in 2000 he has continued to work in the pneumonia field with particular emphasis on vaccines. He was one of the founders of the Global Action Plan for Pneumonia, and one of the leaders of the successful Hib Initiative project that saw the introduction of Hib vaccines into the poorest countries of the world. During the same period he established leading pneumococcal microbiology and immunology laboratories at the Murdoch Children's Research Institute (MCRI), Melbourne, along with major field research programs in Vietnam, Fiji and Mongolia, and growing programs in Indonesia and Laos. He currently holds professorial appointments at the MCRI in Melbourne and the London School of Hygiene and Tropical Medicine in UK.

Jennifer Murphy

Centers for Disease Control and Prevention

Dr. Jennifer Murphy is the Team Lead of the Water, Sanitation, and Hygiene (WASH) Laboratory Team and the Principal Investigator of the Environmental Microbiology Laboratory at the Centers for Disease Control and Prevention (CDC). Dr. Murphy received her Ph.D. degree in Environmental Microbiology from the University of North Carolina at Chapel Hill School of Public Health and her B.S. degree in Biology from Emory and Henry College. Dr. Murphy has more than 18 years of research experience in designing and conducting studies that include microbiological, chemical, and physicochemical testing of water and other types of environmental samples. She has also participated in CDC-led waterborne disease outbreak response both domestically and internationally, as well as performed laboratory-based studies of disinfectants for use in waterborne disease outbreak prevention and response. Dr. Murphy has received various honors, including the CDC NCEZID 2016 Excellence in Public Health Service Award and the CDC 2013 Excellence in International Public Health Impact Award.

Aziza Mwisongo

PATH

Aziza Mwisongo, MD, MSc, PhD, is a Senior Medical Officer in PATH's Center for Vaccine Innovation and Access. She has 19 years of experience in public health work in Africa and Asia. She currently leads the country preparation and introduction work for typhoid conjugate vaccine (TCV) with the Typhoid Vaccine Accelerating Consortium (TyVAC). In this role, she is responsible for supporting countries with decision-making, Gavi applications, TCV implementation, and post-implementation evaluation and research. Presently, she is supporting several countries in sub-Saharan Africa and Southeast Asia with TCV-related activities. Dr Mwisongo's immunization expertise also includes her previous role as a member of the Task Force on Immunization for the World Health Organization-AFRO. In the past, she has provided technical assistance for health systems strengthening activities at the global, regional, and national level. Dr. Mwisongo has worked in Tanzania, South Africa, Ghana, Burkina Faso, Mozambique, and Indonesia. She is also a passionate educator, serving as an Adjunct Clinical Associate Professor at the University of Washington Department of Global Health.

Tin Ohn Myat

University of Medicine 1

Tin Ohn Myat, MBBS; M.Med.Sc (Microbiology), Dip.Med.Micro, is an Associate Professor from the Department of Microbiology, University of Medicine 1, Yangon, Myanmar.

She graduated from the University of Medicine 1 (UM1), Yangon in 1997 and completed the medical training for medicine, surgery, paediatrics, and obstetrics and gynaecology in 1998. She joined the civil service at UM1, Myanmar Ministry of Health and Sports in 2000. She received her master's degree in medical microbiology from UM1 in 2003, and a diploma degree for medical microbiology from the Institute for Medical Research, Kuala Lumpur in 2012. She specialised in infectious diseases and clinical microbiology. As a teaching faculty member of UM1, she is involved in teaching and training both undergraduate and postgraduate medical students in Myanmar, as well as in the departmental research activities. She also participates in the continuing medical education programmes in Myanmar together with health professionals from other medical specialities.

Her main area of interests are in the clinical microbiology, infectious diseases, immunology and molecular biology. Currently, she is completing her PhD from the University of Otago, New Zealand. Her research focuses on bacterial aetiology of febrile illness in Yangon.

Nginache Nampota

Blantyre Malaria Project

Nginache Nampota, MBBS, is a Malawian physician researcher and an avid typhoid fever vaccination advocate in Africa. She leads a research team at Blantyre Malaria Project (BMP), a center of excellence in clinical research established as a multiversity partnership between the Universities of Malawi, Maryland and Michigan State in the USA.

Her passion for public health research sparked during one of Malawi's worst typhoid fever outbreaks as she treated many patients at the largest referral hospital in the country. She joined BMP with the aim of improving the health of her fellow Malawians and the rest of the world by implementing high quality locally conceived and relevant evidence-generating research.

Dr. Nampota is now the on-site investigator for a clinical trial studying the immunogenicity and safety of a novel typhoid conjugate vaccine in African children. She also investigates HIV/AIDS and malaria in vulnerable populations, including studies of malaria prophylaxis in people living with HIV, the impact of HIV on infant immunity and antimalarial and antiretroviral drug interactions. The broad goal of her research is to explore prevention options for prevalent and neglected infectious diseases in sub-Saharan Africa.

Anjali Nayyar

Global Health Strategies

Anjali Nayyar has more than 20 years of experience in global health issues. Her expertise lies in developing integrated advocacy and communications strategies aimed at impacting health policy and practice. She oversees the organization's programs in emerging markets in Asia and Africa working through four offices and independent consultants. Prior to joining GHS, she served as Country Director for Program for Appropriate Technology on Health (PATH) in India. Preceding PATH, she worked with the International AIDS Vaccine Initiative (IAVI) for six years, where she served initially as India Country Director and then as Vice President for Country and Regional Programs in New York. As Vice President, she led field operations and non-research and development programs in India, Brazil, South Africa, China, Kenya, Rwanda and Uganda. Anjali has also worked with the Population Council Regional Office, South and East Asia, as a Communications Specialist and Project Director. She is a member of Confederation of Indian Industry's (CII) National Committee on Public Health, the Expert Group on Tuberculosis set up by a Political Forum called Global Coalition Against TB; Immunization Expert Group, National Health Mission, Ministry of Health and Family Welfare.

Kathleen Neuzil

University of Maryland School of Medicine

Dr. Neuzil is a Professor of Medicine and Pediatrics, Director of the Center for Vaccine Development and Global Health (CVD), and the Division of Geographic Medicine at the University of Maryland School of Medicine. At CVD, Dr. Neuzil leads an academic vaccine research and development enterprise that is engaged in the full range of vaccinology – from basic laboratory science research through vaccine development, early clinical evaluation, large-scale pre-licensure field studies, and post-licensure assessments. Throughout her career, she has conducted clinical and epidemiologic studies on vaccine-preventable diseases – including influenza, rotavirus, respiratory syncytial virus, Japanese encephalitis virus, and typhoid. Dr. Neuzil currently leads the Typhoid Vaccine Acceleration Consortium (TyVAC) whose goal is to accelerate the introduction of typhoid conjugate vaccines into Gavi-eligible countries. TyVAC is a partnership between CVD, the Oxford Vaccine Group at the University of Oxford, and PATH.

Dr. Neuzil has extensive experience in domestic and international policy, including membership on the Centers for Disease Control and Prevention's Advisory Committee on Immunization Practices and the Pandemic Influenza Task Force for the Infectious Disease Society of America. Dr. Neuzil currently serves as a member of the Strategic Advisory Group of Experts, the primary vaccine policy body for the World Health Organization. She has written nearly 200 scientific manuscripts, commentaries and book chapters on vaccines and infectious diseases. She is currently an Associate Editor of the journal Vaccine.

Eric D. Ng'eno

Washington State University

Eric is a research officer at WSU-GH, Kenya where he coordinates a hospital-based, acute febrile illnesses surveillance system. Prior to joining WSU-GH, Eric worked as a research assistant at Kenya Medical Research Institute, International Emerging Infectious diseases Program. He was part of the population-based infectious diseases surveillance and research team, between 2009 and 2017. His research interest focus on understanding epidemiology of typhoid fever in Kenya, including emergence and spread of antimicrobial resistance. Eric has background training in molecular biology and medical microbiology.

Edna Ondari

Swiss Tropical and Public Health Institute

Edna works as a Research Officer at the Kenya Medical Research Institute (KEMRI) – Centre for Global Health Research in the Neglected Tropical Diseases Unit. She is also a doctoral candidate at the Swiss Tropical and Public Health Institute of the University of Basel. The research she is currently involved in investigates immune responses in children infected with schistosomiasis and malaria in Western Kenya.

She completed a Bachelor's degree in Biology from the University of Eastern Africa, Baraton, and a Master's degree in Infectious Diseases, Vaccinology and Drug Discovery from the National University of Singapore. She undertook her doctoral thesis project at the Novartis Vaccines Institute for Global Health (currently under GSK) and the Sanger Institute under the supervision of Prof. Calman MacLennan. Her thesis project aimed at identifying and characterizing factors mediating resistance to antibody-dependent complement-mediated immunity in *S.* Typhimurium, with a focus on bloodstream isolates from Africa.

Win Thandar Oo

University of Otago

Win Thandar Oo is a second year PhD candidate at the Centre of International Health, University of Otago, New Zealand. Her current research focuses on healthcare seeking behaviour, antimicrobial use and causes of fever in Yangon, Myanmar. Win Thandar hold an MBBS from University of Medicine Mandalay, Myanmar and a MMedSci in Medical Microbiology from University of Medicine 1 in Yangon, Myanmar.

Ellis Owusu-Dabo

Kwame Nkrumah University of Science and Technology

Dr Owusu-Dabo is a Public Health Physician, Teacher and Researcher. He is Associate Professor of Epidemiology and Public Health, with research interest in tuberculosis, type II diabetes, and hypertension, sickle cell disease and health systems improvement in low-income country settings. He serves on several boards within and outside Ghana and published extensively in peer-reviewed journals. As Dean, Dr Owusu-Dabo focuses on growing SPH through capacity and skills development of young scientists and faculty. Ellis' research group focuses mainly on Non- Communicable Disease Research.

Dikshya Pant

Patan Academy of Health Sciences

Dr Dikshya Pant is a paediatrician currently working as a Lecturer in Patan Academy Of Health sciences (PAHS). She completed her bachelor in medicine in Nepal and did her postgraduate in pediatrics from Pakistan. She is involved in clinical as well as academic activities including training of the medical students and postgraduates in the department of paediatrics. She has been working as a research paediatrician with TyVAC vaccine study being conducted at PAHS with collaboration with Oxford Vaccine Group, in Nepal since Nov 2017 . Her area of interest, is infectious disease focusing on research related to water borne and vector borne diseases. She is equally interested in vaccine implementation and policy making.

Andrea Parisi

The Australian National University

Dr Andrea Parisi is an infectious-disease epidemiologist based at the Australian Institute of Health and Welfare and a PhD candidate at the Australian National University investigating epidemiology of invasive and multi-drug resistant nontyphoidal Salmonella infections.

Prior to commencing her PhD, Andrea worked as a clinician, researcher, and humanitarian worker in Spain, France, Thailand, and Burkina Faso. Her research interests include infectious diseases and tropical medicine in low-resource settings.

Se Eun Park

International Vaccine Institute

Se Eun has been involved in the typhoid fever surveillance in sub-Saharan Africa since joining the International Vaccine Institute in 2013, and is currently coordinating a multi-country epidemiology study on severe typhoid in Africa. These studies aim to address important research questions of typhoid fever in Africa, including the disease burden, antimicrobial resistance of the causative pathogens, host immune response, chronic carriers, etc. Her research findings have identified the high burden of multidrug resistant typhoid fever and invasive nontyphoidal *Salmonella* diseases in Africa, particularly in children less than 15 years old. Her genomic epidemiological investigation on the emergence and transmission of MDR typhoid fever in 10 countries in sub-Saharan Africa, recently published in Nature Communication, has revealed the regional spread of MDR H58 S. Typhi in East Africa with increasing frequency of reduced susceptibility to fluoroquinolones, and the circulation of a distinct multidrug resistant genotype 3.1.1 in West Africa. Her presentation in this conference exhibits her latest findings in the molecular epidemiology of MDR iNTS infection across sub-Saharan African countries.
Se Eun is an epidemiologist at the International Vaccine Institute and is a DPhil candidate at the University of Oxford.

Chris Parry

University of Liverpool

Chris Parry is a Consultant Clinical Microbiologist and Infection Control Doctor at Alder Hey Children's Hospital, Liverpool, Senior Clinical Lecturer at the Institute of Infection and Global Health, University of Liverpool, Honorary Research Fellow at the Liverpool School of Tropical Medicine and a visiting Professor at the School of Tropical Medicine and Global Health, Nagasaki University, Japan. He has previously worked in the Oxford University South-East Asia Tropical Network and at Nagasaki University, Japan and has a research focus on the epidemiology and management of severe bacterial infections. He is a Trustee of the Royal Society of Tropical Medicine and Hygiene

Clint Pecenka

PATH

Clint Pecenka, PhDE, MPP, is Director of Health Economics and Outcomes Research in the Center for Vaccine Innovation and Access at PATH. Prior to joining PATH, he worked at the Gates Foundation, where he was a Program Officer and Economist on the Development Policy and Finance team. He has also worked at the Federal Reserve Bank of Minneapolis and taught economics at Carleton College. Dr. Pecenka's economic expertise includes costing, impact analysis, cost-effectiveness, and demand forecasting for vaccines. He also has experience in research design and the development and validation of economic tools. He currently works across a range of diseases and interventions, including rotavirus, other diarrheal diseases, respiratory syncytial virus, influenza, pneumonia, malaria. In addition to his work on health economics, he has expertise in development, behavioral and experimental economics and policy. He has a PhD in applied economics and a master's in Public Policy from the University of Minnesota. He received his undergraduate degree from Iowa State University in industrial engineering.

Shaun Pennington

Liverpool School of Tropical Medicine

Shaun holds a PhD in Infection and Immunity from the University of Liverpool. The focus of his doctoral thesis was the assessment of the human immune response to oral vaccination with live-attenuated *Salmonella* Typhi strain Ty21a.

Shaun studied the longevity of vaccine-specific responses in peripheral blood and at the duodenal and colonic mucosa. Shaun also studied the generation of off-target, non-vaccine-specific responses in peripheral blood.

Shaun is currently based at the Liverpool School of Tropical Medicine where he has developed a number of *in vitro* confocal and flow cytometric models of invasive salmonellosis. These models have been used to assess the efficacy of novel treatment strategies and to study factors which influence disease susceptibility.

Maile Phillips

Yale School of Public Health

Maile Phillips is a doctoral student in the Department of Epidemiology of Microbial Diseases at Yale School of Public Health. In the Pitzer Lab at Yale, her work aims to use mathematical models to further the understanding of infectious disease dynamics, particularly typhoid fever. Phillips' dissertation research focuses on evaluating the cost-effectiveness of interventions for typhoid control in different settings. Prior to her time at Yale, Phillips spent much of her time living and working in developing countries, including Sierra Leone, Peru, Guatemala, Honduras, and Nicaragua. Phillips holds a Master of Science degree in Biostatistics from Harvard University and a Bachelor's degree in Mathematics and Hispanic Studies from Hamilton College.

Marie-France Phoba

National Institute for Biomedical Research

Dr Marie-France Phoba is M.D.- microbiologist in the Department of Microbiology at the National Institute for Biomedical Research (INRB)and in the Service of Microbiology of the University Teaching Hospital of Kinshasa (UNIKIN) in the Democratic Republic of the Congo (DRC). She is involved in the surveillance network of antimicrobial resistance in DRC organised by the INRB since 2007 and in the Severe Typhoid in Africa (SETA) Program since 2017. Her research focuses on invasive salmonellosis and antimicrobial resistance.

Virginia (Ginny) Pitzer

Yale School of Public Health

Virginia Pitzer, Sc.D., is an Associate Professor in the Department of Epidemiology of Microbial Diseases at Yale School of Public Health. She received her Sc.D. in Epidemiology from Harvard School of Public Health, and was a postdoctoral fellow at Princeton University and Fogarty International Center/National Institutes of Health prior to joining the Yale faculty in 2012. Her research focuses on mathematical modeling of the transmission dynamics of infectious diseases diseases, including rotavirus and typhoid fever. She studies how interventions such as vaccination, improved treatment of cases, and improvements in sanitation affect disease transmission at the population level.

Andrew J. Pollard

University of Oxford

ANDREW J POLLARD, BSc MA MBBS MRCP(UK) FRCPCH PhD DIC FHEA FIDSA FMedSci, is Professor of Paediatric Infection and Immunity at the University of Oxford, Honorary Consultant Paediatrician at Oxford Children's Hospital and Vice Master of St Cross College, Oxford.

He obtained his medical degree at St Bartholomew's Hospital Medical School, University of London in 1989 and trained in Paediatrics at Birmingham Children's Hospital, UK, specialising in Paediatric Infectious Diseases at St Mary's Hospital, London, UK and at British Columbia Children's Hospital, Vancouver, Canada. He obtained his PhD at St Mary's Hospital, London, UK in 1999 studying immunity to *Neisseria meningitidis* in children and proceeded to work on anti-bacterial innate immune responses in children in Canada before returning to his current position at the University of Oxford, UK in 2001. He chaired the UK's NICE meningitis guidelines development group, the NICE topic expert group developing quality standards for management of meningitis and meningococcal septicaemia. His research includes the design, development and clinical evaluation of vaccines including those for meningococcal disease and enteric fever and leads studies using a human challenge model of (para)typhoid. He runs surveillance for invasive bacterial diseases and studies the impact of pneumococcal vaccines in children in Nepal and leads a project on burden and transmission of typhoid in Nepal, Bangladesh and Malawi, and co-leads typhoid vaccine impact studies at these sites. He has supervised 35 PhD students and his publications includes over 400 manuscripts and books on various topics in paediatrics and infectious diseases. He chairs the UK Department of Health's Joint Committee on Vaccination and Immunisation and the European Medicines Agency scientific advisory group on vaccines and is a member of WHO's SAGE. He received the Bill Marshall award of the European Society for Paediatric Infectious Disease (ESPID) in 2013 and the ESPID Distinguished Award for Education & Communication in 2015. He was elected to the Academy of Medical Sciences in 2016 and is an NIHR Senior Investigator.

Annelies Post

Radboudumc Njmegen & Institute of Tropical Medicine, Antwerp

After obtaining her medical degree and a master's degree in Global Health from Maastricht University (the Netherlands) she went to work for the Institute of Tropical Medicine (ITM) in Antwerp where she was introduced to the topic of invasive non-Typhoidal *Salmonella* among children in sub-Saharan Africa. During her time at the ITM she was involved in several surveillance studies performed in sub-Saharan African countries, including the Democratic Republic of the Congo and Burkina Faso. In 2015 she started her PhD on iNTS and undifferentiated febrile illness in the tropics from RadboudUMC Nijmegen, the Netherlands, which resulted in a collaboration between the ITM and RadboudUMC.

For the past four years her research interests have been centred around neglected tropical infectious diseases – in particular paediatric iNTS - and the imminent threat of antimicrobial resistance in light of global health, poverty and social inequality.

She is currently working as an MD at Rijnstate hospital the Netherlands, while finalizing her PhD. In time, she aspires to become a specialist in internal medicine/ infectious diseases and hopes to continue and expand her research on iNTS and undifferentiated fever in the tropics in academia.

Firdausi Qadri

icddr,b

Dr Qadri is Senior Scientist at the Infectious Diseases Division, at icddr,b in Bangladesh. She also leads the Mucosal Immunology and Vaccinology Unit. Her work includes basic and applied immunology of infectious diseases but also clinical and large field based studies on enteric vaccines. At present her main focus is on enteric vaccines with major emphasis on cholera and typhoid. Understanding the immunological basis on natural infections and correlates of protection is an important component of her group in addition to the reasons for hyporesponsiveness of young children to oral vaccines.

Farah Qamar

Aga Khan University

Farah Qamar is an Assistant Professor in the Department of Paediatrics and Child Health at the Aga Khan University. She works on several large clinical research projects including one, funded by the University of Virginia, to redefine the burden of diarrheal pathogens in children under five. Dr. Qamar is working with the Sabin Vaccine Institute on the Surveillance of Enteric Fever in Asia Project (SEAP), a large, landmark surveillance study to redefine the burden of typhoid in developing countries. Dr. Qamar is also leading a large grant from the WHO for a trial to test the role of antibiotics in childhood diarrhoea. Outside of clinical projects, she conducts numerous research training program workshops all over Pakistan to help build a sustainable pool of infectious disease researchers as part of a grant from the National Institute of Health. Dr. Qamar received her MBBS degree from Dow Medical College, Karachi, Pakistan, and completed a fellowship in paediatric infectious disease and a Masters in Clinical Research (Epidemiology & Biostatistics) from Aga Khan University, Karachi. Her research interests include childhood diarrheal, typhoid, paediatric tuberculosis and antimicrobial resistance. She has authored or co-authored 30 papers in peer-reviewed journals and a chapter in the Hunter's Tropical Medicine and Emerging Infectious Disease text book.

Saqib Hamid Qazi

Aga Khan University Hospital

Dr. Qazi obtained his medical degree from Chandka Medical College, Larkana and completed Pediatric surgery residency at the Aga Khan University, Karachi, Pakistan. Dr Qazi then did his fellowship in Pediatric Laparoscopic Surgery from Capital Institute of Pediatrics, Beijing, China. He is a Fellow of the American College of Surgeons, and holds memberships of International Pediatric Endosurgery Group (IPEG), British Association of Pediatric Surgeons (BAPS), Association of Pediatric Surgeons of Pakistan (APSP) and), and serves on Education Committee of IPEG. He has published more than 15 scientific papers and currently Co-PI of several grants. Dr. Qazi currently serves as the Chief of Pediatric Surgery, Aga Khan University, Karachi, Pakistan.

Eileen Quinn

PATH

Eileen Quinn is the Advocacy and Communications Director for PATH's Center for Vaccine Innovation and Access. She has over two decades of experience advancing issues at the intersection of science and public policy including public health, vaccine uptake, climate change, energy, and biotechnology. Prior to joining PATH in 2006, she spent six years as Deputy Director of the Alliance for Healthy Homes and ten years as Communications Director for the Union of Concerned Scientists. Previously, she was a producer for seven years at C-SPAN, producing the call-in talk shows and coverage of Congress and election campaigns.

Sadia Isfat Ara Rahman

icddr,b

I completed my B.S and M.S in the department of Biochemistry and Molecular Biology from University of Dhaka in 2013 and 2015 respectively. I did my M.S thesis on "The function role of antibody in complement mediated *Salmonella enterica* Serovar Typhi killing after vaccination and typhoid infection" under the supervision of Dr. Firdausi Qadri at icddr,b. After that, I joined icddr,b as Research Officer in 2015 and involved in ETEC vaccine, cholera vaccine study to measure immune responses using immunological techniques such as: ELISA, vibriocidal assay etc. I am also skillful in conducting microbiological and molecular techniques such as: antibiogram, DNA extraction, TaqMan assay. Currently I am pursuing collaborative PhD with University of Dhaka, icddr,b and Wellcome trust Sanger Institute on WGS analysis of *Salmonella* Typhi. I am working with Prof. Gordon Dougan's team for genomic analysis using R programming and different bioinformatics tools. Recently, I have published one article as co-author in the peer-reviewed vaccine journal based on ETEC vaccine. Moreover, I awarded with NST fellowship, Dean's award for academic excellence. The field of biology research made me passionate to develop new ideas for future projects.

Enusa Ramani

International Vaccine Institute

Enusa Ramani is a health economist with epidemiology and public health training from Germany and has worked in the field of infectious disease epidemiology and economics evaluation while working with the Bernhard-Nocht Institute for Tropical Medicine in Hamburg, Germany. Since joining the International Vaccine Institute (IVI) in year 2013, he has been researching in the economics of enteric diseases, cholera and typhoid fever to be precise. He worked on preparing the global typhoid vaccine investment case. He is the current project coordinator for IVI's health economics studies in the framework of the Severe Typhoid in Africa program (SETA) and the Cholera Surveillance in Malawi (CSIMA). Enusa Ramani has an extensive research experience in both the developed and developing countries. He is currently working on addressing the economic burden of typhoid fever in Africa with his research countries being: Madagascar, Ethiopia, Ghana and Burkina Faso. He has also conducted economic evaluation of healthcare interventions in other countries and has published most of his works in different peer-reviewed journals worldwide on typhoid fever and cholera.

Jonathan Rigby

Liverpool School of Tropical Medicine

Working on the Environmental Reservoirs of Salmonella Typhi (ERST) Project with Dr Nicholas Feasey, I am currently doing a PhD with the Liverpool School of Tropical Medicine, developing methods for the recovery of S. Typhi from the Environment. The project involves collecting environmental samples and using novel culture-based approaches for isolation. I am based at the Malawi-Liverpool-Wellcome Trust, the University of Malawi College of Medicine and the Food, Water and Environment Laboratory at Public Health England, Colindale. My background's in environmental and medical microbiology from the University of Portsmouth and London School of Hygiene and Tropical Medicine respectively and worked for the Gastro-Intestinal Reference unit at PHE for three years, focussing on Campylobacter, Salmonella and Antimicrobial resistance.

Samir Saha

Child Health Research Foundation & Dhaka Shishu Hospital

Dr. Samir K. Saha is the Professor and Head of the Department of Microbiology and the Executive Director of The Child Health Research Foundation at the Bangladesh Institute of Child Health, Dhaka Shishu Hospital in Dhaka, Bangladesh. This year, 2017, Dr. Saha has been selected by American Society of Microbiology and the American Academy of Microbiology to receive the award for research in Clinical Microbiology. This year Dr. Saha also received the UNESCO award for his contribution in the field of microbiology and helping the government of Bangladesh to make evidence based decision on introduction of Hib and pneumococcal conjugate vaccine.

Dr. Saha is currently a member of the National Committee for Immunization Policies of the Government of Bangladesh. He is also the member of World Health Organization's (WHO) Technical Advisory Group (TAG) for i) invasive bacterial vaccine preventable diseases, ii) Respiratory Syncytial Virus and iii) Group B Streptococcus.

He has published more than 150 papers in peer-reviewed international journals, mostly relating to childhood typhoid, pneumonia and meningitis. Dr. Saha is conducting several multi-site and multi-country research projects supported by Bill and Melinda Gates Foundation, WHO, Edinburg University, GlaxoSmithKlinee, Pfizer, etc.

Senjuti Saha

Child Health Research Foundation

I am a Bangladeshi-Canadian Microbiologist working at the intersection of Clinical Microbiology and Global Health as a scientist at the Child Health Research Foundation in Bangladesh. I am also a visiting scholar at Stanford University, USA.

I completed my Ph.D. in Molecular Genetics at the University of Toronto, Canada, where my research focused on developing novel therapeutics against the notorious infectious bacteria *Pseudomonas aeruginosa*.

With the aim of pursuing a career that brings both basic science and public health under one umbrella, advancing the cause of health and research equity, I moved to back to Bangladesh. Here, I primarily focus on pediatric vaccine-preventable bacterial infectious diseases. We conduct surveillance studies to monitor disease trends and generate data to guide public health policies. I also lead a group in Dhaka whose aim is to determine etiologies og meningitis in children using cutting-edge metagenomic techniques on site at real time.

Our mission is to break free of the vicious cycle of limited resources that lead to lack of data required for evidence-based policy decisions, which lead back to limited resources in LMICs. We strive to build virtuous cycles of data-generation, that are sustainable and cost-effective.

Sushant Sahastrabuddhe

International Vaccine Institute

Dr. Sushant Sahastrabuddhe (MBBS, MPH, MBA) is the Director of Enteric Fever program at the International Vaccine Institute in Seoul, South Korea. Sushant is working in IVI since last 9 years and is leading the typhoid conjugate vaccine development with multiple manufacturers. Sushant is a medical graduate from India with Masters in Public Health from Johns Hopkins Bloomberg School of Public Health, Baltimore, USA. Before joining IVI, Sushant was working with National AIDS Research Institute (NARI) under the umbrella of Indian Council of Medical Research (ICMR) for 4 years. He has been involved in many phase I/II trials, including that of HIV vaccines. During previous assignment at NARI, Sushant was also involved in monitoring of the HIV sentinel surveillance under National AIDS Control Organization (NACO) for the western states of India. Sushant has wide experience in conducting and managing clinical trials and major public health initiatives. Dr. Sahastrabuddhe has over 10 publications and 2 book chapters.

Md. Saiful Islam Sajib

Child Health Research Foundation

Saiful Islam Sajib has been working as a Microbiologist in Child Health Research Foundation since 2016. He graduated from Stamford University Bangladesh with high distinction. His research interest spans both microbial bioinformatics and molecular biology, mainly focusing on their public health applications. From the beginning of his career, his primary goal is to detect, investigate and prevent infectious diseases which are paralyzing low- and middle-income countries (LMICs). Currently, he is working on developing and testing a low-cost tool which can be utilized to detect *Salmonella* Typhi/

Paratyphi A from drinking water and can act as a supplemental method to detect typhoid burden and differentiate high and low endemic regions. He has also worked on a project where he and his colleagues explored the genomic diversity and antimicrobial resistance of *Salmonella* Typhi in Bangladesh isolated from 1999 to 2013. Additionally, he is analyzing antibiotic susceptibility patterns of *Salmonella* Paratyphi A and their associated DNA-gyrase and Topoisomerase-IV mutations. Also, he has assisted on a study where metagenomic sequencing data of cerebrospinal fluid was exploited to attribute etiologies to pediatric meningitis cases for designing rapid, low-cost, sustainable diagnostic approaches. Most of this work reflect his aims and has already been published in various reputed journals.

Muhammad Salman

National Institute of Health, Pakistan

Dr. Salman has been working in different capacities in NIH since 1995. He is fellow of College of Physicians and Surgeon Pakistan in the discipline of Pathology with specialization in medical microbiology. During his experience in the Public Health Laboratories Division, he has been participating in the implementation of number of projects related to infectious diseases, laboratory diagnosis and surveillance. He has been facilitating the training activities on different aspects of Laboratory medicine including biorisk management, bio-security, bio-safety, antimicrobial resistance, infection control, Quality assurance and quality control, surveillance, IHR and AMR etc. He is also among the visiting faculty for lab systems in the Pakistan Field Epidemiology and Laboratory Training Programme (FELTP). Besides this he also has Bio-risk Management Advanced Trainer certification from the WHO. He also holds certification on Global Health Challenges course, Institute of Health Metrics and Evaluation, University of Washington, USA. Presently he is Head of Microbiology and Virology at NIH and has been designated as focal person for International Health Regulations and Antimicrobial Resistance by the Ministry of National Health Services Regulations and Coordination, Government of Pakistan.

Mathuram Santosham

Johns Hopkins University

Dr. Santosham was born in Vellore, India and obtained his medical degree from the Jawaharlal Institute of Post Graduate Medical Education and Research (JIPMER) in, Pondicherry, India in 1970. He subsequently moved to the USA and obtained Board Certification in Pediatrics and an MPH degree from the Johns Hopkins University. He completed a Fellowship in Pediatric Infectious Diseases at Johns Hopkins Hospital.

Dr. Santosham is professor of Pediatrics and International Health at the Johns Hopkins University (JHU) Medical Institutions. He is also Founder and Director of the Johns Hopkins Center for American Indian. He holds Professorships in the Department of International Health and the Department of Pediatrics at Johns Hopkins University.

Dr. Santosham is internationally known for his work on oral rehydration therapy and for his work on childhood vaccines. He has conducted numerous vaccine efficacy trials, including rotavirus vaccine, H. influenzae type b (Hib) conjugate vaccine, and pneumococcal conjugate vaccine. He has been a global leader in the national and international dissemination of these vaccines worldwide. He was the principal investagator of the GAVI funded Hib Initiative. The latter project was instrumental in increasing the adoption of Hib vaccines in GAVI eligible countries from 20% in 2005 to over 85 % in 2009.

Dr. Santosham serves on numerous national and international committees to promote infant vaccines and oral rehydration therapy. He has acted as consultant for several international agencies including W.H.O., USAID and UNICEF. He has provided consultation in various aspects of child survival in over 30 countries. He is the author of over 200 peer reviewed journals and serves as a reviewer for several international medical journals. He is the recipient of numerous awards including the prestigious Thrasher Research Fund award for excellence in research (1988), Ambassador for Research America 2009 and the Bob Austrian Orator, for International Symposium on Pneumococcas and Pneumococcal Disease, Alice Springs, Australia, April 2006. He was also asked to deliver the Maurice Hillman Memorial Lecture at the CDC, Atlanta on March 17th 2008 during an immunization conference attended by over 1000 delegates. Recently, he was given the Indian Health Service Director's Special Recognition Award for his outstanding contributions to the health of Native Americans and the global impact of his work on immunizations and oral rehydration therapy.

Blanca Perez Sepulveda

University of Liverpool

Dr Blanca Perez-Sepulveda is a Postdoctoral Research Associate at the Jay Hinton's Lab, University of Liverpool. Her interests are understanding the molecular mechanisms of *Salmonella* Enteritidis virulence and the environmental reservoirs & transmission of *Salmonella*. After completing an MSc(Res) in Biochemistry at the University of Chile, she moved to the UK, where she obtained a PhD in Molecular Microbiology at the University of Warwick. Blanca moved to the University of Liverpool in 2016 to join the Hinton Lab. Blanca's research focuses on understanding the virulence determinants of novel *Salmonella* Enteritidis clades identified in sub-Saharan African regions, associated to bloodstream infection, using a combination of phenotypic characterisation, comparative genomics and transcriptomics. Alongside, and in collaboration with the Earlham Institute, Blanca has been leading the 10,000 *Salmonella* Genomes project, a worldwide collaborative effort to understand the epidemiology, transmission and virulence of iNTS. Blanca has been involved in all areas of this project, from technical aspects to administrative tasks, communication and data curation & analysis.

Fatima Serhan

World Health Organization

Fatima Serhan, PhD, is a scientist who joined WHO Expanded Program For Immunization team at Headquarters Geneva in 2010 to coordinate the global laboratory networks for new vaccines surveillance, with a focus on Rotavirus and Invasive Bacterial Vaccine Preventable Diseases (IBVPD).

The main objectives of her work are to ensure that countries that are part of these WHO coordinated surveillance networks have the laboratory capacities to diagnose VPDs and that laboratory data collected are of high quality. Fatima's main role is to ensure that excellent quality assurance and control monitoring systems are in place to enhance laboratory performance and improve VPDs surveillance globally. The new vaccine surveillance systems have adopted the models of the polio and measles laboratory networks where global efforts have contributed to enhancing regional and national capacities for diagnosis and strain characterisation. The data generated through the WHO VPDs surveillance networks help assessing disease trends over time and monitor changes in circulating strains in different countries and regions.

Building trustful working relationships with partners and valuing the great efforts made by countries and regions have been key to establish the surveillance laboratory networks that Fatima and her team coordinate.

Mila Shakya

Oxford University Clinical Research Unit, Nepal

Dr. Mila Shakya is currently working as a Project Lead for Strategic Typhoid Alliance Across Africa and Asia (STRATAA) and Typhoid Vaccine Study – Nepal (TyVAC-Nepal) at Oxford University Clinical Research Unit in Kathmandu, Nepal, which is associated with the Patan Academy of Health Sciences within Patan Hospital. She completed her medical degree in Nepal. She completed her Masters in Public Health from Brown University, USA and is currently doing her DPhil in Pediatrics from University of Oxford. She is interested in infectious disease research.

Ken Simiyu

University of Maryland School of Medicine

Ken Simiyu is a Program Director of TyVAC (typhoid Vaccine Acceleration Consortium) based at the University of Maryland. This is partnership between the Center for Vaccine Development at the University of Maryland School of Medicine, the Oxford Vaccine Group at the University of Oxford, and PATH, an international nonprofit, which aims to accelerate the introduction of new typhoid conjugate vaccines (TCVs) as part of an integrated approach to reducing the burden of morbidity and mortality from typhoid in countries eligible for support from the Global Vaccine Alliance (Gavi), providing expertise, guidance, and leadership to support all program-related activities.

Prior to that he was a Program officer at Grand Challenges Canada where he was responsible for designing, grant making and managing a broad array of portfolios that included the point of care portfolio as well as the stars in Global health.

Dr. Simiyu completed his PhD at the Institute of Medical Sciences, University of Toronto, where he focused on health innovation in developing countries. His research interests focus broadly on how technologies can move from the "lab to village". Dr. Simiyu received a Bachelors degree in Veterinary Medicine and Masters degrees in Veterinary Public Health and Business Administration

from the University of Nairobi, Kenya and completed a Masters in Public Health degree at George Washington University, Washington DC.

Dr. Simiyu has been a guest speaker at several conferences, lectured at several universities in the US and has over 10 publications in peer reviewed journals.

Bireshwar Sinha

Society for Applied Studies

I am working as a Research Scientist at the Centre for Health Research and Development, Society for Applied Studies (CHRD SAS), New Delhi for last 5 years. At CHRD SAS, I was selected as a BMGF PRERNA Research fellow (http://www.prernaindia.in/). I completed my MBBS, from West Bengal University of Health Sciences in 2010 and MD in Community Medicine from Delhi University, India in 2014. I am pursuing my Ph.D. from the University of Bergen, Norway. My research work is focussed within the domain of infection-nutrition under the broad ambit of maternal child heath. Presently, I am involved in a cohort study to estimate the incidence of enteric fever in India (Delhi site, Co-investigator), a study to explore the biological effects of Kangaroo mother care in low-birth-weight infants (as a PI), and monitoring rollout of Rotavirus vaccine in the public health system in Himachal, India (Co Investigator).

Adam Soble

Gavi, the Vaccine Alliance

Adam Soble is a Programme Manager on Gavi's Vaccine Implementation team where he leads the organisation's work on cholera and typhoid vaccines. He also managed Gavi's Vaccine Investment Strategy which was conducted in 2018. Adam previously worked for the Clinton Health Access Initiative where he provided technical assistance to governments in southern Africa to develop national disease elimination strategies. He has spent time working for the Bill and Melinda Gates Foundation where he supported the development and evaluation of projects focused on integration of health services. Adam also has a post graduate degree in Epidemiology from the London School of Hygiene and Tropical Medicine.

Dayoung Song

International Vaccine Institute

Dayoung Song, MPH, is an Associate Researcher at Policy and Economic Research Department of International Vaccine Institute. Her current research focus on cost-of-illness (COI) studies, vaccine cost-effectiveness analysis, vaccine delivery cost estimation, and budget impact analysis to support global and country-level policy decisions. She is currently working on economic evaluation of Typhoid Conjugate Vaccine(TCV) and Measles-Rubella (MR) vaccination in India and Human Papillomavirus (HPV) and Pneumococcal Conjugated Vaccine (PCV) in Thailand. She is also involved in developing costing tools to estimate the delivery and campaign cost for vaccination programs in India.

Dayoung Song has obtained her Master of Public Health from National Cancer Center Graduate School of Cancer Science and Policy (GCSP), South Korea and has background in public health policy and genetic epidemiology.

Sushmita Sridhar

Wellcome Sanger Institute

Sushmita Sridhar is a third-year Wellcome Sanger Institute PhD student in Professor Gordon Dougan's lab at the Department of Medicine, University of Cambridge, UK. Her background is in biology, with an emphasis on microbiology, and her past research experience includes work on molecular characterization of a lung cancer oncogene and intracellular behaviour of *Salmonella* Typhimurium. She is interested in understanding how bacteria respond to antimicrobial pressure and the implications that has for antimicrobial use and resistance. Her PhD project broadly focuses on developing higher throughput methods of analysing phenotypic resistance of *Salmonella* Typhimurium to fluoroquinolones. More specifically, she is working on understanding the development of decreased ciprofloxacin susceptibility in sub-Saharan African ST313s and the effects that has on bacterial fitness and survival. Her project uses a combination of microscopy, transcriptomics, and microbiological phenotyping. Given the growing criticality of antimicrobial resistance in a wide range of bacteria across the world, Sushmita is also interested in researching the potential for vaccine development to decrease the use of antimicrobials and consequent resistance.

Jeffrey (Jeff) Stanaway

Institute of Health Metrics and Evaluation

Jeff Stanaway, PhD, MPH, is Assistant Professor of Health Metrics Sciences and Global Health at the Institute for Health Metrics and Evaluation (IHME) at the University of Washington. He is part of the research team for the landmark Global Burden of Disease (GBD) study. His research focuses on macro-epidemiology with a special interest in understanding connections between the environment (e.g., climate and WASH) and the spatiotemporal distribution of disease. In his role, he models morbidity and mortality from enteric diseases, and environmental risk factors, including water supply, sanitation, and access to handwashing facilities. He has led the GBD burden estimation work for typhoid and paratyphoid for five iterations of the GBD study; and led the work to introduce iNTS as a new cause for GBD 2017. Dr. Stanaway received his PhD in Epidemiology from the University of Washington and his MPH from the University of Arizona.

Duncan Steele

Bill & Melinda Gates Foundation

Duncan Steele, Deputy Director and strategic lead for enteric vaccines in the Enteric and Diarrheal Diseases team, is responsible for an integrated portfolio of vaccine research and development and implementation strategies for the control of diarrhea and enteric fever in vulnerable populations. He coordinates teams across Vaccine Development and Vaccine Delivery for improved and new vaccines against rotavirus, cholera, typhoid fever, and Shigella spp.

Before starting at the foundation in October 2011, Duncan was Senior Technical Advisor at PATH, a global health non-profit organization, where he worked across multiple diarrhea vaccine-related programs, including the Rotavirus Vaccine Program focused on disease burden and clinical trials in Africa and Asia; and in vaccine development for new alternative rotavirus vaccines; and for vaccines against ETEC and Shigella. Previously, as a scientist at the Initiative for Vaccine Research, Department of Immunization, Vaccines and Biologicals, World Health Organization, Dr. Steele was responsible for the diarrheal disease vaccines portfolio, where he coordinated a global strategic agenda for vaccine research for the major diarrheal and enteric diseases.

Duncan is a South African trained microbiologist with extensive experience in virology and microbiology, especially for diarrheal diseases, and has mentored students and postgraduates across the African continent. He is the author of more than 280 scientific publications on diarrheal diseases, epidemiology, clinical research and vaccine development.

William Still

University of Maryland School of Medicine

William Still is a third year PhD student in epidemiology at the University of Maryland, Baltimore. He completed his bachelor's degree in biology at the University of Maryland, College Park, and his master's degree in Biohazardous Threat Agents and Emerging Infectious Diseases at Georgetown University. His research interests include infectious disease epidemiology, pediatric disease surveillance, and data analysis. His thesis involves understanding the epidemiology of invasive bacterial diseases in children in Bamako, Mali, as well as evaluating clinical management of children with sepsis at the national pediatric hospital in Mali. After he graduates, he hopes to work with the CDC as an Epidemic Intelligence Officer and investigate disease outbreaks.

Marcelo B. Sztein

University of Maryland School of Medicine

Dr. Sztein is Professor of Pediatrics, Medicine and Microbiology and Immunology at the University of Maryland (UMB). In addition, Dr. Sztein is Associate Director for Basic and Translational Research, Leader of the Immunology Group, and Chief of the Cellular Immunology Section at the prestigious Center for Vaccine Development. Dr. Sztein is also Director of the Flow Cytometry and Mass Cytometry Core Facility at UMB. Dr. Sztein is an accomplished investigator in the area of immunology of infectious diseases. He has published 213 papers in peer-reviewed journals and written 35 invited chapters.

Dr. Sztein's research focuses on understanding the mechanisms underlying the generation of the innate and adaptive immune responses to infectious organisms and vaccines in humans and animal models. He has studied children, young adults and the elderly following exposure to wild-type organisms and/or

immunization against, among others, *Salmonella* Typhi, *Shigella*, Enterotoxigenic *E. coli*, *V. cholerae*, hepatitis B, *P. falciparum,* influenza, *F. tularensis* and Ebola. Dr. Sztein has over 35 years of experience in performing flow cytometric studies, including mass cytometry. He directs a multidisciplinary center, part of NIAID's Cooperative Center on Human Immunology (CCHI) network, that studies the interplay between Mucosal Immunity, Vaccines and Microbiota.

Arif Mohammad Tanmoy

Erasmus University Medical Center

Arif Mohammad Tanmoy is a PhD candidate at Department of Medical Microbiology and Infectious Disease, Erasmus University Medical Centre in Rotterdam, the Netherlands. He received ARTS scholarship, 2016 from Institut de Recherche pour le Développement (IRD) in France, for his Ph.D. thesis. He completed Master's in 2011, from Molecular Biology Lab, Department of Biochemistry and Molecular Biology, University of Dhaka in Bangladesh and started his career there as a Research Associate. He started working with the Child Health Research Foundation (CHRF) in Dhaka, Bangladesh as a research officer in 2013. Later, he was promoted to Lab manager and then, Research investigator, before leaving for his Ph.D. in 2016. His doctoral project is a part of the collaboration between CHRF in Bangladesh and Fondation Mérieux in France. The project is also part of the COMPARE project, received funding from European Union Horizon 2020 research and innovation program. The project focuses on typhoid fever cases from Bangladesh and uses whole genome sequence data to detect the genetic elements responsible for antimicrobial resistance and phylogenetic inferences. Till now, he has authored nine articles in peer-reviewed journals and 13 conference abstracts.

Ashley Tate

CDC Foundation

Ashley Tate, MPH, MS works with the Global Immunization Division at the Centers for Disease Control and Prevention (CDC), focusing on typhoid and cholera vaccines. She primarily works with the Surveillance for Enteric Fever in Asia Project (SEAP), as well as with other typhoid programs and activities including vaccine safety, outbreak response, and measuring vaccination coverage.

Krista Vaidya

Dhulikhel Hospital

Krista Vaidya received her Masters' in Microbiology from Tribhuvan University. She has over 7 years of experience working in clinical research and 5 years on enteric fever surveillance in Nepal. She is currently the study coordinator for the Surveillance for Enteric fever in Asia project (SEAP) at Dhulikhel Hospital. Her research interest are antimicrobial resistance and its epidemiology in Nepal.

Jennifer Verani

Centers for Disease Control and Prevention

Jennifer Verani is a medical epidemiologist in the Division of Global Health Protection, US Centers for Disease Control and Prevention in Kenya. She is a pediatrician, epidemiologist, and a Captain in the United States Public Health Service. She obtained her medical degree from Harvard Medical School, MPH in International Health from the Harvard School of Public Health, and undergraduate degree in International Development from Brown University. Dr. Verani completed her residency training at the Children's Hospital of New York-Columbia. Dr. Verani joined CDC as an Epidemic Intelligence Service officer in the Parasitic Diseases Branch in 2006. In 2008, she joined the Respiratory Diseases Branch, where she focused on the impact and effectiveness of vaccines against *Streptococcus pneumoniae* and *Haemophilus influenzae* type B in Latin America and Africa, and provided technical assistance for respiratory disease surveillance in low-resource settings. Since 2014, Dr. Verani has been based in Kenya, leading the Population-Based Infectious Disease Surveillance platform in Kibera and Asembo, Kenya, and a network of Acute Febrile Illness sentinel surveillance sites across Kenya. Dr. Verani is also an Adjunct Assistant Professor of Pediatrics at Emory University School of Medicine.

Marije Verheul

University of Oxford

Dr. Marije Verheul works at the Oxford Vaccine Group, where she investigates enteric diseases, in particular typhoidal *Salmonella* infections. More specifically, she investigates changes in cellular characteristics after vaccinations. This includes newly developed vaccines aiming to prevent enteric diseases. Also, she studies the immune response against *Salmonella* (Para)Typhi in a controlled human challenge model of infection.

Her main research interests are in immunology, with a special interest in cellular and humoral responses. Dr. Verheul completed her PhD in Leiden, the Netherlands, focusing on autoantibodies in rheumatoid arthritis.

Merryn Voysey

University of Oxford

Merryn is a Senior Statistician in the Oxford Vaccine Group, University of Oxford. She has extensive experience in vaccines research including clinical trials and observational studies. She is an expert on conducting individual participant data meta-analyses and her current research interests include maternal antibody interference, vaccine correlates of protection, and the forensic seroepidemiology of bacterial infections, in particular, typhoid fever and pneumococcal disease. She is currently Principal Investigator on two large individual participant data meta-analyses of serological data from vaccine clinical trials funded through the NIHR HTA and the MRC/IMPRINT networks.

Huong Minh Vu

PATH

Huong Minh VU MD, PhD, is the Regional Technical Advisor of Vaccine Introduction & Impact,

Center for Vaccine Innovation and Access, PATH (based in Hanoi). Dr. Huong Vu leads PATH's vaccine and immunization-related activities in Vietnam and Myanmar. He provides technical guidance for PATH Mekong Vaccine and Immunization Team and technical advice for National Immunization Programs in designing, managing, monitoring, and evaluating vaccine and immunization related activities including new vaccine introduction, strengthening immunizations systems including vaccine cold-chain system, immunization information systems and disease surveillances. As focal point person for Japanese Encephalitis Vaccine Introduction and Sustainability Project (JEVISP) in the region, he also offers technical assistance to Immunization Programs in Vietnam, Laos, Cambodia and Myanmar in planning and introducing Japanese Encephalitis Vaccine.

Rezwanul Wahid

University of Maryland School of Medicine

Rezwanul Wahid, MBBS, PhD is an Assistant Professor at the Center for Vaccine Development-Global health, University of Maryland School of Medicine. His research is focused on the understanding of the protective human host-immune responses against infectious agents specially those cause enteric diseases. Dr. Wahid studies the role of vaccine-elicited antigen-specific multi-functional T and memory B cells in protection. These studies include comprehensive measurements of the immune responses elicited in volunteers following immunization with licensed (e.g., Ty21a) or candidate vaccines against typhoid (e.g., CVD 908-htrA, CVD 909) as well as paratyphoid A (CVD 1902) fevers. He has also been involved in several phase 1 and 2 trials that evaluated the safety and immunogenicity of the candidate vaccines against *Shigella*, Norovirus, *E.coli*, Malaria and Ebola infection.

Yuke Wang

Emory University

Yuke Wang works as a biostatistician at the Center for Global Safe Water, Emory University. He received his Bachelor's degree in Food Quality and Safety at South China University of Technology and his MSPH from the Department of Biostatistics and Bioinformatics at the Rollins School of Public Health, Emory University. And he is a current PhD student at Department of Mathematics and Statistics at the Georgia State University.

Yuke's research focuses primarily on the mathematical and statistical modeling for infectious disease transmission, multi-pathway microbial exposure assessment, environmental surveillance for enteric pathogen, and social network.

Alison Winstead

Centers for Disease Control and Prevention

Dr. Alison Winstead is an Epidemic Intelligence Service Officer at the Centers for Disease Control and Prevention (CDC) in Atlanta, Georgia. She currently works within the Waterborne Disease Prevention Branch. She obtained her medical degree from Wake Forest University in 2008 and completed a pediatric residency at Children's Hospital of Alabama (Birmingham, Alabama) in 2011. Dr. Winstead worked as a pediatric hospitalist for 6 years, prior to joining the CDC as an Epidemic Intelligence Service Officer in 2017.

Md. Tahir Yousafzai

Aga Khan University

Tahir Yousafzai is trained as epidemiologist from Aga Khan University Karachi and he is currently enrolled in PhD Global health at University of New South Wales Australia. Tahir is working on surveillance of vaccine preventable diseases among children and impact evaluation of newly introduced vaccines. He has published more than 50 research papers in peer reviewed journals and presented his work at more than a dozens of national and international scientific forums.

Alexander Yu

Stanford University

Alexander Yu, MD, MPH, is a post-doctoral fellow at Stanford University Hospital and the Stanford Woods Institute for the Environment. He is interested in the interface between infectious diseases and the environment and has been involved in typhoid fever surveillance as a part of the ongoing Surveillance of Enteric Fever in Asia Project (SEAP) in Nepal. He has focused on the use of hybrid surveillance and environmental sampling as alternatives to traditional disease burden estimation. He completed his residency training at Massachusetts General Hospital in Internal Medicine, earned his medical degree from Texas Tech University and a Masters degree in Public Health from the Harvard T.H. Chan School of Public Health with a focus on Global Health.

Anita Zaidi

Bill & Melinda Gates Foundation

Anita Zaidi is the Director of the Vaccine Development, Surveillance, and Enteric and Diarrheal Diseases program at the Bill and Melinda Gates Foundation. Her teams' work is focused on vaccine development for people in the poorest parts of the world, surveillance to identify and address causes of death in children in the most under-served areas, and significantly reducing the adverse consequences of diarrheal and enteric infections on children's health in low and middle-income countries. She obtained her medical degree from the Aga Khan University in Karachi, residency training in pediatrics and fellowship training in medical microbiology from Duke University, Durham, NC, USA. She undertook further training in pediatric infectious diseases from Children's Hospital, Boston, Harvard Medical School, and Masters in Tropical Public Health from the Harvard School of Public Health. Her research has focused on vaccine-preventable illnesses and newborn infections in resource-limited settings, publishing more than two hundred research papers in these areas.

Prior to joining the Bill and Melinda Gates Foundation, Anita was the Ruby and Karim Bahudar Ali Jessani Professor and Chair, Department of Pediatrics and Child Health, at the Aga Khan University. In 2013 Anita became the first recipient of the $1 million Caplow Children's Prize for work in one of Karachi's poverty stricken fishing communities to save children's lives. She was nominated as a notable physician of the year in 2014 by Medscape.

LUNCHTIME WORKSHOPS

LUNCHTIME WORKSHOPS

Lunchtime workshops are available to pre-registered participants only.

TUESDAY, MARCH 26, 12:25-13:10
PRE-REGISTERED LUNCHTIME WORKSHOPS

Salmonella 101

Ho Tay

ORGANIZED BY: University of Otago

This session is designed to provide a crash course on key and challenging issues in invasive *Salmonella* disease. This session is designed especially for those who are relatively new to the field or who are early in their careers. Speakers include seasoned experts on specific topics that we hope will jump-start your experience at the 11th International Conference on Typhoid and Other Invasive Salmonelloses.

Speakers:

John A. Crump, University of Otago

Patricia I. Fields, Centers for Disease Control and Prevention

Grace D. Appiah, Centers for Disease Control and Prevention

Melita A. Gordon, University of Liverpool & Malawi-Liverpool-Wellcome Trust Clinical Research Programme

Vaccine Introduction Decision-Making, Session 1

Truc Bach

ORGANIZED BY: Typhoid Vaccine Acceleration Consortium (TyVAC)

This lunchtime session, hosted by the Typhoid Vaccine Acceleration Consortium (TyVAC), offers an opportunity to discuss typhoid conjugate vaccine (TCV) introduction decision-making, and explore the various factors that national and sub-national leaders must weigh when making such choices. The session will cover relevant topics such as operational factors, cost estimates and cost-effectiveness, and other considerations that help determine introduction decisions. This interactive conversation with members from the TyVAC team will allow ample discussion to ensure the audience learns about the TCV introduction process, while also sharing their experiences and allowing time for questions to be addressed.

Speakers:

Tony Marfin, PATH

Farzana Muhib, PATH

Aziza Mwisongo, PATH

Clint Pecenka, PATH

WEDNESDAY, MARCH 27, 13:10-13:55
PRE-REGISTERED LUNCHTIME WORKSHOPS

iNTS

Ho Tay

ORGANIZED BY: Malawi-Liverpool-Wellcome Trust

Is invasive non-typhoidal *Salmonella* (iNTS) a Neglected Tropical Disease? The Malawi-Liverpool-Wellcome Trust will convene a discussion of the four WHO criteria for iNTS to be defined as a Neglected Tropical Disease, as a means of strategically advancing advocacy and awareness, and of mobilising funding.

The four WHO criteria for defining a Neglected Tropical Disease are:

1. Disproportionately affect populations living in poverty and cause important morbidity and mortality
2. Primarily affect populations living in tropical and sub-tropical areas
3. Are immediately amenable to broad control, elimination or eradication by the five public health strategies adopted by the Department for Control of NTDs
4. Are relatively neglected by research

Those with a strategic interest in advancing iNTS research and vaccination, those wishing to contribute data to an application for iNTS to be recognised as an NTD, and those with experience in NTDs are all welcome

Speakers:

John A. Crump, University of Otago

Nick Feasey, University of Liverpool

Melita A. Gordon, University of Liverpool and the Malawi-Liverpool-Wellcome Trust Clinical Research Programme

The WHO Typhoid Surveillance Standards

Truc Bach

ORGANIZED BY: World Health Organization, Sabin Vaccine Institute & International Vaccine Institute

The WHO, Sabin and IVI are hosting an interactive workshop to highlight the new WHO surveillance standards for typhoid and other invasive salmonelloses that are part of vaccine preventable diseases surveillance standards. Participants will hear from the Surveillance of Enteric Fever in Asia Project and the Severe Typhoid Fever Surveillance in Africa Program study practitioners about how the standards have worked in different contexts and discuss creative solutions to implement the standards. The target audience for the workshop is those at the health unit who are responsible for implementing the surveillance standards on a day-to-day basis. The workshop will be a great opportunity to discuss in particular the importance of typhoid surveillance and the need for building country capacities for typhoid diagnosis in the context of immunization programs and outbreak response.

Speakers:

Fatima Serhan, World Health Organization

THURSDAY, MARCH 28, 12:40-13:25
PRE-REGISTERED LUNCHTIME WORKSHOPS

Talking About Typhoid: A Crash Course in Advocacy

Ho Tay

ORGANIZED BY: *Take on Typhoid*

This session, hosted by *Take on Typhoid*, focuses on the importance of evidence-based advocacy for typhoid prevention and control. The *Take on Typhoid* team will discuss the importance of setting out with a clear goal, elements of a strategic approach and the best ways to leverage new data and research to advocate for typhoid prioritization and typhoid conjugate vaccine introduction. The conversation will focus on advocacy strategies, messages and how to package the evidence to best inform and influence decision-making. Participants will have a chance to share their experiences and ask questions during this interactive conversation.

Speakers:

Phionah Atuhebwe, World Health Organization Regional Office for Africa

Ashley Latimer, PATH

Eileen Quinn, PATH

Vaccine Introduction Decision-Making, Session 2

Truc Bach

ORGANIZED BY: Typhoid Vaccine Acceleration Consortium (TyVAC)

This lunchtime session, hosted by the Typhoid Vaccine Acceleration Consortium (TyVAC), offers an opportunity to discuss typhoid conjugate vaccine (TCV) introduction decision-making, and explore the various factors that national and sub-national leaders must weigh when making such choices. The session will cover relevant topics such as operational factors, cost estimates and cost-effectiveness, and other considerations that help determine introduction decisions. This interactive conversation with members from the TyVAC team will allow ample discussion to ensure the audience learns about the TCV introduction process, while also sharing their experiences and allowing time for questions to be addressed.

Speakers:

Tony Marfin, PATH

Farzana Muhib, PATH

Aziza Mwisongo, PATH

Clint Pecenka, PATH

POSTER ABSTRACTS

Poster exhibition sponsored by TUBEX®

No.	Presenting Author	Title
1	**Acheampong, Godfred**	Molecular Characterisation of Multidrug-Resistant *Salmonella* by PCR Based Replicon Typing in Ghana
2	**Adewusi, Oluwafemi**	Temporal and Spatial Patterns of Salmonellosis in Ibadan, Southwestern Nigeria
3	**Adikwu, Peter**	Characterisation of Multi-Drug-Resistant *S.* Typhi Isolates From Stool Of Patients in Secondary Health Centres in Benue South Geographical Zone
4	**Aiemjoy, Kristen**	Clinical Predictors for Culture-Positive Enteric Fever in Patients Presenting With Febrile Illnesses in South Asian Settings
5	**Akinyemi, Kabiru Olusegun**	*Salmonella* Bacteremia in Lagos, Nigeria: Incidence of *Plasmodium falciparum*-Associated Co-Infection and Patterns of Antimicrobial Resistance
6	**Aldrich, Cassandra**	Emergence of Phylogenetically Diverse and Fluoroquinolone Resistant *S.* Enteritidis As a Cause of Invasive Nontyphoidal *Salmonella* Disease in Ghana
7	**Anandan, Shalini**	Laboratory Based Surveillance of Enteric Fever in India: Clinical Characteristics and Antimicrobial Resistance Profile – Report From SEFI Network
8	**Anyanwu, Lofty-John**	Spatial Mapping of Cases of Typhoid Intestinal Perforation in Children in Kano Nigeria, Using GIS Techniques
9	**Aroyewun, Eunice**	Malaria, Invasive Salmonellosis and Co-Infections Among Febrile Patients in Ibadan, Nigeria
10	**Arya, Alok**	WASH Practices and Its Association With Enteric Fever – Results From an Ongoing Longitudinal Cohort in an Urban Slum in Delhi (Tier 1 SEFI Site)
11	**Azhar, Muhammad**	Typhoid Intestinal Perforation in Children: A Continues Torture in Developing Country
12	**Baliban, Scott**	Immunogenicity and Efficacy Following Sequential Doses of *Salmonella* Enteritidis COPS:FliC Glycoconjugates in Infant and Adult Mice
13	**Bhuiyan, Md Saruar**	Neutrophil Extracellular Traps (NETs) Involved in Enhanced Killing Capacity in Patients With Enteric Fever Caused by *Salmonella enterica* Serovar Typhi
14	**Bhujbal, Sandeep**	Developing Enterprise Level Multi-Layered National Data Management System for Near Real-Time Surveillance of Enteric Fever Data at Indian Sites
15	**Browne, Annie**	Geospatial Mapping of the Global Prevalence of Antimicrobial Resistant *Salmonella* Typhi and Paratyphi A Isolates
16	**Chattaway, Marie**	Ceftriaxone Resistance in *Salmonella* – The New Threat in *S.* Paratyphi A
17	**Chattaway, Marie**	Distinct Susceptibility and Invasiveness Profiles in *Salmonella* Infantis From South Africa and the United Kingdom
18	**Chatterjee, Pranab**	Lessons From Deploying an Active Surveillance System to Detect Enteric Fever in Urban Slums of Kolkata
19	**Chikwapulo, Victor**	Joint and Marginal Modelling of *Salmonella* Exposure and Immunity Data
20	**Chirambo, Angeziwa Chunga**	Changes in Gastrointestinal Tract Microbiome Profiles of Malawian Children During Exposure to *Salmonella*
21	**Chirambo, Angeziwa Chunga**	Exploiting Anti-Infection Activities of the Early Life Microbiota Member Bifidobacterium Isolated From Malawian Children Against *Salmonella* Infections
22	**Chowdhury, Goutam**	Testing of Sewage Samples for Detection of *S.* Typhi and *S.* Paratyphi A in Kolkata, India
23	**Clarke, Jenny**	VI Polysaccharide Antibody Responses to a Typhoid Conjugate Vaccine in Nepalese Children
24	**Colin-Jones, Rachel**	Logistics of Implementing a Large-Scale Typhoid Vaccine Trial in Kathmandu, Nepal
25	**Cross, Deborah**	Mass Cytometry Analysis of Cellular Responses to VI-Conjugate Vaccination
26	**Cuypers, Wim**	Comparative Genomic Analysis of *Salmonella* Concord From the Horn of Africa Reveals Signatures Related to High Resistance and Invasive Infections
27	**De, Anuradha**	Challenges in Receiving Adequate Blood Volumes for Automated Blood Cultures
28	**Dekker, Denise**	Characterization of *Salmonella* Enterica From Invasive Bloodstream Infections, Water Sources and Poultry in Rural Ghana

No.	Presenting Author	Title
29	**Denis, Ongeng Joseph**	Investigating the Frequency and Sub Categories of Articles on Typhoid Published on Leading On-Line Newspapers in Uganda
30	**Desai, Sachin**	The Nascent Samoa Typhoid Fever Surveillance Initiative Utilizing Public Health Infrastructure
31	**Desai, Stuti**	Making of Typhoid Mary: Understanding Persistence Mechanisms in *Salmonella* Typhi
32	**Dhungana, Gunaraj**	Isolation and Characterization of Novel Bacteriophage Lysing Colistin Resistant *Salmonella* spp., a Promising Solution to Antibiotic Crisis
33	**Drury, Ruth**	Changes to the Small RNA Population in PBMCs in an *S.* Typhi Human Challenge Model Reveal Differences Early After Challenge and at Diagnosis
34	**Dutta, Shanta**	Cluster Analysis of Enteric Fever Cases in Urban Slums of Kolkata
35	**Dyson, Zoe**	Surveillance of Clinical Laboratory and Molecular Characteristics of Typhoidal *Salmonella* Infection in a South Indian Setting
36	**Emary, Katherine**	Investigation of Population Bottlenecks in *Salmonella* Typhi Infection Using an Experimental Human Challenge Model
37	**Freeman, Molly**	Characterization of *Salmonella* Isolates From Invasive Infections Collected During Acute Febrile Illness (AFI) Surveillance in Uganda From 2016-2018
38	**Gaind, Rajni**	Age-Related Clinical and Microbiological Characteristics of Enteric Fever in India (2012-2016)
39	**Gaind, Rajni**	Validation of Pefloxacin and Other Fluoroquinolone Disc for Detection of Low Level Fluoroquinolone Resistance Among *Salmonella* Typhi and Paratyphi A
40	**Gao, Fang**	Establishment of International Standards for Vi Polysaccharide From *Citrobacter freundii* and *Salmonella enterica* subspecies *enterica* serovar Typhi
41	**Gauld, Jillian**	Mathematical Modeling to Investigate Decline of Typhoid Fever in Kibera, Kenya
42	**Getahun Strobel, Aneley**	A Retrospective Study of Patients With Confirmed Typhoid Fever in Fiji: Clinical Features, Case Fatality Rates & Antimicrobial Susceptibility Patterns
43	**Getahun Strobel, Aneley**	Epidemiology of Typhoid Fever in the Northern Division, Fiji: 2014-2017
44	**Gibani, Malick**	Investigation of the Role of Typhoid Toxin in the Pathogenesis of Typhoid Fever Using a Controlled Human Infection Model
45	**Gordon, Melita A.**	*Salmonella* Typhimurium St313 Alters Its Riboflavin Metabolism to Escape Immune Recognition by Mucosal-Associated Invariant T Cells
46	**Husada, Dominicus**	Typhoid Fever Cases in Children at the Tertiary Hospital in Indonesia: A 9-year Experience
47	**Hussain, Mudassar**	Outbreak Investigation of Extensive Drug Resistant Typhoid Fever Hyderabad, Pakistan – 2017
48	**Im, Justin**	Occurrence of Typhoid Fever Complications: Systematic Literature Review and Meta-Analysis
49	**Imad, Hisham**	Severe Typhoid in Maldives
50	**Ingelbeen, Brecht**	Older Age Among Patients with Decreased Ciprofloxacin Susceptibility *Salmonella* Typhi Bloodstream Infection in the Democratic Republic of the Congo
51	**Iqbal, Hina**	Impact Assessment of Typhoid Conjugate Vaccine During Mass Immunization Campaign in XDR Typhoid Outbreak Setting in Pakistan
52	**Jahid, Iqbal**	Antagonistic and Probiotic Properties of Lactic Acid Bacteria Against *Salmonella* Typhimurium and *S.* Enteritidis
53	**Jamka, Leslie**	Accelerating Typhoid Conjugate Vaccine Introduction: What Can Be Learned From Prior New Vaccine Introduction Initiatives?
54	**Jeon, Hyonjin**	Assessing the Burden of *S.* Typhi and iNTS Disease in African Children <5 Years of Age: Implications for Vaccine Formulations and Vaccination Programs
55	**Jin, Celina**	Serological Correlates of Protection Against *Salmonella* Typhi Following Vi-Vaccination

No.	Presenting Author	Title
56	**Jin, Celina**	VI-Specific Memory B Cells Are Detectable in Peripheral Blood Following Vi-Conjugate Vaccination
57	**Jinka, Dasaratha Ramaiah**	Surveillance of Enteric Fever Among Febrile Hospitalizations in a Rural Teaching Hospital, Andhra Pradesh, India
58	**John, Jacob**	Incidence of Typhoid in Chandigarh Estimated in a Hybrid Surveillance System
59	**Junejo, Amber**	Operational Cost-TCV in a Door to Door Campaign: A Case Study From Hyderabad Pakistan
60	**Kamasah, Japhet Senyo**	Influence of Invasive Nontyphoidal *Salmonella* Exposure on Haematological Parameters
61	**Kanungo, Suman**	Water, Sanitation and Hygiene (WaSH) Related Practices in an Enteric Fever Endemic Urban Slum Area in India
62	**Kao, Yu-Han**	Incorporating a Dose-Response Relationship Into Models of Typhoid Fever Transmission
63	**Kapil, Arti**	Antibiotics in the Treatment of Typhoid Fever: Are We Running Out of Options?
64	**Kapoor, Renuka**	Evaluation of Molecular Methods for Detection of *S.* Typhi and *S.* Paratyphi A in Environmental Samples
65	**Kapoor, Renuka**	Optimization of Methods to Detect *S.* Typhi and *S.* Paratyphi A in Sewage
66	**Karim, Sultan**	Cost of Inpatient Treatment of XDR Typhoid in Pakistan
67	**Karim, Sultan**	Typhoid Has Turned Catastrophic for the People of Sindh Pakistan
68	**Khaliq, Asif**	A Systematic Review of Enteric Fever Outbreak Literature Among Asian and African Countries From 1965 to 2018
69	**Khaliq, Asif**	Drug Resistance Pattern of *Salmonella* Typhi and *Salmonella* Paratyphi Among Hospitalized Patients of Aga Khan University Hospital, Karachi, Pakistan
70	**Khan, Ayub**	Use of Geo Spatial Technique to Identify Catchment Area of Patient With Typhoid Dever – A Hybrid Utilization Technique
71	**Khan, Md Arifuzzaman**	Baseline Widal Titer Among Healthy Adult Males From the Greater Mymensingh Division of Bangladesh
72	**Khanam, Farhana**	Immune Response to a Typhoid Conjugate Vaccine: Preliminary Immunogenicity Data From a Cluster-Randomised Controlled Trial of Children in Bangladesh
73	**Khanam, Farhana**	The Strategic Typhoid Alliance Across Africa and Asia (STRATAA): The Burden of Enteric Fever in Mirpur, Dhaka
74	**Khicha, Nikhil**	Catalyzing Uptake of Typhoid Conjugate Vaccine: An Assessment of the Optional Vaccine Market and Distribution Channels in Myanmar
75	**Kim, Jong-Hoon**	A Systematic Review of Typhoid Fever Occurrence in Africa
76	**Kipkirui, Erick**	Antibiotic Resistance Pattern of *Salmonella spp.* Isolated From Stool Samples in a Diarrheal Case-Control Study in Kenya
77	**Koeberling, Oliver**	Development of a Vaccine Based on GMMA Against Invasive Non-Typhoidal *Salmonella* Disease: Towards Phase 1 Testing in Humans
78	**Koeberling, Oliver**	Local and Systemic Immune Response to a Vaccine Against *Salmonella* Typhimurium Based on Generalized Modules for Membrane Antigens (GMMA)
79	**Kulandaipalayam Natarajan, Sindhu**	Impact of Information Pamphlet on Irrational Antibiotic Usage in Children of Urban Vellore, Southern India: A Stepped Wedge Trial in a Closed Cohort
80	**Kumwenda, Benjamin**	Comparative Genomic Analysis of a Sub-Lineage of Multi-Drug Resistant Non-Typhoidal *Salmonella* Typhimurium ST313 That Has Emerged in Blantyre, Malawi
81	**Lagos, Rosanna**	What Elimination of Endemic Typhoid Transmission Looks Like – Chronic Typhoid and Paratyphoid Carrier Prevalence in Santiago, Chile, 2017-2018
82	**Langridge, Gemma**	Metabolic Adaptation of the Human Pathogens *Salmonella* Typhi and Paratyphi ABC.
83	**Li, Jing**	Digital Detection of *Salmonella* Typhi in Large-Volume Environmental Water Samples Using an Asymmetric Membrane

No.	Presenting Author	Title
137	**Rynga, Dabet**	Antimicrobial Susceptibility of Azithromycin Among *Salmonella* Typhi and Paratyphi A: A Report From India
138	**Saddal, Nasir**	Intestinal Perforations From Enteric Fever Among Children and Adults: Data From Prospective Surveillance in Karachi, Pakistan
139	**Saha, Shampa**	Hospitalization of Pediatric Enteric Fever Cases During 2016-2018: Surveillance for Enteric Fever in Asia Project (SEAP), Bangladesh
140	**Salman, Muhammad**	First Characterization of Immunogenic Conjugates of Vi Negative *Salmonella* Typhi O-Specific Polysaccharides With rEPA Protein for Vaccine Development
141	**Samajpati, Sriparna**	Comparative Studies on Molecular Typing Methods and Antimicrobial Resistance for Epidemiological Investigation of *S.* Typhi and *S.* Paratyphi A
142	**Sawant, Pravin**	Antibiotic Usages for Suspected Typhoid Fever in Children Aged Between 6 Months to 14 Years in a Rural Region of Western India
143	**Sawiri-Kanin, Dominic**	Knowledge, Attitude and Practices of Household Contacts and Neighbors of *Salmonella* Typhi Cases in Relation to Typhoid Fever in Peri-Urban Ghana
144	**Shaheen, Ghazala**	Exploring Effective Therapeutic Options Against Extensively Drug Resistant (XDR) *S.* Typhi Infections
145	**Shakya, Mila**	A Detailed Demographic Description of Three Urban Sites With High Typhoid Incidence: The STRATAA Study
146	**Sharma, Supriya**	Association of Climatic Factors With Occurrence of *Salmonella* Typhi in Surface Water of Kathmandu, Nepal
147	**Shastri, Jayanthi**	Isolation and Antibiogram of *Salmonella* Species From Blood and Clot Cultures From Two Tertiary Care Hospital in Mumbai, India
148	**Shenoy, Bhaskar**	Pattern of Antibiotic Susceptibility of *Salmonella enterica* Serovar Paratyphi A in Paediatric Population – Study From India
149	**Sherchand, Jeevan**	Burden of Typhoid Fever in Association With Seasonal Trends and Antimicrobial Susceptibility in Tertiary Care Hospital, Kathmandu Nepal
150	**Sikorski, Michael**	Sampling to Detect *Salmonella* Typhi Within Samoan Concrete Septic Tanks Serving Households of Typhoid Fever Cases - A New Use for Moore Swabs
151	**Sil, Arijit**	Phase I Study to Assess Safety and Immunogenicity of Vi-DT Vaccine Compared to Vi Vaccine in Healthy Filipino Adults and Children
152	**Sil, Arijit**	Phase II Study to Assess the Safety, Reactogenicity and Immunogenicity of Vi-DT Vaccine in 6-23-Month Old Healthy Filipino Infants and Toddlers
153	**Sirima, Sodiomon**	Phase 2 Randomized, Double-Blind, Controlled Safety & Immunogenicity Trial of Typhoid Conjugate Vaccine in Children <2 in Burkina Faso: Study Design
154	**Sjafri Bachtiar, Novilia**	Vi-DT Typhoid Conjugate Vaccine Development Strategy and Update at PT Bio Farma
155	**Smith, Nicola**	Blood Culture Volumes Collected as Part of *Salmonella* Typhi Surveillance Within a Clinical Vaccine Trial in Nepal
156	**Sokairibo, Akosiererem**	A Novel Vaccine Candidate for Non-Typhoidal *Salmonella*
157	**Sokaribo, Akosiererem**	Independent Pathways Leading to Impaired Biofilm Formation Suggests Environmental Niche Specialization in Invasive *Salmonella* Strains
158	**Srinivasan, Manikandan**	Drinking Water and Sanitation in an Urban Community in India
159	**Strugnell, Richard**	Examining the Epidemiology, Drug Resistance and Transmission of Typhoid Fever in Fiji Using Bacterial Genomics
160	**Subramanian, Senthilnathan**	Determination of Fever Defervescence Periods of Ceftriaxone Treated Enteric Fever in Children
161	**Surendranathan, Surekha**	Relationship of Prior Antibiotic Use, Blood Volume and Defervescence Period With Time to Positivity in Blood Culture of Patients With Enteric Fever
162	**Sztein, Marcelo B.**	Effect of Live Oral Attenuated Typhoid Vaccine, Ty21a, on Systemic and Terminal Ileum Mucosal CD4+ T Memory Responses in Humans
163	**Sztein, Marcelo B.**	Manipulation of *Salmonella* Typhi Gene Expression Impacts Innate Cell Responses in the Human Intestinal Mucosa

No.	Presenting Author	Title
164	**Tack, Bieke**	Emerging Antibiotic Co-Resistance in Invasive Salmonellosis: A Need for Clinical Studies, Adapted Treatment Guidelines and Harmonized Policy Documents
165	**Tack, Bieke**	Invasive Non-Typhoidal *Salmonella* Infections in the Democratic Republic of the Congo, a 10 Year Surveillance
166	**Tamrakar, Dipesh**	Lessons Learned From Typhoid Outbreaks in Nepal: Integrating an Outbreak Warning System Into Typhoid Population Surveillance
167	**Tanmoy, Arif Mohammad**	Analysis of Isolates From Bangladesh Highlights Multiple Ways to Carry Resistance Genes in *Salmonella* Typhi
168	**Teferi, Mekonnen**	Typhoid Fever Surveillance in Africa Program (TSAP): Characteristics of Febrile Illnesses Among Children in Butajira, South-Central Ethiopia
169	**Theiss-Nyland, Katherine**	Assessing the Impact of a Vi-Polysaccharide Conjugate Vaccine in Preventing Typhoid in Nepalese Children – Protocol for a Randomised Control Trial
170	**Theiss-Nyland, Katherine**	Assessing the Impact of a Vi-PS Conjugate Vaccine in Preventing Typhoid in Bangladeshi Children – Protocol for a Cluster Randomised Controlled Trial
171	**Thomas, Maria**	The Utility of Real Time PCR for Detection of *Salmonella* Typhi in Suspected Enteric Perforation Cases: A Study From a Hospital in North India
172	**Tracy, Kathleen**	Implementing the Research Electronic Data Capture (REDCap) System in Support of Research in Low and Middle Income Countries: The TyVAC Experience
173	**Truong, Thi Quy Duong**	Antibiotic Resistance and Transmission of *Salmonella* Isolated From Pig Slaughterhouses to Retails Markets in Hanoi, Vietnam
174	**Van Puyvelde, Sandra**	Genomic Insights From *Salmonella* Bloodstream Infections Among Young African Children Identified During the MAL055 RTS,S/AS01 *Salmonella* Ancillary Study
175	**Van Puyvelde, Sandra**	Two Non-H58 *Salmonella* Typhi Lineages From the Democratic Republic of the Congo Show Decreased Ciprofloxacin Susceptibility
176	**Veeraraghavan, Balaji**	An Eighteen Year Retrospective Analysis of *Salmonella* Typhi, *Salmonella* Paratyphi and Invasive Non-Typhoidal *Salmonella* Isolated From Southern India
177	**Verani, Jennifer**	Antimicrobial Susceptibility of Invasive Nontyphoidal *Salmonella* in a Rural and Urban Setting in Kenya, 2007-2017
178	**Voysey, Merryn**	Characteristics of Fever Cases Who Are Blood Cultured and Those Who Are Missed When Presenting to Passive Surveillance Fever Clinics: TyVAC-Nepal
179	**Voysey, Merryn**	The Design and Analysis of Seroefficacy Studies for Typhoid Conjugate Vaccines: A Simulation Study
180	**Watts, Elizabeth**	A Review of the Economic Evidence of Typhoid Fever and Typhoid Vaccines
181	**Wilson, Catherine**	Prevalence and Antimicrobial Resistance Profile of Non-Typhoidal *Salmonella* in Pigs in Kenya and Malawi
182	**Yang, Jae Seung**	Comparison of Anti-Vi IgG Responses Between Two Clinical Studies of Typhoid Vi Conjugate Vaccines (Vi-DT Vs Typbar-TCV)
183	**Yousafzai, Muhammad Tahir**	Multipronged Surveillance Activities for Identification of *S.* Typhi Patients in Hyderabad: Experience From XDR Typhoid Outbreak Setting in Pakistan
184	**Zailani, Mohd Hanif**	Typhoid Fever in Malaysia: An Overview of Trend From 1987 to 2017
185	**Zangoui, Parisa**	The Role of SPI-2 Effectors in *Salmonella* Typhi Pathogenesis
186	**Zhu, Yanzhe**	Development of a Low-Cost Digital Nucleic Acid Amplification Test Platform Using Hydrogel Beads for Environmental Surveillance of *Salmonella* Typhi

1. Molecular Chacterisation of Multidrug-Resistant *Salmonella* by PCR Based Replicon Typing in Ghana

Godfred Acheampong[1], Michael Owusu[1], Alex Owusu-Ofori[2], Isaac Osei[1], Florian Marks[3], Ellis Owusu-Dabo[4], Yaw Adu-Sarkodie[5]

[1]Kumasi Centre for Collaborative Research in Tropical Medicine, [2]Komfo Anokye Teaching Hospital, [3]Department of Epidemiology, International Vaccine Institute, [4]Department of Global Health, School of Public Health, Kwame Nkrumah University of Science and Technology, Ghana, [5]Department of Clinical Microbiology, Kwame Nkrumah University of Science and Technology, Ghana

BACKGROUND

Salmonella infections are known to cause significant morbidity and mortality, especially in resource-limited countries. The situation is worsened by widespread presence of multidrug-resistant (MDR) strains, largely encoded on conjugative plasmids. However, little is known about how these strains are characterized at the molecular level in developing countries. We present findings from ongoing study to characterize multidrug-resistant *Salmonella* plasmids into incompatibility (*Inc*) groups using a multiplex PCR based replicon typing (PBRT) approach.

METHODS

This was a cross-sectional study involving individuals suspected of having *Salmonella* infection. Blood, stool and oropharyngeal swab specimens were taken from these patients between May, 2016 to January, 2018 at Komfo Anokye teaching hospital and Agogo Presbyterian hospital, both located in the middle belt of Ghana. Isolation and identification of *Salmonella* were done using standard microbiological procedures. Genomic DNA were extracted from multidrug-resistant *S.* Typhi and non-typhoidal *Salmonella* (NTS) isolates and PBRT performed using 30 replicons representative of the major incompatibility groups among Enterobacteriaceae.

RESULTS

Of the total number of 2,376 samples collected, 101 *Salmonella* sp. were isolated (4.3%) representing 72 (71.3%) and 29 (28.7%) *S.* Typhi and NTS respectively. Multidrug-resistant *Salmonella* were detected in 34 (33.7%) strains: with *S.* Typhi (23/34; 67.6%) being twice as many as non-typhoidal *Salmonella* (11/34; 32.4%). *Salmonella* MDR investigation showed that 16 (47.1%), 11 (32.3%) and 7 (20.6%) isolates were resistant to 3, 4 and 5 antibiotics respectively. PBRT produced 4 different incompatibility groups identified to be encoding for MDR. Eleven isolates (32.4%), all *S.* Typhi isolated from blood harboured plasmids with *Inc* group HI1 of target size 534bp. Majority (13/34; 38.2%) of the MDR *S.* Typhi isolated tested possessed replicon of size 843bp belonging to *Inc*U. Non-typhoidal *Salmonella* harboured 1 rare *Inc*X2 plasmid and 8 novel *Inc*FIIS plasmids that encode resistance to carbapenems, colistins and several virulence genes.

CONCLUSIONS

This study shows the presence of plasmid variants (belonging to 4 different incompatibility groups) in our study population that confer MDR caused by typhoidal and non-typhoidal *Salmonella* serovars from clinical isolates. This is the first time 3 of 4 variants have been reported in Ghana and are similar to those circulating in Africa but one.

2. Temporal and Spatial Patterns of Salmonellosis in Ibadan, Southwestern Nigeria

Oluwafemi Adewusi[1], Oluwafemi Popoola[1], Aderemi Kehinde[1], Dare Olulana[2], Ondari Mogeni[3], Florian Marks[3], Iruka Okeke[4], Severe Typhoid in Ibadan Research Group (SETA), Nigeria[1]

[1]College of Medicine, University of Ibadan, [2]University College Hospital, [3]International Vaccine Institute, Seoul, [4]Faculty of Pharmacy, University of Ibadan

BACKGROUND

Studies from endemic areas, particularly parts of Asia, have recorded seasonal and microgeographic patterns in typhoid epidemiology but there are such few data from Nigeria. This study aimed to uncover temporal and/or spatial variations in invasive salmonellosis in Ibadan, Southwestern Nigeria.

METHODS

Specimens from 1032 febrile patients enrolled in a February 2017 to January 2018 prospective study at four Ibadan healthcare facilities were subjected to automated blood culture. *Salmonella* enterica serovars were identified by standard bacteriology. An additional 58 patients presenting with signs or symptoms that suggested possible ileal perforation were assessed by surgical teams, who verified perforations surgically and histologically. Data was analyzed using descriptive and Chi-Squared analysis.

RESULTS

Salmonella was cultured from 39 (3.9%) febrile patients but none of the perforation patients. Thirty-four (58.6%) surgically-examined patients had lesions strongly suggestive of typhoid perforation. Of the blood culture *Salmonella* isolates, 36 (92.3%) were *S.* Typhi, 3 (7.7%) were *S.* Paratyphi. Thirty-one (79.4%) blood culture-positive *Salmonella* cases were detected in the rainy season, between the months of March and October, and 25 (73.5%) of the perforation cases were also admitted during these wet months. Altogether, 56 patients with invasive salmonellosis were diagnosed in the rainy season but only 17 in the dry season (p=0.03). Spatial analysis showed that 8.9% of the patients from Southeast Ibadan municipal were culture-positive for *Salmonella* as were 5.3%, 3.2%, 2.0%, 1.1% of patients from Northeast, North, Northwest, Southwest Ibadan municipals respectively. All three of the *S.* Paratyphi were from patients residing in the Northeastern Ibadan. Of the 12 (35.3%) perforation cases that came from inside the Ibadan municipal 4, 5, 1, 2 and 0 were from residents of Southeast, Northeast, North, Northwest, and Southwest municipal Ibadan respectively.

CONCLUSIONS

Recovery rates for *Salmonella* from blood culture showed temporal and spatial associations with ileal perforations in Ibadan. Typhoid predominated during the wet months and in eastern Ibadan. This study points to specific, unidentified risk factors for typhoid associated with time and place. Future work to identify reservoirs and transmission patterns could help inform where to prioritize water, sanitation, hygiene interventions.

3. Characterisation of Multi-Drug-Resistant *S.* Typhi Isolates From Stool of Patients in Secondary Health Centres in Benue South Geographical Zone

Peter Adikwu[1], Ebele Umeh[2], Innocent Ogbonna[2], Obande Godwin[3], Charles Iheukwumere[2], Godwin Oyiwona[1]

[1]Benue State Polytechnic, Ugbokolo, Nigeria, [2]Federal University of Agriculture, Makurdi, Benue State., [3]Federal University, Lafia, Nassarawa State

BACKGROUND

The emergence of Multi-Drug-Resistant (MDR) *Salmonella typhi* to commonly used antibiotics has posed greater challenges in the treatment of typhoid fever. The aim of this study was to characterise MDR *Salmonella typhi* isolated from stool of patients. One thousand and twenty two stool samples were collected from patients attending secondary health centres.

METHODS

Salmonella typhi was isolated using Selenite broth, *Salmonella Shigella* agar and Xylose Lysine Deoxycholate agar. The isolates were purified on Bismuth Sulfite agar and identified using cultural and biochemical characteristics. Characterisation was done using molecular methods

RESULTS

Isolation rate of *S. typhi* in the study area was 43.7% (n=447). Prevalence of *S. typhi* with regards to location (χ^2 = 54.293), age (χ^2 = 15.316), sex (χ^2 = 5.263) and month of sampling (χ^2 = 94.090) differed significantly ($p<0.05$). *S. typhi* infection was most prevalent in subjects aged ≤10 years (52.7%, n=243). Male subjects had a significantly (χ^2=5.263; $p< 0.05$) higher isolation rate (46.8%; n=583) than female (39.6%; n=439). Highest isolation rate was in the month of May (61.8%, n=76). The antibiotic susceptibility pattern of the *S. typhi* isolates showed that 64% (n=286) were resistant to one or more class(es) of antibiotics. The isolates demonstrated the highest resistance to the fluoroquinolone (ciprofloxacin) (55.6%; n=159). All the isolates were however, susceptible to carbapenem (imipenem) and aminoglycoside (chloramphenicol). In addition, 27.3% of the isolates exhibited multi-drug resistance. None showed combined resistance to all the antibiotics at a particular time. There was a significant difference in the occurrence rate of MDR *S. typhi* in the various locations (χ^2 = 27.459, $p < 0.05$). Female subjects had a higher number of MDR strains than the male subjects (χ^2 = 5.662, $p< 0.05$).

CONCLUSIONS

The conjugation experiment showed that the resistant plasmids were transferable. Most MDR *S. typhi* isolates were positive for ESBL production. The S.typhi harboured plasmids of 2027bp, 2322bp and 23130bp molecular weights respectively. The MDR isolates harboured *bla* SHV, *bla* TEM and *QnrA* but lacked *ImpA* and *aac* resistance genes. There is high prevalence of *S. typhi* in the study area and the fact that most of them are MDR calls for concern.

4. Clinical Predictors for Culture-Positive Enteric Fever in Patients Presenting With Febrile Illnesses in South Asian Settings

Isaac Bogoch[1], **Kristen Aiemjoy**[2], Farah Qamar[3], Samir Saha[4,5], Krista Vaidya[6], Caitlin Barkume[7], Denise Garrett[7], Jason Andrews[8]

[1]Toronto General Hospital, [2]Division of Infectious Diseases and Geographic Medicine, Stanford University, [3]Department of Pediatric and Child Health, Aga Khan University, [4]Bangladesh Institute of Child Health, [5]Dhaka Shishu (Children) Hospital, [6]Dhulikhel Hospital, Kathmandu University Hospital, [7] Sabin Vaccine Institute, [8]Division of Infectious Diseases and Geographic Medicine, Stanford University

BACKGROUND

Blood cultures for enteric fever have variable sensitivity ranging between 50-70%. We evaluated clinical predictors for culture-positive enteric fever cases in a prospective sample of patients presenting with an acute febrile illness to hospitals in Nepal, Pakistan, and Bangladesh.

METHODS

We enrolled patients presenting for care at participating hospitals who reported fever for greater than 72 hours. Demographic data, a standardized history, and blood cultures were obtained from consenting patients. We fit a multivariate logit model to evaluate the effects of age, blood volume, prior antibiotic use and duration of fever on the relative risk of testing positive for enteric fever with an interaction term for blood volume and age. We fit a generalized additive model to asses for deviations from monotonicity in the relationship between duration of fever and culture positivity.

RESULTS

Between September, 2016 and September, 2018, 2,402/16,987 (14.1%) of patients with suspected enteric fever tested positive for typhoidal *Salmonella*. The proportion of participants testing positive with a self-reported fever less than 3 days was 10.0% and increased to 21.9% among those with 5-7 days of fever, before declining. The relative risk of testing positive increased with increasing blood volume in Nepal (AOR 1.27; 95% CI: 1.17, 1.36) but not in Bangladesh (AOR 1.02; 95% CI 0.85, 1.17), where there was little variability in blood culture volumes. Self or caregiver report of prior antibiotic was associated with greater probability of positive blood cultures in Bangladesh (AOR 1.29, 95% CI 1.13, 1.45) and Pakistan (AOR 1.51, 95% CI: 1.27, 1.81).

CONCLUSIONS

Among individuals with suspected typhoid, the probability of having culture-confirmed typhoidal *Salmonella* bacteremia peaks at 5-7 days of fever, and is greater among individuals with self-reported prior antibiotic use, likely an indicator of disease severity.

5. *Salmonella* Bacteremia in Lagos, Nigeria: Incidence of *Plasmodium falciparum*-Associated Co-Infection and Patterns of Antimicrobial Resistance

Kabiru Olusegun Akinyemi, Christopher Fakorede, Samuel Ajoseh, Rebecca Abegunrin, Olabisi Adunmo, Bamidele Mutiu

Lagos State University, College of Medicine

BACKGROUND

Typhoidal *Salmonella* is a major health challenge in developing countries. Invasive non-typhoidal *Salmonella* (iNTS) is a febrile bacteremia, usually fatal when associated with malaria and human immunodeficiency virus (HIV) infection. Paucity of Information on *Salmonella* blood stream infections in Lagos necessitated this study, to determine the incidence and prevailing drug resistant invasive *Salmonellae* and *Plasmodium* associated co-infection in febrile patients with or without HIV.

METHODS

A total of 397 patients attending four public hospitals in Lagos, between July, 2016 and June 2017 were recruited. The patients consisted of group A -309 febrile patients and group B - 88 HIV confirmed febrile patients. Blood samples were collected, cultured and isolates identified by standard methods. *Salmonella enterica* serovars were subjected to antimicrobial susceptibility testing by standard procedures. Detection of malaria parasite was by thick blood smear techniques.

RESULTS

The incidence of *Salmonella* blood stream infection in this study is 14.9%. Of 309 in group A, 46 (14.9%) *Salmonellae* were identified comprised of 11 *S.* Typhi, 17 *S.* Typhimurium, 14 *S.* Enteritidis and 4 *S.* Paratyphi. *Plasmodium faciparum* (124) was detected and co-infection with *Salmonella* was recorded in 23 patients. Thirteen (14.8%) of 88 in group B were positive, consisted 4 *S.* Typhi, 6 *S.*Typhimurium and 3 *S.* Enteritidis. *P. falciparum* (37) was detected and co-infection with *Salmonella* isolates occurred in 7 patients. There was no statistical significant difference (p< 0.01) between *Plasmodium* associated co-infection with *Salmonella* in patients with or without HIV. Over 70% of 59 *Salmonellae* (16 typhoidal and 31 iNTS) developed resistance to third generation Cephalosporins (3rdGC) (Cefuroxim, Cefeparezone and Cefotaxime) and fluoroquinolone (Ciprofloxaxin and Ofloxacin). Interestingly isolates from HIV patients and from co-infections with *P. faciparum* in febrile patients were resistant to 3rdGC.

CONCLUSIONS

High incidence of *Salmonella* blood stream infection was recorded which is a threat to public health. *S.* Typhimurium was the prevailing *Salmonella* associated bacteremia in patients with or without HIV. Emerging drug resistant invasive *Salmonellae* co-infection with *P. falciparum* was found and may exacerbate treatment failure. Further studies on *Salmonella* bacteremic strains are on the way and a need for typhoidal and iNTS vaccines in Nigeria are advocated.

6. Emergence of Phylogenetically Diverse and Fluoroquinolone Resistant *S.* Enteritidis As a Cause of Invasive Nontyphoidal *Salmonella* Disease in Ghana

Cassandra Aldrich[1], Hassan Hartman[2], Nicholas Feasey[3,4], Yaw Adu-Sarkodie[5], Florian Marks[6,7], Juergen May[8,9], Timothy Dallman[2], Daniel Eibach[8]

[1]Division of Infectious Diseases and Tropical Medicine, Medical Center of the University of Munich (LMU), [2]National Infections Service, Public Health England, Colindale, UK, [3]Liverpool School of Tropical Medicine, Liverpool, UK, [4]Wellcome Trust Sanger Institute, Cambridge, UK, [5]Department of Clinical Microbiology, Kwame Nkrumah University of Science and Technology, Kumasi, Ghana, [6]International Vaccine Institute, Seoul, Republic of Korea, [7]Department of Medicine, University of Cambridge, Cambridge, United Kingdom, [8]Department of Infectious Disease Epidemiology, Bernhard Nocht Institute for Tropical Medicine, Hamburg, Germany, [9]German Centre for Infection Research (DZIF), Hamburg-Borstel-Luebeck, Germany

BACKGROUND

Salmonella Enteritidis is a global cause of poultry- and egg-associated enterocolitis. Recently, distinct, multidrug-resistant (MDR) genotypes have been described which are associated with bloodstream-invasive nontyphoidal *Salmonella* (iNTS) infections in Africa, often requiring fluoroquinolone treatment. In high-income settings, antimicrobial use in poultry production has led to frequent fluoroquinolone resistance amongst globally prevalent enterocolitis-associated lineages. The study objective was to understand whether diminished ciprofloxacin susceptibility (DCS) observed amongst iNTS-disease associated *S.* Enteritidis isolates in Ghana was associated with African- or globally-circulating clades of *S.* Enteritidis, as treatment and control measures are likely to differ.

METHODS

27 *S.* Enteritidis isolates from patients with iNTS disease and two poultry isolates, collected between 2007 and 2015 in the Ashanti region of Ghana, were whole-genome sequenced. These isolates, many of which exhibited DCS, were placed in the phyletic context of 1,067 sequences from the Public Health England (PHE) *S.* Enteritidis genome database. Single linkage SNP clustering of the isolates within the database was used to derive maximum likelihood phylogenies.

RESULTS

Four major *S.* Enteritidis clades were represented, two global and two African. All 13 DCS isolates, containing a single *gyrA* mutation at codon 87, belonged to a global PT4-like epidemic clade, with distinct clusters identifiable. Apart from two DCS isolates, which clustered with PHE isolates associated with travel to Spain and Brazil, the remaining DCS isolates, including one poultry isolate, belonged to two monophyletic clusters in which *gyrA* 87 mutations appear to have developed within this region of West Africa. 7/15 (46.7%) global PT4-like clade and 4/5 (80%) West African clade isolates were MDR. Isolates from remaining clades showed fully susceptible antimicrobial resistance profiles.

CONCLUSIONS

Extensive phylogenetic diversity is evident amongst iNTS disease-associated *S.* Enteritidis in Ghana. Antimicrobial resistance profiles were diverse and differed by clade, highlighting the challenges of devising empirical sepsis

guidelines. The detection of fluoroquinolone resistance in phyletically-related poultry and human isolates is of major concern and surveillance and control measures within the region's burgeoning poultry industry are required to protect a population at high risk of iNTS disease.

7. Laboratory Based Surveillance of Enteric Fever in India: Clinical Characteristics and Antimicrobial Resistance Profile – Report From SEFI Network

Shalini Anandan, Balaji V, Agila Kumari Pragasam, Anushree Amladi, Jacob John, Gagandeep Kang

Christian Medical College

BACKGROUND

Indian Subcontinent is well known for Enteric fever being endemic in this setting. Typhoid fever is caused by the bacterium *Salmonella enterica* serovar Typhi. Burden of typhoid fever is underestimated due to the lack of diagnostic facilities in resource-limited settings. With this background, a pan India network for Surveillance of Enteric Fever in India (SEFI) has been established to estimate the burden of this dreadful disease. This study presents the surveillance data obtained through the SEFI network from a large tertiary care center in southern Indian region

METHODS

Laboratory based surveillance of typhoid fever was captured by blood culture positivity for *S.* Typhi over a period of 14 months (November 2017 to December 2018) at Christian Medical College, Vellore, India. Individuals with *S.* Typhi positive blood cultures were followed up for hospital admission and recruited in the study after obtaining the consent. Laboratory, clinical and demographic details were captured and follow up was done

RESULTS

During the study period, *S.* Typhi and *S.* Paratyphi constituted for about 2% and 0.4% of all blood culture pathogens identified. High rates of fluoroquinolone non-susceptibility of about 98% were noted. Whereas, three pan susceptible *S.* Typhi and one multi drug resistant *S.* Typhi was isolated. Children <15 years of age accounted for 31%, while 69% were of adult ≥15 years of age. Notably, majority of cases occurred in young adults of age 16-30 years (87%). Overall, hospitalization rates were 45% and 32% for typhoid and paratyphoid cases respectively. Particularly, 56% and 33% of children with typhoid and paratyphoid cases were hospitalized, which was comparatively higher than adult age groups. In this study, azithromycin(38%) and ceftriaxone(22%) were observed to be the first line agents used for management, followed by 33% of combination of azithromycin plus ceftriaxone

CONCLUSIONS

Typhoid fever continues to be a public health problem in Southern Indian region. Increasing incidence of paratyphoid is a cause for concern, which needs close monitoring. Robust typhoid surveillance through SEFI network would improve better understanding of typhoid fever with its disease burden rate estimated precisely, which is vital for vaccination

8. Spatial Mapping of Cases of Typhoid Intestinal Perforation in Children in Kano Nigeria, Using GIS Techniques

Lofty-John Anyanwu[1], Abdulkadir Sani[2], Salisu Mohammed[2], Julius Falola[2], Aminu Mohammad[1,2], Lawal Abdullahi[1,2], Stephen Obaro[4]

[1]Aminu Kano Teaching Hospital, Kano, Nigeria, [2]Bayero University, Kano, Nigeria, [3]University of Nebraska Medical Center, Omaha, USA

BACKGROUND

Although poorly understood, intestinal perforation is a dreadful complication of typhoid fever- a disease transmitted by the faeco-oral route, and commonly reported in developing countries. This study aims to determine the spatial variation of cases of typhoid intestinal perforation in children presenting to our hospital.

METHODS

Data used in this study were from a retrospective chart review of children managed for typhoid intestinal perforation in our hospital between October 2015 and September 2018. Only cases from the hospital's state of domicile were included in the analysis. Secondary data used in the study included topographical maps and land use data. With the use of the ArcGIS software, geocoding techniques were employed to match reported cases with addresses. Analysis of geospatial data was done using the QGIS software.

RESULTS

There were 69 cases of typhoid intestinal perforation in children aged 13 years and less included in the study. Cases were seen from every region of the metropolis, with clustering of cases in high density residential areas close to major fruit and vegetable markets.

CONCLUSIONS

Clustering of cases around vegetable markets may suggest a common food contaminant in the region. We recommend periodic analysis of samples of fruits and vegetables from major markets in the metropolis, in order to detect possible outbreaks of typhoid fever.

9. Malaria, Invasive Salmonellosis and Co-Infections Among Febrile Patients in Ibadan, Nigeria

Eunice Aroyewun[1], Oluwafemi Popoola[1], Oluwafemi Adewusi[1], Veronica Ogunleye[2], Ondari Mogeni[3], Florian Marks[3], Iruka Okeke[4], Severe Typhoid in Ibadan Research Group Severe Typhoid in Africa[2]

[1] College of Medicine, University of Ibadan, [2]University College Hospital, Ibadan, [3]International Vaccine Institute, [4] Faculty of Pharmacy, University of Ibadan

BACKGROUND

Plasmodium and *Salmonella* infections are major public health challenges in tropical countries presenting with similar signs and symptoms. In Nigeria, most fevers are presumed to be malaria and treated accordingly. Additionally, salmonellosis typically diagnosed clinically or by non-specific Widal test is presumed to be a major cause of non-malaria

febrile illness. These presumptions and the overlap of symptomatology often leads to empirical diagnosis of a co-infection in the absence of accurate laboratory investigations thereby, promoting antimalarial and antibiotic misuse. Therefore, this study aimed to determine the prevalence of *Plasmodium*, *Salmonella* and co-infections in febrile patients in Ibadan, Nigeria.

METHODS

We examined malaria and *Salmonella* positivity in an on-going prospective study that recruited 1453 patients from February 2017 to June 2018. The study recruits from four healthcare facilities in Ibadan, Nigeria. Informed consent was obtained from patients with history or current axillary temperatures of ≥37.5°C. Automated blood culture was performed using a BACTEC FX-40 machine and malaria parasites were detected by microscopy.

RESULTS

Blood culture and malaria microscopy results were available for 1078 patients. The overall prevalence of malaria, salmonellosis and co-infection was 9.6%, 3.8% and 1.3% respectively. Other bacteria pathogens were recovered from 4.0% of the patients. Among those who tested positive for malaria, *Salmonella* and co-infection, 75% (78/104), 92.7% (38/41) and 92.8% (13/14) respectively were children aged ≤ 15 years. Malaria and salmonellosis is significantly more common in children ≤15 years (p=0.000) and co-infections are 12 times more likely in children aged 6-10 years than those > 15 years (OR: 12.3; 95%CI: 1.5 to 99.3). In addition, a higher proportion of co-infected patients (60%) had anaemia (haemoglobin < 10g/dl) compared to those with malaria (31.6%) or salmonellosis (40%) only. One of the fourteen co-infected patients needed three days hospital admission but there was no case of mortality.

CONCLUSIONS

Detectable malaria, invasive salmonellosis and their co-infections accounted for 10.9% of febrile illnesses in the study. Efforts should be intensified to reduce exposure to both diseases, particularly in children among whom all three morbidities were common. Diagnostic development is essential for routine detection of these important causes of febrile illness.

10. WASH Practices and Its Association With Enteric Fever – Results From an Ongoing Longitudinal Cohort in an Urban Slum in Delhi (Tier 1 SEFI Site)

Bireshwar Sinha, **Alok Arya**, Nidhi Goyal, Rahul Upadhyay, Mohammad Aslam, Vikas Dubey, Deepak More, Temsunaro Rongsen-Chandola

Society for Applied Studies

BACKGROUND

The community-based-surveillance component of the Surveillance of Enteric Fever in India (SEFI) study was initiated in 2017 in 4 sites in India i.e. Vellore, Pune, Delhi, Kolkata to estimate the burden of culture-confirmed typhoid fever among <15 year-old-children. We present preliminary findings on WASH-practices from the Delhi-site and its association with enteric fever.

METHODS

A prospective cohort of 6000 children (6m-15y) is followed-up in a resource-poor-setting in Delhi for febrile illnesses with a mandatory-weekly-contact for a period of 2-years. Blood culture (BD-BACTEC) is done in children with suspected-typhoid-fever (≥3-consecutive-days; STF) after evaluation in a study-clinic. WASH-practices (safe-water, toilet-use, stool-disposal, food-hygiene) were ascertained by trained-field-workers using a pretested-questionnaire adapted from the WHO-core-questions-on drinking-water-and-sanitation. We present data of 5727 subjects, where information is available. Logistic-regression-analysis was done to examine the effect of WASH-practices on enteric fever. Hosmer-Lemeshow (HL) test was done to assess goodness-of-fit. ROC was assessed for model-predictability.

RESULTS

Of the 5727 subjects, 49% were female; three-fourth belonged to nuclear families with median monthly-income of 136 USD; 2714 (47%) belonged to overcrowded households. 2680 (47%) children had at least one fever-episode, 1030 (17.9%) had STF-episodes and 17 had culture-confirmed typhoid. Around 92% used piped or bottled-water for drinking but, only 33% used a water-treatment method before consumption, most commonly water-filters (18%). Almost all had sanitary-toilet, of which, 21% had flush-systems. In 449/851 (53%) children, not-toilet-trained, the practice of unsanitary-stool-disposal methods was noted. The practice of consuming ready-to-eat-food, unnamed-ice-creams from street-vendors and uncooked food in multiple-days/week was noted in 31%, 12%, and 42%, respectively. Frequent consumption of ready-to-eat-food and ice-creams from street-vendors was significantly associated with enteric fever (RR 3.88; 95%CI 1.37, 11.1). HL-test indicated adequate-fit of the model (p=0.52). The area-under-curve in ROC was 76% (95%CI 65% to 87%). No association of WASH-practices with any fever or STF was observed.

CONCLUSIONS

Preliminary data shows association of ready-to-eat-food and ice-creams from street vendors with enteric fever. As the numbers of enteric fever were less, analysis after completion of the 2-year-follow-up period will be more meaningful. The WASH practices may help to explain the difference in rates of enteric fever across sites.

11. Typhoid Intestinal Perforation in Children: A Continues Torture in Developing Country

Muhammad Tahir Yousafzai[1], **Muhammad Azhar[2]**, Khair Jan[2], Nasir Saddal[2]

[1]Aga Khan University, [2]National Institute of Child Health, Jinnah Sindh Medical University, Karachi

BACKGROUND

To evaluate the pattern of typhoid intestinal perforation and its outcome in the management at NICH Karachi.

METHODS

This is a prospective study of patients who were operated for typhoid intestinal perforation at National Institute of Child Health Karachi between March 2016 and august 2018. Children with other causes of intestinal perforation like TB,

trauma, perforated appendix etc were excluded. Information regarding demographic data, symptoms, pneumoperitonium, perforation single or multiple, perforation to surgery interval, wound infection and mortality were noted. Data collected were analyzed using SPSS computer software version 18.

RESULTS

A total of 69 patients were studied. Males were affected twice more than the females (2.6:1). Their ages ranged from 3 to 14 years with a median age of 10 years. Majority of the patients 80% having perforation within 14 days of illness. Chest and abdominal radiographs revealed pneumoperitonium in 70% of cases. Postoperative complication rate was 45% and surgical site infection was the most frequent complication in 52% of cases. Mortality rate was 5% and it was statistically significantly associated with delayed presentation, inadequate antibiotic treatment prior to admission, shock on admission, low WBC counts, delayed operation, multiple perforations, severe peritoneal contamination and presence of postoperative complications ($P < 0.001$).

CONCLUSIONS

The prevention of typhoid fever can safe our children from this high morbid and killer problem.

12. Immunogenicity and Efficacy Following Sequential Doses of *Salmonella* Enteritidis COPS:FliC Glycoconjugates in Infant and Adult Mice

Scott Baliban, Brittany Curtis, Sharon M. Tennant, Myron M. Levine, Marcela F. Pasetti, Raphael Simon

University of Maryland School of Medicine

BACKGROUND

In sub-Saharan Africa, invasive nontyphoidal *Salmonella* (iNTS) infections with serovars Enteritidis, Typhimurium, and I 4,[5],12:i:- are widespread in children <5 years old. An efficacious vaccine would provide an important public health tool to prevent iNTS disease in this population. Glycoconjugates of *S.* Enteritidis core and O-polysaccharide (COPS) coupled to the homologous serovar phase 1 flagellin protein (FliC) were previously shown to be immunogenic and protected adult mice against death following challenge with virulent Malian blood isolate *S.* Enteritidis R11. This study extends these observations to immunization of mice in early life and also assesses protection with partial and full regimens.

METHODS

Infant (2-week old) or adult (6-8-week old) CD-1 mice received 1, 2, or 3 bi-weekly doses of intramuscular COPS:FliC co-formulated with monophosphoryl lipid A. Serum was collected after each immunization and assessed for anti-COPS and anti-FliC IgG levels by ELISA. One month after the final immunization, mice were challenged intraperitoneally with *S.* Enteritidis R11. To address the contribution of anti-FliC antibodies toward protection, adult mice were immunized with one or two doses of COPS:FliC and challenged with *S.* Enteritidis R11 wild-type or Δ*fliC* (a phase 1 flagellin mutant). In all experiments, control mice were administered PBS.

RESULTS

COPS:FliC was immunogenic in both infant and adult mice, eliciting the highest serum anti-FliC and anti-COPS IgG geometric mean titers (GMTs) after two and three immunizations, respectively. Conjugate-immunized infant and adult mice were protected against lethal S. Enteritidis R11 challenge relative to PBS controls (vaccine efficacy (VE) = 65-94%), for which 2 doses of COPS:FliC were sufficient to achieve robust protection (VE = 65–75%). Robust efficacy was observed in adult mice after 2 doses when the challenge strain lacked phase 1 flagellin (VE = 47%). Finally, we found that acquisition of successively higher serum anti-COPS IgG levels was associated with a proportionate drop in mortality post challenge whereby a COPS-specific IgG GMT >200 ELISA units/mL was associated with mortality in <33% of mice.

CONCLUSIONS

These results further establish that COPS:FliC is a promising pediatric vaccine candidate for use in sub-Saharan Africa and may inform potential immunization strategies for NTS COPS:FliC conjugate vaccines.

13. Neutrophil Extracellular Traps (NETs) Involved in Enhanced Killing Capacity in Patients With Enteric Fever Caused by *Salmonella enterica* Serovar Typhi

Md Saruar Bhuiyan[1], M. Hasanul Kaisar[1], Farhana Khanam[1], Md Wahid Murad[1], Jennifer Hill[2], Andrew Pollard[2], Firdausi Qadri[1]

[1]icddr,b (International Center for Diarrheal Disease Research, Bangladesh), [2]Oxford Vaccine Group, Department of Paediatrics, University of Oxford, Oxford

BACKGROUND

Salmonella enterica serovar Typhi causes typhoid fever and over 21 million cases and 200,000 deaths are reported annually. Neutrophils are the first responders and most abundant innate immune cells in bacterial infections and also thought to be of particular importance for trapping and killing pathogens. NETs consist of DNA along with histones, granular proteins and elastase and myeloperoxidase. Here, we demonstrate the NET-mediated killing capacity of *S.* Typhi in typhoid fever patients.

METHODS

Blood specimens were taken from suspected typhoid fever patient at enrollment and if a patient was culture positive then two more blood specimens were taken at acute convalescence and late convalescence stages. A single blood specimen was taken from healthy participants. Neutrophils were isolated and stimulated with PMA for 2 hrs for NET release. Cytochalsin D and DNase were added to inhibit phagocytosis and NET-mediated killing respectively. Then *S.* Typhi strain was added and incubated for 2 hrs at 37°C. Bacterial count was measured by spread plate technique. NET-mediated killing was expressed as percentage by subtracting total bacteria in the presence of cytochalasin D from total bacteria in the presence of cytochalasin D along with DNase.

RESULTS

We investigated the capacity of NET release ex vivo upon stimulation with PMA by microscopy and observed that 2 hrs of PMA stimulation induced maximum NET release. A range of multiplicity of infection (MOI) was tested (0.5 to 20) and MOI 10 was the highest for efficient killing. NET-mediated killing of *S.* Typhi was highest (42%) at acute stage of typhoid fever. This killing capacity of NET was reducing from infective stage to acute convalescence stage (36%). At late convalescence, the killing capacity was further reduced (21%) that was close to healthy controls (15%). NET-mediated killing capacity of neutrophils isolated from typhoid fever patients coincided with the recovery of patients.

CONCLUSIONS

Our results show that neutrophils isolated from typhoid fever patients are active in entrapping and killing of *S.* Typhi by NET ex vivo. NET assay could be an useful marker to correlate with prognosis of typhoid fever. Further analysis is ongoing in more patients as well as typhoid vaccine recipients (Tybar-TCV).

14. Developing Enterprise Level Multi-Layered National Data Management System for Near Real-Time Surveillance of Enteric Fever Data at Indian Sites

Tathagata Bhattacharjee[1], **Sandeep Bhujbal[1]**, Austin Samuel[2], Venkata Raghava Mohan[2], Sanjay Juvekar[1]

[1]KEM Hospital Research Centre Pune, [2]Christian Medical College, Vellore

BACKGROUND

Electronic data capture systems experience challenge while synchronizing different locations' data at near real-time intervals with appositeness, quality and reporting. By leveraging technology advancement, we built robust data collection system for Tier I community surveillance for enteric fever across four sites in India.

METHODS

The system was designed for community-based cohorts in diverse locations across India for active fever surveillance. People from IT science, Android developers and public health scientists worked together in developing the Application. It was designed on a multi-layered architecture to run on Android tablets, web-browser and secured cloud infrastructure; providing server-side services hosting robust object-relational database.

The android app "*EntericFev*" was developed using *androidstudio*, Java programming language. Version controlling for development process was done on GitHub platform with manual testing for every version. The web-browser based forms for capturing suspected typhoid cases (STF) and clinical lab reports were designed using *CodeIgniter* PHP framework and hosted on Apache web services. Data are pushed to *PostgreSQL*, secured object-relational database configured to provide standard security with fine-grained access control, audit trails, logs and regular backups. User-friendly interface using Adminer database management tool supports Data Managers. An online data visualization tool, *Amazon QuickSight* was deployed with site-level access which provided a good graphical representation of data and some quick pre-defined results of analysis for continued monitoring data quality. Summary tables for visualization process got populated at pre-defined time intervals using *Pentaho Data Integration* tool. Server-side infrastructure is hosted on EC2 instance on Amazon Web Services (AWS). We chose a t2.large type instance with two virtual CPUs, one elastic IP, 300 GiB volume and installed Red Hat Enterprise Linux 7.3 on it.

RESULTS

The architecture works in unison to achieve flawless quality data capture. Since its deployment in July'2017, *EntericFev,* used by 184 users has generated 20,41,230 data points from four sites capturing information of 25,304 participants. Excellent audit trails are instituted that have captured 41,81,614 trails.

CONCLUSIONS

EntericFev provided a robust software for data management of National Surveillance System and is easily scalable to National or Global level for any number of sites with minimal efforts.

15. Geospatial Mapping of the Global Prevalence of Antimicrobial Resistant *Salmonella* Typhi and Paratyphi A Isolates

Annie Browne[1], Michael Chipeta[2], Emmanuelle Kumaran[2], Bahar Kashef Hamadani[2], Catrin Moore[2], Christiane Dolecek[3], Simon Hay[4]

[1]University of Oxford, [2]Big Data Institute, Li Ka Shing Centre for Health Information and Discovery, University of Oxford, [3]Centre for Tropical Medicine and Global Health, University of Oxford, [4]Institute of Health Metrics and Evaluation, University of Washington

BACKGROUND

Antimicrobial resistance of *Salmonella* Typhi and Paratyphi A strains has been reported from multiple countries, negatively impacting our ability to treat and control infections. However, there are gaps in our understanding of the geographic distribution and prevalence of resistant *S.* Typhi and Paratyphi A. Understanding the distribution of resistance is vital for informing policy and combating the spread of disease.

METHODS

We are compiling a dataset of the proportion of *S.* Typhi and Paratyphi A isolates resistant to key antimicrobials, linked to specific times and locations. Data have been extracted from published literature from 1990 to 2017; this will be supplemented by data from additional sources.

A geospatial modelling framework will be used to predict the proportion of *S.* Typhi and Paratyphi A isolates with multidrug resistance and fluoroquinolone non-susceptibility, at a high spatial resolution. Briefly, a stacked generalisation ensemble model will capture the associations between selected covariates and the resistance data; then a Bayesian model based geostatistical model will be fit to the data, accounting for the remaining spatial and temporal correlation and producing pixel level estimates of resistance. Additional covariates on antibiotic use and treatment seeking behaviour are being produced to inform the model.

RESULTS

The majority of data obtained from published literature is from South Asia, with a paucity of microbiological data identified from Africa and the Middle East, and large data gaps in Southeast Asia.

These data show large variations in resistance by antimicrobial, geographic location, year of isolation, and *Salmonella enterica* serovar. Trends of decreasing multidrug resistance and increasing fluoroquinolone non-susceptibility in *S.* Typhi are evident in South Asia, however high heterogeneity within the region is noted. High-resolution maps of resistance will enable a more thorough analysis of resistance patterns.

CONCLUSIONS

We discuss methodological plans to leverage existing data and geospatial modelling techniques to produce robust, validated estimates of resistance in *S.* Typhi and Paratyphi A globally. Heterogeneity within published data highlights the importance of these techniques and the need for additional data to inform the model. A collaborative effort is required to produce accurate estimates of the prevalence of antimicrobial resistant *S.* Typhi and Paratyphi A.

16. Ceftriaxone Resistance in *Salmonella* – The New Threat in *S.* Paratyphi A

Marie Chattaway[1], Satheesh Nair[1], John Wain[2], Samir Saha[3], Gemma Langridge[2]

[1]Public Health England, [2]Quadram Institute, [3]Children's Hospital

BACKGROUND

Concern is growing that widespread carriage of extended spectrum beta-lactamases by *Salmonella* Typhi is spreading. An outbreak in Pakistan of ceftriaxone resistant typhoid fever and surveillance on travellers returning to the UK suggests this fear is being realised. The new Vi-conjugate vaccine for typhoid fever offers real hope for the control of typhoid fever but no human vaccine is available for other invasive salmonelloses. CTX-M enzymes are the most commonly reported from salmonella and so screening for these enzymes is prudent.

METHODS

We have screened all available salmonella referred to PHE between 2014 - Oct 2018 for CTX-M carriage by whole genome sequencing using Illumina Hi-seq protocols (47,872 sequence datasets), analysed in detail the plasmids from enteric fever pathogens and compared them to previously reported cases.

RESULTS

387 Salmonella were found to encode CTX_M enzymes ion their genomes, with CTX-M-9, CTX-M-14 and CTX-M-65, CTX-M-55/TEM-1 & CTX-M-15/TEM-1 as the most common markers. One of these was a *S.* Paratyphi A. Examination of the plasmid revealed close identity to a CTX-M-15 encoding plasmid (PRJEB211992) isolated from a child in Bangladesh. The new plasmid (pSPA440915) was very similar in every respect and also contained the TEM191 gene. We must consider the transmission between these two predominant enteric fever pathogens as highly likely.

CONCLUSIONS

Here report the emergence of ceftriaxone resistant *S.* Paratyphi A seen in a traveller returning to the UK from Bangladesh. Given the lack of a vaccine for paratyphoid fever the surveillance for this strain of *S.* Paratyphi A needs to be prioritised in Bangladesh.

17. Distinct Susceptibility and Invasiveness Profiles in *Salmonella* Infantis From South Africa and the United Kingdom

Marie Chattaway[1], Jenifer Mattock[2], Karen Keddy[3], Anthony Smith[4], John Wain[2]

[1]Public Health England, [2]Norwich Medical School, University of East Anglia, [3]Wits Medical School, University of the Witwatersrand, [4] Centre for Enteric Diseases, National Institute for Communicable Disease

BACKGROUND

Amongst *Salmonella* serovars, *S.* Infantis has become the fourth commonest cause of human salmonellosis in the EU (including the UK), causing 30% of *Salmonella* infections in Israel and is the commonest serovar in domestic fowl worldwide. In South Africa, little is known about the epidemiology of *S.* Infantis.

METHODS

Invasive index of was calculated as the number of all sequenced isolates from blood culture divided by isolates from stool referred to the UK reference laboratory and included historical isolates and all data since 2014. Sequence type was designated according to the standard *Salmonella* MLST scheme (mlsst.net). To investigate this we further sequenced *S.* Infantis isolates from Public Health England between 2004 and 2017 and from the National Institute for Communicable Disease between 2003 and 2016. Whole genome sequencing of isolates was performed on an Illumina NextSeq machine at the Quadram Insitute or on a HiSeq at PHE.

RESULTS

The Invasive Index of selected serovars from 2018 were as follows:Salmonella Paratyphi A = 64.79, Salmonella Typhi = 61.34, Salmonella Dublin = 34.62, Salmonella Typhimurium ST313 = 16.22 and Salmonella Infantis = 1.49.

The Invasive Index of *S.* infantis according to Sequence Type were as follows: ST603 = 18.2, ST32 = 3.2 and ST2283 = 1. Preliminary results from the sequencing of South African isolates suggests a higher burden of resistance in the UK (52.2% MDR) compared to South Africa (19.0%).

CONCLUSIONS

S. Infantis as a serovar is not considered invasive. Of 2579 isolates received with metadata by PHE only 40 were invasive. Interestingly when ST603 and ST32 were analysed separately the invasiveness index (23/888, 2.5%) was much higher suggesting that sub-groups of the *S.* Infantis serovar may be highly invasive. Furthermore antimicrobial resistance appears to be driven by the presence of the pESI plasmid and we are currently exploring this further.

18. Lessons From Deploying an Active Surveillance System to Detect Enteric Fever in Urban Slums of Kolkata

Pranab Chatterjee[1], Suman Kanungo[1], Jayanta Saha[1], Jacob John[2], Gagandeep Kang[3], Shanta Dutta[1]

[1]ICMR National Institute of Cholera and Enteric Diseases, [2]Christian Medical College, Vellore, [3]Translational Health Science and Technology Institute

BACKGROUND

Enteric fever sickens 20 million people and claims over 140,000 lives annually, with the highest burden in South Asia. Indiscriminate use of antibiotics, often prescribed by non-formal practitioners, has led to an apparent decline in the burden as isolation rates have fallen. This multi-site, active surveillance was undertaken to characterise the burden of enteric fever in India.

METHODS

The study enrolled a cohort of 6017 children aged between 6 months and 13 years 364 days; active weekly fever surveillance is being undertaken by trained enumerators. In children with fever, a daily follow-up is initiated till 3 consecutive fever-free days are documented. Suspected Typhoid (STF) fever is defined as a period of fever of 3 or more consecutive days; all children suffering from STF are clinically evaluated at the study clinics on the fourth day and a blood culture will be requested if there is history of fever in the last 12 hours. If there is no fever in the last 12 hours the culture request will be deferred. Prior antimicrobial drug consumption does not exclude blood culture.

RESULTS

Community mobilization and rapid census activities were conducted in the study sites and 6017 children were recruited from three wards in the Kolkata Municipal Corporation (KMC) area. Of these, 2017 were aged between 6 months to <5 years, and 2000 each were in the age groups of 5 to <10 years and 10 years to <14 years each. The mean family size was 5.11 (SD1.7), with 2.02(SD0.88) children/family; most families were nuclear (63%), and only few were joint (22%); most houses were a mix of kutcha and pucca (61%). Most houses did not have a separate kitchen (59%) and cooked indoors (64%) using gas (59%) or kerosene (31%). The median years of education was 8.5 in the highest educated family member; median total family income was INR 8000 (IQR7000-10000). Only 2% held cattle and 4% had backyard poultries.

CONCLUSIONS

Recruiting and maintaining a cohort for conducting active surveillance of enteric fever represents several scientific, socio-cultural, financial, political and logistics challenges. Our experiences, contextualised with local factors, may inform future efforts to plan studies.

19. Joint and Marginal Modelling of *Salmonella* Exposure and Immunity Data

Victor Chikwapulo[1], Marc Henrion[1], Jupiter Simbeye[2], Tonney Nyirenda[3], Melita Gordon[1]

[1]Malawi Liverpool Wellcome Trust Clinical Research Programme, Blantyre, Malawi, [2]Chancellor College, [3]College of Medicine

BACKGROUND

In Malawi exposure to Nontyphoidal Salmonella during early childhood is common and this provides an opportunity to investigate immunity development. The dataset for Nontyphoidal Salmonella, presents several challenges for modelling: (i) exposure events are only known up to monthly intervals (an interval censoring problem), (ii) immunity status is measured by Serum Bactericidal Activity(SBA), a quantitative measurement, but if dichotomized using a clinical threshold of effective immunity, the exact time point of immunity acquisition is also subject to interval censoring, but with 3 months intervals rather than 1 month, (iii) repeated measurements, (iv) the data contain missing values. To address these challenges, we interrogated the applicability and performance of longitudinal mixed methods for single and multivariate response variable, survival methods and joint modelling.

METHODS

Data were obtained from a cohort of 60 children recruited from Zingwangwa health center at 6 months of age and followed-up until 18 months of age. Exposure events were determined by stool culture and Polymerase Chain Reaction (PCR) from samples collected monthly. Serum Bactericidal Activity (SBA) and antibody levels were measured from blood samples collected every 3 months while clinical and environmental data were recorded on a monthly basis.

RESULTS

The linear mixed method fitted the data better than other methods. The Cox hazard model fell short as it does not incorporate time-varying covariates, whereas joint modelling for the first time to event fails to incorporate immunity measurements after the first exposure (event).

CONCLUSIONS

The linear mixed method can be adopted as a modelling framework for similar kind of data. Future work needs to be done to extend both the survival methods for interval censoring using Cox hazard regression method and Joint model for the time to event to naturally incorporate the time-varying events and measurements after the first event respectively.

20. Changes in Gastrointestinal Tract Microbiome Profiles of Malawian Children During Exposure to *Salmonella*

Angeziwa Chunga Chirambo[1], Tonney Nyirenda[2], Miren Iturriza-Gomara[3], Arox Kamngona[2], James Nyirenda[1], Ndaru Jambo[1], Melita Gordon[3]

[1]Malawi Liverpool Wellcome Trust Clinical Research Programme, [2]Biochemistry Section, Basic Medical Sciences Department, University of Malawi College of Medicine, [3]Institute of Infection and Global Health, University of Liverpool

BACKGROUND

The gastrointestinal tract microbiota plays important roles in human health including colonization resistance against enteric infections. Some changes in the gut microbiota may favor the survival and proliferation of enteric pathogens such as *Salmonella*. In Malawi, a recent cohort study of Malawian children aged 6 to 18 months has demonstrated that up to 47% of the children were exposed to *Salmonella* within the gut at least once over a 12 months period. Animal model work suggests that *Salmonella* colonization depends on metabolic competition with the microbiota in an inflammatory environment. It is however not known whether changes in gut microbiota composition in Malawi children is associated with *Salmonella* exposure.

METHODS

Sixty healthy Malawian children were recruited in a longitudinal cohort study at 6 months of age and followed up every month up to the age of 18 months. *Salmonella* exposure was determined by testing stool samples for *Salmonella* using culture and molecular based methods. Illumina sequencing of the V1V2 regions of the 16S rRNA gene was done on 336 stool DNA samples to determine the microbiome profiles of the children. Qiime version 1.8.0 was used to analyze sequence reads.

RESULTS

Seventeen and 310 Salmonella positive and negative samples respectively were included in the analysis after quality filtering. Twelve genera which were greater than 1% in abundance and constitutes 86% of the sequence reads were used in the analysis. Of these, Bifidobacterium and Streptococcus contributed 29% and 23% respectively. Marked changes in the profiles of Bifidobacterium and Bacteroides were observed. Salmonella exposure was associated with a 200% increase in the abundance of Bacteroides and a 50% decrease in the abundance of Bifidobacterium. No significant changes were observed in the other genera.

CONCLUSIONS

Salmonella exposure in Malawian children is associated with changes in microbiome profiles mainly the abundance of Bifidobacterium and Bacteroides.

21. Exploiting Anti-Infection Activities of the Early Life Microbiota Member Bifidobacterium Isolated From Malawian Children Against *Salmonella* Infections

Angeziwa Chunga Chirambo[1], Lindsay Hall[2], Tonney Nyirenda[3], Arox Kamng'ona[3], Miren Iturizza-Gonzalez[4], Happy Chimphako[1], Melita Gordon[4]

[1]Malawi Liverpool Wellcome Trust Clinical Research Programme, [2]Quadram Institute Bioscience, Norwich Research Park, [3]Biochemistry section, Basic Medical Sciences Department, University of Malawi College of Medicine, [4]Institute of Infection and Global Health, University of Liverpool

BACKGROUND

Bifidobacterium is a key member of the gastrointestinal tract (gut) microbiota that plays a beneficial role in controlling enteric infections during early life. Several *Bifidobacterium* species and strains have previously been shown to directly inhibit growth of other enteric organisms including *Salmonella* by the production of novel anti-microbials. In Malawi, as in other developing countries, episodes of enteric infections are highest in the under-5 age group. *Bifidobacterium* strains found in the gut of Malawian children and their antimicrobial properties are however not known. This study aims to isolate novel *Bifidobacteria* strains from Malawian children and carry out in-depth genomic and phenotypic testing to probe their anti-microbial activities with the aim of developing new cost-effective, non-toxic therapies.

METHODS

We carried out a single centered prospective cross-sectional pilot study at Ndirande Health Centre in Blantyre where 30 exclusively breastfed healthy children were recruited. A stool sample was collected from each participant. Isolation of *Bifidobacterium* was done anaerobically and isolates were confirmed using Fructose-6-phosphate Phosphoketolase assay and 16S rRNA Sanger sequencing. Whole genome Sequencing, 16S rRNA sequencing of stool DNA and invitro competitive assays of *Bifidobacterium Longum sub-species infantis* and *Suillum* against the invasive *Salmonella Typhimurium*, D23580 is being done.

RESULTS

Thirty healthy exclusively breastfed participants were recruited into the study with a mean age of 2.2 (0.5 – 3.8) months. Sixty eight isolates comprising of Bifidobacterium Longum, Breve, Bifidum and Pseudocatenulatum were 66.7%, 2.9%, 2.9% and 1.4% respectively were confirmed. *Bifidobacterium Longum sub-species Suillum* was isolated for the first time from humans. *Bifidobacterium Suillum* was able to inhibit *in vitro* the invasive *Salmonella* strains whilst Bifidobacterium Longum sub-species Infantis was not.

CONCLUSIONS

Bifidobacterium Suillum was identified from Malawian infants, this is the fist time this subspecies has been detected from humans. The *Bifidobacterium suillum* isolated from a Malawian infant was able to inhibit in vitro the invasive *Salmonella* strains first isolated in Malawi.

Further work will aim to further characterise and compare WGS of Bifidobacteria found in Malawian infants against global collections and to further characterise them for their inhibitor properties against diverse *Salmonella* including *Salmonella Enteritidis* and *Salmonella Typhi*.

22. Testing of Sewage Samples for Detection of *S.* Typhi and *S.* Paratyphi A in Kolkata, India

Goutam Chowdhury[1], Renuka Kapoor[2], Asish K. Mukhopadhyay[1], Suman Kanungo[1], Pranab Chatterjee[1], Shanta Dutta[1], Christine L. Moe[2]

[1]National Institute of Cholera and Infectious Diseases, [2]Center for Global Safe Water, Sanitation, and Hygiene, Rollins School of Public Health, Emory University

BACKGROUND

Enteric fever caused by *S.* Typhi (ST) and *S.* Paratyphi A (SPT) remains a major public health concern in many countries. This study focused on detection of ST and SPT in sewage samples in Kolkata, India in order to develop environmental surveillance for typhoid.

METHODS

Samples from septic tanks of shared toilets (PL) (1 L) and sewage pumping station (PS) (40 L) were collected from different locations within a ward of Kolkata known to have ST cases by clinical surveillance. Samples were tested for *E. coli* (EC) and total coliforms (TC) by membrane filtration, bacteriophage against *Bacteroides fragilis* (strain GB-124) and *E. coli* (strain WG-5) to differentiate origin of fecal contamination, and ST and SPT by quantitative real-time PCR (qRTPCR). ST and SPT were concentrated from sewage samples by polyethylene glycol (PEG) precipitation for PL samples and ultrafiltration followed by PEG precipitation for PS samples. After concentration, total DNA was extracted using Qiagen DNeasy PowerWater kit. qRTPR used Taqman-based platform, primers described by Nga et al. (2010), and plasmid DNA controls for ST and SPT.

RESULTS

32 PL samples and 35 PS samples were tested. EC concentration ranged from 10^4-10^7 CFU/mL in PL samples and 10^4-10^5 CFU/mL in PS samples. The concentration of TC ranged from 10^5-10^7 CFU/mL in PL samples and 10^4-10^6 CFU/mL in PS samples. Phages against GB-124 were detected in 20/32 (62.5%) PL samples at levels ranging from 5 to 2.8×10^4 PFU/mL and in 31/ 35 (88.5%) PS samples at levels ranging from 5 to 5.5×10^2 PFU/mL. Somatic coliphages (WG-5) were detected in 100% of the samples, at levels ranging from 80 to 10^5 PFU/mL and 4 to 10^3 PFU/mL in PL and PS samples, respectively. ST and SPT were not detected by qRTPCR in any of the 67 samples.

CONCLUSIONS

This study demonstrates the successful use of GB-124 phage for detection of human fecal contamination for the first time in India. Lack of ST and SPT detection, despite occurrence of ST cases, may be due to rapid die-off or low concentrations in sewage and indicates the need for further standardization of the protocols to improve the limit of detection.

23. VI Polysaccharide Antibody Responses to a Typhoid Conjugate Vaccine in Nepalese Children

Jennifer Hill[1], Mila Shakya[2,3], **Jenny Clarke[1,4],** Tan Trinh Van[5], Rachel Colin-Jones[1,4], Buddha Basnyat[2,3], Andrew Pollard[1,4]

[1]Oxford Vaccine Group, Department of Paediatrics, University of Oxford, [2]Oxford University Clinical Research Unit - Nepal, [3]Patan Academy of Health Sciences, Lalitpur, [4] NIHR Oxford Biomedical Research Centre, Oxford, [5]The Hospital for Tropical Diseases, Wellcome Trust Major Overseas Programme, Oxford University Clinical Research Unit, Ho Chi Minh City

BACKGROUND

Nepal suffers a significant typhoid fever burden, with the highest morbidity and mortality in children. A recently WHO pre-qualified typhoid conjugate vaccine (TCV) offers potential to reduce this burden, however effectiveness data are needed. In a randomised controlled trial currently underway in Nepal 20,019 children aged 9 months to ≤16 years of age were randomised 1:1 to receive the TCV or a capsular group A meningococcal vaccine. A subset of children were enrolled into an immunogenicity sub-study for assessment of immune responses to the TCV.

METHODS

1,441 children randomised on a 2:1 basis (TCV:MenA) were enrolled to provide samples for assessment of immunogenicity at day 0, and 28 days after vaccination. Further samples will be collected at 18 and 24 months post-vaccination. Day 0 and 28 plasma samples were shipped to Oxford University for measurement of Vi-specific IgG and IgA antibody by ELISA (VaccZyme Human Anti-*Salmonella* Typhi Vi IgG Enzyme Immunoassay Kit, The Binding Site). A modification of this kit is used to measure anti-Vi IgA.

RESULTS

Both day 0 and day 28 samples were obtained from 1063 children, while for 246 children it was possible to obtain a day 0 sample only, and for 34 a day 28 sample only. Preliminary analysis of 940 paired samples showed that at day 0, 73% of participants had Vi IgG below the lower limit of detection. By day 28, 62% of paired samples had a > 4-fold rise in Vi IgG. Sample analysis is continuing and full results will be available for presentation in Hanoi. We will present the full unblinded Vi IgG and IgA immunogenicity results stratified by age group, comparing the responses (absolute titres and fold changes) between recipients of the TCV and meningococcal control vaccine.

CONCLUSIONS

This study will characterise the immune response of children in an endemic setting to vaccination with a TCV, which can later be related to population protection. Through comparisons with other datasets these results have the potential to increase our understanding of the immunological correlates of protection against typhoid fever, and will provide important information needed to support the global roll out of TCV immunisation programs.

24. Logistics of Implementing a Large-Scale Typhoid Vaccine Trial in Kathmandu, Nepal

Rachel Colin-Jones[1], Mila Shakya[2], Nicola Smith[1], Katherine Theiss-Nyland[1], Shrijana Shrestha[3], Buddha Basnyat[2], Andrew J Pollard[1], The study team TyVAC[4]

[1]Oxford Vaccine Group, University of Oxford, [2]Oxford University Clinical Research Unit - Nepal, [3]Patan Academy of Health Sciences, [4]TyVAC consortium

BACKGROUND

Typhoid fever is estimated to affect over 20 million people per year worldwide, with infants, children and adolescents in south-central and south-east Asia experiencing the greatest burden of disease. The Typhoid Vaccine Acceleration Consortium (TyVAC) aims to support the introduction of typhoid conjugate vaccine (TCV) into Gavi eligible countries in an effort to reduce morbidity and mortality from typhoid.

METHODS

TyVAC-Nepal is a large-scale participant- and observer-blind, individual randomised controlled trial evaluating the efficacy of a newly developed typhoid conjugate vaccine in an urban setting in Nepal. In order to effectively deliver the trial, the clinical trial team had to be proactive in their approach to implementation, whilst being dynamic in responding to a changing environment. Three areas in which specific adaptations are needed included public engagement, training, and recruitment management.

RESULTS

Public engagement strategies were considered early, and involved the implementation of a tiered approach. Approximately 300 staff were employed and trained in order to achieve the mass vaccination of 20,000 children aged 9 months - ≤16 years old. Only 7 members of staff had previously worked in research. On the 20th of November 2018, the first vaccination clinic was opened. The original plan was to operate 15 clinics for the duration of the 4-month recruitment phase. However, clinics recruited at different rates and recruitment dropped over time as the proportion of children vaccinated in each area increased. Therefore a total of 19 vaccination clinics were established across the Lalitpur metropolitan city in Kathmandu valley. On the 9th of April 2018, target enrolment was completed with 20, 019 children vaccinated in just over 4 months. Participants will be followed-up for two years post-vaccination to measure the rate reduction of blood culture confirmed typhoid fever in the vaccination arm as compared to the control arm.

CONCLUSIONS

In conducting this large scale vaccine trial, experience has suggested that comprehensive planning, continuous monitoring and an ability to adapt plans in response to feedback has been key. Taken with expert opinion, the logistical elements of implementation highlighted may be important for other researchers in the planning and delivery of similar large-scale trials in the future.

25. Mass Cytometry Analysis of Cellular Responses to VI-Conjugate Vaccination

Deborah Cross[1], Marije Verheul[1], Irina Mohorianu[1], Michael Leipold[2], Gerlinde Obermoser[2], Jennifer Hill[1], Andrew J Pollard[1]

[1]University of Oxford, [2]Stanford University

BACKGROUND

A Vi-tetanus toxoid conjugate vaccine (Vi-TT) has been recently pre-qualified by the WHO for use against typhoid fever. In a human typhoid challenge model, vaccination induced strong anti-Vi IgG titres, however the nature of the cellular response to Vi-TT vaccination has not been previously described. Herein, we present a study examining the changes in peripheral blood mononuclear cells (PBMCs) following immunisation with Vi-TT and draw comparisons with responses to a plain Vi-polysaccharide vaccine (Vi-PS).

METHODS

Healthy volunteers received a single dose of either Vi-TT or Vi-PS. PBMCs were collected at baseline (D0), seven (D7) and 28 days post-vaccination (D28). Cells were stained for 37 surface markers defining cell lineage, activation status and homing potential and assessed using mass cytometry. Analyses were carried out using both manually gated subsets and populations defined through unsupervised learning on marker expression.

RESULTS

Preliminary analyses identified a 5.2-fold expansion in plasmablasts following Vi-TT vaccination with a weaker response also seen in the Vi-PS recipients. Plasmablast homing marker profiles were similar between vaccine groups at D7, highlighting a systemic- but not gut- homing phenotype of the early vaccine response. Fold change in plasmablast frequency correlated with Vi IgG antibody titres.

In addition, increased T follicular helper cell (Tfh) activation was observed in Vi-TT vaccinees at D7 versus baseline, suggesting a germinal centre (GC)-dependent response. Circulating Tfh cells with an activated phenotype also exhibited reduced expression of CCR7 after vaccination, indicative of recent GC activity. No significant changes in the Tfh compartment were observed in the Vi-PS recipients. Combined, these observations highlight key features of the immunological response to Vi-TT and Vi-PS vaccination. These differences are of major relevance to immunogenicity in young children and production of immunological memory.

CONCLUSIONS

Vi-TT vaccination induces a productive, GC-dependent plasmablast response which correlates with antibody titres post-vaccination. Plasmablast localisation within the body may be critical for protective responses, therefore further investigation of observed changes in plasmablast homing marker expression is warranted.

26. Comparative Genomic Analysis of *Salmonella* Concord From the Horn of Africa Reveals Signatures Related to High Resistance and Invasive Infections

Wim Cuypers[1,2], Gordon Dougan[3], Jan Jacobs[2], Pieter Meysman[1], Kris Laukens[1], Stijn Deborggraeve[2], Sandra Van Puyvelde[2]

[1]University of Antwerp, [2]Institute of Tropical Medicine, Antwerp, [3]Wellcome Trust Sanger Institute

BACKGROUND

The non-typhoidal *Salmonella* serotype Concord is particularly linked to the Horn of Africa, causing both gastrointestinal infections and invasive infections. Most isolates show high antimicrobial resistance (AMR), but little is known about the genetic nature of AMR in this serotype, nor its capacity to cause invasive infections.

METHODS

Two *Salmonella* Concord isolates from Ethiopian adoptees who presented in 2008 and 2012 at the Institute of Tropical Medicine Antwerp, Belgium, were phenotypically profiled for antibiotic resistance and whole genome sequenced using the PacBio RSII and Illumina HiSeq platform. We determined the genetic markers explaining the observed AMR as well as associated mobile genetic elements. In a next phase, we characterized genomic signatures underlying increased invasive infection potential in both coding and non-coding regions by a comparison with reference genomes of *Salmonella* serotypes that are either associated with gastroenteritis or invasive infections.

RESULTS

The first high-quality reference genomes of *Salmonella* Concord generated in this work contain a large set of AMR genes underlying the high resistance phenotype. The genes *CTX-M-15*, *qnrB*, and *mphA*, located on IncHI2 and IncA/C type plasmids, encode resistance to the third generation cephalosporins, fluoroquinolones, which are both recommended treatment options for invasive *Salmonella* infection and azithromycin, a reserve antibiotic. Preliminary results also point to the presence of patterns that have been linked to invasive infection in *Salmonella* in other studies, including impactful mutations in genes involved in establishing infection, and several metabolic pathways.

CONCLUSIONS

This is the first genomic analysis of *Salmonella* Concord and shows presence of an elaborate antibiotic resistance gene repertoire combined with genomic signatures associated with invasive infections.

27. Challenges in Receiving Adequate Blood Volumes for Automated Blood Cultures

Anuradha De, Jayanthi Shastri, Sachee Agrawal

T. N. Medical College & Nair Hospital, Mumbai

BACKGROUND

Enteric fever is endemic in many developing countries including India and other Southeast Asian countries, where 80% of the world's typhoid fever cases occur due to overcrowding with poor drinking water system and unhygienic conditions. A confirmative culture-based diagnosis is critical, which will help to ensure appropriate and effective treatment. One of the challenges in isolation of *Salmonella* species is receiving adequate blood volumes for blood culture. Most public hospitals do not have dedicated phlebotomists for blood collection and doctors are required to do blood collection. Recommended volume is 20 ml from either arm in adults and 1 ml/kg body weight in pediatric age group. However, this important aspect is not factored in blood culture for enteric fever. In addition to patients taking prior antibiotics, reduced volume of blood collection contributes to very poor isolation rates of salmonella.

Hence, a study was conducted at a tertiary care public hospital in Mumbai, India for a period of three months in 2018, to compare the difference in isolation rates and contamination, before and after training for collection of adequate blood volumes for blood cultures, following all aseptic precautions.

METHODS

Advocacy and training with mannequins were given to all staff in medical wards (adult and pediatric), to those who are responsible for blood collection for blood cultures, to avoid skin contamination. Importance of collection of adequate volumes of blood was also emphasized upon.

Blood was collected in Tryptic soy broth for culture in Automated blood culture system. Any growth was identified using standard biochemical tests. All *Salmonella* isolates were identified by standard biochemical tests and confirmed by agglutination with specific antisera.

RESULTS

A significant decrease in contamination rate and increase in isolation of *Salmonella* species was observed following the training sessions.

CONCLUSIONS

Training of staff resulted in collection of adequate volumes of blood for blood culture after appropriate skin preparation with all aseptic precautions. Contamination rates also decreased considerably. Thus, we can conclude that regular training sessions will definitely help in improving the quality of blood cultures received in the laboratory, which will lead to timely diagnosis and proper management of the patients.

28. Characterization of *Salmonella* Enterica From Invasive Bloodstream Infections, Water Sources and Poultry in Rural Ghana

Denise Dekker[1], Nimako Sarpong[2], Kennedy Boahen[2], Charity Wiafe-Akenten[1], Florian Marks[3], Jürgen May[1]

[1]Bernhard Nocht Institute for Tropical Medicine, [2]Kumasi Center for Collaborative Research, [3]International Vaccine Institute

BACKGROUND

Nontyphoidal *Salmonella* (NTS) cause the majority of bloodstream infections in Ghana, however the mode of transmission and sources of invasive NTS in Africa are poorly understood. The study compares NTS from invasive bloodstream infections to NTS from drinking water sources and poultry meat in rural Ghana.

METHODS

Blood from hospitalised, febrile children, meat from imported and locally-produced poultry and samples from drinking water sources were analysed for *Salmonella enterica*. Strains were serotyped to trace possible epidemiological links between human, poultry and water-derived isolates. Antibiotic susceptibility testing was performed.

RESULTS

In 2,720 blood culture samples, 165 (6%) NTS were isolated. *S.* Typhimurium (70%) was the most common serovar followed by *S.* Enteritidis (8%) and *S.* Dublin (8%). Multidrug resistance was found in 95 (58%) NTS isolates. Five *S.* Enteritidis and one *S.* Typhimurium showed reduced fluoroquinolone susceptibility.

In 511 water samples, 19 (4%) tested positive for S. enterica with two isolates being resistant to ampicillin and one isolate being resistant to cotrimoxazole. Serovars from water samples were not encountered in any of the clinical specimens.

Among 200 meat samples, comprising 34% (n=68) from the Ghanaian poultry industry and 66% (n=132) from imports, 9% (n=17) contained *Salmonella*. Most common serovars identified included Kentucky (n/N=5/16; 32%), Poona (n/N=4/16; 25%) and Agama (n/N=3/16; 19%). Resistance to fluoroquinolones was high with 63% (n=10).

CONCLUSIONS

Our study results demonstrate a rather broad serovar distribution of *Salmonella* found in drinking water and poultry. Serovars found were mainly types not commonly associated with human infections. This suggests anthroponotic transmission as the major transmission route of *Salmonella* in sub-Saharan Africa, which urges to be further investigated. Even though no major link was established, *Salmonella* in drinking water and poultry present a potential health risk. Of major concern is the overall high level of fluoroquinolone resistance seen in poultry as this may lead to the increase of resistance in the human population. The substantially high level of multidrug- and emerging fluoroquinolone resistance seen in the invasive NTS strains poses a challenge to current treatment strategies.

29. Investigating the Frequency and Sub Categories of Articles on Typhoid Published on Leading On-Line Newspapers in Uganda

Ongeng Joseph Denis[1], Oloi Christine[2], Opio Emanuel[3]

[1]NewVision Newspaper, [2]Favor of God Ministry, [3]The Nation Media Group (Daily Monitor Newspaper)

BACKGROUND

The Media industry plays a pivotal role in raising awareness about Typhoid, which remain a major global cause of morbidity in low and middle income countries. Information available suggests that the media fraternity has limited knowledge and information on Typhoid fever, a fact occasioned with publishing wrong or in accurate information to the public and the divers group of stakeholders. These has the effect of ultimately derailing efforts to combat the disease. A well informed media is essential in the fight against Typhoid fever, especially in terms of creating public awareness with informed , up to date in-depth articles on issues such as outbreaks , sanitation and hygiene and vaccine development. In this abstract, we review the content of Uganda's leading on-line newspapers to understand the frequency of reporting on Typhoid fever and sub categories those articles appeared.

METHODS

A review of Uganda's leading newspapers with on- line publications (New Vision, Daily Monitor and Observer) were conducted using internet based archives of articles to identify publications reporting about Typhoid fever outbreaks, sanitation and hygiene and vaccine development. The publications reported about Typhoid fever in districts across Uganda, a country with a population of over 40 million people between the periods of January 2015- March 2018. Selected publications were analyzed according to agreed guidelines.

RESULTS

Three leading newspapers were sampled and a total of 180 articles were identified. However, when we screened the stories for a second time, we ended up with 126 articles. Out of the 126 articles, sanitation and hygiene had 40.5%, 6.3% of articles were on outbreaks while only about 4% were on vaccine development. Besides the limited coverage on outbreaks and vaccine development by the media houses, gaps were also seen in areas such socioeconomic impact of Typhoid and Policy response.

CONCLUSIONS

Media capacity building programs forms an ideal platform for rejuvenating a more robust and informed reporting and awareness raising on Typhoid fever in Africa. An informed media can report from the point of knowledge about wide ranging issues, such treatment and drug resistance, economic impacts of Typhoid, risk factors, epidemiology and surveillance.

30. The Nascent Samoa Typhoid Fever Surveillance Initiative Utilizing Public Health Infrastructure

Sachin Desai[1], Robert Thomsen[2], Take Naseri[2], Michael Sikorski[1], Ben Howden[3], Roy Robins-Browne[3], John Crump[4], Myron Levine[1]

[1]University of Maryland, [2]Samoa Ministry of Health, [3]University of Melbourne, [4]University of Otago

BACKGROUND

Typhoid fever is endemic in Oceania, including Samoa where remote villages have less access to health care and there is no bacteriology capability; thus suspect typhoid cases remain unconfirmed. Quantifying with greater precision the burden of typhoid and characterizing the local epidemiology is critical to guide future control activities.

METHODS

Strengthened bacteriology infrastructure and enhanced capacity to undertake epidemiologic investigations of cases underpin the nascent Samoa Typhoid Fever Surveillance Initiative. Systematic surveillance for febrile illnesses (temperature ≥39 °C for > 3 days) at remote sentinel sites will trigger collection of blood cultures that will be transported to the main hospital laboratory. Automated blood culture capacity is being established *de novo* in the hospital laboratory on Savaii island and will be strengthened in the hospital laboratory on Upolu island. A Samoa Typhoid SWAT (Special Weapons and Tactics) Team will visit households (or school or workplace) of confirmed cases to identify co-incident cases and possible chronic carriers among contacts, gather risk factor and exposure information and culture human fecal waste. The SWAT Team consists of four professionals including two nurses. Household (or school or workplace) visits will include: epidemiologic questionnaire, obtaining blood cultures from febrile household contacts, screening for acute and chronic carriers by stool (or rectal swab) cultures, serum Vi antibody measurement, ultrasound examinations to detect gallstones, duodenal fluid cultures (if indicated), and environmental (septic tank) sampling. Identified putative chronic carriers are offered treatment (Samoan *S.* Typhi are quinolone-sensitive).

RESULTS

Circa 70-100 blood culture-confirmed typhoid cases occur annually (almost all from Upolu). Visits to ~20 households have been undertaken to document the feasibility of applying these 'weapons and tactics.' The visits have revealed shared contact and exposure relationships among sporadic cases previously considered unrelated; one putative chronic carrier has been identified.

CONCLUSIONS

The Samoa Typhoid Fever Surveillance Initiative will provide more precise typhoid burden estimates and epidemiologic information to guide future interventions to lower typhoid transmission. As countries implement typhoid control with vaccine and WASH interventions, and as burdens diminish, they may consider establishing SWAT teams to identify and treat chronic carriers (the long-term reservoir) and subclinical acute cases.

31. Making of Typhoid Mary: Understanding Persistence Mechanisms in *Salmonella* Typhi

Stuti Desai, Linda Kenney

Mechanobiology Institute, National University of Singapore

BACKGROUND

Salmonella enterica serovar Typhi is an intracellular pathogen that infects only humans to cause typhoid fever. In order to survive in humans for prolonged periods, it has evolved the ability to form hardy multicellular structures on gallstones of asymptomatic patients who then act as carriers to disseminate *S.* Typhi. In Singapore, chronic carriers of *S.* Typhi also introduce typhoid to non-endemic populations; in the United States the notorious example was the case of Typhoid Mary. The problems associated with typhoid carriage are compounded by the observation that colonized individuals have a much higher risk of developing hepatobiliary carcinomas. However, an understanding of how *S.* Typhi switches on its dormant lifestyle to form gallstone biofilms is completely lacking. We recently deciphered the molecular pathways involved in the establishment of the carrier state in *S.* Typhimurium and determined biofilm regulation by atypical signaling events.

METHODS

Crystal violet staining, chromosomal deletions using lambda *red gam* engineering, fluorescence microscopy, zebrafish husbandry

RESULTS

We have now examined whether similar mechanisms were involved in the development of gallstone biofilms in serovar Typhi. To our surprise, we discovered that *S.* Typhi required a completely different set of environmental conditions, and thereby different molecular players, to form gallstone biofilms. Our preliminary experiments also indicate that *S.* Typhi, as well as serovar Typhimurium, was able to successfully colonize and persist in the intestines of zebrafish larvae. We are now identifying the biofilms components (structural and regulatory) in *S.* Typhi using genetic approaches. We will also utilize the superior imaging potential of zebrafish as a heterologous host to follow the real-time progression of infection in the primary targets of intestine and gall bladder, in order to characterize the extracellular persistence of *S.* Typhi in chronic infections.
Supported by RCE in Mechanobiology, NUS Ministry of Education, Singapore, NIHR21-AI123640 and VA 5IO1BX000372 to LJK.

CONCLUSIONS

As part of the results and conclusions section above.

32. Isolation and Characterization of Novel Bacteriophage Lysing Colistin Resistant *Salmonella* spp., a Promising Solution to Antibiotic Crisis

Gunaraj Dhungana, Elisha Upadhyaya, Madhav Regmi, Apshara Parajuli, Rajani Malla

Tribhuvan University

BACKGROUND

Resistance to traditional antibiotics in Salmonella spp. is steadily increasing including carbapenem and even colistin, the last resort of available antibiotic. Thus, because of the difficulty to treat these "superbug" and menace and some term as "apocalypse" of the post-antibiotic era, an alternative approach to controlling this pathogen is prudent and one of the approaches is bacteriophage-mediated control and/or treatment. This study aimed to isolate and characterize novel lytic bacteriophages against colistin resistant Salmonella spp. a probable solution to the current antibiotic crisis.

METHODS

Total six molecularly characterized colistin resistant Salmonella enterica serotype typhi were used as host for the isolation of bacteriophage. Bacteriophages were isolated from sewage water from Kathmandu, Nepal by double layer agar assay method. Phages were identified using transmission electron microscope and further characterized according to physiochemical, proteomic and molecular properties, like one step growth curve, burst size, multi host range, protein profiling, thermal and pH stability. Whole genome sequencing was done using the Illumina platform.

RESULTS

Two lytic bacteriophages were isolated against colistin resistant *Salmonella enterica serotype typhi*. Among them, Phage_TU Sal2 was selected for further characterization on the basis of lysis pattern and multi-host range, which effectively lyzed 9 strains of bacteria other than its primary host. Phage_TU Sal2 showed good thermal tolerance ranging from 4°C to 60°C and stable wide range of pH (2-11). Electron microscopy confirmed that the phage was tailed and belonged to caudovirales family. Major capsid protein band (110kda) and minor band (54kda) were observed in SDS-PAGE. Whole genome sequencing revealed its genome size to be 164.2 kb with total 267 predicted proteins. The G+C content of phage genome was 40.58%. Bioinformatic analysis further confirmed that the phage genome did not contain any bacterial genes within the phage genome, which ruled out the concern for transfer of virulent genes during phage therapy.

CONCLUSIONS

Novel bacteriophages, Phage TU_Sal 2 showing broad host range, good pH and thermal tolerance, the absence of virulent genes of bacterial origin and presence of lysin proteins within phage genome makes the phage as an excellent candidate for therapeutics.

33. Changes to the Small RNA Population in PBMCs in an *S.* Typhi Human Challenge Model Reveal Differences Early After Challenge and at Diagnosis

Ruth Drury, Christoph Blohmke, Celina Jin, Daniel O'Connor, Irina Mohorianu, Andrew Pollard

Oxford Vaccine Group, University of Oxford

BACKGROUND

A human challenge model offers a uniquely controlled environment for the longitudinal study of host-pathogen interactions. We investigated whether exposure to *Salmonella* Typhi induces changes in the expression of small non-coding RNAs (sRNAs) in peripheral blood mononuclear cells (PBMCs). We focused on two classes of sRNA: microRNAs (which inhibit mRNA translation) and small nucleolar RNAs. MicroRNAs regulate genes involved in host immune responses, e.g. genes involved in innate and adaptive responses including antibody production, but little is known about their role in enteric fever. This is the first study on sRNA expression in a human infection model.

METHODS

Participants were vaccinated with a plain Vi-polysaccharide vaccine (Vi-PS) or Vi-polysaccharide conjugated to tetanus toxoid (Vi-TT). Twenty-eight days later the volunteers were exposed to *S.* Typhi by oral challenge. Small RNA-sequencing was conducted at baseline, 7 and 10 days after vaccination, day of challenge, 1 day after challenge, at diagnosis, and 7 days after challenge in participants not developing typhoid. Results were deemed significant when adjusted p-values (FDRs) were <0.05.

RESULTS

Samples were obtained from 53 participants.

Preliminary analysis identified changes in the expression of several microRNAs that were associated with outcome. MicroRNAs were more differentially expressed 1-day post challenge in participants not developing typhoid compared with those who did. Among differentially expressed microRNAs was hsa-miR-6852-5p. Functional enrichment analysis revealed that differentially expressed microRNAs target genes involved in FcεRI signalling. Several microRNAs were differentially expressed at diagnosis. One of the most differentially expressed microRNA was hsa-miR-1303; this microRNA targets genes involved in NF-κβ activation.

Other classes of sRNAs, including small nucleolar RNAs, were differentially expressed after challenge and/or during infection e.g. SNORD107.

To gain biological insights into host responses to *S.* Typhi, we are investigating the role of sRNAs as part of wider regulatory networks using integrative approaches.

CONCLUSIONS

We found changes in microRNA expression after *S.* Typhi exposure is associated with outcome, we identified potential microRNA-based correlates of vaccine protection, and we have discovered candidate biomarkers of typhoid fever. In the long term these findings could be useful in vaccine development, diagnostics, and/or creating microRNA-based treatments that augment the host response to *S.* Typhi.

34. Cluster Analysis of Enteric Fever Cases in Urban Slums of Kolkata

Shanta Dutta[1], Suman Kanungo[1], Pranab Chatterjee[1], Jayanta Saha[1], Jacob John[2], Gagandeep Kang[3]

[1]ICMR National Institute of Cholera and Enteric Diseases, [2]Christian Medical College, Vellore, [3]Translational Health Science and Technology Institute

BACKGROUND

South Asia contributes maximally to the global burden of enteric fever. An active surveillance was initiated in typhoid endemic urban slums of Kolkata to assess the burden of enteric fever in this ecosystem. The collected data was geotagged. In the current analysis, we explore the clustering of the cases of confirmed typhoid fever, diagnosed based on a positive blood culture.

METHODS

Geotagged household level data was collected in course of active surveillance of febrile illness in children aged between 6 months and <14 years. A child suffering from fever for 3 consecutive days was defined to be a case of suspected typhoid fever; when *Salmonella* spp was isolated in microbiological culture of blood specimen collected from a fever case, it was defined to be a case of confirmed enteric fever. For first order spatial randomness to identify general clustering, a Nearest Neighbourhood Analysis (NNA) was undertaken to conduct a Nearest Neighbourhood Index; an index value of <1 was expected to be observed in case of clustering. To assess local clustering, a Ripley's K function analysis was conducted; the K function was transformed to an L(d) function such that the reference for complete spatial randomness was linear and horizontal (at zero). To determine significance, the L(d) function was compared to a confidence limit for random distribution generated using Monte Carlo simulations. Significant clustering was indicated if the observed L(d) function exceeded the calculated upper confidence limit. Spatial analyses were done using CrimeStatIV.

RESULTS

6017 children were recruited since October 2017; 37 cases of confirmed enteric fever were accrued in the study period. NNA revealed a mean nearest neighbour distance of 95m compared to an expected distance of 192m, giving an NNI of 0.5, which indicated significant clustering (P=0.0001, Z=-5.8613). In Ripley's K function analysis, clustering was strongly seen.

CONCLUSIONS

Considering that only 37 cases had accrued these findings need to be interpreted with caution. However, the occurrence of clusters of cases in an endemic area, where there is little difference in the risk profiles of susceptible children, calls for closer examination of transmission pathways and agent-host-environment interactions.

35. Surveillance of Clinical Laboratory and Molecular Characteristics of Typhoidal *Salmonella* Infection in a South Indian Setting

Carl Britto[1], **Zoe Dyson[2],** Sitarah Mathias[3], Jose Sanju[3], Savitha Nagaraj[3], Gordan Dougan[4], Kathryn Holt[2], Andrew Pollard[1,5]

[1]Oxford Vaccine Group, Department of Paediatrics, University of Oxford, [2]Department of Biochemistry and Molecular Biology, Bio21 Molecular Science and Biotechnology Institute, University of Melbourne, [3]Department of Microbiology, St. John's Medical College Hospital, [4]Department of Medicine, University of Cambridge,, [5]NIHR Oxford Biomedical Research Centre

BACKGROUND

India is endemic for enteric fever and recent reports suggest a rise in enteric fever cases, particularly in areas of the South.

METHODS

Blood culture surveillance was conducted at St. John's Medical College Hospital, Bengaluru, between July 2016 and June 2017. Clinical, laboratory and demographic data were collected from each case and linked to the molecular characteristics of the respective bacterial isolate to gain insight into the host-pathogen biology. The resulting pathogen genomic data were also used to place these isolates into a worldwide context.

RESULTS

Typhoidal *Salmonella*e constituted 3.4% of all significant blood cultures. Young adults (16-30 years) and children <15 years accounted for 46.9% and 37% of cases respectively. Anaemia on presentation was seen in 46.2% of cases and 18.7% had an abnormal leucocyte count. Adults had a significantly longer duration of admission when compared with children (p=0.002). Atypical presentations included arthritis, acute haemolysis and repeated typhoid infection with two distinct genotypes. A total of 101 *S.* Typhi and 14 *S.* Paratyphi A isolated from patients treated in both inpatient and outpatient settings were subjected to whole genome sequencing and antimicrobial susceptibility testing. Fluoroquinolone resistance was seen in 95% of *S.* Typhi and all *S.* Paratyphi A isolates and was mediated via SNPs in the quinolone resistance determining region of genes *gyr*A, and *par*C. There were no acquired MDR genes among these isolates. The molecular structure of the *S.* Typhi pathogen population was dominated by H58 strains particularly those belonging to lineage II. The Paratyphi A strains mostly belonged to lineage A. Global contextualisation of these strains revealed that local *S.* Typhi and *S.* Paratyphi A strains had close genetic relatives in other South Asian countries, indicating regional circulation.

CONCLUSIONS

Enteric fever in South India continues to be a major public health issue and requires robust surveillance as well monitoring of pathogen population structure to inform treatment and preventive strategies. The on-going inter- and intra-regional transmission in South Asia, highlights the need for regional coordination of intervention strategies. The absence of a *S.* Paratyphi A vaccine is concerning, given its prevalence as a fluoroquinolone resistant enteric fever agent in this setting.

36. Investigation of Population Bottlenecks in *Salmonella* Typhi Infection Using an Experimental Human Challenge Model

Katherine Emary, Maria Moore, David Smith, Jennifer Hill, Marije Verheul, Richard Moxon, Andrew Pollard

Oxford Vaccine Group, Department of Paediatrics, University of Oxford, and NIHR Oxford Biomedical Research Centre

BACKGROUND

The essential steps in the pathogenesis of bloodstream infection for Salmonella Typhi are inadequately understood. The bottleneck hypothesis suggests that bacteraemia is initiated by a sole 'founder' bacterium; i.e. the entire population of bacteria found in the blood are derived from this single cell. There are data to support this concept from animal models of S. Typhimurium and other bacterial pathogens. The aim of this study is to explore the bottleneck hypothesis in the pathogenesis of bacteraemia in a human challenge model of infection with S. Typhi.

METHODS

We will use an established, experimental outpatient human challenge model of S. Typhi to examine potential population bottlenecks in typhoid. Volunteers (n=15) will orally ingest an inoculum containing an equal ratio of two characterised variants of Salmonella Typhi: a wild-type strain (Quailes), and a typhoid toxin knockout mutant of the Quailes strain. Previous studies show that oral challenge with these strains induces the same attack rate and similar disease severity. Blood cultures will be performed daily for 14 days post challenge and additionally if symptoms occur. Bacteria will be isolated from the blood of the volunteers and will undergo genotypic analysis using PCR to identify the presence of each variant in a given bacteraemia.

RESULTS

Based on observations in previous challenge studies we expect approximately 60-70% of volunteers to become bacteraemic following challenge. From animal data we might expect to isolate either variant but not both.

CONCLUSIONS

The outcome predicted by animal models would suggest that there is a population bottleneck in the development of S. Typhi bacteraemia. This would be the first evidence of a population bottleneck in a human model of bacteraemia.

37. Characterization of *Salmonella* Isolates From Invasive Infections Collected During Acute Febrile Illness (AFI) Surveillance n Uganda From 2016-2018

Molly Freeman[1], Henry Kajambula[2], Hannington Tasimwa[2], Susan Van Duyne[1], Hayat Caidi[1], Ana Lauer[1], Matthew Mikoleit[1]

[1]Centers for Disease Control and Prevention, [2]Makerere University

BACKGROUND

Acute febrile illness (AFI) is a common syndrome among sick children in Uganda and may have a variety of diverse etiologies, including invasive *Salmonella enterica* infections. Diagnosing such infections remains challenging due to scarcity of reagents, equipment and expertise and difficulty of culturing bloodborne bacteria. However, in hospital settings that lack microbiology capacity, it is possible to inoculate and incubate blood culture bottles on site and transport positive cultures to a central laboratory for microbiological isolation and identification.

METHODS

Salmonella enterica was isolated from the blood of febrile children in 6 sites across Uganda from 2016-18. 49 isolates underwent traditional phenotypic characterization including antibiotic susceptibility testing (AST) by disc diffusion and broth microdilution, as well as additional molecular characterization via pulsed-field gel electrophoresis (PFGE) and whole genome sequencing (WGS). WGS confirmed serotype and antibiotic resistance profiles. PFGE patterns and WGS data determined relationships amongst strains.

RESULTS

The most common *Salmonella* serotype identified was Enteritidis (21/49, 42.8%), followed by Typhi (14/49, 28.5%), Typhimuirum (13/49, 26.5%) and I4,5,12:i:- (1/49, 2%). 16 of 21 (76.2%) of Enteritidis exhibited an "atypical" phenotype characterized by trace H2S production, inability to produce gas from glucose, and delayed citrate utilization, which complicated differentiation from Typhi. Notably, 11/13 (84.6%) of Typhimuriums belong to ST19 rather than ST313. 16/19 (84.2%) of Typhi belong to the haplotype 58 group. Antibiotic resistance to at least one drug used to treat *Salmonella* bacteremia was detected in 29 of 49 strains (59%). While PFGE and WGS subtyping methods revealed similarity to other strains from East Africa, these isolates belong to their own clade and displayed limited strain diversity.

CONCLUSIONS

Invasive *Salmonella* infections are an important cause of febrile illness in Ugandan children. No clusters of illness were detected as heterogeneity across serotypes, antibiotic susceptibility patterns and WGS subtypes was observed. In addition, some strains isolated in different years appear highly related which suggests those strains are continuing to circulate in the population. Sustaining capacity for isolation and characterization of *Salmonella* is crucial for detecting (re) emerging strains, developing empiric therapy guidelines, and identifying effective interventions.

38. Age-Related Clinical and Microbiological Characteristics of Enteric Fever in India (2012-2016)

Rajni Gaind

VMMC and Safdarjung Hospital

BACKGROUND

The epidemiology of typhoid and paratyphoid fever is evolving with introduction of immunization and improvement and of sanitation. The clinical and microbiological spectrum enteric fever also varies with etiological agent.

METHODS

A retrospective, hospital-based study at Safdarjang Hospital, India, was undertaken between January 2012 and December 2016 to estimate age-related epidemiological, clinical and microbiological characteristics in enteric fever cases.

RESULTS

A total of 670 blood-culture-proven cases of enteric fever were studied. The majority of cases occurred in children aged 5–12 years and 24.8% of cases were in children up to 5 years of age. *Salmonella* serotypes showed an age-related predilection, with paratyphoid fever more common in adults. Classically-described clinical features of the disease were comparable among patients under and above 5 years of age. Hepatomegaly, anaemia and complications in general were more frequent in children up to 5 years of age. The antimicrobial resistance pattern, irrespective of *Salmonella* serotype, did not reveal a statistically significant difference across age groups for the different antibiotics tested. Multidrug resistance was seen only in *Salmonella enterica* serotype Typhi but not in *S.* Paratyphi A isolates. However, resistance to fluoroquinolones was comparable in both serotypes. Azithromycin MIC were higher for S. Paratyphi A. There was a significant increase in S. Typhi and Paratyphi A isolates with Azithromycin MIC $\geq$ 16 during study period. No resistance to cephalosporin's was observed in both serotypes.

CONCLUSIONS

Age-related differences of serotype isolation rates, clinical presentation and associated complications are noteworthy for better case management and policy planning. More epidemiological studies regarding reasons for age-related differential serotype patterns would enable and guide public health strategies to contain enteric fever in endemic locations.

39. Validation of Pefloxacin and Other Fluoroquinolone Disc for Detection of Low Level Fluoroquinolone Resistance Among *Salmonella* Typhi and Paratyphi A

Rajni Gaind, Shakila Banu

VMMC and Safdarjung Hospital

BACKGROUND

Fluoroquinolones (FQ) have been recommended for treatment of enteric fever as they are available as oral formulation, economical and excellent intercellular activity. Emergence of low level resistance to FQ is associated with therapeutic failure. Laboratory detection of these isolates is thus important for optimal patient care. Low level resistance among S. Typhi and S. Paratyphi A is mostly due to mutations in *gyr*A and or parC of the quinolone resistance-determining region and Nalidixic acid (NA) disc till recently was found to be a reliable method for detection. The current methods for susceptibility testing are not adapted to the detection of new resistance determinants, which also confer low levels of resistance.

The aim of this study was to validate different quinolones by disk diffusion and MIC determinations to detect fluoroquinolone resistance.

METHODS

A total of 200 S. Typhi and Paratyphi A strains, characterized for mechanism of resistance (Gyr A /GyrB and ParC) were selected. Disk diffusion assays and MIC (E-test) were performed using nalidixic acid, ciprofloxacin, ofloxacin, and levofloxacin. Pefloxacin disc was also evaluated.

RESULTS

The results showed a trimodal distribution of the MICs for both S. Typhi and S. Paratyphi A. The MIC distributions for the isolates varied with the compounds tested. Screening for nalidixic acid resistance by MIC testing or disk diffusion assay was not efficient for the detection of isolates with gyrB mutation. Decreased susceptibility to FQ mediated by gyrB mutation was best detected by testing for the MIC of ciprofloxacin or ofloxacin and pefloxacin disk diffusion only. Testing for the MICs of levofloxacin fail to detect these isolates.

CONCLUSIONS

In conclusion, screening with nalidixic acid is efficient for the detection of mutants with gyrA mutants only. Detection would be maximized by screening with either ciprofloxacin or ofloxacin by both MIC determination and disk diffusion assays. Pefloxacin disks seemed to increase the sensitivity of the disk diffusion assay

40. Establishment of International Standards for Vi Polysaccharide From *Citrobacter freundii* and *Salmonella* enterica subspecies *enterica* serovar Typhi

Fang Gao, Carolyn Swann, Peter Rigsby, Kay Lockyer, Alastair Logan, Sjoerd Rijpkema, Barbara Bolgiano

NIBSC/MHRA

BACKGROUND

Plain Vi polysaccharide (PS) and Vi PS conjugate vaccines are primarily evaluated by physicochemical methods to determine quality, safety and potency and ensure that batches are consistently manufactured. As different assays may be employed to quantify the PS content of final formulations and bulk intermediates, there is a demand for a Vi PS International Standard (IS) to calibrate internal reference standards used in different laboratories and so NIBSC as a Collaborating Center of the World Health Organization (WHO) initiated a project to establish a Vi PS IS.

METHODS

Vi polysaccharides from *Citrobacter freundii* and *Salmonella enterica* subspecies enterica serovar Typhi were filled at NIBSC and distributed to participating laboratories to evaluate the candidate standards. Unitage of these two standards was assigned by quantitative NMR. Fitness-for-purpose evaluation of the standards was also carried out to assess their performance in various methods for quantifying PS content in vaccine relevant samples.

RESULTS

Both PS were established by the WHO Expert Committee on Biological Standardization (ECBS) in Oct 2017 as the First WHO International Standards of *C. freundi*i Vi PS and *S.* Typhi Vi PS with contents of 1.94$\pm$0.12 and 2.03$\pm$0.10 mg Vi PS per ampoule respectively.

CONCLUSIONS

The intended use of both standards is for the quantification of the Vi saccharide component of Vi oligo- and PS-containing vaccines, for which they are potentially suitable for use in HPAEC-PAD, ELISA, rate nephelometry and rocket immuno-electrophoresis assays, on the basis of results from the collaborative study.

The standards are available from NIBSC (www.nibsc.org/products/brm_product_catalogue.aspx as Enteric disease standards 12/244 and 16/126), who act as guardians and distributors of the material under the auspices of WHO.

41. Mathematical Modeling to Investigate Decline of Typhoid Fever in Kibera, Kenya

Jillian Gauld[1,2], Margaret Lind[3], Godfrey Bigogo[4], Geoffrey Masyongo[4], Adam Akullian[2], Eric Mintz[5], Jennifer Verani[6]

[1]Institute for Disease Modeling, [2]Lancaster University, [3]University of Washington, [4]Kenya Medical Research Institute- Centre for Global Health Research, [5]Centers for Disease Control and Prevention- Division of Foodborne, Waterborne and Environmental Diseases, [6]Centers for Disease Control and Prevention- Division of Global Heath Protection

BACKGROUND

A high burden of typhoid fever (TF) was described in Kibera, an urban slum in Nairobi, Kenya, beginning in 2007. However, incidence decreased dramatically in 2013, and has remained relatively low. The cause of this reduction is poorly understood. Kibera has inadequate sanitation, drinking water primarily comes from illegal connections and an unregulated distribution network, and no typhoid vaccine was implemented. We undertook a mathematical modeling investigation to explore potential drivers of decline.

METHODS

We utilized an individual-based, mathematical model (EMOD) fit to age distribution, endemic incidence, and seasonality of TF in Kibera. Data for the model came from the Population-Based Infectious Disease Surveillance (PBIDS), which monitors the health and demographics of ~25,000 Kibera residents. PBIDS participants receive free medical care at a centrally located clinic. TF cases were identified through routine blood culture of clinic patients presenting to a central clinic with pneumonia or acute febrile illness. Person-time incidence by age, month, and year were estimated between 2007 to 2017 to explore potential contributions to decline, including immunity from a prior outbreak, changes in the population due to migration or mortality, and environmental exposure changes.

RESULTS

TF incidence was highest in 2012 (189/100,000 person-years-observation), and after falling to 60.1/100,000 in 2013, continued to decline through 2014-2017, reaching a low of 1.8/100,000 person-years-observation in 2017. Simulated outbreak-related immunity contributed to a decline in TF, but failed to capture the sharp drop in incidence observed in 2013. Modeled changes in migration patterns were also unable to explain the decline observed. A simulated reduction in environment exposure in 2013 resulted in the best fit to data, assuming that ≥80% of cases pre-2013 were infected through an environmental route (long-cycle transmission) rather than direct (short-cycle) transmission.

CONCLUSIONS

Kibera experienced a dramatic reduction in TF incidence without any targeted intervention; mathematical modeling suggests declines in environmental exposure as a likely explanation. Although data measuring *S.* Typhi in the environment are not available, reported changes to water source and piping materials occurring before 2013 are consistent with this finding. Further investigation into environmental exposures and their impact on TF in Kibera is underway.

42. A Retrospective Study of Patients With Confirmed Typhoid Fever in Fiji: Clinical Features, Case Fatality Rates & Antimicrobial Susceptibility Patterns

Aneley Getahun Strobel[1], Christopher Parry[2,3], Ravi Naidu[4], Varanisese Rosa[5], John Crump[6], Richard Strugnell[7], Kim Mulholland[3,5]

[1]Fiji National University, [2]Nagasaki University, [3]Liverpool School of Tropical Medicine, [4]Ministry of Health and Medical Services, [5]Murdoch Children's Research Institute, [6]University of Otago, [7]University of Melbourne

BACKGROUND

Typhoid fever is endemic in Fiji. There has been a dramatic increase in reported cases of typhoid fever over the last two decades. This study examined the clinical features, fatality and antimicrobial susceptibility patterns in typhoid patients.

METHODS

A standardised case investigation form was used to record epidemiological, clinical and laboratory information from culture confirmed typhoid patients from January 2014 to December 2015.

RESULTS

There were 551 culture confirmed typhoid patients of whom 95.6% were ITaukei/indigenous Fijians and 52.6% males. The median age was 25 years (inter quartile range 16-38). Children <15 years of age accounted for 22% of the cases. Clinical information was obtained for 75% (368/492) of patients who were treated in hospitals. Mean time from the onset of illness to admission was 11.1 ±6.9 days. The common presenting symptoms were fever (97%,) diarrhea (66.9%), loss of appetite (52.2%), rigors (52.0%), headache (44.1%) and vomiting (33.2%). Adult patients were more likely to report history of headache and rigors than children. At admission, 47.3% patients had anemia. Leukopenia and thrombocytopenia were reported in 39.7% and 44.8% of patients, respectively. The prevalence of severe disease was 13.3% (49/368) which included: hypovolemic shock (4.7%), hepatitis (3.1%), severe anemia (2.8%), gastrointestinal bleeding (2.5%), pneumonia (1.7%), encephalopathy (1.1%) and myocarditis (0.3%). The overall case fatality rate was 1.6% (9/551) with higher fatalities (8, 2.9%) among adults. The local S. Typhi strains were fully susceptible to ampicillin, chloramphenicol, gentamicin, ceftriaxone and cephalothin. Resistance to ciprofloxacin and nalidixic acid was 0.5%. Ciprofloxacin resistance may be under-reported as approximately 30% of samples were not tested for nalidixic acid and ciprofloxacin susceptibility.

CONCLUSIONS

In our study, anaemia, thrombocytopenia and complications such as shock and hepatitis appear to be common in culture-confirmed typhoid patients. Significant delay in seeking treatment may have contributed to ongoing transmission and increased fatality. There was a gradual increase over time in resistance to nalidixic acid and fluoroquinolones. Thorough antimicrobial drug resistance surveillance with whole genome sequencing of local isolates will provide accurate information on the current antimicrobial susceptibility pattern in Fiji.

43. Epidemiology of Typhoid Fever in the Northern Division, Fiji: 2014-2017

Aneley Getahun Strobel[1], Josese Limaono[2], Tevita S. Qoriniasi[2], Varanisese Rosa[3], Adam Jenney[4], Richard Strugnell[4], Kim Mulholland[3,5]

[1]Fiji National University, [2]Ministry of Health and Medical Services, [3]Murdoch Children's Research Institute, [4]University of Melbourne, [5]London School of Hygiene and Tropical Medicine

BACKGROUND

Fiji Island is an archipelago in the South Pacific consisting of over 300 islands. The Northern division (including the islands of Vanua Levu and Taveuni) reports the highest incidence and absolute number of typhoid fever cases compared to the main island (Viti Levu). This study aims to describe the epidemiology of typhoid fever in the Northern division from January 2014 to December 2017.

METHODS

We analysed all culture-confirmed typhoid fever cases which were reported as part of the routine laboratory based *Salmonella* surveillance from Labasa divisional hospital. Additional data was collected from typhoid case investigation reports provided by health inspectors. Overall and age specific incidence rates were computed using the 2017 population census.

RESULTS

A total of 437 confirmed typhoid cases were analysed. The average incidence rate was 81.2/100,000 population. Majority (96%) were ITaukei/indigenous Fijians and 54% were males. The highest average age specific incidence of 132.1 per 100,000 population was reported among young people between 20 and 24 years of age. A second peak in incidence (118/100,000 population) was observed among 45-49 years old individuals. Thereafter, incidence steadily declined and reached its lowest level of 27.1/ per 100,000 population in the age group 60 years and above. No seasonal or temporal trends were seen during the 4-year study period. Analysis of data by the location of residence indicated significant cluster and outbreaks following community gathering. Several outbreaks were attributed to foodborne transmission such as in Bua (2014-15) associated with end of the year feasts and in Cakaudrove (2017) linked to food served during funeral, birthday and health workers training.

CONCLUSIONS

Surveillance data showed a high burden of typhoid fever among young people and especially the ITaukei population. The findings of our study suggest foodborne transmission to a main mode of transmission and appropriate investigation of outbreaks in the community is warranted to identify, and treat, subclinical cases as well as carriers who could be implicated in foodborne transmission.

44. Investigation of the Role of Typhoid Toxin in the Pathogenesis of Typhoid Fever Using a Controlled Human Infection Model

Malick Gibani[1], Elizabeth Jones[1], Susana Camara[1], Jennifer Hill[1], Jorge Galan[2], Andrew Pollard[1]

[1]Oxford Vaccine Group, Department of Paediatrics, University of Oxford and the NIHR Oxford Biomedical Research Centre, [2]Department of Microbial Pathogenesis, Yale University School of Medicine

BACKGROUND

The typhoid-toxin is postulated to be a key virulence factor in the pathogenesis of acute typhoid fever and could be evaluated as a vaccine or therapeutic target. We studied the role of typhoid-toxin in disease pathogenesis using a typhoid controlled-human infection model.

METHODS

We conducted a randomised, double-blinded controlled human infection study in which 40 healthy volunteers were randomised (1:1) to oral challenge with 10e4 colony forming units (CFU) of either wild-type or an isogenic typhoid-toxin deficient variant of *Salmonella* Typhi Quailes strain prepared under GMP, to assess differences in clinical and microbiological features of infection. The primary composite endpoint was the rate of typhoid infection (attack rate), defined as *S.* Typhi bacteraemia and/or persistent fever ≥38°C for ≥12hrs.

RESULTS

Wild-type and isogenic typhoid-toxin deficient strains displayed comparable phenotypic properties in vitro, with the exception of typhoid-toxin activity assays. Using the primary diagnostic endpoint there was no significant difference in the rate of disease between participants challenged with wild-type or typhoid-toxin deficient *S.* Typhi (15/21[71%] vs. 15/19[79%]; relative risk 1.11;95%CI 0.8–1.6;p=0.58) and no significant difference in time to diagnosis from the day of challenge. The clinical syndrome was indistinguishable between wild-type and typhoid-toxin deficient groups when measured using a range of clinical and microbiological endpoints, including time of fever; fever clearance time and time to bacteraemia. The duration of bacteraemia was significantly longer in participants challenged with the typhoid-toxin deficient strain compared with wild-type (47.6 hrs[28.9-97.0] vs. 30.3[3.6-49.4];p=<0.001). No challenge related serious adverse events were observed. Five participants met the criteria for severe typhoid fever, of whom one participant was randomised to wild-type (1/15;7%) and four (4/15;27%) were randomised to the typhoid-toxin knock-out challenge. IFNɣ-ELISPOT responses to toxin sub-units CdtB, PltA and PltB were detectable at Day 28 post-challenge in participants challenged with wild-type but not toxin-negative *S.* Typhi.

CONCLUSIONS

Using a controlled human infection model, the absence of typhoid-toxin did not affect the likelihood of acute presentation of typhoid fever. The precise role of the typhoid-toxin in disease pathogenesis remains to be determined, but further clinical data may be required prior to the development of vaccines and therapeutics targeting this virulence factor.

45. *Salmonella* Typhimurium St313 Alters Its Riboflavin Metabolism to Escape Immune Recognition by Mucosal-Associated Invariant T Cells

Lorena Preciado-Llanes[1], Rocio Canals[2], Anna Aulicino[3], Ndaru Jambo[4], Jay C. D. Hinton[2], **Melita A. Gordon[4],** Mariolina Salio[5], Alison Simmons[3]

[1]University of Oxford, [2]Institute of Integrative Biology, University of Liverpool, [3]Medical Research Council (MRC) Human Immunology Unit, Weatherall Institute of Molecular Medicine, University of Oxford., [4]Malawi-Liverpool-Wellcome Trust Clinical Research Programme, University of Malawi College of Medicine

BACKGROUND

To date, the role of innate-like lymphocytes has been poorly addressed in the settings of *Salmonella* infections. Mucosal-associated invariant T (MAIT) cells represent the most abundant subset of innate-like lymphocytes. MAIT cells recognise metabolites from the bacterial riboflavin synthesis pathway and are important effector lymphocytes against bacterial infections. We endeavoured to study the ability of MAIT cells to respond to different *Salmonella* serovars, in particular the highly invasive and multi-drug resistant *S.* Typhimurium sequence type 313 (ST313).

METHODS

Blood mononuclear cells and gut mucosal cells were obtained from healthy volunteers, from *Salmonella* infected patients and from HIV+ patients. Cells were infected *ex-vivo* with a wide variety of *Salmonella* isolates. MAIT cells were assessed by flow cytometry for their capability to become activated and secrete cytokines. Transcriptomic and proteomic analysis were performed to disclosure changes on bacterial genes involved in the riboflavin pathway.

RESULTS

MAIT cells fail to become activated and produce cytokines when exposed to *Salmonella* isolates from the ST313 lineage II (such as D23580) but become activated by the ST313 lineage I, as well as by other Typhimurium and Typhoidal strains. Competitive experiments showed that ST313-D23580 was not blocking the surface receptor on MAIT cells, but was failing to produce the riboflavin intermediate metabolites that trigger MAIT cell activation. RNAseq and proteomics confirmed that the *ribB* gene involved in the riboflavin pathway, is overexpressed in the ST313-D23580 strain but not in the ST19-4/74 strain. In agreement, infection with a 4/74 *ribB* overexpressing construct resulted in lack of MAIT cell responses, replicating the phenotype observed with ST313-D23580. Our results were further validated in the field with samples from Malawi, confirming that this phenomenon occurs in *Salmonella* infected individuals and is independent of the HIV status.

CONCLUSIONS

Our study suggests that lack of MAIT activation may account for disease spread and severity among immunosuppressed individuals, in whom classical T cell responses are already impaired. Our findings represents the first example of a specific signature embedded into *Salmonella* ST313 lineage II isolates.

46. Typhoid Fever Cases in Children at the Tertiary Hospital in Indonesia: A 9-year Experience

Dominicus Husada, Dwiyanti Puspitasari, Leny Kartina, Parwati Basuki, Ismoedijanto Moedjito

Faculty of Medicine, Airlangga University and Dr. Soetomo Hospital

BACKGROUND

Typhoid fever remains a big problem in Indonesia, including in children. The trend in the modern world showed a lower incidence but this is not always the case in the developing world. Dr. Soetomo Hospital is the second largest in Indonesia with around 200 beds for pediatrics, and most were hospitalized because of infectious diseases. The hospital collected and analyzed the data from these patients continuously and routinely. The aim of the study was to report a hospital surveillance data of typhoid fever cases in children.

METHODS

This surveillance study was based on the hospital data from 2010 until 2018. Demography aspects such as name, sex, age (18 years or less), and address were recorded together with the main complaint, length of stay, the treatment, and discharge condition. Serology and microbiology data were also collected. This study used descriptive analysis.

RESULTS

There were 389 children for 9 year period who had typhoid fever as the main or additional final diagnosis. Most patients were from the early years and the incidence tend to become lower each year. Boys (52.2%) slightly outnumbered girls. Almost all of the children came from Surabaya area. The majority of patients were more than 2 years of age (86.1%); however, there were 54 patients with the age of 2 or less. All patients except one were discharged in good condition. One child died because of congenital heart disease. Most children were hospitalized more than 5 days (91.8%). Twenty-three patients had a double infection with dengue virus. All patients had serology data as the primary diagnostic method. The microbiological culture showed positive results from less than 10% and nearly all isolates were completely sensitive to chloramphenicol.

CONCLUSIONS

The incidence of typhoid fever tends to be lower, indicating the impact of modernized world. The majority of age remains above two years old, as known previously. The culture result was low, but almost all isolates were sensitive to chloramphenicol. The antibiotics policy should not be modified in the near future.

47. Outbreak Investigation of Extensive Drug Resistant Typhoid Fever Hyderabad, Pakistan – 2017

Mudassar Hussain, Santosh Kumar, Munza Qadri, Sandeep Kumar, Naveed Masood, Musa Raheem, Mirza Amir Baig
FELTP

BACKGROUND

On 9th January 2017, Directorate General Health Services, Sindh received a report of 14 confirmed cases of Extensive-Drug-Resistant Typhoid Fever (XDR-TF) from Hyderabad district. On the same day FELTP fellows were deputed to identify additional cases, determine risk factors and implement control measures.

METHODS

A case was defined as clinically suspected typhoid fever, positive on ELISA (IgM/IgG), confirmed on culture for *Salmonella enterica* serotype typhi; demonstrating resistance to first line drugs as well as fluoroquinalones and third generation cephalosporins on sensitivity testing, in a resident of District-Hyderabad between 10th November 2016 to 31st December 2017. Age and sex-matched matched case-control study was conducted. Active-case-finding was conducted in the community. Environmental assessment was done and water samples sent to Aga Khan University Hospital Lab for microbial analysis.

RESULTS

Out of total of 1,378 suspected cases, 629 (45.6%) were confirmed XDR-TF on blood culture, however only 438 (69.3%) consented and were enrolled. Median age was four years (range 1-55 years) and 60% were males. Overall attack rate was 2 per 10,000 population and the most affected age group was 2-4 years (AR 11/10,000). Taluka Qasimabad was most affected (AR=7.2/10,000) followed by Latifabad (AR=2.1/10,000). On multivariate analysis, history of prior antibiotics use (aOR 8.0; 95%CI 5.2-12.0), consumption of water from community filter plants (aOR 3.2; 95%CI=2.0-5.1), history of exposure to XDR-TF cases (aOR 2.8; 95%C-I 1.5-5.1), presence of dilapidated water lines (aOR 2.7; 95%CI 1.9-3.9), presence of open sewage lines outside the house (aOR 2.5; 95%CI 1.7-3.7), and consumption of municipal tap water (aOR 2.4; 95%CI 1.6-3.7) were associated with XDR-TF. Environmental assessment revealed filtration plants with unauthorized punctures, leaking pipelines and illegal vacuum suction. Of the 55 water samples from the filtration plants, handpumps and community taps, 12 were positive for Salmonella *typhi* DNA strands on PCR testing.

CONCLUSIONS

Injudicious use of antibiotics was the most probable cause of the outbreak. Sewage contamination of drinking water contributed to the spread. Prohibition of over-the-counter sales of antibiotics and chlorination with repair of the filtration plants & supply lines was proposed. As recommended a Typhoid vaccination campaign was carried out from August 2017.

48. Occurrence of Typhoid Fever Complications: Systematic Literature Review and Meta-Analysis

Ligia Maria Cruz Espinoza[1], Ellen McCreedy[2], Marianne Holm[1], **Justin Im[1],** Prerana Parajulee[1], Ondari D. Mogeni[1], Christopher M. Parry[3], Florian Marks[1]

[1]International Vaccine Institute, [2]School of Public Health, Brown University, [3]Clinical Sciences, Liverpool School of Tropical Medicine

BACKGROUND

Complications from typhoid fever disease have been estimated to occur in 10 to 15% of hospitalized patients with evidence of a higher risk when there is a delay in implementing effective antimicrobial treatment. The objective of the study was to estimate the prevalence of complications in hospitalized typhoid fever patients and the effect of disease duration at hospitalization on the prevalence of complications.

METHODS

A systematic review and meta-analysis of the prevalence of complications in hospitalized culture confirmed typhoid fever cases was performed using studies from the PubMed database. We rated risk of bias of relevant publications and conducted random-effects meta-analyses to estimate the prevalence of complications. Group analysis stratified by disease duration at hospital admission (< 10 *versus* ≥ 10 median/mean days of disease) was implemented. Differences in risk between groups were assessed using odds ratios and 95% confidence intervals. Heterogeneity and publication bias were evaluated with the I2 value and funnel plot analysis, respectively.

RESULTS

Publications meeting the selection and risk of bias criteria required for inclusion in this meta-analysis was limited to 12. The pooled prevalence of complications estimated among hospitalized typhoid fever patients was 25% (95% CI:20–29%, I^2 = 88.2%, p=0.000). The meta-analysis stratified by groups revealed a higher prevalence of complications among patients with an average of 10 or more days of disease at hospitalization (36%, 95% CI:29–43%, I^2 = 22.3%, p=0.257) than among cases arriving earlier (16%, 95% CI:13–18%, I^2 = 23.9%, p=0.268). The group of patients with longer disease progression showed three times higher risk of complications (OR= 3.00, 95%CI: 2.14–4.17, p<0.0001). Similar higher risks were observed in specific complications.

CONCLUSIONS

Good quality evidence concerning typhoid fever complications is limited. This meta-analysis identified a higher overall prevalence of complications than previously reported and a higher prevalence and risk among patients with long disease progression before hospitalization. These results should be interpreted with caution because of the limited number of publications included. In high-risk countries with limited access to healthcare and high prevalence of antimicrobial-resistance, vaccination should be considered part of a comprehensive prevention and control strategy.

49. Severe Typhoid in Maldives

Hisham Imad[1], Shifa Riza[2], Fathimath Reesha[3], Azna Ali[2], Moosa Muaz[4], Ibrahim Sujau[4], Ali Latheef[4]

[1]Thai Travel Clinic, Hospital for Tropical Diseases, [2]Indira Gandhi Memorial Hospital, Department of Surgery, [3]Indira Gandhi Memorial Hospital, Department of Microbiology, [4]Indhira Gandhi Memorial Hospital, Department of Medicine

BACKGROUND

Comprising a complex nomenclature, there are two major groups *Salmonella bongori* and *Salmonella enterica*. The *Salmonella enterica* subtype *enterica* is virulent and causes most infection in humans. It is an acquired infection through contaminated food and water. The manifestation of illness presents as an undifferentiated febrile illness, complicating the clinical course with the involvement of various systems, mainly the gastrointestinal system. With recent improvements in diagnostics and access to medical services, more cases are now being diagnosed and managed in the Maldives. However, we are still at the infancy of understanding complications of enteric fever with no such reported cases treated in the Maldives.

METHODS

On 21st December 2018, our subject was recruited following an informed written consent at Indira Gandhi Memorial Hospital located in Male', Maldives.

RESULTS

We present a case of enteric fever with complications in a 28 years old man from the Indian subcontinent, who traveled to the Maldives for employment a month prior to presentation with endotoxemia and peritonitis. Having no features of perforation at the time of admission or from the imaging, the subject was managed conservatively with antimicrobials. The hemoculture isolated *Salmonella enterica* spp. enterica sensitive to ceftriaxone. Despite the good clinical response to treatment a week into the hospital stay, our subject developed acute abdominal pain and was taken up for emergency laparotomy which revealed a single perforation at distal ileum, 5cm from ileocecal junction.

CONCLUSIONS

Although, to our knowledge this is the first case of enteric fever who developed complication while being hospitalized for treatment in Maldives, this unexpected clinical course of events may be present and unaccounted for the proportion of patients discharged early or managed as outpatient service. This case brings to attention the need for our clinicians to further understand complications of enteric fever and to be cautious in looking for complications such as perforations when treating enteric fever in both in-patients and out-patients.

50. Older Age Among Patients with Decreased Ciprofloxacin Susceptibility *Salmonella* Typhi Bloodstream Infection in the Democratic Republic of the Congo

Brecht Ingelbeen[1], Marie-France Phoba[2], Bieke Tack[3], Lisette M. Kalonji[2], Jan Jacobs[3], Octavie Lunguya[2], Marianne A.B. van der Sande[4]

[1]Institute of Tropical Medicine, [2]Department of Microbiology, National Institute for Biomedical Research, Kinshasa, [3]Department of Clinical Sciences, Institute of Tropical Medicine, Antwerp, [4]Department of Public Health, Institute of Tropical Medicine, Antwerp, Belgium

BACKGROUND

Salmonella Typhi is a key pathogen causing bloodstream infections (BSI) in DRC. Decreased ciprofloxacin susceptibility (DCS) was observed in DRC since 2007, and can complicate treatment. To inform treatment of typhoid fever and suspected BSI, we analysed DCS dynamics.

METHODS

Using BSI surveillance data from Kisantu (Kongo-Central province), systematically collected throughout 2008-17, we analysed distribution of age, sex, municipality of origin and antibiotic use among DCS *Salmonella* Typhi patients and used time-series analysis to assess trends in the number of DCS cases over time.

RESULTS

330 non-duplicate *Salmonella* Typhi cases were reported, in 101 (86%) of 117 months; median 2 cases/month (range 0-11). 85 (28%) tested *Salmonella* Typhi cases had DCS, reported in 54 (46%) months; median one case/month (range 0-8). The percentage DCS increased from 11% (2008) to 56% (2015), then decreased but again at 53% in 2017. Yearly seasonal variation was less outspoken for DCS than for susceptible cases. DCS infected patients were older than ciprofloxacin susceptible *Salmonella* Typhi patients ($p<0.01$): median 15 years (IQR 6-30) vs 11 years (IQR 5-19) respectively. We found no temporal or geographical outbreak linked to this age difference. DCS patients' median age decreased from 18 years (IQR 7-33) during 2008-12, to 13.5 years (IQR 6-29) during 2013-17, similar to the decrease among ciprofloxacin susceptible patients (12.5 to 9 years, $p=0.02$). Also among non-Typhi BSI patients, median age decreased from 2 (IQR 0-8) to 1 year (IQR 0-4; $p<0.01$). 47 (57%) DCS infected patients were male, not different from susceptible patients ($p=0.97$). Of 8 municipalities reporting >1 DCS case, in one the percentage DCS was significantly higher (72.5%, 29/40): an urban municipality where the hospital is based, reporting systematically more DCS since 2010. Antibiotic use prior to admission was reported among 45 (57%) DCS and 78 (40%) susceptible cases ($p=0.01$).

CONCLUSIONS

DCS *Salmonella* Typhi BSI were reported throughout the year during the ten years of surveillance, without distinguishable temporal epidemic patterns. The older age of patients with DCS *Salmonella* Typhi BSI and their geographical clustering close to one hospital throughout several years could suggest increased fluoroquinolone use with age, which needs to be explored further.

51. Impact Assessment of Typhoid Conjugate Vaccine During Mass Immunization Campaign in XDR Typhoid Outbreak Setting in Pakistan

Hina Iqbal, Farah Qamar, Tahir Yousafzai, Sultan Karim, Amber Kashif, Anayat Baig, Najeeb Rahman

Aga Khan University

BACKGROUND

Hyderabad (Pakistan) is facing the world largest outbreak of ceftriaxone resistant (XDR) *S. typhi*. More than 2000 cases of XDR Typhoid reported since November 2016. The outbreak predominantly affected two sub-districts in Hyderabad and 85% of the cases are children aged 10 years and below. The Aga Khan University in collaboration with ministry of health Sindh initiated mass immunization with typhoid conjugate vaccine (TCV) in January 2018. Here we report the impact of TCV against culture proven typhoid (irrespective of antimicrobial resistance) in target communities of Hyderabad, Pakistan.

METHODS

Immunization campaign with TCV was initiated in Latifabad and Qasimabad. Children aged 6 months to 10 years, were elegible to receive a single dose of 0.5ml IM injection of TCV. Suspected cases of typhoid with 3 or more days of fever, without any other focus of infection were identified from the sentinel hospitals and blood cultures were collected. Culture proven cases of typhoid also identified from laboratory network of AKU and Liaquat University of Health Sciences. Culture proven typhoid cases before and after vaccination campaign are compared. Vaccination status were ascertained through vaccination cards.

RESULTS

Total 86 cases of culture proven typhoid, aged ≤ 10 years were identified during November 30, 2016 to January 30, 2018. Out of which, (65/86 (75.5%) were XDR. During January to October 2018, the preliminary results shows, 79 cases aged ≤ 10 years, out of which 53/79 (67%) are XDR. Cases were enrolled from only 3 hospitals and lab network of AKU in Hyderabad before vaccination campaign. However, surveillance was enhanced after campaign increasing the hospitals from 3 to 10 including the laboratory network of LUMHS in Hyderabad. Data was obtained from 180 culture proven cases, 5/180(2.8%) and 310 test negative controls, 39/310(12.6%) were vaccinated with TCV. Crude measure of vaccine effectiveness against culture proven typhoid was 78% without adjustment for potential confounders and age.

CONCLUSIONS

The cases of culture proven typhoid has substantially decreased after the TCV campaign among children aged ≤ 10 years. Preliminary unadjusted results from a subset of cases and test negative controls showed that vaccine is 78% effective against culture proven typhoid.

52. Antagonistic and Probiotic Properties of Lactic Acid Bacteria Against *Salmonella* Typhimurium and *S.* Enteritidis

Reuben Rine[1], Shovon Sarkar[2], Pravas Roy[2], **Iqbal Jahid[2]**

[1]Department of Science Laboratory Technology, Nasarawa State Polytechnic, [2]Department of Microbiology, Jessore University of Science and Technology

BACKGROUND

Salmonella is one of the major causes of foodborne illnesses in humans worldwide with poultry as the primary source of outbreaks. The administration of Lactic Acid Bacteria (LAB) as probiotics has become a safe and promising alternative to antibiotics in *Salmonella* reduction in poultry. This study sought to select the most suitable LAB strains with anti-*Salmonella* activities as probiotics in poultry.

METHODS

LAB strains were isolated from the gastrointestinal tract of broilers and identified by API 50 CHL, 16S rRNA, and bacteriocin genes sequencing. The antagonistic activities of LAB isolates against *S.* Typhimurium and *S.* Enteritidis, characterization of inhibitory substances, co-aggregation and competitive exclusion of these pathogens were determined using standard techniques. Other probiotic properties including survival of LAB strains in stimulated gastric juice (pH of 2), tolerance to phenol, bile salts and NaCl, adhesion to ileum epithelial cells, auto-aggregation, hydrophobicity, and antibiotic susceptibility were also evaluated.

RESULTS

Out of the 58 LAB strains isolated, 15 showed antagonistic activities against *S.* Typhimurium and *S.* Enteritidis, as a result of organic acid production and bacteriocins. Only 6 LAB strains were able to survive in stimulated gastric juice, tolerate 0.4% phenol, 0.3% bile salt and 6.5% NaCl. The selected LAB were identified as *Lactobacillus paracasei ssp paracasei*, *Pediococcus pentosaceus*, *Lactobacillus plantarum*, *Lactococcus lactis ssp lactis*, and *Lactobacillus pentosus* showed significant (P<0.005) co-aggregation abilities with *S.* Typhimurium and *S.* Enteritidis ranging from 36.2 to 78.5%. The selected LAB strains significantly decreased (P<0.001) the capacity of *S.* Typhimurium and *S.* Enteritidis to adhere to and invade broiler intestinal epithelial cells. Furthermore, the antibiotic susceptibility test showed 100.00% resistance of the LAB strains to oxacillin, and 83.33% resistance to oxacillin, erythromycin, vancomycin, ciprofloxacin, streptomycin, and tetracycline with multiple antibiotic resistance indixes above 0.5. The antagonistic activity by *Pediococcus pentosaceus* and *Lactobacillus paracasei ssp paracasei* were majorly as a result of bacteriocin production

CONCLUSIONS

The isolated *Pediococcus pentosaceus* and *Lactobacillus paracasei ssp paracasei* might be promising probiotics candidates for the successful control of *Salmonella* in poultry, hence reducing human infections. Further research will be conducted in the field to evaluate the selected strains on poultry.

53. Accelerating Typhoid Conjugate Vaccine Introduction: What Can Be Learned From Prior New Vaccine Introduction Initiatives?

Leslie Jamka[1], Kenneth Simiyu[1], Adwoa Bentsi-Enchill[2], Aziza Mwisongo[3], Helen Matzger[2], Anthony Marfin[3], Andrew Pollard[4], Kathleen Neuzil[1]

[1]University of Maryland School of Medicine, [2]World Healt Organization, [3]PATH, [4]University of Oxford

BACKGROUND

Typhoid, a serious enteric fever caused by *Salmonella* Typhi (*S.* Typhi), disproportionately impacts children and marginalized populations in sub-Saharan Africa and Asia. The health consequences of typhoid, including the increase of drug-resistant strains, can stress health care systems. Vaccination can be one of the most cost-effective interventions for typhoid control, but accelerated vaccine introduction – the introduction of a new vaccine, through public health immunization delivery services into a national immunization program – is a complex process.

METHODS

The Typhoid Vaccine Acceleration Consortium employs an integrated, proactive approach to accelerate the introduction of a new typhoid conjugate vaccine in countries eligible for support from Gavi, the Vaccine Alliance. We built on prior successful vaccine introductions, coupled with typhoid- and typhoid vaccine-specific gaps and challenges, to develop an accelerated vaccine introduction strategy.

RESULTS

Each new vaccine introduction is unique and requires a strong human component to ensure the necessary relationships and data exchange between global, regional, and local entities. The status of vaccine availability varies and countries have different interests, readiness, willingness, capabilities, and capacities to support introduction. It is important to recognize the need to seek input and achieve buy-in from a broad range of global, regional, and local stakeholders.

CONCLUSIONS

The Typhoid Vaccine Acceleration Consortium is fortunate to have the legacy of prior successful vaccine introductions. While no approach can guarantee successful introduction, our broad schema includes a diverse array of tools and resources to facilitate introduction. A general framework identifying important components of vaccine introduction versus a step-by-step process has greater transferability to different scenarios. The framework of evidence to support typhoid conjugate vaccine introduction, global policy recommendations and financing, country willingness and readiness to introduce, local uptake and sustainability, and an adequate, stable supply of affordable vaccine highlights broad components of vaccine introduction used to navigate the intricate process of typhoid conjugate vaccine introduction. Understanding this complexity, level of detail, and uniqueness is critical to accelerating vaccine introduction.

54. Assessing the Burden of *S.* Typhi and iNTS Disease in African Children <5 Years of Age: Implications for Vaccine Formulations and Vaccination Programs

Hyonjin Jeon[1], Octavie Lunguya[2], Abdramane Soura Bassiahi[3], Ellis Owusu-Dabo[4], Raphael Rakotozandrindrainy[5], Abraham Aseffa[6], Iruka Okeke[7], Florian Marks[1]

[1]International Vaccine Institute, [2]Institut National de Recherche Biomédicale, [3]Institut Supérieur des Sciences de la Population, [4] Kwame Nkrumah University of Science and Technology, [5]University of Antananarivo, [6]Armauer Hanssen Research Institute, [7]University of Ibadan

BACKGROUND

A typhoid conjugate vaccine (TCV) was recently prequalified by the World Health Organization (WHO), who recommends its use in persons aged ≥6 months to 45 years residing in typhoid fever-endemic areas. We explore data from the Typhoid Fever Surveillance in Africa (TSAP), the Severe Typhoid Fever in Africa (SETA) programs and other typhoid surveillance efforts to investigate the burden in very young children to determine how TCVs can have the greatest impact in the most vulnerable populations in Africa.

METHODS

The Typhoid Fever Surveillance in Africa Program (TSAP, 2011-2014) in 10 sub-Saharan African countries included blood culture-based surveillance in febrile people presenting at healthcare-facilities originating from defined catchment areas; the follow-on program, the Severe Typhoid in Africa (SETA) program particularly focused on disease severity and mortality in the Democratic Republic of the Congo, Nigeria, Madagascar, Ethiopia, Ghana and Burkina Faso from 2015 to 2019. The typhoid fever/invasive non-typhoidal *Salmonella* (iNTS) disease incidences were estimated for 0-10 year-old children in yearly increments.

RESULTS

In both studies, *Salmonella* Typhi and iNTS were the most frequently isolated pathogens. TSAP identified 135 and 94 and SETA 213 and 269 cases, respectively. In TSAP, we excluded 12 and 4 isolates from Ethiopia, Sudan and Senegal due to absence of person-years of observation (PYO) data. After exclusion, 37/123 (30.1%) typhoid fever and 71/90 (78.9%) iNTS disease cases were found among children <5 years. No typhoid fever and 8/90 (8.9%) iNTS infections were observed in children aged <9 months. Typhoid fever incidences (/100,000 PYO) for children aged <1 year and 1-<2 years were 5 and 39, respectively; the highest incidence was 304/100,000 PYO in children 4-<5 years of age. For iNTS disease, the incidence in the same age groups ranged between 81 and 233/100,000 PYO; the highest incidence occurred in 1-<2 year-old children. Results from the SETA program will be incorporated and presented at the conference.

CONCLUSIONS

We observed a high burden of typhoid fever in both studies that merits TCV introductions. Considering the additional iNTS disease burden, a trivalent vaccine targeting *S.* Typhi, *S.* Typhimurium, and *S.* Enteritidis may be a future solution.

55. Serological Correlates of Protection Against *Salmonella* Typhi Following Vi-Vaccination

Celina Jin[1], Jennifer Hill[1], Bronwyn Gunn[2], Lindsay Dahora[3], Wen-Han Yu[2], Georgia Tomaras[3], Galit Alter[2], Andrew Pollard[1]

[1]Oxford Vaccine Group, Department of Paediatrics, University of Oxford, and NIHR Oxford Biomedical Research Centre, [2]Ragon Institute of MGH, MIT, and Harvard,, [3]Duke Human Vaccine Institute, Duke University Medical Center

BACKGROUND

In 2017, Vi-conjugate vaccines (TCVs) were recommended for use in children up to 15 years of age living in high burden typhoid fever regions by the World Health Organisation. TCVs have been shown to be immunogenic and efficacious in children and adults, however, a widely accepted correlate of protection, which could be used to expedite the development and licensure of new TCVs further assisting with disease control, has not been established. We applied a systems serology approach using samples obtained from Vi-vaccinated participants that underwent *Salmonella* Typhi challenge, to provide the first comprehensive characterisation of the serological response to Vi-vaccination, enabling the identification of Vi-specific correlates of protection.

METHODS

Serum samples were obtained from healthy typhoid-naïve adult volunteers enrolled in a randomised-controlled TCV human challenge efficacy trial. Samples included in this study were obtained from Vi-tetanus toxoid conjugate (Vi-TT n=37) or Vi-polysaccharide (Vi-PS n=35) vaccinees. A panel of >20 antibody features, which encompassed antibody quantification and characterisation of biophysical and functional properties, were evaluated prior to vaccination and on the day of *S.* Typhi challenge. Feature reduction and partial least squares discriminant analyses were performed to identify vaccine-specific humoral signatures and serological correlates of protection.

RESULTS

Vi-TT vaccinees had significantly higher anti-Vi antibody titres, avidity indices, functional responses and Fc-receptor binding than Vi-PS vaccinees one-month post-vaccination. Hierarchical clustering using the panel of Vi-specific antibody features described above, separated samples from Vi-TT and Vi-PS vaccinees. Preliminary multivariate analyses suggest that antibody-dependent neutrophil phagocytosis and IgA titre were associated with protection in both vaccine groups. Increased antibody-dependent cellular phagocytosis, IgG2 and IgG3 titres also reduced the risk of infection in Vi-PS vaccinees.

CONCLUSIONS

This in-depth evaluation of Vi-specific humoral responses is the first to demonstrate that Vi-TT and Vi-PS vaccines may mediate protection from typhoid fever through induction of neutrophil phagocytosis and IgA-mediated mechanisms. Further work is required to identify the primary antibody type responsible for driving neutrophil phagocytosis and to understand the mechanisms by which IgA antibodies mediate protection. Identification of a threshold of protection using either serological marker could accelerate the assessment and deployment of novel TCVs to regions requiring typhoid fever control.

56. VI-Specific Memory B Cells Are Detectable in Peripheral Blood Following Vi-Conjugate Vaccination

Celina Jin, Joshua Starr, Elizabeth Jones, Andrew Pollard

Oxford Vaccine Group, Department of Paediatrics, University of Oxford, and NIHR Oxford Biomedical Research Centre

BACKGROUND

The short duration of persistence of anti-Vi antibody titres following Vi-polysaccharide (Vi-PS) vaccination has resulted in the recommendation for revaccination every 2-3 years. This is a major shortcoming of Vi-PS vaccines and has contributed to the poor uptake of Vi-PS immunisation programmes in typhoid fever endemic regions. As Vi-conjugate vaccines (TCVs) induce T-dependent immune responses, anti-Vi antibody persistence, in theory, should be greater due to the induction of Vi-specific memory B cells and long-lived plasma cells from germinal centres. Identifying Vi-specific memory B cells following vaccination may allow us to predict the duration of antibody persistence, however, to-date no such studies have been performed in the context of TCV vaccination.

METHODS

Peripheral blood mononuclear cells (PBMCs) were isolated from healthy typhoid-naïve adult volunteers enrolled in a randomised-controlled phase IIb TCV human challenge efficacy trial. Samples included in this study were obtained from Vi-tetanus toxoid conjugate (Vi-TT n=36) or Vi-polysaccharide (Vi-PS n=34) vaccinees prior to vaccination, 10 and 28 days post-vaccination and one-month post-challenge. Thawed PBMCs were cultured for five-days with media supplemented with polyclonal mitogens. Vi-specific memory B cells were detected from cultured PBMCs using an enzyme-linked immunosorbent spot assay.

RESULTS

Following Vi-TT vaccination, a significant increase in the frequency of Vi-specific memory B cells was detected on day 10 (median 43.3 Vi-specific ASCs/10^6cultured PBMCs) when compared with pre-vaccination frequencies (3 ASCs/10^6cultured PBMCs), $p<0.0001$. Vi-specific memory B cells were identified in 23/36 (63.9%) Vi-TT vaccinees 10-days post-vaccination and 11/36 (30.6%) participants 28-days post-vaccination. One-month post-challenge, 10/36 (27.8%) Vi-TT vaccinees had detectable Vi-specific memory B cells. No significant changes in the frequencies of Vi-specific memory B cells were observed in Vi-PS vaccinees at the measured time points.

CONCLUSIONS

This is the first study to report the detection of Vi-specific memory B cells following vaccination with a TCV. These findings provide evidence that effective T-dependent germinal centres are induced by TCV vaccination. Evaluating potential correlations between post-vaccination Vi-specific memory B cell responses and anti-Vi antibody persistence and booster responses in children is needed and will assist with the evaluation of TCVs in the future.

57. Surveillance of Enteric Fever Among Febrile Hospitalizations in a Rural Teaching Hospital, Andhra Pradesh, India

Dasaratha Ramaiah Jinka, Raghu Prakash Nayakanti, Mohammad Jubair Katika, Somusekhara Sakivela

RDT Hospital

BACKGROUND

Typhoid remains endemic in developing countries like India especially in rural areas with inadequate water supply, poor hygiene and sanitation. Data on blood culture confirmed enteric fever, antibiotic susceptibility and cost of illness among febrile hospitalizations is limited for the rural population. Rural Development Trust hospital, part of a comprehensive development program, serve their main catchment: Anantapur district, one of India's 250most backward districts (2006). In this rain-shadow district that is heavily dependent on agriculture, 61.3% of the population have access to safe drinking water and 46.5% to sanitation facility (2015 NFHS4)

METHODS

Hospitalized cases with acute febrile illness or temperature > 380C were enrolled in the surveillance study if older than 6 months and consented. Blood culture, malaria and dengue serology, neutrophil and platelet count were routinely tested unless not required for a definitive diagnosis. Key clinical findings, treatment and direct out-of-pocket (OOP) expenditure was documented at discharge and at two subsequent follow ups at 2 and 4 weeks

RESULTS

Febrile hospitalizations were 10.92% (1166) of all admissions during the seven month study period. The study recruited 1035 cases and carried out blood cultures for 702 cases (67.83%). Proportion of S. Typhi and S. Paratyphi among blood cultures were 2.71% (19) and 0.14% (1), respectively. Enteric fever accounted for 11.55% of all positive cultures. Ciprofloxacin was not sensitive in 70% (14) while ampicillin, chloramphenicol, co-trimoxazole and ceftriaxone were sensitive for all cases. Patients were treated with ceftriaxone for 10 days on average, two patients were given azithromycin and one co-trimoxazole as well, simultaneously. Four cases had co-infections (amoebiasis, viral hepatitis A, two dengue cases) and one had acute kidney injury with circulatory failure while the others recovered with no complication. Although hospital rates are subsidised by about 80% and a median of 6 days of hospitalization (4-12 days), the average direct OOP expenditure was 3.21% of the family's annual income

CONCLUSIONS

Enteric fever accounts for 2.85% of all blood cultures among febrile hospitalizations and 70% of cases were not sensitive to ciprofloxacin. Treating an episode of enteric fever costs 3.2% of a family's annual income at a not-for-profit rural hospital in south India

58. Incidence of Typhoid in Chandigarh Estimated in a Hybrid Surveillance System

Jacob John

Christian Medical College, Vellore

BACKGROUND

The lack of recent, representative geographic data on disease burden in India has delayed consideration of typhoid vaccines for national immunization. We report incidence of hospitalized enteric fever from a population-referenced hybrid surveillance in a peri-urban setting in India.

METHODS

The Surveillance for Enteric Fever in India (SEFI) network established hybrid surveillance in six sites across India. Preliminary data from the peri-urban Chandigarh site is reported. All consenting patients hospitalized with acute febrile illness had age appropriate volumes of blood processed using a Bactec® system. The catchment area of the hospital was constructed from prior hospitalization data and its population determined from the most recent census. A healthcare utilization survey (HUS) was performed in 100 randomly selected clusters. The incidence estimates were adjusting for the proportion of acute febrile hospitalizations in the catchment that sought care at the study facility.

RESULTS

At the study hospital, over 223 days of surveillance, there were 1390 acute febrile hospitalizations, 600 belonged to the catchment area and 585 (97.5%) were recruited. 581 (99.3%) had a blood culture, with 76 (13.1%) culture confirmed enteric fevers (51 Typhoid, 25 Paratyphoid). Additionally, 12 patients (2.1%) had a clinical diagnosis of enteric fever that was not confirmed by culture. The population of the catchment area is 1,23,577. The HUS included 21978 persons from 5000 households in 100 clusters. In a one-year recall, 759 hospitalizations included 223 (29.4%) for acute febrile illness, with 85 (38.1%) admitted to the study hospital. The minimum incidence of hospitalized culture-confirmed enteric fever is 64.7 (95% CI 48.2-85.1) per 100,000-person years. Assuming that the 61.9% acute febrile hospitalizations at non-study facilities had a similar risk and that the risk was similar across the year, we estimate the incidence of culture-confirmed hospitalized typhoid fever at 169.54 per 100,000 person-years. These preliminary estimates will need to be refined accounting for potential sources of bias.

CONCLUSIONS

Chandigarh is one of the few planned cities in India and has good access to safe water and sanitation, but still has a high disease burden. The use of typhoid conjugate vaccines is likely to be beneficial to its population.

59. Operational Cost-TCV in a Door to Door Campaign: A Case Study From Hyderabad Pakistan

Amber Junejo, Farah Qamar, Tahir Yousafzai, Sultan Karim, Hina Memon, Anayat Baig

Aga Khan University

BACKGROUND

Hyderabad is suffering with XDR typhoid since November 2016. In January 2018 Aga Khan University in collaboration with health department of Sindh Pakistan has started emergency mass vaccination campaign against Typhoid with Typhoid conjugate vaccine. The campaign was door to door activity and has been happening for the first time in Pakistan.

METHODS

To estimate the cost of campaign we have analyzed the total cost incurred on the campaign, initially we did the micro-level costing of each component (Vaccine cost, Human resource, transportation, devices and stationary , cold chain maintenance, vaccination cost(syringes, dry cotton) training cost and health education), and combined all the total cost incurred which was in Pakistani rupees, converted it to dollar and conversion rate was taken as 106 as per the price of dollar at January 2018 kept as standard during the whole course of calculation. The total cost incurred is further divided by the number of vaccinations doses to find the average operational cost incurred on each dose of typhoid conjugate vaccine.

RESULTS

The results showing the average operational cost in campaign activity which is door to door is 2.48$ per dose and if we assume to get the vaccine at 2 $ the total cost of 1 vaccine dose comes out to be 4.48$. The operational cost can be decreased further to 1.26$ in a campaign if the speed is increased to 120 vaccination per team/day. Moreover the operational cost of additional 0.20$ would be required to immunize the child in routine immunization alongside measles 1 or measles 2.

CONCLUSIONS

The operational cost of vaccine is very minimal as the XDR typhoid cost is too high and also the opportunity cost and spread of infection of XDR typhoid cannot be eliminated from the calculations. Moreover the operational cost can also be decrease if the vaccination is speed up to double the operational cost comes to half. It's very safe to administer with measles vaccine and operational cost is minimum which is 0.20$/dose of Typhoid conjugate vaccine.

60. Influence of Invasive Nontyphoidal *Salmonella* Exposure on Haematological Parameters

Japhet Senyo Kamasah[1], Michael Owusu[1], Isaac Osei[1], Godfred Acheampong[1], Portia Boakye Okyere[1], Calman MacLennan[2], Florian Marks[3], Ellis Owusu-Dabo[4]

[1]Kumasi Centre for Collaborative Research In Tropical Medicine, [2]Jenner Institute, Nuffield Department of Medicine, [3]International Vaccine Institute, [4]Kwame Nkrumah University of Science and Technology, Department of Public Health

BACKGROUND

Bacteremia has been reported to cause abnormal haematological conditions in patients. These conditions are manifested in the form of cytopenia and are influenced by age, sex, state of the immune system as well as type of bacterial infection. The purpose of this study was to evaluate the variation of Full Blood Count (FBC) as a presumptive assessment for invasive nontyphoidal salmonella infection.

METHODS

A case-control study was conducted on patients in two hospitals in the Ashanti Region of Ghana (Komfo Anokye Teaching Hospital and Agogo Presbyterian Hospital). These patients were selected based on a previous cross-sectional study which recruited 1688 patients of which 8.12% (n=18) positivity rate for invasive nontypoidal *Salmonella* was recorded. All patients diagnosed with nontyphoidal *Salmonella* infection from May 2016 to October 2018 were recruited and their controls matched according to sex and age. Their full blood counts were performed using Sysmex Hematology analyzer

RESULTS

Out of the 18 cases, 50% (n=9) were males and 50% (n=9) were females. In the control group of 32 patients 43.8% (n=14) were males and 56.3% (n=18) were females. The median ages of cases and controls were 2 years (IQR = 1-14) and 5 years (IQR = 3-27) respectively. The neutrophil count among the cases was statistically significantly higher than in the control group (U = 110, p = 0.002). Blood count parameters that were significantly higher in the control group than the cases were eosinophils (U = 106.5, p = 0.014), haemoglobin (U = 60.5, p<0.001) and red blood cells (U = 45.5, p<0.001). No significant differences were observed between cases and controls for total white blood cell count (U = 224, p = 0.196), lymphocytes (U = 237, p= 0.829), basophils (U = 189, p= 0.747), monocytes (U = 177, p = 0.5) and platelets (U=260, p=0.983).

CONCLUSIONS

Neutrophilia, eosinopenia, low red blood cell count and low haemoglobin level are associated with invasive nontyphoidal *Salmonella* infection among the study population.

61. Water, Sanitation and Hygiene (WaSH) Related Practices in an Enteric Fever Endemic Urban Slum Area in India

Suman Kanungo[1], Pranab Chatterjee[1], Jayanta Saha[1], Jacob John[2], Gagandeep Kang[3], Shanta Dutta[1]

[1]ICMR National Institute of Cholera and Enteric Diseases, [2]Christian Medical College, Vellore, [3]Translational Health Science and Technology Institute

BACKGROUND

In the current evaluation, we assessed the WaSH practices in an urban slum in Kolkata, which is endemic for enteric fever, and experiences a high burden of enteric infectious diseases.

METHODS

This survey was conducted as a part of the baseline evaluation of a cohort of 6017 children who were recruited to study the incidence of enteric fever under the National Surveillance System for Enteric Fever in India (NSSEFI). A pre-tested questionnaire based survey was conducted on all households to assess the WaSH-related practices in the area.

RESULTS

Most families accessed potable water from shared piped connections (43%); similar trends were seen for water for other domestic uses (shared pipe: 46%). Most commonly, the women (65%) in the families fetched water, spending a median of 10 minutes to walk to the source (IQR0-20). Most families did not process the water before drinking (88%). Sanitary toilets with piper sewer system (50%) or septic tanks (48%) were most common. Most toilets were shared (80%), with each toilet being shared by a median of 6 households (IQR3-10); 13% of the households accessed toilets which were used by the general public. Most children were reported to use toilets (73%); disposal in drains (8%) or garbage dumps (7%) was common. 45% of the children consumed street food at least once a week; 50% had breakfast outside; 57% had ice-creams from street vendors at least once a week. Eating uncooked food was common (37%) with high self-reported levels of washing (94%) and peeling (75%). In univariate binary logistic regression, family type ($p=0.01$), number of people in family ($p=0.01$), number of rooms ($p<0.01$), presence of separate kitchen ($p=0.03$), cooking indoors ($p=0.02$), source of water for domestic use (0.01), presence of toilet facility ($p=0.01$), sharing toilets ($p=0.01$), toilet open to public use ($p=0.01$), disposal of children's stool ($p=0.04$) were significantly associated with confirmed typhoid fever.

CONCLUSIONS

Despite high access to WaSH, and knowledge regarding the need to maintain food hygiene, the study area experiences a high burden of enteric fever. This indicates the need for further studies on factors affecting disease transmission, practice adherence and understanding other environmental transmission pathways.

62. Incorporating a Dose-Response Relationship Into Models of Typhoid Fever Transmission

Yu-Han Kao[1], Marina Antillón[2], Andrew Pollard[3], Virginia Pitzer[1]

[1]Department of Epidemiology of Microbial Diseases, Yale School of Public Health, [2]Swiss Tropical and Public Health Institute, [3]Oxford Vaccine Group, Department of Pediatrics, University of Oxford

BACKGROUND

The age distribution of typhoid cases varies across settings with different levels of (unadjusted) incidence. Previous transmission models have estimated different reporting fractions for different settings. Accounting for the association between the incidence of typhoid fever and the probability of symptomatic infection may better explain the variation of age-specific incidence due to transmission intensity, and provide more accurate estimates for the impact of typhoid vaccination.

METHODS

We incorporated a dose-response function in a previously developed transmission model in order to explicitly model the relationship between the force of infection and the probability of symptomatic disease. The model was fitted to published population-based incidence data from studies conducted in South Asia and Sub-Saharan Africa with different levels of typhoid incidence. The model was then used to evaluate the potential impact of typhoid conjugate vaccine strategies in each setting.

RESULTS

Under this revised model structure, we were able to better explain the distribution of age-specific incidence across different magnitudes of typhoid transmission intensity. By reducing the force of infection and thus also the probability of symptomatic disease, vaccination was predicted to lead to a larger and more sustained decline in typhoid fever incidence compared to previous models.

CONCLUSIONS

The inclusion of a simple dose-response function in a mathematical model of typhoid transmission is able to reproduce the distribution of typhoid cases in different transmission settings. This has important implications for model predictions for the impact of vaccination. More importantly, the simplicity and generalizability of the model provides a powerful and easy-to-use tool for decision makers to evaluate control strategies against typhoid fever across different incidence settings.

63. Antibiotics in the Treatment of Typhoid Fever: Are We Running Out of Options?

Arti Kapil, Sushila Dahiya, Priyanka Sharma, Rakesh Lodha, Sushil Kabra

All India Institute of Medical Sciences

BACKGROUND

With emerging antimicrobial resistance treatment of typhoid fever remains a challenge. Present study was undertaken to determine current practices of antibiotic use in children attending a tertiary care hospital of North India.

METHODS

This was an observational study, including children meeting case definition of Typhoid fever and giving consent. Antibiotic treatment was based on the protocols of the treating unit. Blood cultures positive isolates were identified by standard methods and antimicrobial susceptibility done by CLSI guidelines. Antibiotic use was measured as days of therapy (DoT) standardized to 1000 patient days

RESULTS

Among the 30 hospitalized patients, 18 were found to be culture (S Typhi in 13 and S Paratyphi A in 5), while in 7 Typhi point IgM was positive and 5 were diagnosed clinically. Prior antibiotic history was available in 5 patients of which 2 had cefixime and 1 each ciprofloxacin, azithromycin and ceftriaxone without clinical response. Only the clinically diagnosed severe typhoid cases were hospitalized.
The duration of hospital stay ranged from 2-35 days (ALOS – 10 days) Of these 28 patients were treated with ceftriaxone. The mean duration of defervescence of fever was 6.4 days (SD$\pm$3.9) and mean duration of treatment with ceftriaxone was 7 days (range 2 to 14 days). We found that DoT for ceftriaxone was 845/1000 patient days as compared to ofloxacin and azithromycin, being 198 and 90 /1000 patient days. On discharge, no antibiotics were prescribed in 22 patients, while 6 were discharged on cefixime, 1 each on ciprofloxacin and azithromycin There was an addition of another antibiotic besides ceftriaxone (ofloxacin or azithromycin) sequentially in 6 patients and 3 antibiotics in 1 patient due to clinical non response or worsening clinical condition.

CONCLUSIONS

We found that *S.* Typhi continues to be a major etiological agent of enteric fever remaing 100% susceptible to ceftraixone and 10% to ciprofloxacin. The MDR phenotypes have declined to about 10% but ceftriaxone remains the empirical choice of antibiotic. However, 10% patients needed a second antibiotic and 2% needed a third antibiotic, based on clinical parameters. The rationale to use of combination therapy requires more clinical studies.

64. Evaluation of Molecular Methods for Detection of *S.* Typhi and *S.* Paratyphi A in Environmental Samples

Renuka Kapoor[1], Shanta Dutta[2], Ashutosh Wadhwa[3], Yuka Wang[1], Goutam Chowdhury[2], Asish Mukhopadhyay[2], Christine Moe[1]

[1]Emory University, [2]National Institute of Cholera and Enteric Diseases, [3] Centers for Disease Control and Pervention

BACKGROUND

Enteric fever is a serious systemic infection caused by *Salmonella* Typhi (ST) and *Salmonella* Paratyphi A (SPA), and acquired via fecal-contaminated food and water. Quantitative microbial risk assessment (QMRA) requires quantitative estimates of exposure to the pathogens of interest. Here we present results from methods studies to quantitatively detect ST and SPA in environmental samples representative of different pathways of transmission of enteric fever. These methods will be used in a large exposure assessment study in Kolkata, India.

METHODS

Ten-fold serial dilutions of ST and SPA cultures were seeded into samples of surface water, soil, raw produce (tomatoes, cucumber), and street food. The samples were concentrated by membrane filtration, and total DNA was extracted using Qiagen DNeasy PowerWater kit. Samples were tested by quantitative real-time PCR (qPCR) using a Taqman-based platform and primers described by Nga *et al*. (2010). Standard curves generated from plasmid DNA containing the target genes were used to determine the limit of detection for ST and SPA.

RESULTS

ST and SPA were detected in all seeded samples: ST Ct values= 12- 35 and SPA Ct values=14-35. ST recovery was reduced by 1- to 2-$\log_{10}$ in surface water, soil, and cucumbers, and by 2- to 3-$\log_{10}$ in tomatoes and street food for the different seeding concentrations. SPA recovery was reduced by 1- to 2- $\log_{10}$ in surface water, 1- to 3- $\log_{10}$ in soil, and cucumber, 2- to 3- $\log_{10}$ in tomatoes, and 3-$\log_{10}$ in street food for the different levels of seeding. Sequencing of the amplified product from seeded soil samples confirmed the ID of the recovered target pathogens. Extrapolated data using standard curves, suggested that for most of the sample types the range of detection was 10^3 to 10^9 genomic copies. Methods for surface swabs are in development.

CONCLUSIONS

These methods provide quantitative estimates of the target pathogens in relevant food and environmental samples and could be used to inform "dose" estimates in QMRA analyses. Next steps include testing environmental samples in Kolkata, and optimizing protocols to improve the limit of detection of the target pathogens in environmental samples.

65. Optimization of Methods to Detect *S.* Typhi and *S.* Paratyphi A in Sewage

Renuka Kapoor[1], Shanta Dutta[2], Ashutosh Wadhwa[3], Pengbo Liu[1], Yuke Wang[1], Suman Kanungo[2], Christine Moe[1]

[1]Emory University, [2]National Institute of Cholera and Enteric Diseases, [3]Centers for Disease Control and Pervention

BACKGROUND

Enteric fever is a serious systemic infection caused by *Salmonella* Typhi (ST) and *Salmonella* Paratyphi A (SPA) that is transmitted by fecal-contaminated food and water. Detection of ST and SPA in sewage or wastewater can be used to complement clinical surveillance for enteric fever. We describe methods to detect ST and SPA in sewage by quantitative real-time PCR (qPCR) using different sample volumes and sample processing protocols. We evaluated sample concentration and DNA extraction methods in order to optimize the limit of detection of ST and SPA in sewage by qPCR.

METHODS

50 mL to 100 L of sewage were seeded with various levels of ST and SPA ranging from 10^0 to 10^{10} cells. Four different concentration protocols were evaluated: membrane filtration (50-100 mL); polyethylene glycol (PEG) precipitation (500 mL); ultrafiltration (5 – 100L) followed by PEG precipitation; and Moore swabs (2L) followed by culturing in Universal Pre-enrichment broth and membrane filtration. After concentration, total DNA was extracted using Qiagen DNeasy PowerWater kit. Samples were tested using a Taqman-based quantitative real-time PCR (qPCR) platform and primers described by Nga *et al.* (2010). Standard curves generated from plasmid DNA containing the target genes were used to determine the limit of detection.

RESULTS

The range of detection for both ST and SPA was 10^3 to 10^9 genome equivalents. PEG precipitation was more effective than membrane filtration, as indicated by an average 6 Ct difference between the two methods. Positive Ct values (22-30) were obtained on 5- 100L samples concentrated by ultrafiltration. Moore swabs were able to detect 102 ST cells in 2 L.

CONCLUSIONS

The present study validates sample processing and DNA extraction protocols for detection of $\geq 10^3$ cells of ST and SPA in seeded sewage samples. Ultrafiltration followed by PEG precipitation can be used to quantify ST and SPA in large volume sewage samples for environmental surveillance of enteric fever. Moore swabs used with enrichment broth is a sensitive method to detect presence/absence of ST and SPA in sewage.

66. Cost of Inpatient Treatment of XDR Typhoid in Pakistan

Sultan Karim, Farah Qamar, Tahir Yousafzai, Hina Memon, Amber Kashif, Anayat Baig

Aga Khan University

BACKGROUND

Pakistan is facing the largest outbreak of extensive drug resistance XDR stain of s. typhi, this isolate is only sensitive to Azithromycin and Meropeneum making treatment options limited and expensive. Our aim was to estimate direct out of pocket health care expenditure on XDR typhoid.

METHODS

The data was collected retrospectively from Aga khan maternal and child health (AKMCC) Hyderabad November 2016-August 2018. The children who were aged 6 months to 15 years and admitted for minimum of 24 hours, less than 24 hours children and aged >15 are excluded. The data is collected from billing department of AKMCC upon the consent of the family of the child, those who refused for the consent are also excluded from the study. So the total number of children whose data was obtained from the department N=84.

RESULTS

The Mean cost of hospitalization excluding opportunity cost and all indirect costs incurred during the treatment of ceftriaxone resistant S.typhi is PKR39086.16, SD PKR26361.88233 while Mean hospitalization was 4.14 days with SD 2.52 days. The median cost incurred was PKR 34071, median hospitalization is 4. Minimum PKR 7890 and 1, while maximum value was PKR 154,052 and 15 for cost and no of days of hospitalization respectively. The average daily cost of medication with IV Meropenum is 6000 PKR and with Azithromycin Oral is 500 PKR.

CONCLUSIONS

Data from the private hospital shows there is marked increase in cost of treatment and number of days of hospitalization, eventually family becoming prey of catastrophic expenditure. If the outbreak further spreads to the country it further stretch the inflation as resources for treatment are scarce, only two antibiotics can treat. The oppurtunity cost of increasing XDR is way higher than what we assume and what we could calculate.

67. Typhoid Has Turned Catastrophic for the People of Sindh Pakistan

Sultan Karim, Tahir Yousafzai, Hina Mirza, Hina Iqbal, Najeeb Rehman, Farah Qamar

Aga Khan University

BACKGROUND

Resistance to antibiotics is very known phenomena, S.typhi has been prominent in development of resistance against different antibiotics resulting in narrowing of options of treatment causing inflation. This in result exerts the pressure on poor community in terms of financial loss and sometime

loss of human life. Since 2016, resistance to ceftriaxone has narrowed the treatment options to carbapenum and macrolide antibiotics and the cost has almost doubled in XDR typhoid compared to Sensitive s.typhi cases.

METHODS

Data was collected from patients who were admitted to hospital with c/s confirmed salmonella S.typhi enrolled in Surveillance of enteric in Asia project SEAP Pakistan from September 2016 to July 2018 in Government and private hospitals (JPMC and NICH), (KGH and AKU) respectively . Jinnah Post graduate medical college hospital JPMC is largest government sector hospital in Karachi, National Institute of child health NICH is children hospital at government sector. Kharadar General Hospital KGH is charity base hospital in under privileged population of kharadar Liyari. Aga Khan University Hospital AKU is largest private sector hospital of Karachi.

RESULTS

The direct mean cost of treatment, the mean age and mean no of days admitted, gender distribution at JPMC, NICH, KGH and AKU is (194,125,173, and 708$), The mean age (26.8, 7.2,16 and 19.3) years, hospital stay (15.7, 12.4, 6.4, and 4.9) days, and (89.6 &10.4, 63&37, 58&42, 59&41 males and females) respectively. The results showing highest mean expenditure in dollars and least no of days of hospitalization at AKU while JPMC the no of hospitalization is highest and least out of pocket expenditure in dollars.

CONCLUSIONS

43% of Sindh population living at less than 2$/day in such scenario 125$ spending on a single disease is catastrophic to the family, in Karachi this is 10% of the population. On the other hand in Pakistan people go into poverty due to expenditure in health is 32%.This showing that the social indicators are very weak in Pakistan although some places the economic indicators appears healthy. This can easily be prevented with 4.48$ intervention on a single dose of Typhoid conjugate vaccine for the children of aged <10 years of Pakistan.

68. A Systematic Review of Enteric Fever Outbreak Literature Among Asian and African Countries From 1965 to 2018

Asif Khaliq[1], Salman Haq[2], Tahir Yousafzai[1], Momin Kazi[1], Farah Naz Qamar[1]

[1]Aga Khan University Hospital, [2]Ziauddin University

BACKGROUND

Enteric fever is a highly endemic but a neglected disease among the Asian and African countries. Lack of sanitation, unsafe drinking water, rapid urbanization and changing pattern in the resistance pattern of antimicrobial agents made this disease very dangerous. In Pakistan, there is an extensive drug-resistance (XDR) typhoid outbreak that led us to review the studies on enteric fever outbreaks to identify the changing pattern in case definitions, diagnostic criteria, antimicrobial resistance and methods used for outbreaks control in different regions of Asia and Africa over last 5 decades.

METHODS

Studies regarding enteric fever outbreaks events that occurred either in Asian or African countries from 1965 to 2018was searched by using PubMed and Google Scholar. Studies that represent single outbreak event and have described either the epidemiological features, screening or laboratory confirmatory test, antibiotics resistance/ susceptibility pattern, therapeutic outcomes, disease transmission, and prevention strategies were reviewed. A total of 4414 articles were extracted out of which 79 studies were selected for final review.

RESULTS

There were more than 75% Asian studies .43% studies showed enteric fever outbreak event from 1995-2018. The drug resistance pattern was described by32% studies, while the outcomes like hospitalization and mortality were reported by 27% and 25% studies respectively. Fever is the hallmark clinical symptom and was present in 92% studies. Other symptoms like diarrhea, abdominal pain, and Nausea & vomiting were presented by more than 50% studies. Blood and stool culture were major laboratory confirmatory test depicted by77% and 52% studies respectively. Contaminated water, food, carrier, and inappropriate sanitation were the 4 different identified sources of transmission. And health education, mass immunization, water chlorination, and legislation etc. were major preventive measures that were either proposed or implemented.

CONCLUSIONS

Different factors are involved in disease transmission. The case-definition, clinical detection method and laboratory test for enteric fever diagnosis is not standardized. Thus, this review highlights the need to develop a syndromic case-definition of enteric fever for both adult and pediatric population and guidelines for the proper management and prevention of disease outbreaks

69. Drug Resistance Pattern of *Salmonella* Typhi and *Salmonella* Paratyphi Among Hospitalized Patients of Aga Khan University Hospital, Karachi, Pakistan

Asif Khaliq, Muhammad Hadi Usmani, Tahir Yousafzai, Sonia Qureshi, Farah Naz Qamar, Zulfiqar Bhutta

Aga Khan University Hospital

BACKGROUND

Enteric fever is a major public health concern especially for the Asian countries, where it accounts for more than 90% deaths. The antimicrobial susceptibility profile for the organism causing enteric fever has been dramatically changed. The increased antimicrobial resistance to Salmonella Typhi and Salmonella Paratyphi has hampered the effective treatment; thereby it posed a serious treatment challenge. Therefore we aim was to review the trends of antimicrobial susceptibility pattern in patients with culture-proven enteric fever cases.

METHODS

A retrospective study was carried out among all lab confirmed culture proven enteric fever in-patients admitted at Aga Khan University Hospital(AKUH) from 2007-2017 irrespective of age, gender, and level of care, while all the suspected cases, non-typhoidal salmonella positive cases, and of ambulatory care patient data were excluded.

RESULTS

A total of 6350 patients were hospitalized with a complaint of Enteric fever from 2007 to 2017, of which 914(14.4%) had a laboratory-confirmed enteric fever. Among enteric fever confirmed cases, 694(76%) had Typhoid and 220(24%) were of paratyphoid. The multidrug-resistant (MDR) cases of Salmonella Typhi and Paratyphi in 2007were 61.5% and 8.6% that increased to 71.4% and 52.6% respectively. The resistance of both organisms for fluoroquinolones was high i.e., 84.3% for Salmonella Typhi and 80% Salmonella Paratyphi. Since 2012, the fluoroquinolone-resistance to Salmonella Typhi and Paratyphi amplify to 98.6% and 100%. Till 2016, both organisms were 100% sensitive to Cephalosporin. But by 2017, 25.7% extensive drug-resistant (XDR) cases were reported for Salmonella Typhi.

CONCLUSIONS

An increasing number of antimicrobial-resistant cases was reported from 2007 to 2017 for both organisms. This increased in antimicrobial resistance to the drugs depicts a serious threat especially for treating Typhoid fever because of sudden XDR cases. Thus, this study suggests the need for Typhoid vaccination and for an integrated approach for the prevention of enteric fever

70. Use of Geo Spatial Technique to Identify Catchment Area of Patient With Typhoid Dever – A Hybrid Utilization Technique

Abdul Momin Kazi, **Ayub Khan**, Tahir Yousufzai, Sultan Karim, Farah Qamar

Aga Khan University

BACKGROUND

Typhoid fever is a systemic infection caused by subspecies of Salmonella enterica The disease remains a health problem in developing countries like Pakistan. In this study, a geospatial technique is being used to identify the catchment area of patients with typhoid fever, using a hybrid surveillance technique. This involves data collection via smartphones which have an installed GPS system which is cross-referenced to geographic information system (GIS) maps.

METHODS

Patients who came to the AKUH OPD with a fever of 3 days or more, with a positive blood culture were assessed and heat maps were generated which showed that approximately 60% of the cases lied in 3 catchment areas: Gulshan-e-Iqbal, Jamshed town, and Gulberg. Using the hybrid surveillance method, each catchment area was divided into clusters/ rectangles, which covered an area of 56.8 by 61.2 meters. 120 clusters were randomly selected and a sample size of 5000 was reached. Data collectors were given smartphones which had incorporated digitalized maps with individual clusters and their central point (landmark) and SAEP data entry program. The staff selects a cluster, navigates to its central point and then proceeds according to protocol. The collected data is projected as visual maps and evaluated daily

RESULTS

It was found that using smartphones incorporated with GIS maps and SAEP data entry program can be an accurate and reliable way for data collection; which covers a large sample size in remote areas and allows rapid assessment of data.

CONCLUSIONS

The study shows that employment of geospatial techniques along with hybrid surveillance method can be an efficient and convenient technique which enables investigators to carry out a far-reaching survey in a short and cost-effective way.

71. Baseline Widal Titer Among Healthy Adult Males From the Greater Mymensingh Division of Bangladesh

Md Arifuzzaman Khan[1], Fahim Ashher[2], Muhammad Akram Hossain[3]

[1]The University of Queensland and Public Health Unit, [2]icddr,b, [3]NIPSOM

BACKGROUND

Widal test is the most widely used laboratory investigation for diagnosis of typhoid. However, the test interpretation remains controversial in the context of endemic regions such as Bangladesh, as agglutination occurs at varied titrations among a large percentage of healthy population. Paired Widal tests are often not feasible; hence single unpaired test has to be used for screening, diagnosis and treatment.

We aimed to assess the normal range of baseline titre for Anti TO, TH, AO, AH, BO agglutinins among healthy population in an endemic country with a view to guide the researchers and the clinicians, facilitating further investigation on updating cut off points of single Widal test for screening and diagnosis of typhoid fever in the context of Bangladesh.

METHODS

A cross-sectional study was carried out in Mymensingh Medical College, Bangladesh among 2925 male immigration applicants. A single blood sample was collected for Widal test and interpreted using standard guidelines.

RESULTS

The highest baseline titer for Anti TO, TH, AO, AH, BO agglutinins among 95% of the healthy participants was found to be 1:80 for each respectively. A titre of 1: 40 was observed for BH antigen.

CONCLUSIONS

In case of singular Widal test, baseline values for the normal range was found to be 1:20 - 1:80 for all the antigens (TO, TH, AO, AH, BO, BH), except BH, for which it was 1:20-1:40. Further studies, inclusive of other sociodemographic groups and positive controls are required to determine the updated cut off values.

72. Immune Response to a Typhoid Conjugate Vaccine: Preliminary Immunogenicity Data From a Cluster-Randomised Controlled Trial of Children in Bangladesh

Farhana Khanam[1], Katherine Theiss-Nyland[2], Xinxue Liu[2], Andrew Pollard[2], Firdausi Qadri[1], John Clemens[1], TyVAC Team[1]

[1]icddr,b, [2]Oxford Vaccine Group, Department of Paediatrics, University of Oxford

BACKGROUND

Typhoid fever remains a major public health concern in Bangladesh. In a geographically defined catchment area of Dhaka, Bangladesh, a large scale, double-blind cluster randomised controlled trial of Vi-TCV is being conducted, using a live Japanese encephalitis (JE) vaccine as the control. The study consists of over 40,000 children, in 150 clusters, randomised to receive either JE or Vi-TCV, and followed over two years, to assess the effectiveness of Vi-TCV immunisation at preventing typhoid infections in an endemic setting. Twenty-five vaccination sites were used to enrol and vaccinate children into the study. As part of this study, a subset of children was enrolled in an immunogenicity sub-study to assess the immune response to vaccination.

METHODS

Six vaccination sites, covering 34 clusters, were selected to take part in the immunogenicity sub-study based on the site capacity to collect and manage blood samples. A subset of 18 clusters were randomly selectedon a 2:1 basis (Vi-TCV vs JE) from the 6 sites. The selection of participants for the sub-study was age-stratified (< 5 years vs ≥ 5 years of age with an allocation ratio of 1:1). Children who consented to participate in the immunogenicity sub-study provided blood samples at day 0 before vaccination, and at day 28 following vaccination. Later samples will be collected at 18 months, and at 2 years, at the completion of the trial follow-up period. The day 0 and day 28 sample analysis is presented here.

RESULTS

We enrolled 1514 children into the immunogenicity sub-study, among whom 1433 attended the 28-day visit. The unblinded immunogenicity results from day 0 and day 28 will be presented. This will consist of a comparison of assay of anti-Vi IgG antibodies in plasma samples, stratified by age groups, between those participants who received Vi-TCV as compared with those participants who received JE vaccine.

CONCLUSIONS

While there is no agreed serological threshold of protection following vaccination against typhoid, analysing the anti-Vi IgG antibodies of children provides evidence of immune responses against Vi-TCV that may later be useful in predicting population protection.

73. The Strategic Typhoid Alliance Across Africa and Asia (STRATAA): The Burden of Enteric Fever in Mirpur, Dhaka

Firdausi Qadri**, Farhana Khanam**, K. Zaman, John Clemens, STRATAA Consortium

icddr,b

BACKGROUND

Enteric fever causes over 21 million cases of febrile illness and 200,000 deaths annually worldwide. Current burden of enteric fever is mainly in South and South East Asia. Rate of multidrug resistant (MDR) infections is also increasing. Currently available data on enteric fever in Bangladesh are limited. As part of STRATAA consortium, multicomponent study was designed to characterize burden and transmission of enteric fever and to generate evidence for implementation of typhoid vaccine in Bangladesh.

METHODS

Following baseline census a passive surveillance for typhoid was implemented. Blood and stool specimens were collected from febrile patients for culture and antibiotic sensitivity. An age-stratified cohort of over 8,000 individuals was randomly selected for serological surveillance and blood was collected to measure Vi-antibodies to identify suspected chronic typhoid carriers. Over 700 households were randomly selected for two healthcare utilization surveys (HUS) to assess healthcare seeking behaviour for prolonged fever.

RESULTS

Baseline census was conducted in the study area and 110,731 individuals were enumerated. Among census population 50% were female and 9% were children of <5 years of age. In passive surveillance 4675 patients were enrolled; among them 322, 84, and 1 patient had *S.* Typhi, *S.* Paratyphi A, and *S.* Paratyphi B infection respectively. Incidence rate of *S.* Typhi infection was 220,000 person years of follow-up.
MDR was observed in 34%, nalidixic acid resistance in 96%, ciprofloxacin resistance in 1% and azithromycin resistance in 12% of *S.* Typhi, *S.* Paratyphi A, and *S.* Paratyphi B isolates. Reduced susceptibility to ciprofloxacin and azithromycin was seen in 97% and 9% of the isolated strains, respectively.

Among 204 serosurvey participants with high Vi, followed-up with stool cultures chronic carriage was confirmed in one participant, for a population prevalence of only .01%.
Preferred first line source of care for persistent fever, most respondents indicated 'self-treated with traditional medicine' or "pharmacy" in HUS.

CONCLUSIONS

High disease burden and MDR typhoid fever in this population argue for introduction of typhoid conjugate vaccine in efforts to control this disease. Data from this study will be used to parameterize dynamic, population-based disease transmission models to predict optimal use of the vaccine in the community.

74. Catalyzing Uptake of Typhoid Conjugate Vaccine: An Assessment of the Optional Vaccine Market and Distribution Channels in Myanmar

Nikhil Khicha

IQVIA

BACKGROUND

In 2018, IQVIA conducted a vaccine market assessment in Myanmar in order to identify priority manufacturer investments, trends in adoption and sales, and trace vaccine journeys in the country. The assessment included retrospective analysis from 2013 to present, and a forecast to 2023. Both scheduled and optional vaccines, including the Typhoid conjugate vaccine (TCV) were considered. Our assessment yielded insights into the adoption and sales patterns for optional vaccines.

Our presentation will provide a high-level summary of the study and its key findings. We will conclude with specific recommendations to increase uptake of optional vaccines in the Myanmar market, including TCV.

METHODS

Primary data was collected using expert interviews with experts, doctors, and consumers. Secondary research drew from existing demographic information, scientific literature, and IQVIA's sales and prescription database.

RESULTS

Our assessment generated significant insights vis-à-vis: 1) optional vaccine market growth potential; 2) vaccine awareness; 3) distribution channels. In the private market, the nascent healthcare infrastructure means that private reimbursement options are limited, and payments are mostly out of pocket. Optional vaccines, including typhoid, comprise the largest share of the private vaccine market. These are administered at private hospitals and clinics, which grew by 5.7% between 2013 and 2017. Growing income combined with an increase in the number of private facilities will lead to increased vaccine affordability and access. Primary market research indicates that Yangon and Mandalay are the main growth points for optional vaccines.

Consumer vaccine awareness is generated primarily through Facebook and recommendations from health care providers. Pediatricians and General Practitioners are the most influential health care providers for decision-making, and they are also the main prescribers of optional vaccines. Cost and quality are key brand choice criteria for these providers.

CONCLUSIONS

We project high growth in the optional vaccine market; we conservatively estimate 8% compound annual growth, bringing the value of the optional vaccine market to approximately 18 million EUR in 2023. Given patterns of consumer awareness, vaccine brand selection, and administration, health care providers should be the primary focus of efforts to increase the uptake of optional vaccines, including the conjugate Typhoid vaccine.

75. A Systematic Review of Typhoid Fever Occurrence in Africa

Jong-Hoon Kim[1], Justin Im[1], Marianne Holm[1], Prerana Parajulee[1], Ligia Cruz Espinoza[1], Nimesh Poudyal[1], Florian Marks[1,2]

[1]Department of Epidemiology, International Vaccine Institute, [2]University of Cambridge

BACKGROUND

Our current understanding of the burden and distribution of typhoid fever in Africa relies on extrapolation of data from a small number of population-based incidence rate estimates. Many other records on the occurrence of typhoid fever are, however, available and those records may contain information to enrich our understanding of the epidemiology of the disease.

METHODS

We provide an overview of the typhoid fever occurrence in Africa, reflected in public records identified through PubMed, Embase, and ProMED (Program for Monitoring Emerging Diseases).

RESULTS

Typhoid fever has been reported in 42 countries since 1900. The overall number of reports has increased over time in Africa with substantial heterogeneity between country and over time. Outbreaks were reported in 15 countries and their frequency and size have increased over time.

CONCLUSIONS

The epidemiology of typhoid fever seems to be independent of the frequency and distribution of reported occurrences, which makes it a challenge to study the disease only through public records. Efforts should be made to leverage existing typhoid data, for example, by incorporating them into models for estimating the burden and distribution of typhoid fever.

76. Antibiotic Resistance Pattern of *Salmonella spp.* Isolated From Stool Samples in a Diarrheal Case-Control Study in Kenya

Erick Kipkirui[1], Mary Kirui[1], Nancy Kipkemoi[1], Abigael Ombogo[1], Elizabeth Odundo[1], Jim Managbanag[2]

[1]Kenya Medical Research Institute (KEMRI)/US Army Medical Research Directorate-Kenya, Microbiology Hub Kericho, [2]Walter Reed Army Institute of Research, Silver Spring, MD, USA

BACKGROUND

Salmonellosis is mainly caused by *Salmonella spp* transmitted through consumption of contaminated water and food. In Kenya, the burden of this disease as at 2016 is estimated as 97,762 cases and 1,075 deaths of which 62% and 66% were among children under 15 years of age respectively. This situation can be worsened by the spread of multidrug resistant *Salmonella spp.* strains around the world. This is becoming a major threat to public health in developing countries Kenya included. The aim of this study was to determine the antibiotic susceptibility patterns of *Salmonella spp.* isolated from stool in a case-control diarrheal surveillance study in Kenya.

METHODS

A retrospective analysis was done on antibiotic susceptibility profiles of 42 *Salmonella spp.* isolates from stool specimens from 2011-2015 from seven county hospitals spread across Kenya. Susceptibility testing to various classes of antibiotics was done using the Microscan WalkAway® Plus gram negative combo panel according to manufacturer's instructions. The minimum inhibition concentrations were interpreted according to the Clinical & Laboratory Standards Institute guidelines.

RESULTS

Salmonella spp. isolates were mostly in cases than in controls (71.4% v 28.6%; p<0.05). A total of 45.2% *Salmonella spp.* were multidrug resistant while 19 % of the isolates were extended spectrum beta Lactamase producers. There was no significant difference between multidrug resistant isolates from cases (50%) and controls (33.3%) and also those from subjects less than five years of age (45.5%) and those five or more years(45%). High resistance was observed to ampicillin 64.3%, trimethoprim/sulfamethoxazole 62% and tetracycline 57.1%. Low resistance was detected to amoxicillin/clauvanate (21.4%), cefotaxime (19%), cefipime (19%), ceftriaxone (9.5%), imipenem (2.4%), meropenem (2.4%) and ciprofloxacin (2.4%). Levofloxacin was a 100% sensitive. Majority of the subjects with *Salmonella spp.* obtained their water for human use from municipal sources (62%).

CONCLUSIONS

As multidrug resistant *Salmonella spp.* evolve it presents difficulty in treatment and management of salmonellosis. This calls for continuous monitoring of antibiotics use, an approach towards prevention focusing on safe drinking water, good sanitation and hygiene and increasing access to vaccines.

77. Development of a Vaccine Based on GMMA Against Invasive Non-Typhoidal *Salmonella* Disease: Towards Phase 1 Testing in Humans

Oliver Koeberling, Anna Maria Colucci, Francesca Micoli, Claudia Vitali, Vito Di Cioccio, Allan Saul, Laura Martin

GSK Vaccines Institute for Global Health

BACKGROUND

Invasive non-typhoidal Salmonella disease (iNTS), is one of the leading causes of bacteremia in sub-Saharan Africa. It is a neglected and poverty-related disease causing at least 45,000 deaths per year in <5 year olds. Young children and immunocompromised individuals of all ages are at highest risk. *Salmonella enterica* serovars Typhimurium and Enteritidis account for >90% of iNTS cases. Wide spread multidrug resistance, high case fatality rate and difficult diagnosis advocate for the development of a vaccine against iNTS.

METHODS

GSK Biologicals SA trough the GSK Vaccines Institute for Global Health (GVGH) is developing a vaccine against iNTS based on a technology platform called GMMA, outer membrane exosomes released by genetically engineered bacteria. The iNTS vaccine contains GMMA from the two most prevalent African *Salmonella* serovars, Typhimurium and Enteritidis, respectively formulated on Alhydrogel and combined to provide the 2-component iNTS-GMMA.

RESULTS

In mice and rabbits, iNTS-GMMA induced high levels of serovar specific anti-O-Antigen responses with high functional activity against *S.* Typhimurium and *S.* Enteritidis. The GMMA were well tolerated in rabbits at the highest dose tested containing 40 µg of total O-Antigen. We developed a simple and robust process for GMMA production and formulation readily transferable to contract manufacturing organizations for manufacture of GMP material for clinical use. Analytical tests for in-process controls, release and stability testing have been developed. GMMA drug substance and drug product were shown to be stable at elevated temperatures for the test time of 56 days. The process was used to generate formulated Typhimurium and Enteritidis GMMA lots which are currently being tested in a repeat dose GLP toxicology study in rabbits. Plans for Phase 1 testing to demonstrate safety and immunogenicity of this vaccine in European adults prior to African populations are in place. With our collaborators we work on plans to further raise public awareness for iNTS.

CONCLUSIONS

A comprehensive preclinical package for the iNTS-GMMA vaccine was established enabling us to proceed with clinical development of this urgently needed vaccine.

78. Local and Systemic Immune Response to a Vaccine Against *Salmonella* Typhimurium Based on Generalized Modules for Membrane Antigens (GMMA)

Fabio Fiorino[1], **Oliver Koeberling[2],** Elena Pettini[1], Annalisa Ciabattini[1], Francesca Necchi[2], Laura B. Martin[2], Donata Medaglini[1]

[1]University of Siena, [2]GSK Vaccines Institute for Global Health

BACKGROUND

Salmonella enterica serovar Typhimurium (STm) is one of the predominant causes of invasive nontyphoidal *Salmonella* (iNTS) disease. The O-antigen portion of STm lipopolysaccharide (O:4,5) has been recognized as an important target for vaccination. In this work, we characterized the murine immune response to a vaccine against STm based on the GMMA (Generalized Modules for Membrane Antigens) technology as a delivery system for O:4,5.

METHODS

C57BL/6 mice were immunized with Alhydrogel formulated STmGMMA using two doses of vaccine by subcutaneous or intranasal route. Systemic and local O:4,5-specific antibodies, serum bactericidal activity and cellular immune response were characterized.

RESULTS

Following primary immunization, high levels of O:4,5-specific serum IgG were observed with both doses of STmGMMA administered by subcutaneous route and with the higher dose by intranasal route. Boosting after 10 weeks induced, in all groups, an increase of O:4,5-specific serum IgG and bactericidal activity against the homologous strain. The analysis of IgG subclasses showed a balanced Th1/Th2 response following subcutaneous immunization and a Th1 response after intranasal. At intestinal level, the higher

vaccine dose elicited O:4,5-specific IgG by SC administration, and O:4,5-specific IgA by intranasal route. A significant production of IL-2, IFN-γ, and IL-17A by CD4+ T cells was observed in splenocytes of mice immunized with STmGMMA using both doses and administration routes.

CONCLUSIONS

These data demonstrate the ability of the STmGMMA vaccine to induce local and systemic, humoral and cellular, immune responses and highlight the modulation of the immune response driven by different routes of immunization.

79. Impact of Information Pamphlet on Irrational Antibiotic Usage in Children of Urban Vellore, Southern India: A Stepped Wedge Trial in a Closed Cohort

Sindhu Kulandaipalayam Natarajan, Manikandan Srinivasan, Sathyapriya Subramaniam, Jacob John, Gagandeep Kang

Christian Medical College, Vellore

BACKGROUND

There is an increasing irrational use of antibiotics for conditions in children which are predominantly of viral etiology such as upper respiratory tract infections, fevers and diarrheas in the urban community of Vellore, and these rates are alarmingly high. Parents or primary caregivers perceive early initiation of antibiotics for any fever episode hastens recovery. Awareness on long term impact of irrational antibiotic usage, especially with regards to the threatening anti-microbial resistance is poor. Easy availability of antibiotics over-the-counter (OTC) and early initiation by general practitioners, operate together with the existing poor public awareness, leading to high rates of antibiotic use. This study aims to investigate if the introduction of an information pamphlet in the community will have an impact on irrational antibiotic usage.

METHODS

Through a step wedged design, awareness pamphlets will be provided to the parents/primary caregivers whose children are under follow-up by SEFI (Surveillance for Enteric Fever in India). Over a duration of 11 months, information pamphlets will be introduced to the study areas in a stepped-wedge manner. Antibiotic usage rates captured in the background of SEFI, will serve as a baseline to the rates that will be available after the roll out of intervention. Rates of antibiotic usage before and after the intervention at each time point will be compared. To account for the effect of time over antibiotic usage, a multilevel model analysis will be performed with time as a cluster variable.

RESULTS

With the study ongoing, an overall reduction in antibiotic usage is expected in the community. The increase in awareness among parents/primary caregivers about cautious use of antibiotics is expected to bring down antibiotic prescription rates by general practitioners.

CONCLUSIONS

To achieve antibiotic stewardship, it is imperative to instil awareness both at the level of the community as well as general practitioners, and this is challenging. Awareness at community level that is impactful as well as cost-effective, is the need of the hour to curb irrational antibiotic usage. The results derived from this study, which is first of its kind to be done in a semi-urban slum setting, can serve as a pivotal tool in antibiotic stewardship.

80. Comparative Genomic Analysis of a Sub-Lineage of Multi-Drug Resistant Non-Typhoidal *Salmonella* Typhimurium ST313 That Has Emerged in Blantyre, Malawi

Benjamin Kumwenda[1], Jay Hinton[2], Melita Gordon[2], Chisomo Msefula[1], Carsten Kroger[3], Rocio Canals Alvarez[2], Olexandr Predeus[2]

[1]College of Medicine, University of Malawi, [2]University of Liverpool, [3]Moyne Institute

BACKGROUND

Invasive non-typhoidal *Salmonella* Typhimurium (iNTS) is a major cause of bloodstream infections in sub-Saharan Africa that target immune-compromised individuals. iNTS accounts for over 388, 000 deaths annually in Africa. Surveillance data from Blantyre, Malawi revealed an emergence of a new group of iNTS S. Typhimurium ST313 strains in 2006 that we have designated as lineage 2A. The lineage 2A isolates share the same multi-drug resistance profile as lineage 2. The two strains were isolated from patients with similar demographic and clinical characteristics. The reasons for the emergence of lineage 2A strains remain unclear.

METHODS

We used two representative isolates D23580 (lineage 2) and D37712 (lineage 2A) to perform a comparative genome analysis to search for the genetic differences that explained emergence of lineage 2A. The genomes of the representative strains were sequenced using PacBio technology. Using comparative genome analysis, we identified the differences in SNPs, accessory genes, and plasmids, phages and pseudogenes that distinguish the two lineages.

RESULTS

Comparison between the genomes of D23580 and D37712 revealed differences in the number and composition of plasmids, accessory genes and SNPs. The D37712 chromosome lacks two genes that are present in D23580. There are 27 core genome SNP differences between the two lineages. Both D23580 and D37712 shared a similar prophage profile. The two isolates also carried two identical plasmids pSLT-BT and pBT3. However, plasmids pBT1 and pBT2 were absent from D37712, which carried two novel plasmids, pBT4 and pBT5. The two new plasmids share high levels of homology with *Salmonella*Weltevreden and *E.coli*plasmids consistent with acquisition by horizontal gene transfer.

CONCLUSIONS

We identified genetic differences that distinguish lineage 2 from lineage 2A isolates of iNTS S. Typhimurium ST313. Further work is in progress to establish the biological importance of the genetic differences observed using differential gene expression and laboratory experiments.

81. What Elimination of Endemic Typhoid Transmission Looks Like – Chronic Typhoid and Paratyphoid Carrier Prevalence in Santiago, Chile, 2017-2018

Rosanna Lagos[1], Juan Carlos Hormazabal[2], Catterina Ferreccio[3], Michael Sikorski[4], Sergio Duarte[2], Ellen Higginson[4], Marcela Pasetti[4], Myron Levine[4]

[1]Centro para Vacunas en Desarrollo-Chile, [2]Instituto de Salud Pública, Chile, [3]Pontificia Universidad Católica de Chile, [4]University of Maryland School of Medicine

BACKGROUND

In the 1970s and 1980s enteric fever due to *Salmonella* Typhi and *S.* Paratyphi (mainly B) were highly endemic in Santiago, Chile, and the disease was highly seasonal (warm, rainless summer). In 1980, bile cultures of 1000 consecutive patients undergoing cholecystectomy yielded *S.* Typhi in 3.8% and *S.* Paratyphi in 3.5% of specimens. Amplified long-cycle transmission of typhoid declined precipitously following strictly enforced prohibition of crop irrigation with untreated sewage water after a cholera outbreak in 1991. Enteric fever cases are now rare in Santiago (7 cases in 2017 in a population of 7.2 million). We studied cholecystectomized patients in Santiago age 15-34 years (who grew up in Santiago when typhoid was no longer endemic) and > 55 years (who resided in Santiago when typhoid was hyper-endemic). We hypothesized that we would not detect *S.* Typhi or Paratyphi in bile specimens from the former but might detect some persisting chronic carriers in the latter older age group.

METHODS

Patients scheduled for cholecystectomy in four Santiago hospitals were approached to join the study. Participants were enrolled after informed consent. Pre-surgery stool specimens and blood (to measure anti-Vi IgG serum antibody titer) were obtained. Bile and gallstones collected at surgery and stools were cultured and tested by qPCR to detect *S.* Typhi and *S.* Paratyphi.

RESULTS

742 cholecystectomy patients in the younger age group and 917 in the older age group provided specimens from June 2017-November 2018. *S.* Paratyphi was cultured from stool and bile of one subject age 70 years. 12 persons (8 older, 4 younger) had elevated anti-Vi IgG titers.

CONCLUSIONS

Only one older and no younger patient yielded typhoidal *Salmonella*. Modern routine pre-operative cefazolin administration may have inhibited culture but qPCRs were also negative. Treatment over the years with fluoroquinolones for urinary tract and gastrointestinal infections may have eliminated typhoidal *Salmonella* from the gallbladders of chronic carriers who had acquired their infections during the endemic era. The lack of a notable prevalence of chronic carriers correlates with the near disappearance of cases of typhoid in Santiago.

82. Metabolic Adaptation of the Human Pathogens *Salmonella* Typhi and Paratyphi ABC.

Gemma Langridge, John Wain

Quadram Institute Bioscience

BACKGROUND

Host adaptation in salmonella is a metabolic phenomenon, as confirmed by Leif et al this year. We know this to be the result of degradation of metabolic function over time for S. Gallinarum and S. Pullorum in their adaptation to galliforme birds. We also know this is true in S. Typhi and S. Paratyphi A but it hasn't been studied in depth in the less common human-adapted serovars S. Paratyphi B and C.

METHODS

Representative S. Paratyphi B and C genome sequences were selected. Disrupted coding sequences were identified in these genomes and the impact of these disruptions upon metabolic pathways was assessed using Pathway Tools software and compared with S. Typhi and S. Paratyphi A.

RESULTS

Neither S. Paratyphi B nor C showed any significant overlap with S. Typhi or S. Paratyphi A in metabolic degradation. Indeed, S. Paratyphi B displayed very few disrupted coding sequences at all. S. Paratyphi C had a larger complement of disrupted genes but these were largely ancestral to the O6,7:c:1,5 group which also includes S. Choleraesuis. This is in contrast to S. Typhi and S. Paratyphi A which share disruption across pathways including vitamin B12, sugar utilisation and transporters.

CONCLUSIONS

S. Typhi and Paratyphi A are host adapted and restricted to humans. S. Paratyphi C shows hallmarks of being host adapted to pigs whilst S. Paratyphi B shows no evidence for host adaptation.

83. Digital Detection of *Salmonella* Typhi in Large-Volume Environmental Water Samples Using an Asymmetric Membrane

Jing Li, Xingyu Lin, Xiao Huang, Yanzhe Zhu, Katharina Urmann, Michael Hoffmann

California Institute of Technology

BACKGROUND

A simple and cost-effective membrane based on digital loop-mediated isothermal amplification (mLAMP) method was developed to simultaneously concentrate and detect *Salmonella* Typhi in large-volume of drinking water samples. Compared to traditional real-time polymerase chain reaction (qPCR) method, mLAMP shows higher tolerance against inhibitors (e.g., heavy metals, organic matters) and provides absolute quantification results without the need of standard curve calibration. Briefly, mLAMP holds great potential for microbial water quality analysis in resource-limited settings.

METHODS

The bilayer asymmetric membrane was prepared by combining two commercial polycarbonate (PC) membranes of different pore sizes (top: 25 µm and bottom: 600 nm) through simple heating at 170°C. Drinking water samples spiked with different concentrations of *Salmonella* Typhi were used as model water and tested with the mLAMP method. For each test, 1-100 mL water sample can be filtered through the bilayer membrane. Bacteria were enriched and randomly partitioned into the top 25-µm micropores, while smaller particles were washed away through the bottom 600-nm nanopores. The filtered asymmetric membrane was then loaded with the LAMP reagents, followed by heat incubation at 65°C for 60 min for nucleic acid amplification. The endpoint fluorescence images of the asymmetric membrane were taken using a fluorescence microscope. The concentrations of *Salmonella* Typhi in original samples were calculated by the number of positive pores (pores exhibit increased fluorescence) and the total number of pores using Poisson distribution. For comparison, the same water samples were also tested by qPCR.

RESULTS

It took less than 20 min for the asymmetric membrane to filter up to 100 mL water sample and the recovery rate of *Salmonella* Typhi cells was around 60%. The detection limit of mLAMP was as low as 0.1 cells/mL, which was 1000-fold lower than qPCR. Overall, a good linear correlation was observed between the detected absolute number of *Salmonella* Typhi and the actual number of cells spiked into the sample.

CONCLUSIONS

Our study provides a novel analytical method for *Salmonella* Typhi quantification in large-volume of water samples. This development has a promising prospect of being applied for microbial water quality analysis in low-resource settings due to its portability, cost-effectiveness and user-friendliness.

84. Comparison of Different Randomisation Methods in a Cluster Randomised Vaccine Effectiveness Trial: A Simulation Study Using Real-World Data

Xinxue Liu[1], Merryn Voysey[1], K Zaman[2], Farhana Khanam[2], Firdausi Qadri[2], Andrew Pollard[1], John Clemens[2], the TyVAC Study Team[1]

[1]Oxford Vaccine Group, Department of Paediatrics, University of Oxford, [2]International Centre for Diarrhoeal Disease Research – Bangladesh (icddr,b)

BACKGROUND

Cluster randomised controlled trials (CRCTs) of vaccine effectiveness randomly allocate all individuals in a geographically-defined cluster to receive either the test vaccine or a control vaccine according to their cluster of residence. Randomisation by cluster rather than by individual can result in the baseline characteristics of individuals being imbalanced between the two treatment groups. The lack of balance at baseline will increase the variance of the estimated effect and thus reduce the efficiency of the study. We compared different cluster randomisation methods in a typhoid vaccine CRCT (Typhoid Vaccine Acceleration Consortium-Bangladesh, TyVAC-Bangladesh) and assessed the degree of imbalance present in the baseline characteristics.

METHODS

We conducted a simulation study using TyVAC-Bangladesh baseline census data to compare three randomisation methods (simple block randomisation, stratified block randomisation, and restricted randomisation) in three different scenarios: all 150 clusters in TyVAC-Bangladesh, or a subset of 50 or 20 randomly selected clusters. For each randomisation method, we generated 1000 randomisation lists allocating each cluster to either typhoid vaccine or control. For each baseline characteristic, imbalance was defined as ≥10% difference between the two arms. We assessed the performance of each randomisation method by comparing the proportion of simulated randomisation lists with that were imbalanced for each selected baseline characteristics.

RESULTS

For individual-level continuous normally distributed variables, such as age, all randomisation methods achieved perfect balance. The proportions of imbalance among 1000 simulations are 0% in all three scenarios. For continuous cluster-level variables (such as the number of male participants in the cluster), the performance of the randomisation method depended on the variable's distribution. For highly skewed variables, most methods had imbalance proportions >70%. However, when restricted randomisation was used with the skewed variable as a design variable, the imbalance proportion dropped to 20%. Scenarios with large numbers of clusters were less likely to be imbalanced.

CONCLUSIONS

Choosing the right design variables for cluster randomisation is important to achieve good baseline balance in CRCTs. Outcome predictors with highly skewed distribution at cluster-level should to be incorporated as a design variable.

85. The Strategic Typhoid Alliance Across Africa and Asia: The Burden of Enteric Fever in Lalitpur, Nepal

Mila Shakya[1], Pallavi Gurung[1,2], **Archana Maharjan[1,2],** Sabina Dongol[1,2], Christiane Dolececk[3], Stephen Baker[4], Buddha Basnyat[1,2]

[1]Oxford University Clinical Research Unit - Nepal, [2]Oxford University Clinical Research Unit - Nepal, Patan Academy of Health Sciences, [3]Nuffield Department of Medicine, Oxford University, [4]Oxford University Clinical Research Unit, Vietnam

BACKGROUND

Enteric fever causes 12-21 million infections and 100,000-200,000 deaths globally each year. It is a serious public health concern in many low and middle-income countries, especially in South Asia. However, estimates of incidence of the typhoid in South Asia are uncertain due to lack of data on culture-proven disease and lack of specificity of clinical diagnosis. As part of the Strategic Typhoid Alliance across Africa and Asia (STRATAA) consortium, a multicomponent study was designed to improve understanding of key data gaps around the burden and transmission of enteric fever and generate the evidence for vaccine implementation.

METHODS

A demographic census was enumerated in Lalitpur Metropolitan City, Kathmandu Valley. A census update was conducted at one and two years. Passive surveillance was conducted from a tertiary hospital (Patan Hospital), and blood-cultures were collected from children and adults with febrile illness. Healthcare utilisation surveys were conducted in a sample of households to enable adjustment of incidence estimates for health care seeking behaviour. Community-based serological surveillance was performed on an age-stratified cohort of over 6,000 individuals randomly selected from the census, with blood samples collected at baseline and 3 months.

RESULTS

Between 2/06/2016 and 30/09/2016, 102.963 participants within 32,401 households were enrolled into the demographic census, from this population 142 S Typhi and 13 S paratyphi were cultured from the blood of 1541 febrile patients. The overall incidence rates for blood culture confirmed S. Typhi per 100,000 person-years of observation were 66.2. Adjusted incidence rates were highest in the 10-14 year age group.

27.5% of febrile patients recruited gave a history of prior antimicrobial usage. From healthcare seeking questionnaires only 8.6% of the population used government health facilities with 42.5% self-treating with anti-microbials or purchased directly from pharmacy. Fluoroquinolone resistance was observed in 71.5% of isolates and azithromycin resistance in 2.9 % of isolates.

CONCLUSIONS

A high burden of typhoid was identified in children especially those 5 – 15 years of age. The high rates of anti-microbial resistance were also further confirmed in the study. Introduction of an effective typhoid vaccine has the potential to reduce the disease burden and control antimicrobial resistance.

86. Global Typhoid Fever Incidence: A Systematic Review and Meta-Analysis

Christian Marchello, John Crump, Chuen Yen Hong

University of Otago

BACKGROUND

Contemporary incidence estimates of typhoid fever are needed to guide policy decisions, control measures, and improve future epidemiological studies.

METHODS

We systematically reviewed three databases (Ovid MEDLINE, PubMed, and Scopus) without restriction on age, country, language, or time for studies reporting the incidence of blood culture-confirmed typhoid fever. Outbreak, travel-associated, and passive government surveillance reports were excluded. We performed a meta-analysis in MetaXL using a random effects model to calculate estimates of pooled incidence, stratifying by studies that reported the incidence of typhoid fever and those that estimated incidence by using multipliers.

RESULTS

Thirty-three studies were included in the analysis. There were 25 sites from 17 countries reporting typhoid cases from active, population-based incidence studies; 17 sites in 9 countries used multipliers to adjust sentinel surveillance data for under-ascertainment. Among active, population-based studies the overall pooled estimate of incidence (95% CI) was 159.8 (119.7-205.6) typhoid cases per 100,000 per year and was highest in Asia (270.2, 182.8-368.2). Among multiplier studies, the overall pooled incidence estimate was 141.8 (85.3-212.2) typhoid cases per 100,000 per year. We also identified several gaps in the consensus of adjustments being used in incidence studies and case definitions for blood culture.

CONCLUSIONS

Typhoid fever incidence remains high at many sites. Additional and more accurate typhoid incidence studies are needed to support country decisions about typhoid conjugate vaccine use.

87. Using Hospital-Based Studies of Community-Acquired Bloodstream Infections to Make Inferences About Typhoid Fever Incidence

Christian Marchello[1], John Crump[1], Ariella Perry Dale[2], Sruti Pisharody[3]

[1]University of Otago, [2]Colorado Department of Public Health and Environment, [3]Duke University Medical School

BACKGROUND

Hospital-based studies of community-acquired bloodstream infections (BSI) are less resource-intensive and more widely available than population-based typhoid fever incidence studies. We sought to investigate whether hospital-based study metrics are useful in predicting typhoid fever incidence by location.

METHODS

We systematically reviewed three databases (Pubmed, Web of Science, and Scopus) for hospital-based studies of community-acquired BSI without restriction on date, country, or language. We determined by study the prevalence of Salmonella Typhi among participants and the rank order of Salmonella Typhi among bloodstream isolates. We also calculated the prevalence ratio of Salmonella Typhi to the stably endemic organism Escherichia coli. We then examined the relationship between these hospital-based study metrics and population-based typhoid fever incidence data from a separate systematic review.

RESULTS

Forty-four studies met the inclusion criteria. Data were collected from 1987 through 2015 in 19 countries. The median (range) number of pathogenic organisms causing BSI per study was 10 (2-21). Salmonella Typhi was isolated in 23 (52.3%) studies and was the most frequently isolated organism in 9 (20.5%) studies. Among studies isolating Salmonella Typhi, the median (range) prevalence of Salmonella Typhi BSI among participants was 1.2% (<0.1-13.0%). The median (range) rank order of Salmonella Typhi compared to other pathogenic organisms in BSIs was 4 (1-14). The median (range) prevalence ratio of Salmonella

Typhi to E. coli was 0.2 (<0.1-13.3). One prevalence study from Pemba, Tanzania, 2010, overlapped in place and time with an incidence study indentified by our separate typhoid incidence systematic review. In this setting where typhoid incidence was 110.1 cases per 100,000 per year, hospital-based Salmonella Typhi prevalence was 2.1%, rank order was 1, and the Salmonella Typhi : E. coli ratio was 9.2.

CONCLUSIONS

We describe considerable variation over place and time for Salmonella Typhi prevalence, rank order, and Salmonella Typhi : E. coli ratio among hospital-based studies of community-acquired BSI. We found insufficient concurrent, collocated prevalence and incidence studies to examine associations. More data from simultaneous typhoid prevalence and incidence studies are needed to establish whether data from prevalence studies could offer insights into typhoid incidence in hospital catchment areas.

88. Genotypic Diversity of *Salmonella* Typhi Carried Isolates of Two Kampala Markets and 2015 Isolates Outbreak at Kampala Uganda

Bumano Mark[1,2], Henry Kajumbula[1], Welly Ssengooba[1], NAJJUKA Christine[1]

[1]Makerere University College of Health Science, [2]Upper Nile University South Sudan

BACKGROUND

With an estimated of 27 million cases of typhoid and 200,000 death globally every year. In Uganda Typhoid fever is thought to be highly endemic with the national Health Management information system recording a total of 248,783 cases country wide and 34,109 cases in Kampala during 2014. Its magnitude was underscored by a large outbreak in Kampala City from February to May 2015. We therefore set out to estimate the genotypic diversity among carried strain and 2015 isolates outbreak strain using the Molecular Technique, Multiple Locus Variable Number of Tandem Repeat Analysis to determine the relatedness.

METHODS

This was a descriptive Cross -sectional Study involving stored *Salmonella Typhi* carried isolates from vendors of two markets Kalerwe and Nakasero and it was sampled between July- September 2016, the isolates was obtained from carried Stool Sample and it was stored at 4°C and the Stored isolates from the 2015 outbreak in Kampala and other sporadic isolates was stored at Makerere University College of Health Science Microbiology laboratory were genotypicaly relatedness using Multiple Locus Varialble Number of Tandem repeat Analysis

RESULTS

Multiple Locus Variable Number of tendem Repeat analysis grouped the 44 carriages, outbreak and sporadic isolates analyzed into **15 profiles** and demonstrated that the isolates did not cluster on the basis of these 3 epidemiological backgrounds

CONCLUSIONS

The carrier strains are genotypicaly diverse but cluster together with the outbreak and sporadic strain. Indicating that either the carriers formed the source of the outbreak and the sporadic infections or they arose from resolving sporadic or outbreak cases. The *Salmonella Typhi* Strain from different epidemiological backgrounds are related and widely dispersed.

89. Evidence of *Salmonella* Paratyphi C Found for the First Time in Medieval Northern Europe

Muganga Mark[1], Mark Achtman[2]

[1]Uganda Youth Alliance for Family Planning and Adolescent Health (UYAFPAH), [2]University's Warwick Medical School

BACKGROUND

Genome research suggests that enteric fever, a potentially lethal disease more commonly found in hot countries, was present in medieval Europe. Salmonella Paratyphi C causes enteric fever, a life-threatening infection, and has been detected in a 800 year old human skeleton discovered in Trondheim, Norway

The research was to reshape the understanding of Salmonella enterica and to trigger intriguing speculations about historical host jumps during the Neolithic period between humans and their domesticated animals.

METHODS

Salmonella *Paratyphi C* causes enteric fever, a life-threatening infection, and has been detected in a 800 year old human skeleton discovered in Trondheim, Norway.

Now scientists are speculating that the evolution of enteric fever could be linked to the domestication of pigs across northern Europe.

According to Prof Achtman and his team analysed bacterial DNA found in the teeth and bones of the skeleton of a young woman who is believed to have migrated to Trondheim from the northernmost areas of Scandinavia or Northwest Russia by her early teens only to die there around the age of 19-24 years.

RESULTS

The new results included comparative analyses of the *Paratyphi C*genome found in the skeleton against modern Salmonella genome sequences from EnteroBase, an online database developed at the University of Warwick and used internationally. This revealed that *Paratyphi C* represents the evolutionary descendants of a common ancestor, or clade, within the Para C lineage. The Para C Lineage includes Choleraesuis, which causes septicaemia in pigs and boar and Typhisuis which causes epidemic swine salmonellosis (chronic paratyphoid) in domestic pigs. These different host specificities likely evolved in Europe over the last 4,000 years and coincide with the timing of pig domestication in Europe.

CONCLUSIONS

Genome research suggests that enteric fever, a potentially lethal disease more commonly found in hot countries, was present in medieval Europe and through the use of EnteroBase, researchers were able to define the Para C lineage from 50,000 modern *Salmonella enterica* genomes and find that over its 3,000 year history only a few genomic changes occurred within the Para C lineage.

90. Social Media Impacts to Behavior Change Among Adolescents

Muganga Mark

Uganda Youth Alliance for Family Planning and Adolescent Health (UYAFPAH)

BACKGROUND

In Uganda, 78% of the population are adolescents who face numerous sanitation and hygienic challenges which results from lack of accurate and timely health related services. Currently, adolescents are the leading social media users almost at 72% and subscription varies at 81.34% for Facebook, 4.22% Twitter and You Tube 1.79%. Use of social media has become a new trend used for sharing and empowering young people with information.

METHODS

The internet and social media are now pervasive and ubiquitous. By the end of 2015, the Internet had been used by 3.2 billion people, 2 billion of them from developing countries, with over 78% of social media users being young people in Uganda. As young people we always prefer the use of social platforms such as Facebook, Twitter, Instagram, WhatsApp and Wordpress to empower our peers with health information and this is done through on daily basis disseminating of health related information.

This same idea can as well be integrate in the battle against typhoid, paratyphoid and nontyphoidal Salmonella. On Facebook I / we can reach up to 370 young people and Twitter over 10000 young people per day, Instagram over 10-15 and on Wordpress over 20-30 per month.

We can also reach the communities via radio and TV talk show always hosted for radio on a monthly basis as a way to amplify social media.

RESULTS

The number of young people accessing accurate health information and services will increase hence to choose right health behaviors; the uptake of health services will also increase among adolescents thus improving on the economical standard or the county and also to harnessing Uganda's Demographic Dividend.

CONCLUSIONS

Many young people will have access health information through social media helping in their behavior change processes and to stay alive. There is also a need to address issues hindering adolescents from using social media especially in developing countries.

Use of social media and improving access to online accurate information is highly recommended to avert some of the typhoid, paratyphoid and nontyphoidal Salmonella myth among the adolescents.

91. Low-Endotoxic Apyrogenic LPS From *Salmonella* Typhi as Immunogen and Adjuvant for Vi-Antigen

Anna Markina, Petr Aparin, Vyacheslav Lvov

National Research Center Institute of Immunology, Federal Medical Biological Agency of Russia

BACKGROUND

The main carbohydrate antigens of the outer membrane of the cell wall of *Salmonella typhi* -capsular polysaccharide (Vi-antigen) and lipopolysaccharide (LPS) are involved in all stages of the interaction with the host organism (invasion, local inflammation, introduction into phagocytic cells, febrile syndrome, induction of an adaptive immune response). LPS is the main factor determining the development of the pathological process in typhoid fever: it stimulates the production of proinflammatory cytokines and other biologically active substances, which, having a vasoactive effect, lead to the development of microcirculatory disorders. Serum antibodies against LPS and Vi-antigen may confer protective immunity to this enteric pathogen. LPS is also known as a natural adjuvant, which can increase numbers of long-lived antigen-specific T cells, but its mechanism of action is not understood. However, the use of LPS is limited due to its high endotoxicity. *S. typhi* LPS with tri-acylated lipid A represent a clinically-applicable variant of LPS and the aim of this work was to study its immunogenic and adjuvant properties.

METHODS

Vi-antigen was obtained from *S. typhi* extracellular fluid by Gotshchlich method. LPS was obtained from *S. typhi* cells by Westphal method. Purified LPS was partially deacylated under alkaline conditions to give LPS with mainly a tri-acylated lipid A moiety (Ac_3-LPS). Both preparations were apyrogenic. Mice (CBA×C57B1/6)F1 were intraperitoneally immunized with sterile saline (control group) and *S. typhi* Vi-antigen, Ac_3-LPS and combination thereof at a ratio of 1:1 (Vi-Ac_3-LPS) two times (0, 14 day) at a dose of 50 μg. Serum IgG and IgM were determined after 14 days after secondary immunization.

RESULTS

Immunization with Vi-Ac_3-LPS elicited 2-fold increases of anti-Vi-antigen IgM and IgG over those following the immunization with single Vi-antigen preparation. Vi-Ac_3-LPS and Ac_3-LPS both elicited high levels of LPS-specific IgM and IgG, which were 5-fold and 8-fold higher over those for control group.

CONCLUSIONS

Parenteral immunization with Vi-Ac_3-LPS increase Vi-antigen-specific antibodies that may indicate adjuvant properties of LPS. Given that Ac_3-LPS in Vi-Ac_3-LPS has the same immunogenicity as a single Ac_3-LPS allows us to consider the Vi-Ac_3-LPS as a preparation to protect against both *S. typhi* antigens.

92. Assessment of Immune Avidity to Determine the Course of Disease in Acute and Chronic State of Natural *S.* Typhi Infection

Ayan Dey, Ju Yeong Park, Sunha Song, Ursula Panzner, Se Eun Park, Manki Song, **Florian Marks**

International Vaccine Institute

BACKGROUND

Antibody avidity is a measure of the overall strength of an antibody-antigen complex, the increase in affinity maturation and the somatic hyper mutation after repeated antigen exposure due to infections or vaccinations. Antigen-antibody complexes present in the serum of typhoid fever patients with chronic infections bind strongly to Vi antigens with low antigen antibody dissociation in the presence of chaotropic agents, whereas in recent infection, antibodies dissociate quickly. The objective of the study was to assess immune avidity of natural *S.* Typhi infection using an avidity assay based on the Vi antigen ELISA and using a chaotropic agent Guanidine hydrochloride.

METHODS

We developed and pilot tested an ELISA based IgG and IgM antibody avidity measurement method for the *Salmonella* Typhi Vi-polysaccharide antigen. The avidity assay was internally qualified based on the parameters including linearity, range, inter-plate and intra-plate variations. Febrile and typhoid fever cases serum samples from Ghana and Madagascar were tested for anti-Vi IgG and IgM ELISA and avidity. In addition, we also tested neighboring healthy controls and healthy household contacts.

RESULTS

Initial data on pilot testing of 471 and 978 samples from Ghana and Madagascar for avidity assay suggests all positive blood cultures and other febrile cases from Ghana and Madagascar had high anti-Vi IgM titers and IgG titers. Many of these subjects with high Vi antibody titers also have high antibody avidity suggesting the probability of repeated infection or a persistent chronic state.

CONCLUSIONS

An avidity assay was established and pilot tested for the prediction of natural infection disease states and the duration of exposure. Avidity Index was used to classify the samples into groups based on their IgM and IgG antibody affinity. The next step is to validate this method using more samples and also to compare results with blood, stool culture, bone marrow and bile or gall bladder specimens collected at different points in time during one year after infection.

93. Epidemiologic and Antimicrobial Resistance Patterns of *Salmonella enterica* Serotype Typhi Isolates From Zimbabwe From 2009 to 2014

Tapfumanei Mashe[1], Robert Kingsley[2], Sekesai Zinyowera[1], Marleen M Kock[3], David Gally[5], Valerie Robertson[5], Babill Stray-Pedersen[6], Marthie M Ehlers[3]

[1]National Microbiology Reference Laboratory, Ministry of Health and Child Care Zimbabwe, [2]Quadram Institute Bioscience,, [3]Department of Medical Microbiology, University of Pretoria, [4]Roslin Institute, University of Edinburgh, [5]Department of Medical Microbiology, University of Zimbabwe, [6]Institute of Clinical Medicine, University of Oslo

BACKGROUND

Typhoid fever remains a major public health problem in Zimbabwe with recurrent outbreaks reported since 2009. To provide guidance on appropriate treatment choice in order to minimise the morbidity and mortality of typhoid fever and prevent large-scale outbreaks, we investigated the antimicrobial susceptibility patterns and molecular subtypes of *S.* Typhi from Zimbabwean outbreak strains isolated from 2009 to 2018 and compared these to isolates from neighboring African countries.

METHODS

Antimicrobial susceptibility testing was performed on all isolates from stool and blood using disk diffusion and E-test, and results were interpreted using the 2017 Clinical Laboratory Standards Institute guidelines. Pulsed-field gel electrophoresis (PFGE) was performed on 91 isolates.

RESULTS

Altogether 22036 suspected cases and 805 confirmed cases of typhoid fever were notified in Zimbabwe. An increase in ciprofloxacin resistance was observed in isolates collected from 2012 to 2017 (0% to 22.0%). In 2018 and outbreak of a *S.* Typhi strain was reported which showed 73% and 100% ciprofloxacin resistance amongst the isolates obtained from Kuwadzana and Gweru respectively. These ciprofloxacin-resistant isolates had minimum inhibitory concentrations ranging from 1 mg/L to 2 mg/L. In Gweru a cumulative total of 1943 suspected typhoid cases, 21 confirmed cases and eight deaths were recorded. The Mabvuku *S.* Typhi 2009 subtype was noted to be circulating in Harare during 2013 and 2016, in Mutawatawa during 2014, in Chitungwiza during 2012, in Mutare during 2016, in Rusape during 2014 and in Inyanga during 2013, demonstrating a relationship between isolates across a wide area and timeline. The PFGE analysis of isolates collected in 2013, 2014 and 2016 revealed a dominant strain with an indistinguishable PFGE pattern previously identified in strains isolated from South Africa, Zambia and Tanzania.

CONCLUSIONS

Resistance to ciprofloxacin, which is the first line antimicrobial for typhoid fever management in Zimbabwe, is emerging. A better understanding of the molecular epidemiology of *S.* Typhi can greatly contribute to the prevention and control of outbreaks as well as to determine cross-border spread of specific strains. Comprehensive and integrated strategies as part of infection control and prevention can be developed using the molecular surveillance data.

94. Clinical Management of a Typhoid Fever Outbreak With Differing Sensitivity Patterns, Sept 2017 to July 2018

Kudzai Masunda[1], Clemence Duri[1], Annamercy Makoni[1], Prosper Chonzi[1], Emmaculate Govore[1], Ibraheem Adebayo[2], Innocent Mukeredzi[1], George Mtahwa[1]

[1]City of Harare, [2]MSF-Belgium

BACKGROUND

Harare has had Typhoid fever outbreaks yearly since 2010 and the drivers have been consistent. Clinical management has been with Ciprofloxacin in all the previous outbreaks. However, when differing sensitivity patterns emerge, they pose a challenge to clinical management.

METHODS

Epidemiological Investigations were done in Mbare and Kuwadzana suburbs that had most cases in the outbreak. A case control study was done in Mbare and in Kuwadzana to determine the risk factors. Laboratory specimens were taken of stool and blood to diagnose *S.* Typhi and for sensitivity testing using the Clinical Laboratory Standards Institute (CLSI) method at Beatrice Road Infectious Disease Hospital laboratory in Harare. Environmental assessments were done in the suburbs and samples were taken for analysis. Case definitions were set, and line-lists created and analysed together with the spot maps of cases and water sources. Treatment centres were setup at Mbare and Kuwadzana polyclinics

RESULTS

At the end of the outbreak there were 4389 cases line-listed with 251 of them confirmed and a Case fatality rate of 0%. The top three suburbs with cases were Mbare (39%), Kuwadzana (18%) and Glen View (15%). Of the 251 confirmed samples, 231 were analysed for sensitivity and 69/215 (32%) and 22/215 (10%) showed intermediate sensitivity. This resistance pattern varied by suburb where Mbare (8/71), Glen View (8/24) and Kuwadzana (45/65) had 11%, 33% and 69% resistance to Ciprofloxacin respectively. The varied sensitivity pattern led to adjusting recommended treatments for patients from different suburbs, with Cefixime replacing Ciprofloxacin where Ciprofloxacin resistance was high. The drivers of the outbreak were contaminated boreholes and burst sewer lines. The contaminated boreholes were decommissioned and some fit with online Chlorinators. Males and children aged less than 15 years had highest cumulative attack rates.

CONCLUSIONS

Poor municipal water supply, broken-down sewer lines and contaminated boreholes propagated the typhoid outbreak. Correction of these drivers led to the end of the outbreak. Clinical management with a mixed sensitivity pattern is challenging logistically and clinically. Importance of laboratory surveillance led to good clinical outcomes.

95. Controlling a Typhoid Fever Outbreak in the Midst of a Cholera Outbreak, Sept 2018 to Date

Kudzai Masunda, Innocent Mukeredzi, Clemence Duri, Hilda Bara, Emmaculate Govore, Israel Makwara, Ruby Tapera, Phillomina Chitando

City of Harare

BACKGROUND

In Sept 2018 a Typhoid Fever outbreak started concurrently with a Cholera outbreak in Harare and containing both was the main objective. They share similar risk factors and ciprofloxacin is the medicine of first choice in Zimbabwe.

METHODS

Outbreak investigation at the start of a cholera outbreak revealed cases of Typhoid fever. Case definitions for both diseases were disseminated to clinics, and line-lists were developed and analysed to describe the outbreaks and to determine sources and identify potential to spread to new areas. Spatial analysis of cases and risk factors including water sources was instituted. An environmental assessment was done to assess the water and sanitation with laboratory sampling of water samples. Stool and blood samples were analysed to confirm cases and assess antibiotic sensitivity.

RESULTS

As of 6 Jan 2019, there are 1 642 typhoid cases with 39 of them confirmed and 2 deaths (Case Fatality Rate= 0.12%) compared to 9 974 cholera cases with 216 confirmations and 43 deaths (case Fatality rate 0.43%). The typhoid outbreak started in two adjacent suburbs on the 5th of Sept 2018 and then spread to a third suburb in Nov 2018. Lab analysis showed 81/160 (51%) samples were resistant to Cipro for vibrio cholerae specimens and for typhoid fever sensitivity to Ciprofloxacin was 90% (19/21). 42 boreholes in affected areas were contaminated with faecal coliforms or *Salmonella* species,20 boreholes had *E. Coli* and 3 had *Vibrio Cholarae.* Males and children <15 years had higher attack rates in both outbreaks compared to their comparative group respectively. However, the differences in attack rates were more significant in the typhoid outbreak compared to the cholera outbreak.

CONCLUSIONS

This was a common source outbreak for both typhoid and cholera with contaminated boreholes being the source. Differentiating the clinical management of the cases was difficult and follow up of cholera cases took precedence with less samples tested for Typhoid as most resources were channeled to cholera diagnosis. Contamination of borehole water at such a level has been prevalent in Harare for almost 4 years and requires urgent attention to reduce the spread of Typhoid fever and cholera.

96. Safety of a New *Salmonella* Typhi Polysaccharide-Diphtheria Toxoid (Vi-DT) Conjugate Vaccine: A Randomized Clinical Trial-Phase I Study in Indonesia

Bernie Endyarni Medise[1], Soedjatmiko Soedjatmiko[1], Iris Rengganis[2], Sri Rezeki Hadinegoro[1], Jean-Louis Excler[3], Sushant Sahastrabuddhe[3], Mita Puspita[4], Rini Mulia Sari[4]

[1]Child Health Department, Faculty of Medicine, University of Indonesia, Dr. Cipto Mangunkusumo General National Hospital, [2]Department of Internal Medicine, Faculty of Medicine University of Indonesia, Dr. Cipto Mangunkusumo General National Hospital, [3]International Vaccine Institute, [4]PT. Bio Farma, Bandung

BACKGROUND

Prevalence of typhoid fever remains high globally, with mortality rate of 200,000 deaths per year which affecting younger age children especially in endemic and developing countries. Typhoid vaccination is an important prevention tool against typhoid fever. Current polysaccharide typhoid vaccines are not recommended for children under 2 years. A new typhoid conjugate Vi-diphtheria toxoid (Vi-DT) vaccine has been developed for infant immunization. We aimed to define the safety of Vi-DT vaccine among adults and children in Indonesia.

METHODS

We conducted an observational blinded, comparative, randomized, phase I safety study in two age de-escalating cohorts in Jakarta, Indonesia, from April 2017 to February 2018. We enrolled 100 participants in 2 age groups: 18 to 40 years (adults) and 2 to 5 years old (children), which were divided into 4 arms. Two interventional groups received two doses of Vi-DT vaccine whereas two control groups received Vi-polysaccharide (Vi-PS) and another additional vaccine (influenza-HA vaccine for adult group and 13-valent Pneumococcal polysaccharide conjugated vaccine for children). Vaccine was administered twice 4 weeks apart. All subjects were provided with observation diary card to assess and record information for local and systemic reaction for 28 days following immunization, with special attention within the first three days.

RESULTS

All healthy 100 participants completed the study. The Vi-DT and Vi-PS vaccines showed no difference in terms of intensity of any immediate local and systemic events within 30 minutes post vaccination. Overall, pain occurred as the most common local reaction and muscle pain was the most common systemic reaction in the first 48 hours. Most of the local and systemic event intensities were mild. No serious adverse event was deemed related to vaccine administration.

CONCLUSIONS

The new typhoid conjugate Vi-diphtheria toxoid (Vi-DT) vaccine is safe in adults and children above two years of age.

97. Burden of Enteric Fever in Three Urban Sites Across Africa and Asia: A Prospective Epidemiological Study With Over 600,000 Person-Years of Observation

James Meiring[1], Mila Shakya[2], Farhana Khanam[3], Tikhala Makhaza Jere[4], Melita Gordon[4], Buddha Basnyat[2], Firdausi Qadri[3], Andrew Pollard[5]

[1]Oxford Vaccine Group, [2]Oxford University Clinical Research Unit Nepal, [3]icddr,b, [4]Malawi Liverpool Wellcome Trust, [5]Oxford University

BACKGROUND

Estimated to cause 12-21 million infections and 100,000-200,000 deaths globally each year, enteric fever is a major public health problem in many low and middle-income countries. With recent World Health Organisation recommendation to use an efficacious Vi-conjugate vaccine against *Salmonella enterica* serovar Typhi (*S* Typhi), global control of this pathogen is now possible. In the Strategic Typhoid Alliance across Africa and Asia (STRATAA) programme, we designed a comprehensive epidemiological study to accurately determine the burden of disease and generate evidence for vaccine implementation.

METHODS

A demographic census of approximately 100,000 individuals was enumerated in each of three urban sites in Africa (Malawi) and Asia (Nepal and Bangladesh). Documenting individual and household level data by GPS location provided a detailed denominator population within which to conduct surveillance. Facility-based passive surveillance was conducted from June 2016 to September 2018 in primary health clinics and referral hospitals, providing over 600,000 person-years of observation. Cases were detected by blood-culture confirmation in participants reporting fever for 2days or more or a documented temperature of at least 38oC.

RESULTS

Between June and October 2016, 311,105 participants were enrolled into the demographic census. From this population 573 *S.* Typhi and 84 *S.* Paratyphi isolates were cultured from the blood of 7,787 febrile participants. The unadjusted incidence rates for blood-culture-confirmed *S.* Typhi per 100,000 person-years of observation were 143.1 in Bangladesh, 66.2 in Nepal and 61.1 in Malawi. Incidence rates were highest in the 0-4year age group in Bangladesh (562.6/100,000), 10-14 in Nepal (220/100,000), and 5-9 in Malawi (151/100,00).

Multi-drug resistance (resistance to amoxicillin, chloramphenicol and co-trimoxazole) was observed in 45.2% (97% Malawi, 36.9% Bangladesh, 1.8% Nepal) of isolates, naldixic acid resistance in 55.6% (0% Malawi, 95.5% Bangladesh, 71.5% Nepal) of isolates and azithromycin resistance in 8% (0% Malawi, 21.1% Bangladesh, 2.8% Nepal) of isolates.

CONCLUSIONS

This accurate description of the burden of *S.* Typhi and *S.* Paratyphi A demonstrates high incidence of disease in all 3 sites, but with markedly different age profiles and resistance patterns. The introduction of typhoid conjugate vaccines will rely on these accurate incidence estimates across different epidemiological contexts to maximise vaccine impact.

98. Community Engagement Before Initiation of Typhoid Conjugate Vaccine Trial in Two Urban Townships in Blantyre, Malawi – Experience and Lessons

James Meiring[1], Rodrick Sambakunsi[2], Elvis Moyo[2], Theresa Misiri[2], Pratiksha Patel[2], Priyanka Patel[2], Melita Gordon[2]

[1]Oxford Vaccine Group, [2]Malawi Liverpool Wellcome Trust

BACKGROUND

To determine the efficacy of a new typhoid conjugate vaccine in an endemic setting in sub-Saharan Africa, the Typhoid Vaccine Acceleration Consortium is conducting a phase 3 randomized controlled trial in Blantyre, Malawi. We describe community and stakeholder engagement activities performed before and during the trial, challenges and lessons learned.

METHODS

Our engagement strategy included meetings with Ministry of Health and Education officials, local community leaders, and parent teacher association groups six months prior to trial initiation. Media outlets including local and international television, radio, and print media were approached and community members were informed directly through a study jingle played via loudspeaker from a van and by community-based activities. The Typhoid Vaccine Acceleration Consortium team held focus group discussions and met regularly to assess effectiveness of engagement.

RESULTS

Between February and September 2018, 28,142 children 9 months through 12 years were vaccinated at two health centres and multiple primary schools in Ndirande and Zingwangwa townships of Blantyre. The school-based vaccine campaign increased community participation exceeding recruitment targets of, on average, > 200 children/day.

CONCLUSIONS

Community engagement plays an important role in recruitment and in communicating research goals and objectives to participants. Multiple channels of communication are required to reach the community and deliver information needed for participation and provide an opportunity for dialogue with the trial team. The use of engagement modalities a community is already familiar with further increases acceptance and promotes ownership among local stakeholders. From this experience, community engagement played a critical role in meeting recruitment targets within 6 months.

99. Evaluation of Population-Based Serological Surveillance for the Identification of *S.* Typhi Chronic Carriers Using an Anti-Vi IgG ELISA

James Meiring[1], Merryn Voysey[2], Buddha Basnyat[3], John Clemens[4], Melita Gordon[5], Robert Heyderman[6], Firdausi Qadri[4], Andrew Pollard[2]

[1]Oxford Vaccine Group, [2]University of Oxford, [3]Oxford University Clinical Research Unit Nepal, [4]icddr,b, [5]Malawi Liverpool Wellcome Trust, [6]University College London

BACKGROUND

Between 1 and 5% of acute typhoid fever cases are thought to develop chronic carriage of *Salmonella* Typhi. Identification of these individuals is challenging due to their asymptomatic state and the intermittent nature of stool shedding. Previous attempts to identify carriers by population-level serological screening for anti-Vi (virulence capsule) IgG has produced mixed results. With the introduction of Vi-conjugate vaccines into endemic countries, understanding the epidemiology of typhoid carriage and its impact on indirect and overall vaccine efficacy is of high importance.

The Strategic Typhoid Alliance across Africa and Asia (STRATAA) programme has performed the largest ever serological survey for typhoid infection aiming to identify potential chronic carriers suitable for further stool shedding assessment. Here we present the initial anti-Vi IgG results.

METHODS

Using a demographic census of approximately 100,000 individuals in Blantyre (Malawi), Dhaka (Bangladesh) and Lalitpur (Nepal), 8,500 participants at each site were randomly selected using an age-stratified approach. Blood samples were collected at baseline and 3 months over an 18month period.

Serum anti-Vi immunoglobulin G (IgG) antibody levels were tested using the commercially available VaccZyme enzyme-linked immunosorbent assay kit (The Binding Site) according to the manufacturer's instructions.

An age-stratified cut-off for high Vi-IgG antibody was set independently for each site after the first 1000 samples had been processed. Individuals with values above this cut-off were followed up to provide two stool samples over 48 hours for microbiological testing.

RESULTS

21,184 participants provided at least one plasma sample for analysis. 167 reported having received a typhoid vaccine. Cut-off levels were set at 96.3EU/ml for 0-14yr-olds and 57.1 EU/ml for >15yr-olds in Bangladesh, 141.5 EU/ml for 0-14yr-olds and 101.4 EU/ml for >15yr-olds in Nepal and 91.3EU/ml for 0-14yr-olds and 65.1 EU/ml for >15yr-olds in Malawi with anti-Vi antibody increasing with age across all three sites. Currently, 410 participants have been followed up with stool culture, with 1 positive for *S.* Typhi. Follow-up is ongoing.

CONCLUSIONS

A large-scale serological survey has been undertaken from which individual follow-up is ongoing. Preliminary results indicate very low rates of microbiologically-confirmed chronic carriage among individuals with high Vi-IgG antibody titres.

100. High Rates of Enteric Fever and Anti-Microbial Resistance Following an Epidemic in Blantyre, Malawi: The STRATAA Study

James Meiring[1], Tikhala Makhaza Jere[2], Maurice Mbewe[2], Harrison Msuku[2], Deus Thindwa[2], Robert Heyderman[3], Melita Gordon[2]

[1]Oxford Vaccine Group, [2]Malawi Liverpool Wellcome Trust, [3]University College London

BACKGROUND

Estimated to cause 3-5million infections in Africa each year, enteric fever is a serious public health concern throughout much of the continent. Blantyre, Malawi had an epidemic rise in cases secondary to the introduction of a multi-drug resistant strain from South Asia. Here we present data following the recent epidemic as part of the Strategic Typhoid Alliance across Africa and Asia (STRATAA) Consortium.

METHODS

A demographic census was enumerated in the large township of Ndirande, Blantyre. Facility-based passive surveillance was conducted from a primary health care clinic and central referral hospital. Blood-culture collection for febrile illness was conducted for two years with repeat census following this. Healthcare utilisation surveys were conducted in a sample of households to enable adjustment of incidence estimates for healthcare seeking behaviour. Community-based serological surveillance was performed on an age-stratified cohort of over 8,000 individuals randomly selected from the census, with blood samples collected at baseline and 3 months.

RESULTS

Between July and October 2016, 97,410 participants within 23,567 households were enrolled into a demographic census with average household size of 4.4, and 43% of the community less than 15years of age. From this population, 120 *S.* Typhi and 20 *S.* Typhimurium were cultured from the blood of 2304 febrile participants. The unadjusted incidence rates for blood culture confirmed *S.* Typhi per 100,000 person-years of observation were 61.1. Adjusted incidence rates were highest in the 5-9year age group.

93% of the population used shared pit latrines for defecation and the majority collect drinking water from communal taps and boreholes. 45% of the population use government healthcare facilities for febrile illness, with self-treatment and private clinics also used.

29% of febrile participants recruited gave a history of prior antimicrobial usage. Multi-drug resistance was observed in 97% of isolates with no nalidixic acid resistance documented.

CONCLUSIONS

Following an epidemic we have identified that S. Typhi continues to be a major cause of febrile illness notably within school aged children. Combined with the high rates of anti-microbial resistance and the presence of many known risk factors for enteric infection, the introduction of typhoid conjugate vaccines is a necessity.

101. Passive Surveillance for a Phase III Clinical Efficacy Trial for a Typhoid Conjugate Vaccine: TyVAC Malawi

James Meiring[1], Priyanka Patel[2], Pratiksha Patel[2], Maurice Mbewe[2], Kathleen Neuzil[3], Melita Gordon[2]

[1]Oxford Vaccine Group, [2]Malawi Liverpool Wellcome Trust, [3]University of Maryland

BACKGROUND

Blood culture is the most common diagnostic method for detecting *Salmonella enterica* serovar Typhi (*S.* Typhi) and Typhimurium (*S.* Typhimurium) in surveillance studies and clinical trials. The diagnostic sensitivity of a blood culture is estimated at around 60%. Recent meta-analysis suggests this sensitivity is affected by the volume of blood collected and prior antimicrobial usage. We present data on blood culture surveillance from the Typhoid Vaccine Acceleration Consortium phase 3 clinical trial for a new typhoid conjugate vaccine in Malawi.

METHODS

In Blantyre, Malawi, we are conducting a two-year facility-based passive surveillance on 28,143 children vaccinated as part of the first efficacy trial of a new typhoid conjugate vaccine in Africa. A blood sample is collected when vaccinated children present to a study facility with either a temperature of at least 38 degrees or fever for at least three days. The volume of blood collected was calculated and compared to the volume documented in the electronic case report form. Every febrile child also has a malaria rapid diagnostic test performed.

RESULTS

Between 21 February 2018 and 2 November 2018, a total of 2173 blood samples were collected and cultured from eligible children of which 823 of the blood samples were collected in pre-weighed culture sample bottles. There have been 15 *S.* Typhi and 5 *S.* Typhimurium cases to date with the majority of cases in children under 5 years of age. For *S.* Typhi cases, mean volume collected was 6.78 ml compared to 4.9 ml for culture negative cases. 7.1% of children received anti-microbials prior to their clinic visit and over 80% were prescribed anti-microbials after consultation. 209 children had a positive malaria rapid diagnostic test.

CONCLUSIONS

Comprehensive passive surveillance is essential for the success of any vaccine efficacy trial. Here we demonstrate adequate blood culture volume collection, with larger volumes in culture positive cases. This trial is ongoing.

102. TyVAC Malawi: Phase 3 Randomized, Double-Blind, Controlled Trial of Clinical Efficacy of Typhoid Conjugate Vaccine in Children: Study Protocol

James Meiring[1], Matthew Laurens[2], Pratiksha Patel[3], Priyanka Patel[3], Theresa Misiri[3], Kenneth Simiyu[2], Melita Gordon[3], Kathleen Neuzil[2]

[1]Oxford Vaccine Group, [2]University of Maryland, [3]Malawi Liverpool Wellcome Trust

BACKGROUND

Typhoid fever is an acute infection characterized by prolonged fever, following the ingestion and subsequent invasion of *Salmonella enterica* serovar Typhi (*S.* Typhi). The incidence of typhoid fever has been most-reported in children 5-15 years of age, but is increasingly recognized in children younger than 5 years old, and on the African continent. Current estimates indicate nearly 12 million cases and more than 128,000 related deaths occurring worldwide annually.

Typhoid conjugate vaccine was recently recommended by the World Health Organization for use in routine immunization programs based on data from Asia. No typhoid conjugate vaccine had been previously tested in Africa. Here we present the protocol for an on-going trial to determine the efficacy of Typbar-typhoid conjugate vaccine in children in Blantyre, Malawi.

METHODS

We designed a phase III, individually randomized, controlled, double-blind trial of the clinical efficacy of a typhoid conjugate vaccine, among children 9 months through 12 years of age, randomised in a 1:1 ratio, to receive a typhoid conjugate vaccine or a meningococcal serogroup A conjugate vaccine. A subset of 600 of these children were enrolled in a vaccine immunogenicity and reactogenicity sub-study and had blood drawn before vaccination and at two timepoints after vaccination. All children are under passive surveillance for at least 2 years, or until x number of cases are accrued to determine the primary outcome, which is blood culture confirmed *S.* Typhi illness. All children will be followed actively for adverse events and serious adverse events.

RESULTS

Between February 21, 2018 and September 28, 2018, 28,142 children were enrolled in the trial. Children are currently being followed for febrile illness. As of October 31, 2018, 13 typhoid cases were blood-culture confirmed.

CONCLUSIONS

This trial, the first of a typhoid conjugate vaccine in Africa, seeks to demonstrate the impact and programmatic use of typhoid conjugate vaccines within an endemic setting. The trial is fully recruited, and is expected to yield efficacy results in 2020.

103. Monitoring and Evaluation of a Multi Country Surveillance Study: The Severe Typhoid in Africa Program

Daniel Ondari Mogeni[1], Ligia María Cruz[1], Se Eun Park[1], Justin Im[1], Ursula Panzner[1], Raphaël Rakotozandrindrainy[2], Iruka N. Okeke[3], Florian Marks[1]

[1]International Vaccine Institute, [2]University of Antananarivo, [3]University of Ibadan

BACKGROUND

There is limited information on best practices to monitor multi-country epidemiological studies. We describe the monitoring and evaluation procedures created and implemented in the multi-country study, The Severe Typhoid in Africa (SETA) Program and its impact. SETA involves various core activities such as disease surveillance, cost-of-illness assessment and long-term patient follow-up. Ensuring successful project outcomes in high quality and cross-site comparability requires the adequate monitoring of these activities.

METHODS

A dedicated monitoring team was formed, and two main monitoring components were developed: SETA databases at the International Vaccine Institute (IVI) and core activities in the field sites. The SETA databases are monitored as a collaborative effort between IVI and each study site. A monthly report is generated for identified study indicators based on the objectives. The core activities are monitored in the field in each country at least twice per year. Each core activity is observed in detail during the routine work of study staff and a report is written highlighting issues requiring attention. Phlebotomy process is one of the sample collection core activities that is monitored.

RESULTS

Continuous monitoring activities have resulted in enhanced compliance to the protocol and standard operating procedures. Repeat trainings have been conducted where necessary as has been support supervision. For instance, in 2017 the proportion of contaminated blood cultures rose from 5.9% to 12% in 2 months in Nigeria and 5.6% to 6.2% in Madagascar within a month. Following monitoring visits and corrective actions, contamination rates in both countries reduced to less than 1%.

CONCLUSIONS

Unique conditions exist in multi-country surveillance studies such as SETA and site-specific adaptations are required to ensure successful study implementation. Continued monitoring and evaluation efforts are required to ensure that the procedures are harmonized across sites. Flexibility, continuous feedback and team participation is important to find sustainable solutions.

104. Analysis of Nontyphoidal *Salmonella* Isolated at a Tertiary Care Hospital in Northern Sri Lanka

Nasmiya Mubarak[1], Niroshy Kandasamy[1], Sinthuja Mahalingam[1], Sujatha Pathirage[2]

[1]Teaching Hospital Jaffna, [2]Enteric Reference Laboratory, Medical Research Institute, Colombo

BACKGROUND

Invasive nontyphoidal Salmonelloses is gaining interest globally. Limited data from Sri Lanka reports *Salmonella Enteritidis* as the predominant serotype (invasive and non-invasive) showing 66.6% ciprofloxacin resistance. Intermediate resistance to ceftriaxone has been detected in few nontyphoidal *Salmonella*. We analyzed serotypes, antimicrobial susceptibility, epidemiology, and invasive disease profile of nontyphoidal *Salmonella* isolates in northern Sri Lanka.

METHODS

Stool and blood cultures of adult and paediatric patients received to the microbiology laboratory, Teaching Hospital Jaffna from June 2014 to September 2018 were analyzed. Specimen processing, organism identification and antimicrobial susceptibility testing followed standard laboratory methods. The enteric reference laboratory in Colombo, Sri Lanka performed serotype determination.

RESULTS

Twenty-two (7 blood and 15 stool) nontyphoidal *Salmonella* were isolated. Nontyphoidal *Salmonella* accounted for 0.29% (7/2403) bacteraemic patients consisting of four adults and three children. All adults (two male, two female) were above 60 years. Serotypes detected were *S.Enteritidis* (3 patients) and *S.Stanley* (1 patient). One *S.Enteritidis* bacteraemic patient was diagnosed with prosthetic valve endocarditis and didn't survive. Other three patients had underlying comorbidities and survived. The three children were males below 1 year. Serotypes identified were *S.Enteritidis*, *S.Filmore* and *S. Chester.* The infant with *S.Enteritidis* bacteraemia had Kawasaki's disease. The other two were previously healthy. Stool culture from the infant with *S.Chester* bacteraemia yielded *S.Chester* and *Campylobacter jejuni*.

15/1952 (0.77%) of the total stool cultures yielded nontyphoidal *Salmonella*. Majority (10/15) belonged to the paediatric age group and 70% (7/10) were below 1 year. 3/5 adult patients were above 60 years. Gender predominance not noted in any age group. 7 different serotypes were identified among the 15 isolates.

All invasive isolates were sensitive to ampicillin, co-trimoxazole, chloramphenicol and ceftriaxone with complete/intermediate resistance to ciprofloxaxin. All stool isolates were sensitive to furazolidone and mecillinam. 80% (12/15) were not susceptible to ciprofloxaxin. Two stool isolates were resistant by disc diffusion to ceftriaxone with ESBL production detected in one.

CONCLUSIONS

Despite high prevalence of gastroenteritis and typhoid in this region, nontyphoidal *Salmonella* detection was low. Nontyphoidal *Salmonella* bacteremia was 0.29% (7/2403) compared to 3.08% (74/2403) *S.Typhi* bacteremia. Detection of high rate ciprofloxacin resistance and reduced 3rd generation cepholosporin susceptibility is of concern.

105. Development and Application of Methods to Detect *Salmonella* Typhi in Water and Drainage Samples in an Urban Informal Settlement in Kenya

Jennifer Murphy[1], Jennifer Verani[2], Patricia Akers[3], Eric Mintz[1], Jothikumar Narayanan[1], Elizabeth Hunsperger[2], Loicer Achieng[3]

[1]Centers for Disease Control and Prevention, [2]CDC-Kenya, [3]Kenya Medical Research Institute

BACKGROUND

Typhoid fever substantially contributes to the burden of enteric disease in sub-Saharan Africa. To better understand typhoid fever transmission dynamics in Kibera, an informal settlement in Nairobi, Kenya, a longitudinal environmental study was conducted to detect *Salmonella* serotype Typhi in sewage-impacted drainage streams and drinking water and using both traditional culture-based and new advanced molecular-based methods.

METHODS

Drainage and drinking water samples were collected in triplicate from four sampling sites over the course of one year. General physical, chemical, and microbial water quality parameters were measured and dead end ultrafiltration was used to concentrate up to 100 L of water. Ultrafilter concentrates were submitted to standard culture methods to obtain presumptive positive *Salmonella* colonies. Enrichments and colonies will be analyzed using existing and newly-developed *Salmonella* and *S.* Typhi real-time polymerase chain reaction (PCR) assays. Preserved aliquots of concentrates and cultures will be further analyzed using a modified sequence-independent single primer amplification (mSISPA) technique followed by next generation sequencing. High-throughput targeted amplicon sequencing will also be performed.

RESULTS

A total of 72 drainage and 72 drinking water samples were collected over six sampling events from 2017 to 2018. Average free chlorine in drinking water was 0.3 mg/L; turbidity, pH, conductivity, and fecal indicator bacteria concentrations were within expected ranges for surface and drinking waters. A total of 253 and 42 presumptive positive *Salmonella* colonies were isolated from 58 (81%) drainage and 12 (17%) drinking water samples, respectively. Initial PCR analysis of a subset of presumptive positive colonies indicates *Salmonella* species. Molecular analyses are on-going and a comprehensive dataset will be presented.

CONCLUSIONS

S. Typhi isolated from drainage streams and drinking water in Kibera may provide insight into environmental exposure routes and possibly the extent of asymptomatic carriers and cases not fully captured by surveillance in the community. Advanced molecular detection methods will provide tools for monitoring low concentration pathogens directly from environmental samples at a genomic resolution that may allow for trace back to clinical cases and in turn allow for the development of rapid remediation strategies in the event of future outbreaks.

106. Prevalence of Fecal Carriage of Non-Typhoidal *Salmonella* in Kenya

Esther Muthumbi[1], Arthur Mwanzu[2], Geoffrey Bigogo[3], Cecelia Mbae[4], Samuel Kariuki[4], Jennifer R. Verani[5], Anthony Scott[2]

[1]KEMRI-Wellcome Trust Research Programme, [2]KEMRI-CGRMC, [3]KEMRI-CGHR, [4]KEMRI-CMR, [5]CDC-DGHP

BACKGROUND

The routes of transmission of non-typhoidal *Salmonellae* (NTS) causing invasive disease in Africa are unknown. Carriers who shed NTS in stool may be important host reservoirs for both endemic and epidemic disease. Knowledge of the prevalence of NTS carriage and circulating strains can provide insight on sources of infection and guide vaccine development.

METHODS

To estimate the age-stratified prevalence of fecal carriage of NTS in Kenya, we conducted a cross-sectional study across 3 sites in Kenya with high (Siaya), moderate (Nairobi) and low (Kilifi) incidence of invasive NTS disease. We randomly selected 100 participants from age-bands: 0-11months, 12-59months, 5-14years, 15-54years and >55years using the Kilifi Health Demographic Surveillance System (HDSS) and the KEMRI/CDC HDSS in Siaya. In Nairobi, we used high-resolution maps and a GPS system to randomly select prospective participants' homes. We collected a fresh stool sample from 1500 healthy children and adults across all sites, venous blood for HIV-1 and HRP-2 rapid tests and administered a questionnaire on risk factors. Stool samples were cultured within 8 hours of collection on selective agar following standard protocol.

RESULTS

Overall, 53 isolates of NTS were cultured (53/1500, 3.5%). Forty-six NTS isolates were recovered in Kilifi (46/494, 9.4%), 6 in Siaya (6/496, 1.2%) and 1 in Nairobi (1/510, 0.2%). The age and sex specific prevalence was highest among females aged 15-54 years (19.5%, 95% CI 8.8-34.9). Of the 53 isolates, 5 were *S.* Enteritidis, 1 was *S.* Typhimurium. The rest could not be typed by the panel of antisera available. There was no *S.* Typhi isolated in any of the sites. All isolates were susceptible to all the antibiotics tested including ampicillin, chloramphenicol, ciprofloxacin and co-trimoxazole. Prevalent NTS carriage was not associated with recent malaria (Prevalence ratio (PR) 0.91 95%CI [0.23,3.61]) or malnutrition (WAZ<-3) (PR 1.51 [0.22,10.52]).

CONCLUSIONS

There was a relatively high prevalence of fecal carriage of NTS in Kilifi, an area of low incidence of invasive NTS disease. Prevalent carriage strains (non-typable by antisera panel used) differ from those that cause invasive disease (primarily MDR *S.* Enteritidis and *S.* Typhimurium). Further research is needed to explore the sources of incident invasive NTS disease.

107. Prevalence of Enteric & Nontyphoidal Salmonellae & Their Antimicrobial Susceptibility Pattern From 2014-18: Laboratory Based Study From South India

Savitha Nagaraj, Sanju Jose, Aruna Sethuraman, Ratnamala Choudhury, Mary Dias

St Johns Medical College and Hospital

BACKGROUND

The disease burden in South Asia, where access to safe water and sanitation is suboptimal, is believed to be high with an estimated incidence of 394 cases per 100,000 person-years. The emergence of the multidrug resistant H58 clade in the Indian subcontinent and recent reports of resistance to last line antibiotics suggest that typhoid will be increasingly difficult and expensive to treat. This study describes the experience of a tertiary care teaching hospital in South India.

METHODS

Retrospective lab based surveillance of cultures and WIDAL. The culture &susceptibility data of all samples received in the laboratory from 2014 till August '18 were retrieved from the Laboratory information system& analysed for S.Typhi,S. Paratyphi A (Enteric Salmonellae ES)& Non typhoidal Salmonellae(NTS). All blood cultures were processed by automated System and other samples by recommended manual methods and antisera.Antimicrobial susceptibility was reported using Kirby Bauer disc diffusion method, according to specific CLSI guidelines.MIC for Ciprofloxacin was documented by VITEK 2 or by Etest when required.The laboratory is accredited by the National body since 2006 &followed appropriate quality assurance procedures.Data was expressed as percentages.

RESULTS

In addition to other samples,83115 blood cultures were received during this period, 7784(11% showed growth,596 isolates of S.Typhi(6.08%),143 of S.ParatyhiA(1.6%)& 32 of NTS (.4%,S.typhimurium).Additional19 isolates of Enteric &10 of NTS were identified from other samples eg discharges,urine etc.No difference in the isolation rates was noticed. Resistance to ciprofloxacin significantly increased from 22% in 2014 to 90% in'17& 96% in '18 among ES and in NTS from 37%to 50%.All ES were susceptible to Ceftriaxone. Most of culture positives were from inpatient adults(379/596 S.Typhi & 217/596 S.Paratyphi A).Seasonal trends were peaks in Jan-July('14&'15) & additional peaks in Oct-Dec('16&'17) 20612 serum samples were tested by WIDAL.Additional 795 patients had titres of >160 suggestive of Enteric fever (S.Typhi O& H, significant in our region) &122 of S.Paratyphi A.

CONCLUSIONS

This study demonstrates the continued presence of Salmonellae both Enteric &NTS from adults &paediatrics in an endemic urban region &the need for hospitalisation. Resistance to Ciprofloxacin has increased over the years.The study highlights the increased risk of infection even in well developed cosmopolitan cities, need for surveillance of the susceptibility pattern& vaccines.

108. *Salmonella* Genomics: A Revolution in Public Health Microbiology

Satheesh Nair, Hassan Hartman, Tim Dallman, Martin Day, Kathie Grant, Marie Chattaway

Public Health England

BACKGROUND

Salmonella is a major human pathogen and a global public health burden. Emerging multidrug resistant (MDR) *Salmonella* are increasing the stress on global health care systems. As part of the public health action to control *Salmonella*, a rapid, high throughput, high resolution Whole Genome Sequencing (WGS) approach for routine service delivery at Gastrointestinal Bacterial Reference Unit, Public Health England (PHE) has been adopted since April 2015 to interrogate c.10,000 *Salmonella* isolates annually.

METHODS

Sequence data derived from WGS by Illumina HiSeq for c.40,000 *Salmonella* isolates between 2015 -2018 was analysed to determine Multi locus Sequencing Typing (MLST) for serovar identification, the presence of known resistance genes, and single nucleotide polymorphisms (SNP) for strain discrimination. Sequence data were also used to develop Real-Time PCR assays for rapid isolate identification.

RESULTS

1. *Salmonella* identification : MLST provided an insight into the genetic population structure of all *Salmonella* serovars in England and Wales during a 4 year period . *S.* Enteritidis and *S.*Typhimurium were the predominant serovars, with a significant number of *S.*Typhi and *S.*Paratyphi A
2. Detection and surveillance of antimicrobial resistance (AMR): The use of an in-house AMR pipeline for the detection of drug resistance genes and characterisation of resistance mechanisms/regions. WGS was used to determine the first reported cases of ESBL resistance in S. Typhi and S.Paratyphi A in the U.K. Prevalence of azithromycin, ESBL and fosfomycin resistance in the U.K population of non-typhoidal *Salmonella* (NTS) has been highlighted. A cause of concern as azithromycin and ESBL are being used as the drug of choice for enteric fever and invasive NTS treatment in many parts of the world.
3. Development of a RT-PCR assay: A RT-PCR assay to differentiate typhoidal and NTS serovars and to identify typhoidal pathogens was developed

CONCLUSIONS

In the last 5 years WGS has transformed *Salmonella* routine service delivery at PHE, revolutionising public health microbiology. Rapid advances in WGS methodologies have resulted in the ability to perform robust high throughput sequencing of bacterial genomes at low cost making WGS an economically viable alternative to traditional typing methods for public health surveillance, outbreak and AMR detection.

109. Clinical Manifestations and Antimicrobial Treatment of XDR Typhoid Patients: Experience From Outbreak in Pakistan

Farah Qamar, Sarwat Ansari, **Abdullah Naveed**, Sultan Karim, Aiman Mukhtar, Tahir Yousafzai

Aga Khan University and Hospital

BACKGROUND

Enteric fever due to Salmonella Typhii is one of the leading causes of febrile disease in Pakistan and with the emergence of extreme drug resistant (XDR) Salmonella Typhii, it poses an even greater risk. Here we report the clinical manifestations and the treatment response of different antibiotics in treating patients with XDR Typhoid in Pakistan.

METHODS

We retrospectively reviewed the outpatient and inpatient records of culture proven XDR typhoid patients who visited Aga-Khan Hospital Karachi and Aga-Khan Secondary Care Hospital Hyderabad between March 2017 to June 2018. Only cases who had complete records on treatment, dosage, frequency and duration of treatment were included in this study. Clinicopathologic data was analyzed to assess efficacy of used antibiotics and incidence of different clinical symptoms was also documented.

RESULTS

72 patients were enrolled into this study. 47/72 (65%) were treated as inpatients. 42/72 (58%) were male and 56/72 (78%) were children aged less than 18 years old. Clinical symptoms most prevalent were vomiting (71%), headache (51%), abdominal pain (46%) and diarrhea (46%). The two antibiotics (Azithromycin and Meropenem) that this strain of Salmonella Typhii was not resistant to were compared. Dosage of Azithromycin and Meropenem for pediatric population was 10mg/kg and 20mg/kg respectively whereas for adults it was 500mg twice daily and 500mg thrice daily respectively. Parameters used to assess efficacy were relapse within 28 days, time to defervescence and treatment duration. Patients only administered Azithromycin had a mean time to defervescence of 7.29 $\pm$ 0.787 with 0 relapses and median duration of treatment with IQR 7(2). Patients only administered Meropenem had a mean time to defervescence of 7.00 $\pm$ 2.17 with 0 relapses and median duration of treatment with IQR 8.5(5). Patients who received both Meropenem or Azithromycin had a mean time to defervescence of 7.89 $\pm$ 1.08 with 1 relapse. In this group Azithromycin was given for a median duration with IQR for 7(4) and Meropenem for 9(6). Only 1 patient developed complication and died.

CONCLUSIONS

This observational study showed no significant difference in clinical outcomes when being treated with either Azithromycin, Meropenem or both. Clinical trials are needed for further evidence.

110. Cold Chain Management at Vaccination Sites During a Phase 3 Controlled Trial for the Clinical Efficacy of a Typhoid Conjugate Vaccine

John Ndaferankhande[1], Maureen Ndalama[1], Andreas Singini[1], Brian Ngwira[1], James Meiring[2], Markus Gmeiner[1], Melita Gordon[1]

[1]Malawi Liverpool Wellcome Trust, [2]Oxford University

BACKGROUND

The cold chain is an integral part of managing pharmaceutical products in clinical trials. However, it is a challenge to maintain the cold chain at the quality levels required in the field. Here we present temperature control aspects of cold chain management in a phase 3 trial in Malawi that seeks to determine the efficacy of a new typhoid conjugate vaccine in an endemic setting.

METHODS

The study enrolled 28,143 participants, randomized 1:1, to receive a typhoid conjugate vaccine in 2.5 ml pre-filled syringes or MenAfrivac Meningococcal Group A conjugate vaccine. We used temperature monitoring and control devices with short message service and email alarm systems and instituted clearly defined accountability measures. During the study, 1440 vials of an investigational typhoid conjugate vaccine and 770 vials of Meningococcal Group A conjugate vaccine were stored at the Malawi-Liverpool Wellcome Trust research pharmacy. The vaccines were transferred daily to field vaccination sites.

Temperature records of credo cubes used for transportation of vaccines from the research pharmacy to field sites were analyzed from February 28 through to July 08, 2018. These records were compared to the research pharmacy vaccine refrigerator temperature recordings from a Beyond Wireless remote temperature monitoring system.

RESULTS

The research pharmacy temperature ranged from 2.0°C to 5.3°C with a mean of 3.5°C. The temperature in the credo cubes used to transport vaccine to the field ranged from 4.2°C to 12°C with a mean of 5.6°C. The recommended temperature for cold chain is 2°C to 8°C.

CONCLUSIONS

Temperature recordings for both the pharmacy and the credo cubes were well within the recommended temperature range except on a single occasion when the credo temperature was 12°C. As evidenced here, the cold chain can be well managed at different sites provided staff involved in investigational medicinal product handling are well trained in conditioning credos, temperature monitoring and transportation. Clearly defined accountability processes are critical.

Good cold chain management ensures vaccine quality and gives confidence that pharmaceutical compounds are managed according to Good Pharmaceutical Practice. Data on field site vaccine administration from clinical trials will support national vaccination programs in managing cold chain on a large scale.

111. Immunogenicity of a Novel Typhoid Conjugate Vaccine in African Infants and Children

Nginache Nampota[1], Maurice Mbewe[2], Lameck Khonde[1], **Osward Nyirenda[1],** James Meiring[3], Kathleen Neuzil[4], Melita Gordon[2], Matthew Laurens[4]

[1]Blantyre Malaria Project, [2]Malawi-Liverpool-Wellcome Trust Clinical Research Programme, [3]Oxford Vaccine Group, University of Oxford, [4]University of Maryland School of Medicine

BACKGROUND

Human vaccination with two or more antigens simultaneously may invoke a different immune response compared to single antigen vaccination. Vaccine response may also differ based on demographic and genetic factors that vary by region. For these reasons, new vaccines are routinely tested in clinical studies where the novel vaccine is given with routine immunizations in different geographic settings. For the newly recommended typhoid conjugate vaccine, studies in Indian children to date, show no interference of the typhoid conjugate vaccine with immune response to measles-containing vaccines. Immunogenicity data in African children, including co-administration with routine vaccination are needed by stakeholders and health officials to inform decision-making. Here we present the first immunogenicity data from African children vaccinated with typhoid conjugate vaccine.

METHODS

The Typhoid Vaccine Acceleration Consortium conducted a phase 3 randomized, blinded, controlled clinical efficacy trial of typhoid conjugate vaccine in Malawian children ages 9 months to 12 years. Participants were randomized in a 1:1 ratio to receive typhoid conjugate vaccine or a meningococcal serogroup A conjugate vaccine. A subset of 600 children (200 in each of three age groups: 9-11 months, 1-5 years, and 6-12 years) were included in a safety and immunogenicity sub-study with more stringent exclusion criteria, including no known HIV exposure or infection. In this sub-study, we collected serum before vaccination and 28 days after vaccination to measure anti-Vi (VaccZyme™ Binding Site), anti-measles, and anti-rubella antibody by enzyme-linked immunosorbent assay (ELISA). Blood specimens collected were processed and serum stored on the day of collection.

RESULTS

By the close of recruitment in September 2018, 602 children were enrolled in the sub-study. Two hundred children ages 9 to 11 months received measles-rubella vaccine together with their assigned study vaccine. The remaining 402 children, ages 1-12 years, received their assigned study vaccine alone. Immunogenicity results are currently being generated and analyzed.

CONCLUSIONS

Typhoid conjugate vaccine is not expected to interfere with the immune response to measles-rubella vaccine. Immunogenicity data for the entire cohort of 602 children enrolled in the sub-study will be presented.

112. *Salmonella* Exposure in the Gut Elicits Protective Serum Bactericidal Immunity Against Invasive *Salmonella* Disease in a Cohort of Malawian Children

Tonney Nyirenda[1], Victor Chikwapulo[2], Ndaru Jambo[2], Angeziwe Chirambo[2], Marc Henrion[2], Wilson Mandala[3], Robert Heyderman[4], Melita Gordon[2]

[1]College of Medicine, University of Malawi, [2]Malawi Liverpool Wellcome Trust, [3]Malawi University of Science and Technology, [4]University College London

BACKGROUND

Invasive nontyphoidal *Salmonella* (iNTS) disease is an important cause of death in African children. Defining the events leading to natural acquisition of protective immunity to iNTS remains elusive, yet understanding this is critical for generation of an effective vaccine. Opsonic IgG antibodies against *Salmonella* lipopolysaccharide (LPS) facilitate efficient killing of *Salmonella* in the extracellular (cell-free) and intracellular space. We hypothesized that natural, asymptomatic *Salmonella* exposure within the gastrointestinal tract (GIT) children induces the generation of NTS-specific antibodies, which mediate the acquisition of protective serum bactericidal immunity against iNTS disease.

METHODS

We recruited a cohort of 60 healthy children from Zingwangwa Health Centre, in Blantyre at 6 months of age, and followed-up until 18 months of age. *Salmonella* exposure events in stool samples were determined by standard stool culture and PCR at monthly intervals. We quantified serum bactericidal activity (SBA) against *S.* Typhimurium strain D23580, and *S.* Typhimurium anti-LPS antibody titres (IgA, IgM, IgG, IgG1-4) in blood samples collected at 3-month intervals. We analysed data using (generalised) linear mixed models.

RESULTS

Importantly, Akaike Information Criterion (AIC) models revealed that robust SBA was directly associated with current *Salmonella* exposure (p=<0.001), age (p=<0.001) and IgG2 titre (p=<0.05), and inversely associated with IgA titre (p=<0.05). We detected a total of 33 *Salmonella* exposure events in 23 children over the study period. We found that current *Salmonella* exposure increases in children with recent history of antimalarial drugs use (p=<0.05) while previous *Salmonella* exposure increases in children with recent history of antimalarial use (p=<0.001) and antibiotic drug use (p=<0.001). Current *Salmonella* exposure was associated with an increase in IgG2 (p=< 0.05) and IgA (p=< 0.05) antibodies.

CONCLUSIONS

We have shown using principled statistical models in a longitudinal cohort of Malawian children that asymptomatic *Salmonella* exposure within the GIT triggers the generation of *S.* Typhimurium LPS-specific IgG2 antibodies which are instrumental for mounting functionally effective serum bactericidal immunity against iNTS. Transient asymptomatic gut exposure to *Salmonella* is an event that could either be beneficially immunising, or could result in invasive disease. Further work on the determinants of mucosal protection or mucosal invasion is warranted.

113. Genomic Characterization of Invasive *Salmonella enterica* Serovar Typhi Isolates From Kibera, Kenya, 2007 – 2017

Caroline Ochieng[1], Elizabeth Hunsperger[2], Mike Osita[1], Victor Omballa[1], Godfrey Bigogo[1], Bonventure Juma[2], Jennifer Verani[2], Heather Carleton[2]

[1]Kenya Medical Research Institute, Center for Global Health Research, [2]Centers for Disease Control and Prevention

BACKGROUND

More than 7 million cases of typhoid fever are estimated to occur each year in sub-Saharan Africa. A high burden of *Salmonella enterica* serovar Typhi (*S.* Typhi) bacteremia has been demonstrated in Kibera, an urban informal settlement in Nairobi, Kenya, characterized by high population density, limited access to safe water, and poor sanitation. However, the incidence in recent years has declined. We genetically characterized invasive *S.* Typhi from ongoing surveillance in Kibera.

METHODS

From 2007 to 2017, S. Typhi was isolated from blood culture of 379 patients with acute febrile illness or pneumonia though Population Based Infectious Disease Surveillance in Kibera; 324 (85.5%) isolates were revived, and 322 (85%) sequenced. Genomic DNA was extracted using Wizard Genomic DNA Purification kit (Promega), library prepared using Illumina Nextera XT Kit followed by paired end sequencing on a Hiseq platform (Illumina) in 300 cycle reaction. Serotype was confirmed using SeqSero v1 and resistance genes and classes identified using ResFinder implemented in BioNumerics 7.6. Sequence data was further analyzed by core genome MLST (cgMLST, EnteroBase scheme) and wgMLST.

RESULTS

A total of 267 (82.9%) isolates were confirmed to be Typhi. Up to 216 cgMLST allelic differences and 3 major clades were identified. One clade contained 93% (247/267) of isolates and a median of 11 allele differences (range 0-40). The frequency of predicted resistance gene classes were aminoglycosides (211 isolates), tetracycline (203 isolates), phenicol (212 isolates), sulphonamide (212), trimethoprim (212 isolates), fluoroquinolones (49 isolates) and β-lactams (211 isolates). Predicted plasmids included IncQ1 (211), IncHI1B (202 isolates) and IncHI1A (203 isolates). All these plasmids are linked to antibiotic resistance. Forty-two isolates lacked resistance genes and plasmids while 8 had only flouroquinolones resistance.

CONCLUSIONS

One *S.* Typhi clade predominated throughout the study period. However, from 2015 onwards, tetB and IncHI1 were no longer detected in most isolates and the gyrA83 mutation that confers fluoroquinolone resistance was present in the isolates. These differences in antibiotic resistance gene carriage coincided with a decline in *S.* Typhi bacteremia in Kibera.

114. Bacteremia Among Febrile Patients Attending Selected Health Facilities in Ibadan, Nigeria

Oluwafemi Popoola[1], Aderemi Kehinde[2], **Veronica Ogunleye[2],** Ondari D. Mogeni[3], Florian Marks[3], Iruka N. Okeke[1], the Severe Typhoid in Ibadan Research Group (SETA)[1]

[1]University of Ibadan, [2]University College Hospital Ibadan, [3]International Vaccine Institutue

BACKGROUND

Infectious diseases are important causes of morbidity and mortality, particularly in Africa. Estimating the burden of invasive bacterial infections in Nigeria and many other African countries is hampered by diagnostic limitations. This study screened pediatric and adult patients attending four health care facilities in Ibadan, South Western Nigeria for bacteremia, including invasive salmonellosis, and malaria parasitaemia.

METHODS

We conducted a cross-sectional study of the aetiology of febrile illnesses in the core municipal and outlying metropolitan areas of Ibadan. The study enrolled patients from four health care facilities between 16 June and 16 October 2017. Febrile patients underwent clinical diagnosis, blood culture, and malaria parasite testing. Bacteria in positive blood cultures were isolated and identified to at least species level.

RESULTS

A total of 682 patients were recruited and the majority, 467 (68.5%), were under 18 years of age. Bacterial pathogens were cultured from the blood of 116 (17.0%) patients with *Staphylococcus aureus* (69; 59.5%) and *Salmonella enterica* (33; 28.4%) being the most common species recovered. Twenty-seven (81.8%) of the *S. enterica* isolates were serovariety Typhi and six *Salmonella* belonged to the Paratyphi serotypes. Invasive non-typhoidal *Salmonella* were not recovered. Thirty-four individuals were found to be co-infected with *Plasmodium* and bacteria. Five (14.7%) of these co-infections, all of them in children under five years of age, involved

CONCLUSIONS

The study demonstrates that bacteria, *S.* Typhi in particular, were commonly recovered from febrile patients with or without malaria. Focused and extended disease burden studies are needed for typhoid conjugate vaccine introductions that may potentially generate significant impact on prevention of this severe community-acquired febrile disease in our locality.

115. Attitudes and Factors Influencing Participation in Enteric Fever Controlled Human Infection Trials: A Pooled Analysis of Six Nested Surveys

Blanche Oguti[1], Malick Gibani[1], Christopher Darlow[1], Emma Plested[1], Tom Darton[1,2], Andrew Pollard[1]

[1]Oxford Vaccine Group, [2]Florey Institute

BACKGROUND

Salmonella Typhi and *S.* Paratyphi controlled human infection models (CHIM) have recently been re-established to improve the understanding of host-pathogen interactions and to accelerate vaccine and diagnostic development. The primary motivations for participants to take part in these studies, which are often perceived to be 'high-risk', remain unknown. Here, our aim was to examine participant motivations and attitudes to identify factors influencing their decision to participate in human challenge research and to enable us to optimise the participant experience.

METHODS

Participant surveys were nested in six controlled human infection model studies conducted at a single research centre in Oxford between November 2011 and August 2017. The studies recruited from the same population of adults >18-years old in Oxfordshire. All participants were invited to complete an anonymous, self-administered paper or online survey at one predefined time-point. A descriptive analysis was performed using data pooled from these comparable studies.

RESULTS

A total of 201/447 (45.0%) challenge participants returned questionnaires and were included in the analysis. Overall, 57.0% of the cohort were educated to at least Bachelor's level and 62.6% described themselves as employed. Prior knowledge of enteric fever was reported as low by 88.5% of participants, however 100.0% of participants considered the written and verbal study information easy to understand. The most commonly cited motivations for participation were a desire to contribute to the progression of medicine (170/201: 84.6%), the prospect of financial reimbursement (166/201: 82.6%) and curiosity about clinical trials (117/201: 57.2%). Half of respondents developed enteric fever during study participation and 69.5% of these participants considered the experience of infection to be as expected or better than anticipated. All participants were either very satisfied (94.2%) or satisfied (5.8%) with the care received during the study.

CONCLUSIONS

These data indicate that participants felt that adequate information was provided during the informed consent process. Motivation to take part in the challenge studies was multi-factorial and heavily influenced by internal drivers beyond monetary reimbursement alone. Further studies are needed to determine whether high educational attainment and employment were protective factors against financial inducement, particularly if these studies are to be expanded to low-income and middle-income countries.

116. Antimicrobial Drug Administration, Salmonellosis and Antimicrobial Resistance in Broiler Production Value Chain, Oyo State, Nigeria

Nurudeen Olalekan Oloso[1], Ismail Adewuyi Adeyemo[2], Ismail Ayoade Odetokun[3], Adebola Olayemi Odeseye[4], Henriette Van Heerden[5], Folorunso Oludayo Fasina[6]

[1]University of Pretoria, South Africa, [2]Department of Veterinary Microbiology, Faculty of Veterinary Medicine, University of Ibadan, [3]Department of Public Health and Preventive Medicine, Faculty of Veterinary Medicine, University of Ilorin, [4]Department of Microbiology, Nigerian Institute of Science Laboratory Technology, Federal Ministry of Science and Technology, [5]Department of Veterinary Tropical Diseases, Faculty of Veterinary Science,University of Pretoria, [6]Emergency Centre for Transboundary Diseases (ECTAD-FAO), Food and Agricultural Organization of the United Nation, Dar es Salaam

BACKGROUND

Salmonella has been recognized globally to be on the high priority list for the study of bacterial antimicrobial resistance (AMR) circulating within human, food-animals and environment. Information on the use of antibiotics in food animals especially in broiler production are under-represented and the antibiotic usage pattern is considered a strong factor and contributor to AMR pool in one health status. This study is to explore the interaction between purposes and pattern of antimicrobial drug administration (usage) and circulating antimicrobial resistance of prevalent Salmonella isolates from Nigeria broiler production value chain.

METHODS

Study was conducted along the Nigeria broiler production value chain by using 181 antimicrobial usage questionnaires of 21 antimicrobial in 151 locations. Simultaneously, antimicrobial resistance testing of 18 commonly used antibacterials in humans was conducted on 507 isolates belonging to 261 (23%) samples that are positive for Salmonella out of the 1135 samples of broiler input, products and environmentally collected for the detection of Salmonella (modified ISO 6579 and invA PCR) from 60 of the locations. The data collected were subjected to descriptive statistics and presented as percentages, histogram and bar chart.

RESULTS

Overall, over 80% of the responses revealed the purposes of antimicrobial drugs were not for therapy based on laboratory confirmation with live-bird-market (100%), hatchery (86.7%), grow-out-farm (75%) and breeder (66.7%).

Wide spread prophylactic and metaphylactic used of antimicrobials without laboratory tests or and veterinarian prescription were recorded with the highest in enrofloxacin (63% and 24%), followed by tetracycline (58% and 33%) and erythromycin (50% and 17%) respectively. Antimicrobial resistance was highest in flumequine (100%), penicillin (95%) and perfloxacin (89%).

CONCLUSIONS

We observed high use without laboratory recommendation in higher generation of a class of antibiotics conferred high resistance on lower generation of the same class such as in enrofloxacin (2nd generation) and fumequine (first generation) which are both quinolone. This pattern is reflected in all the classes of antibiotics studied suggesting a link in antimicrobial usage pattern with AMR development. We therefore recommend the institutionalization of antimicrobial usage framework in one health platform that will incorporate an alternative source to replace prophylactic use of antimicrobial in animal production.

117. Safety and Immunogenicity of Typhoid Conjugate Vaccine in Nepal: Preliminary Results From a Randomised Controlled Trial

Dikshya Pant[1], Nicola Smith[2], Mila Shakya[3], Merryn Voysey[2], Rachel Colin-Jones[2], Buddha Basnyat[3], Andrew J Pollard[2]

[1]Patan Academy Of Health Sciences, Patan Hospital, [2]Oxford Vaccine Group, Department of Paediatrics, University of Oxford, and the NIHR, [3]Oxford University Clinical Research Unit - Nepal, Patan Academy of Health Sciences

BACKGROUND

Enteric fever caused by *Salmonella enterica* serovar Typhi is a major public health problem in developing countries, which could be controlled through widespread deployment of typhoid conjugate vaccine (TCV). Vaccine safety and tolerability is an important consideration in vaccine rollout. The recently WHO-prequalified TCV has been reported to be safe in infants, young children and adults in trials in India, though data remain limited.

METHODS

A randomised controlled trial is underway in Nepal to assess safety and efficacy of TCV in children from 9 months to 15 years of age, in which participants were randomised 1:1 to TCV or a capsular group A meningococcal vaccine. Blood samples were collected from a subset of consenting children on days 0 and 28 to assess immunogenicity. Further samples will be collected at 18 and 24 months. Telephone follow-up seven days after vaccination was conducted to solicit local and systemic reactions in all participants. All serious adverse events (SAE) were assessed in person or via telephone, recorded, and reported by the local study paediatrician.

RESULTS

20,019 children were randomised and vaccinated. 1441 children provided blood samples for immunogenicity. In the first seven days after vaccination, fevers occurred in 7.8% of children under-5 years and 4.2% of children aged 5-15 years. 6% of children felt pain at vaccination, 0.8% experienced swelling, and 0.2% experienced redness. Systemic reactions were experienced in a small proportion of children, the most common being nausea and diarrhoea in 1.4% and 1.8% of children respectively.

86 participants experienced 93 SAEs, all of which were due to participants requiring hospitalisation. The most common events were pyrexia, pneumonia, and febrile convulsions. One SAE was identified as vaccine-related by the investigators. The participant developed high-grade fever within 24 hours of vaccination and was admitted to the local hospital. The participant was given antipyretics and the fever subsided after 12 hours, investigations were within normal limits and the participant was discharged.

CONCLUSIONS

The unblinded data show that TCV and the control vaccine were well tolerated, and an interim unblinded analysis is in preparation. Immunogenicity data will also be available.

118. Increasing Incidence of Invasive Nontyphoidal *Salmonella* Infections in Queensland, Australia, 2007-2016

Andrea Parisi[1], John A. Crump[2], Russell Stafford[3], Kathryn Glass[4], Benjamin Howden[5], Martyn Kirk[4]

[1]Australian Institute of Health and Welfare, [2]University of Otago, [3]Queensland Health, [4]Australian National University, [5]University of Melbourne

BACKGROUND

Nontyphoidal *Salmonella* is a major contributor to the global burden of foodborne disease, with invasive infections contributing substantially to illnesses and deaths.

METHODS

We analyzed notifiable disease surveillance data for invasive nontyphoidal *Salmonella* disease (iNTS) in Queensland, Australia. We calculated an invasiveness index as the proportion of invasive isolates to the total number of isolates recovered for each serotype. To determine the effect of age group, gender, geographical area, time, and serotype on invasiveness, we calculated crude and adjusted odds ratios comparing invasive and non-invasive NTS infections. We used Poisson regression to estimate incidence rate ratios by gender, age group, and geographical area over 2007–2016.

RESULTS

There were 995 iNTS cases, with 945 (92%) confirmed by blood culture. *Salmonella* Virchow accounted for 254 (25%) of 1,001 unique iNTS isolates. *Salmonella* serotypes Choleraesuis, Dublin, and Panama had the highest invasiveness index. Invasive NTS disease incidence rates peaked among males, infants, during the summer months, and in outback Queensland where the incidence rate (95% CI) was 17.3 (14.5–20.1) cases per 100,000 population. Overall, there was a 6% annual increase (p<0.001) in iNTS disease incidence.

CONCLUSIONS

Our study provides an important insight into the epidemiology of iNTS disease in Australia. High rates of iNTS among males, infants, and elderly require further investigation of spatial clusters of disease, and clarification of patient and household risk factors through the conduct of case-control studies. In addition, there is a particular need to investigate and control food, animal, and environmental sources of *Salmonella* Virchow.

119. The Phylogeography and Incidence of Multi-Drug Resistant Typhoid Fever in Sub-Saharan Africa

Se Eun Park[1], Duy Thanh Pham[2], Christine Boinett[3], Vanessa K. Wong[4], Gi Deok Pak[1], Ursula Panzner[1], Florian Marks[1], Stephen Baker[2]

[1]International Vaccine Institute, [2]The Hospital for Tropical Diseases, Wellcome Trust Major Overseas Programme, Oxford University, Ho Chi Minh City, [3]Centre for Tropical Medicine and Global Health, Oxford University, Oxford, [4]The Wellcome Trust Sanger Institute, Hinxton

BACKGROUND

There is paucity of data on the geographical distribution, incidence, and phylogenetic structure of multi-drug resistant (MDR) *Salmonella* Typhi (*S.* Typhi) in sub-Saharan Africa. Here, by utilizing organisms and data generated through the Typhoid Surveillance in Africa Programme (TSAP) and from other African typhoid fever studies, we aimed to investigate the phylogeography and incidence of MDR *S.* Typhi across sub-Saharan Africa.

METHODS

Whole genome sequencing was performed on genomic DNA extracted from 249 contemporaneous *S.* Typhi isolates from 11 sub-Saharan African countries, followed by a phylogenetic reconstruction, in context of the 2,057 global *S.* Typhi genomic framework. Investigations of genes associated with antimicrobial resistance (AMR) and their geographical distribution were conducted. Population-based data were combined with genotypic and phenotypic data to calculate the incidence of MDR *S.* Typhi.

RESULTS

We identified 12 different *S.* Typhi genotypes circulating in 11 different countries. Despite this genetic diversity, most organisms (225/249; 90%) belonged to only three genotypes, 4.3.1 (H58) (99/249; 40%), 3.1.1 (97/249; 39%), and 2.3.2 (29/249; 12%). Organisms belonging to genotype 4.3.1 were found only in East Africa, whilst genotypes 3.1.1 and 2.3.2 were found only in West Africa. The majority (129/249; 52%) of organisms were MDR, with this phenotype being entirely confined within the dominant circulating genotypes in East (4.3.1) and West Africa (3.1.1). IncHI1 plasmids were the most common vehicle of MDR associated genes, but some isolates from Tanzania harboured an MDR-associated chromosomal insertion. High incidences (>100/100,000 person-years of observation) of MDR *S.* Typhi were calculated in sites with high burdens of typhoid fever, mainly among children aged <15 years.

CONCLUSIONS

MDR *S.* Typhi is widespread in sub-Saharan Africa and MDR organisms circulate across national borders within, but not between, East and West Africa. MDR was common in nearly all investigated countries and MDR *S.* Typhi incidences largely mirror typhoid incidences. AMR national action plans, including ongoing surveillance of antimicrobial usage and resistance, as well as antimicrobial stewardship policies and conjugate vaccines will be critical to control MDR typhoid in Africa.

120. The Severe Typhoid in Africa Program Protocol: Assessing the Burden, Severity, Host Immunity and Carriage Associated With Invasive Salmonellosis

Se Eun Park[1], Trevor Toy[1], Ligia Maria Cruz Espinoza[1], Ursula Panzner[1], Justin Im[1], Ondari D. Mogeni[1], John D. Clemens[2], Florian Marks[1]

[1]International Vaccine Institute, [2]International Centre for Diarrheal Disease Research

BACKGROUND

Typhoid and paratyphoid fever, and invasive nontyphoidal *Salmonella* disease are among the most common community-acquired bloodstream infections in children and adults in Africa. Invasive salmonellosis accounts for a high global disease burden, but there is paucity of data on the severity of disease, long-term host immune response mechanisms following natural infection and the prevalence of carriage.

METHODS

A prospective healthcare facility-based passive surveillance of enteric fever and clinically-suspected severe typhoid fever with complications will be performed in six countries: Burkina Faso, the Democratic Republic of Congo, Ethiopia, Ghana, Madagascar, and Nigeria. Defined inclusion criteria will be used, and enrolled patients with confirmed invasive salmonellosis by blood culture will form a cohort for clinical follow-up visits for one year to investigate host immunity, chronic carriage and socio-economic burden. Asymptomatic neighborhood controls and immediate household contacts of each case will be enrolled and assessed for level of *Salmonella*-specific antibodies and shedding patterns. Healthcare utilisation surveys and post-mortem questionnaires will be conducted in selected sites.

RESULTS

Incidences of TF/PF/iNTS disease and severe typhoid will be estimated, using blood-culture confirmed TF/PF/iNTS data and laboratory-confirmed severe typhoid cases (numerator) and pre-determined study catchment population (denominator). Several adjustment factors such as the proportion of eligible patients enrolled, healthcare utilization, and blood culture sensitivity. Death attributable to suspected invasive salmonellosis will be determined based on the post-mortem questionnaires and case report forms. Host immune response and acute/chronic carriage will be analysed using the immune assays and stool culture results of blood and stool specimens collected from a cohort of study participants.

CONCLUSIONS

This protocol has been ethically approved by the International Vaccine Institute Institutional Review Board and all site-specific institutional and national ethics committees. Informed consent will be obtained prior to study enrolment. Results will be presented at academic conferences and submitted to international peer-reviewed journals. Research data generated through SETA will address the scientific knowledge gap concerning long-term host immune responses and carrier patterns associated with the natural infection of invasive *Salmonella* disease and further support public health policy on typhoid immunization strategy in Africa.

121. Serious Adverse Events in Children Vaccinated With Typhoid Conjugate Vaccine or Meningococcal A Vaccine During Passive Surveillance

Pratiksha Patel[1], Priyanka Patel[1], James Meiring[2], Matthew Laurens[3], Robert Heyderman[4], Kenneth Simiyu[3], Kathleen Neuzil[3], Melita Gordon[1]

[1]Malawi Liverpool Wellcome Trust, [2]Oxford University, [3]University of Maryland, [4]University College London

BACKGROUND

The Typbar™ (Bharat) typhoid conjugate vaccine, recently pre-qualified by the World Health Organisation, is the leading typhoid Vi conjugate vaccine. Safety and tolerability data, including co-administration with routine measles-rubella vaccination, are needed by stakeholders and health officials to inform decision-making. As part of the Typhoid Vaccine Acceleration Consortium (TyVAC), we vaccinated >28,000 children in a 1:1 randomised double-blind controlled clinical phase 3 efficacy trial in Malawi, the first site to test a typhoid conjugate vaccine in Africa. Here, we present safety data from the first 18,491 participants.

METHODS

Healthy children aged 9 months through 12 years were randomly assigned in a 1:1 ratio to receive the Typbar Vi-conjugate vaccine or the meningococcal A conjugate vaccine. All participants were observed for 30 minutes post-vaccination for any immediate adverse event (AE). For safety evaluation, all children will be under passive surveillance for six months to identify serious adverse events (SAEs).

RESULTS

Between 21 February and 29 June 2018, 18,491 participants were vaccinated. Data were locked and analysed for review by the DSMB. Upto 29 June, one related AE (rash) and one unrelated AE (diarrhoea) occurred within 30 minutes post-vaccination. 24 serious adverse events including one death occurred in 23 participants, none related to vaccination. Most SAEs were hospitalisations due to acute childhood illnesses. These SAEs fell into categories of neurological problem or fit (5), chest or respiratory infection (6), abdominal or diarrhoea problem (4), febrile illness or malaria (5) and other (4). Among the 656 blood cultures collected, 6 were positive for *Salmonella* Typhi, with 4 occurring in participants in the 1-5 age category. All participants with *S.* Typhi were followed up every 2 weeks until illness resolved. No associated complications of *S.* Typhi bacteraemia were documented.

CONCLUSIONS

In a large cohort, the detection of 24 SAEs representing common childhood illnesses indicates comprehensive passive surveillance, and gives a high confidence of detecting any potentially related serious adverse events. Vaccinations were well-tolerated and no safety signal in terms of related serious adverse events was detected. The trial is ongoing, and updated data for the entire cohort of 28,000 children will be presented.

122. Forecasting Demand for the Typhoid Conjugate Vaccine in Low- and Middle-Income Countries

Frédéric Debellut[1], Nathaniel Hendrix[2], Virginia E. Pitzer[3], Kathleen M. Neuzil[4], Dagna Constenla[5], Naor Bar-Zeev[5], Anthony Marfin[1], **Clint Pecenka[1]**

[1]PATH, [2]The Comparative Health Outcomes, Policy, and Economics (CHOICE) Institute, University of Washington, [3]Yale School of Public Health, [4]Center for Vaccine Development and Global Health, University of Maryland, [5]Department of International Health, Johns Hopkins Bloomberg School of Public Health

BACKGROUND

The World Health Organization released a position paper in March 2018 calling for integration of a novel prequalified typhoid conjugate vaccine into routine immunization along with catch-up campaigns for children up to age 15. Gavi, the Vaccine Alliance has committed funding to help resource-constrained countries introduce this vaccine. In this paper, the Typhoid Vaccine Acceleration Consortium (TyVAC) forecasts demand for typhoid conjugate vaccine if World Health Organization recommendations are followed.

METHODS

We built a model of global typhoid conjugate vaccine introductions between 2020 and 2040 to estimate the demand for the vaccine in 133 countries. We projected each country's year of introduction by examining the estimated incidence of typhoid, the history of introducing new vaccines, and any information on engagement with typhoid prevention, including intent to apply for Gavi funding. Our model predicted use in routine infant vaccination programs as well as campaigns targeting varying proportions of the unvaccinated population up to 15 years of age.

RESULTS

Between 2020 and 2025, demand will predominantly come from sub-Saharan African countries, many receiving Gavi support. After that, Asian countries generate most demand until 2030, when campaigns are estimated to end. Demand will then track the birth cohort of participating countries, suggesting an annual routine demand between 90 and 100 million doses. Peak demand is likely to occur between 2023 and 2026, approaching 300 million annual doses if campaign implementation is high.

CONCLUSIONS

There is some risk of exceeding presently estimated peak production capacity of 200 million doses per year. Therefore, it will be important to carefully coordinate typhoid conjugate vaccine introductions, especially when accompanied by campaigns targeting large proportions of the eligible population.

123. Changes in Historical Typhoid Transmission Across 16 U.S. Cities, 1889-1931: Quantifying the Impact of Investments in Water and Sewer Infrastructures

Maile Phillips[1], Katharine Owers[2], Bryan Grenfell[3], Virginia Pitzer[1]

[1]Yale School of Public Health, [2]Department of Biology, Colorado State University, [3]Department of Ecology and Evolutionary Biology, Princeton University

BACKGROUND

Historical investments in water and sanitation systems are thought to have led to the decline in typhoid fever in developed countries, such that most of the global burden of disease now occurs in regions with poor sanitary conditions and inadequate access to clean water and sanitation. Exploring seasonal and long-term patterns in historical typhoid time series from the United States can offer a deeper understanding of the factors that drive disease transmission and elimination.

METHODS

Weekly mortality counts reportedly due to typhoid from 1889-1931 were extracted from the Project Tycho database for 16 U.S. cities. All other data were obtained from the U.S. Census Bureau and individual municipal sources. We fit a modified Time-series Susceptible-Infectious-Recovered (TSIR) model and extracted the seasonal and long-term typhoid transmission rates for each city. We examined seasonal transmission parameters separately and aggregated by water source. We then fit generalized linear models to measure the association between long-term typhoid transmission rates and water and sewer financial variables.

RESULTS

From 1889-1931, there were a total of 86,023 deaths from typhoid fever across the 16 cities. Annual typhoid transmission generally peaked in the late summer or early fall months. Seasonality in the estimated typhoid transmission rate varied depending on the city's water source, with the highest peaks occurring in cities that relied on reservoirs for their water supply. Annual investments in the acquisition/construction and operation/maintenance of water supply and sewer systems were associated with a 4-16% decrease in typhoid transmission for every $100,000 spent. Every $1 million increase in the total value and/or debt accrued to build and maintain the water supply and sewer systems was associated with an 8-16% decrease in typhoid transmission.

CONCLUSIONS

The results from our analysis aid in the understanding of typhoid transmission dynamics and potential impact of improvements in water and sanitation infrastructure. Resource-poor countries must prioritize spending on public health issues, weighing the costs and benefits of interventions. Our results can help to inform comparative cost-effectiveness analyses of different interventions to reduce the global burden of typhoid fever.

124. Cost-Effectiveness of Typhoid Conjugate Vaccine Delivery Strategies in Gavi-Eligible Countries

Joke Bilcke[1], Marina Antillón[1], Zoë Pieters[2], Kathleen Neuzil[3], Andrew Pollard[4], A. David Paltiel[5], **Virginia Pitzer[5]**

[1]University of Antwerp, [2]Hasselt University, [3]University of Maryland School of Medicine, [4]University of Oxford, [5]Yale School of Public Health

BACKGROUND

Typhoid fever is a major cause of morbidity and mortality in low- and middle-income countries. The World Health Organization recently recommended the programmatic use of typhoid conjugate vaccine (TCV) in endemic settings, and Gavi has pledged support for vaccine introduction. Country-level health economic evaluations are now needed to inform decision-making.

METHODS

We compared four strategies: no vaccination; routine immunisation at 9 months; or routine immunisation at 9 months with catch-up campaigns to either age 5 or 15 years. For each of 54 Gavi-eligible countries, output from an age-structured transmission dynamic model was combined with country-specific treatment and vaccine-related costs, treatment outcomes, and disability weights to estimate disability-adjusted life-years (DALYs) and identify the 'preferred' strategy that maximized average net benefit across a range of cost-effectiveness thresholds, as quantified by the willingness-to-pay (WTP) value. We also estimate and explore the uncertainties surrounding our findings, and identify the economic and epidemiological conditions under which vaccination might be preferred.

RESULTS

Whenever typhoid vaccination is considered cost-effective, including a catch-up campaign is always preferred over routine vaccination alone. Routine immunisation with a catch-up campaign to age 15 years is preferred in 34/48/51 countries at WTP values of >=US$200/500/1000 per DALY averted and in 38/47/48 countries at WTP values >=25/50/100% of the gross domestic product per capita per DALY averted, assuming the country-specific share of the Gavi-supported vaccine cost (US$0.20-1.50 per dose). Vaccination is likely to be cost-effective in countries with >=300 typhoid cases per 100,000 person-years. For all countries, uncertainty around typhoid incidence and/or case fatality rate have the greatest influence on the preferred strategy.

CONCLUSIONS

Routine TCV immunisation with a catch-up campaign is preferred over no vaccination and routine immunisation alone in countries with high incidence. Obtaining improved estimates of age-specific typhoid incidence and mortality might be economically justifiable in some countries.

125. A Systematic Review of Outcome Reporting in Randomized Controlled Trials for the Treatment of Enteric Fever

Sunil Pokharel[1], Amit Arjyal[2,3], Elinor Harris[1], Stephen Baker[4], Abhilasha Karkey[2], Buddha Basnyat[2], Christiane Dolecek[1]

[1]University of Oxford, [2]Oxford University Clinical Research Unit Nepal, [3]Patan Academy of Helath Sciences, [4]Oxford University Clinical Research Unit Vietnam

BACKGROUND

Due to the high mortality and morbidity associated with enteric fever globally, and rapid evolution and spread of antimicrobial drug resistance, the continuous evaluation of antimicrobials in the fight against enteric fever remains crucial. Randomized controlled trials (RCTs) are the cornerstone for evaluating efficacies of antimicrobial treatments. There exists no consensus or guidelines on the selection and definition of outcome endpoints for RCTs comparing enteric fever treatments. Outcomes are selected and defined at the discretion of investigators.

METHODS

In order to systematically delineate the prevailing practice in selecting and defining the outcome measures used in RCTs for the treatment of enteric fever, we conducted a systematic review and descriptive analysis of currently used measures to report outcomes. We searched PubMed database for enteric fever RCTs published between January 1990 and October 2018. Two reviewers independently screened for the eligibility of the publications and extracted the data on outcome endpoints used to measure the treatment effect.

RESULTS

We retrieved 341 studies from the initial search. After screening for eligibility, 52 papers recruiting 5096 patients were included in final analysis. Common outcome domains reported by the studies included fever clearance time (n=50, 96%), clinical cure or treatment failure (n=47, 90%), microbiological cure or treatment failure (n=44, 85%), relapse (n=43, 83%) and carrier status (n=28, 54%). There were large inconsistencies in the selection of outcome sets and the definition of component outcome domains. The definitions varied largely with regard to detail and completeness, and the time-points at which they were evaluated.

CONCLUSIONS

The heterogeneity in the selection and definition of outcomes impedes comparison between studies. It is critical that outcome measures are standardized to ensure future reproducibility and meaningful comparison. It will allow studies to be pooled in meta-analysis with greater statistical power and opens the possibility for individual patient data analysis to generate more reliable estimates of treatment effect. This systematic review forms a strong case and foundation for the development of standardised, consensus-based core outcome sets for enteric fever trials.

126. Evaluation of a New Real-Time PCR Assay in Africa for Measuring Typhoid Disease Burden

Stephane Pouzol, Hubert Endtz

Fondation Mérieux

BACKGROUND

Enteric fever is a severe illness mainly caused by *Salmonella typhi* or *Salmonella* paratyphi A. The disease is still of utmost importance in Asia and Africa where nearly 21 million cases and more than 220,000 deaths are estimated to occur annually. In addition, invasive non-typhoidal *Salmonella* infections are particularly important in immunosuppressed populations especially in sub-Saharan Africa. Diagnosis in endemic region is challenging due to the non-specific clinical presentation and the lack of rapid, standardized and sensitive laboratory assays, highlighting the need for the development of alternative diagnostics.

METHODS

We combined a short pre-enrichment step with a real-time multiplex polymerase chain reaction to identify *S.* Typhi, *S.* Paratyphi A and *Salmonella* spp. directly from 2-3 ml of whole blood specimen. 1000 suspected Typhoid Fever cases older than 3 months old with any history of fever ≥ 3 days and 200 controls were enrolled from Ghana, Malawi and Burkina Faso and their blood was subjected to culture and molecular identification.

RESULTS

Preliminary results from Ghana and Malawi indicate that 979/1979 cases were female (49.4%) with median age of 10 years (range 3-29 years). However, cases from Malawi were older (19.0 years) than those reported from Ghana (6.0 years) with longer fever duration and higher total medication rate (6.0 days vs 4.0 days and 87% vs 53% respectively) prior consultation. 162/1979 (8.2%) blood samples were positive for culture of Salmonella and 226/1813 (12.5%) by qPCR assay. None of the tests performed identified S. Paratyphi A in blood specimens while 34 cultures (21%) and 86 PCRs (38%) were positive for non-typhoidal Salmonella. 18 positive cultures (14 S. Typhi and 4 S. spp) showed discrepancies in species identification with PCR. Considering true positive as having a positive blood culture or qPCR test, sensitivity of qPCR assay was 88% and 59% for culture with specificity ≥ 94% for both assays.

CONCLUSIONS

We observed good performance of the qPCR assay in a setting where both S. Typhi and non-typhoidal Salmonella rates are reported high. This method has the potential for worldwide use (alone or in combination with blood culture) for surveillance and vaccine interventions studies.

127. Genomic Insights on Emergence of the Multiple-Drug Resistance-Associated *Salmonella* Typhi Haplotype H58 in Southern India

Agila Kumari Pragasam[1], Derek Pickard[2], Gordon Dougan[2], Gagandeep Kang[1], Jacob John[1], Balaji Veeraraghavan[1], Ankur Mutreja[2]

[1]Christian Medical College, Vellore, [2]Wellcome Trust Sanger Institute, Hinxton

BACKGROUND

Typhoid fever caused by *S.* Typhi is a major public health concern, and is endemic in India. Phylogenetic analysis of *S.* Typhi indicated that South Asia might be the site of the original emergence of the H58 haplotype, but this hypothesis was based on sequence data from a limited number of *S.* Typhi isolates from India and adjacent countries. The objective of our study was to investigate the evolution and relationship of *S.*Typhi, isolated from Southern Indian region over the past two decades, within the global phylogenetic framework

METHODS

A total of 194 *Salmonella enterica* serovar Typhi isolates covering a 25-year period (1991-2016) in a major referral hospital in Vellore, South India were included. Genomic DNA was extracted from these isolates and subjected to deep whole genome sequencing using the HiSeq Illumina platform. Haplotyping and antibiotic resistance characterization were performed at both phenotypic and genotypic level

RESULTS

Out of the 194 *S.* Typhi isolates sequenced, 13 different haplotypes were identified, indicating a broad representation across the serovar phylogenetic population structure. Interestingly, 77 % (n=149) of the isolates belonged to the H58/4.3.1 haplotype indicating that this was dominant in the population. Other haplotypes were generally represented by less than 5 isolates. MDR and fluoroquinolone resistance mutations were found in the H58 isolates and no MDR phenotype was detected in non-H58/4.3.1 isolates. Genomic comparison with *S.* Typhi isolates with global collection shows that there were two Vellore associated H58/4.3.1 sub-groups, I and II, and shared similarity with isolates from countries adjacent to India and from Southeast Asia, respectively

CONCLUSIONS

This is one of the earliest reports of H58/4.3.1 *S.* Typhi and provides support for the hypothesis that this globally dominant haploptype emerged in this region a little earlier than previously speculated. This study provides insights into the population of *S.* Typhi circulating in this Southern India region over the past 25 years. The H58/4.3.1 clade in Vellore is now the major lineage in the region and presents a serious public health concern

128. Frequency and Associated Factors of Typhoid Carrier on Duodenal Fluid Culture in a Tertiary Care Hospital, Karachi

Sonia Qureshi, Farah Naz Qamar, Tahir Yousafzai, Shafquat Rozi, Shahida Qureshi, Kamran Sadiq

Aga Khan University Hospital

BACKGROUND

Typhoid fever is a serious public health problem and remains a major cause of morbidity and mortality worldwide. Typhoid carriers serve as a reservoir in the ongoing transmission of typhoid fever. This study aims to determine the frequency of typhoid carriers in a typhoid endemic country by performing duodenal fluid culture in patients undergoing upper gastrointestinal (GI) endoscopy

METHODS

We conducted a crossectional study at Aga Khan University Hospital, Karachi from February-August 2017. Individuals of age ≥1 year who underwent upper GI endoscopy for any reason were included. Duodenal fluid culture was performed for identification of *Salmonella. typhi* and *paratyphi*. Statistical analysis carried out using Stata. For socioeconomic status factor analysis was performed. Overcrowding was assessed by estimating crowding index. GIS mapping was done for visualizing distribution of study participants.

RESULTS

Out of 801 participants, 477 were enrolled. The mean±SD age (years) of the individuals was 42.4±15.5. Majority 287/477 (60.2%) were males. Two thirds (74.5%) of the Participants were from the province of Sindh (54% from Karachi), 13.6%, 3.4% and 3.4% from Baluchistan, Punjab and KPK respectively. 205/477(42.9%) reported use of unsafe water for drinking in their homes. 389/477 (81.5%) underwent upper gastrointestinal endoscopy for the diagnosis of gastrointestinal illness. 73(15.3%) reported past history of typhoid fever. Only 9/477 (1.9%) stated that they had received antibiotics in last two weeks of the procedure. Out of 477 cultures, 250 (52.4%) were positive for a bacterial isolate. None of the cultures showed growth of *salmonella. typhi* or *paratyphi* . However, common pathogens isolated were *Escherichia coli* 68 (27.2%) followed by *Pseudomonas species* 58(23.6%), *Klebsiella pneumonia* 35 (14%).

CONCLUSIONS

We were not able to identify any typhoid carrier on duodenal fluid culture among subjects undergoing upper GI endoscopy. Carrier detection remains one of the best ways to stop transmission of salmonella. We propose molecular detection methods to determine the prevalence of carrier state after an episode of typhoid.

129. Inclusion Criteria for Enteric Fever Surveillance – Are We Underestimating This Disease?

Hafiz Rahman[1], Afiour Rahaman[1], Stephen Luby[2], Jason Andrews[2], Denise Garrett[3], Samir Saha[1]

[1]Child Health Research Foundation, [2]Stanford University School of Medicine, [3]Sabin Vaccine Institute

BACKGROUND

Typhoid remains a neglected disease, despite being the most common invasive bacterial disease in South Asia and many African countries. Recently, multiple surveillance studies have been initiated to understand the disease burden and establish the baseline for the vaccine impact studies. The inclusion criteria for these studies requires three consecutive days of fever, which is the World Health Organization definition of a suspected typhoid case in endemic areas; however, the basis for this fever duration threshold is unclear. We sought to understand the culture positivity proportion according to the duration of fever and the impact of alternative fever duration thresholds on the total yield of surveillance.

METHODS

This study was conducted at 2 hospitals in Dhaka, Bangladesh, in the context of the Surveillance for Enteric Fever In Asia (SEAP) project, a prospective surveillance study, from 2016 to 2018. All children presenting to the hospital with 3 or more consecutive days of fever in the last 7 days are offered enrollment. In addition, we also collected blood from children with <3 days fever, if the clinician suspected invasive bacterial disease. We analyzed the data to determine positivity rates of confirmed enteric fever among the cases with <3 days fever and its comparison with the cases with >3 days.

RESULTS

Blood culture results showed 3% (9/351) growth from patients with only 1 day fever, 6% (20/354) with 2 days fever, that averages to 4% growth from <3 days fever group. In contrast, the proportion with culture-confirmed enteric fever among all enrolled patients with >3 days of fever was 18%. Restricting to <3 days of fever would have missed 3% (29/1057) of all cases.

CONCLUSIONS

These results illustrate that the common surveillance eligibility criteria of at least 3 days of fever misses enteric fever cases. The additional 29 cases identified in this analysis is a minimal estimate because blood culture was not routinely conducted among all children with a briefer duration of fever. Although it is unlikely to be cost-effective for surveillance to collect blood samples from every child with pre-fever, these data provide further evidence that counting positive blood cultures underestimates typhoid incidence.

130. Severe Typhoid in Africa Program Cost of Illness Study: Preliminary Results From Two African Countries

Enusa Ramani, Seeun Park, Ursula Panzner, Justin Im, Ondari D. Mogeni, Florian Marks, Vittal Mogasale

International Vaccine Institute

BACKGROUND

Typhoid fever (TF) cost of illness (COI) study estimates public, private expenditures for treatment and productivity losses associated with the illness. COI studies addresses cost saved through TF control measures and is essential in measuring the cost-effectiveness of vaccination or disease control interventions. Severe Typhoid in Africa (SETA) health economic study was implemented using platform for typhoid surveillance in four African countries, to generate data for Africa. Here, we present preliminary results.

METHODS

The SETA health economics component is conducted in Burkina Faso, Ethiopia, Ghana and Madagascar. The out-of-pocket expenditure of participants (private cost: made up of direct medical and non-medical costs), of health facilities (public cost) and lost productivity due to illness (indirect cost) were collected from laboratory confirmed TF cases and complicated TF cases (special case), using a pretested COI survey instrument. Costs are collected from day of fever onset to day of self-declared recovery by participant.

RESULTS

In total, 99 TF and Special Cases from Ghana (n=46, 46.47%) and Madagascar (n=53, 53.54%) were analyzed. Mean direct medical cost per TF case during <30-day and <90-day follow-up was estimated to be USD 24.1 (SD=39.4) and USD 29.7 (SD 45.1) for Ghana with Madagascar having USD 8.4 (SD=13.5) and USD 8.4 (SD=13.4), respectively. For Special cases the estimate was USD 41.3 (SD=73.2) and USD 135.7 (SD=97.7) for Ghana and USD 9.9 (SD=15.8) and USD 27.5 (SD=27.8) for Madagascar, respectively. The average direct non-medical cost per TF case during <30-day and <90-day follow-up was estimated for Ghana to be USD 4.60(SD=8.18) and USD 4.90 (SD 8.18) whereas Madagascar had USD 2.69(SD=11.14) and USD 2.69 (SD=11.14). For Special cases, the estimate for Ghana was USD 65.20(SD=69.69) and USD 66.20 (SD=81.03); for Madagascar USD 19.14(SD=16.64) and USD 21.66 (SD=14.49)].

CONCLUSIONS

This study provides new data on cost of laboratory confirmed TF and its complications in Ghana and Madagascar. Typhoid complication was identified as a major out-of-pocket cost driver for participants in both direct medical and non-medical cost categories. Ongoing analysis will present results on other private cost components of TF in the near future.

131. Relationship Between Positive Typhoid Rapid Diagnostic Test and Clinical Symptoms Suggestive of Typhoid

Nirmal Ravi[1], Toluwalase Tomi-Adeboye[2], Ameh Akoji[2], Musa Abdulmutalab[2]

[1]EHealth Africa, [2]EHA Clinics

BACKGROUND

Typhoid is one of the most commonly diagnosed diseases among adults in Nigeria. Anyone with subjective fever and abdominal symptoms is widely presumed to have Typhoid and treated with antibiotics. Even though blood cultures are the Gold standard for diagnosing Typhoid, they are seldom done in Nigeria due to lack of quality-assured microbiology laboratories and patients' inability to pay for the test. An alternative is immunochromatographic rapid diagnostic tests which detect IgM/IgG antibodies against Salmonella antigens. We tested if there was any correlation between patient reported presumptive symptoms of Typhoid and a positive Typhoid rapid diagnostic test result.

METHODS

A cross sectional analysis was done of 93 adult patients who were tested for Typhoid using rapid diagnostic tests between July and October 2018 in a primary care clinic in Kano, Nigeria. Laboratory test results and patient information were obtained from the clinic's electronic medical records. Patients' serum samples were tested using Solid™ Rapid Diagnostic Kits according to the manufacturer's instructions. The test manufacturer reported a relative sensitivity of 91%, and specificity of 99.3%. Chi-squared tests were done to look for statistical correlation between presumptive symptoms of Typhoid and laboratory test results.

RESULTS

The 93 patients tested for Typhoid ranged in age from 18 - 76 years (median 33). Males constituted 56% of the patients. Twelve of 93 patients (13%) had a positive Typhoid test. Of these 12, 5 (42%) reported presumptive symptoms of Typhoid (subjective fever and abdominal pain/diarrhea/constipation). Of the 81 patients (87%) with a negative Typhoid test, 22 (27%) reported presumptive symptoms of Typhoid. No statistically significant correlation was seen between a positive Typhoid test and the presence of presumptive symptoms.

Among all 27 patients who reported presumptive symptoms including fever, only 1 was found to have a temperature >38 Celsius. No statistically significant correlation was seen between the presence of temperature >38C and a positive Typhoid test.

132. Antimicrobial Resistance in Typhoidal *Salmonella* in Nepal - Past and Present

Nisha Rijal[1], Jyoti Acharya[1], Bishnu Prasad Upadhaya[1], Shailaja Adhikari[1], Supriya Sharma[2]

[1]National Public Health Laboratory, [2]Central Department of Microbiology, Tribhuvan University

BACKGROUND

Enteric fever, caused by *Salmonella enterica* serovars Typhi (*S.* Typhi) and Paratyphi A (*S.* Paratyphi A), is the most common cause of bloodstream infection in Nepal. There is an estimated 11–21 million cases of typhoid fever and approximately 128 000–161 000 deaths annually. The emergence of antimicrobial resistance is a significant challenge, with several outbreaks caused by multidrug-resistant S. Typhi in Africa and Asia. The present study was undertaken to compare the change in trend of antimicrobial resistance among Typhoidal Salmonella in a decade

METHODS

The laboratories participating in the Antimicrobial Resistance Surveillance network contributed results (organism identification, date of isolation, antimicrobial susceptibility profile, etc.) on Salmonella positive blood cultures to the National Focal point laboratory. All the recovered isolates were confirmed by serotyping. The data thus collected during 2008 was analyzed and compared to the data collected in 2017.

RESULTS

A significant decline in the number of Typhoidal *Salmonella* was observed in 2017 (677) as compared to that of 2008 (1561). Of the total, 66% were *Salmonella enterica* serovar Typhi and 33% were *Salmonella enterica* serovar Paratyphi A. S.Typhi outnumbered S.Paratyphi A in both years. Males were predominantly affected. In 2008, infection was higher in 10-19 years age group in both sexes whereas in 2017, age group variation among gender was seen. Although Ampicillin resistance showed a significant decline in both S.Typhi (11.5% in 2008 to 1% in 2017) and S.Paratyphi A (25.2% in 2008 and 5.1% in 2017), the opposite was true for Ciprofloxacin, where a significant increase in resistance was observed in both species. Decrease in resistance to Chloramphenicol and Cotrimoxazole (1% and 0.4% in 2008 to 0 in 2017 respectively) was observed. All the isolates were susceptible to Ceftriaxone in 2017.A decline in Multidrug Resistant Salmonella isolates is noted over the years.

CONCLUSIONS

Antimicrobial non-susceptibility along with changing epidemiology reflects the need for continuous monitoring of Antimicrobial Resistance in Salmonella. Also, these data highlight the need of molecular surveillance in endemic regions and calls for prudent strategies aimed at conserving the currently effective drugs along with vaccine deployment

133. Anti-*Salmonella* Activity of Metabolites From African Soldier Termites, *Macrotermes bellicosus*

Esther Afolayan[1], Hausatu Babayi[2], **Rine Reuben[3]**

[1]Department of Microbiology, Ahmadu Bello University, Zaria, [2]Department of Microbiology, Federal University of Technology, Minna, [3]Department of Science Laboratory Technology, Nasarawa State Polytechnic, Lafia

BACKGROUND

The global emergence and rapid dissemination of multidrug-resistant *Salmonella* strains necessitate research to find new antimicrobials that can be effectively used against these pathogens. Insects, been the most abundant animals on earth, have lately been recognized for having potent immune defenses that produce constitutive and inducible antimicrobial compounds to combat various pathogens. In the present study, anti-*Salmonella* activity of metabolites from African Soldier Termites, *Macrotermes bellicosus* was demonstrated and subsequently compared with antibiotic, ciprofloxacin.

METHODS

Hexane, ethylacetate, methanol and aqueous extracts of metabolites from the *M. bellicosus* were assayed for anti-*Salmonella* activity using the agar dilution method as well as the determination of the minimum inhibitory concentration (MIC) by broth dilution. The inhibitory activities of the extracts were compared to ciprofloxacin (256µg/ml). Also, the bioactive components of the extracts were determined using standard techniques.

RESULTS

At 4000µg/ml hexane extract inhibited the growth of *S.* Typhi, *S.* Paratyphi A, B and C while ethylacetate extract was able to inhibit *S.* Paratyphi A and C. Methanolic and aqueous extracts at the same concentration were unable to inhibit these strains of *Salmonella*. Furthermore, our findings revealed that the MIC of hexane extract was 2000µg/ml for *S.* Paratyphi B and C, 250µg/ml for *S.* Paratyphi A, and 125µg/ml for *S.* Typhi. Also, the MIC of ethylacetate extract was 4000µg/ml for *S.* Paratyphi B, 2000µg/ml for *S.* Paratyphi C, 500µg/ml for *S.* Typhi and 250µg/ml for *S.* Paratyphi A respectively. The screening of bioactive components revealed the presence of cardiac glycosides and alkaloids.

CONCLUSIONS

Our results provide evidence of anti-*Salmonella* action of metabolites from African Soldier Termites, *M. bellicosus*. Hexane and ethylacetate extracts can be used as novel antimicrobials for the treatment of typhoid and paratyphoid fevers thereby reducing the pressure exerted on the available antibiotics and combating multidrug strains.

134. Occurrence and Antibiogram of *Salmonella* Species From Locally Fermented Milk (*Nono*) and Locally Pasteurized Milk (*Kindirimo*) Sold in Lafia, Nigeria

Reuben Rine[1], Aliyu Yakubu[2], Esther Afolayan[3]

[1]Department of Science Laboratory Technology, Nasarawa State Polytechnic, [2]Department of Science Laboratory Technology, Federal Polytechnic, Nasarawa, [3]Department of Microbiology, Ahmadu Bello University, Zaria

BACKGROUND

Salmonella is a major bacterial agent of food poisoning in Nigeria with antibiotic-resistant strains resulting in treatment failure, increased hospitalization, and increased risk of death. Milk and milk products can harbor a variety of microorganisms and can be important sources of foodborne pathogens which may result in large outbreaks. This study was carried out to determine the presence of antibiotic-resistant Salmonella in locally fermented milk (*Nono*) and locally pasteurized milk (*Kindirmo*) sold in Lafia, central Nigeria.

METHODS

Samples collected from Shabu, a suburban area and Lafia city main market were examined for the presence of *Salmonella* spp using conventional microbiological procedures. Confirmed *Salmonella* isolates were tested for antimicrobial susceptibility using the agar-disc diffusion technique as recommended by the Clinical and Laboratory Standard Institute (CLSI).

RESULTS

Results obtained from this study showed that 33.3% of the samples examined were contaminated with *Salmonella* spp; with 13.3% and 20.0% from *Nono* and *Kindirmo* respectively. Also, there was an insignificant difference (P>0.05) in the occurrence of *Salmonella* spp from samples obtained from Shabu (20.0%) and Lafia city main market (13.3%). The antibiotic susceptibility of *Salmonella* isolates to some commonly used antibiotics revealed 80.0% resistance to amoxicillin, norfloxacin, streptomycin and rifampicin, and a 60.0% resistance to ampicillin. Five different resistance phenotypes expressed by the isolates were: erythromycin-gentamycin-streptomycin-rifampicin, ciprofloxacin-norfloxacin-rifampicin, norfloxacin-gentamicin, amoxicillin-ampicillin, and amoxicillin-streptomycin. The multiple antibiotic resistance indexes of these resistant *Salmonella* strains were 0.4, 0.3 and o.2 respectively, indicating misused of antibiotic in the study area.

CONCLUSIONS

These results provide preliminary data on milk products contamination, suggesting the possibility of public health threat of antibiotic-resistant *Salmonella*. This serves as a prelude for the development of preventive strategies for foodborne pathogens and prudence in antibiotics usage in the study area.

135. Incidence of and Factors Associated With Suspected Typhoid Fever in Children Aged Between 6 Months to 14 Years in a Rural Region of Western India

Ankita Shrivastava[1], **Sudipto Roy[1],** Bharat Chaudhari[1], Sonali Sanghavi[1], Sanjay Juvekar[1], Jacob John[2], Ashish Bavdekar[1]

[1]KEM Hospital Research Centre, Pune, [2]Christian Medical College, Vellore

BACKGROUND

A National Surveillance System for Enteric Fever in India has been set up at four sites to estimate the burden of typhoid and paratyphoid fever. While confirmation of typhoid in blood cultures of fever cases is dependent on many factors, suspected typhoid fever (STF) can act as an indicator of confirmed typhoid cases. Here, we determine the incidence of and risk factors associated with episodes of STF and the clinical diagnosis.

METHODS

A community-based rural cohort of children aged between 6 months and 14 years at Vadu, KEM Hospital Research Centre Pune, has been under active weekly surveillance for the past one year in order to detect fever episodes. All fever cases are followed up with daily contacts till the end of the episode. Fever lasting for three consecutive days and more is defined as suspected Typhoid Fever (STF) which is further investigated for diagnosis of typhoid and paratyphoid through blood cultures.

RESULTS

The Suspected Typhoid Fever (STF) episode incidence rate was 4 per 100 child-months of follow-up. Among a cohort of 5962 children, 1832 (30.7%) reported at least one STF episode and 423 (7.1%) reported multiple episodes. Not washing uncooked food item (O.R. 1.326 with 95% C.I. 1.087 – 1.618), age less than four years (O.R. 3.588 with 95% C.I. 3.077 – 4.183), shared toilet facility (O.R. 1.174 with 95% C.I. 1.037 – 1.328) and unprotected well and trucked water delivery as drinking water sources (O.R. 1.855 with 95% C.I. 1.290 – 2.669 and O.R. 1.745 with 95% C.I. 1.285 – 2.369 respectively) were associated with a higher risk while middle and upper-middle socio-economic class (O.R. 0.812 with 95% C.I. 0.661 - 0.997 and O.R. 0.743 with 95% C.I. 0.602 – 0.916 respectively) were associated with lower risk of STF episodes. Clinical diagnosis was available for 1644 episodes of which 1028 (62.5%), 227 (13.8%), 257 (15.6%) and 85 (5.2%) were viral fever, upper-respiratory tract infection, lower-respiratory tract infection and acute gastro-enteritis respectively. Salmonella Typhi and Paratyphi was detected through blood cultures in three STF episodes.

CONCLUSIONS

Sanitation and hygiene are important factors associated with fever episodes in children with respiratory tract infection being the commonest cause of fever.

136. Development of a 16S Ribosomal RNA Reverse Transcriptase Real-Time PCR for *Salmonella* Detection in Blood Stored in PAXgene® Blood RNA Tubes

Jean Pierre Rutanga[1,2,3], Sandra Van Puyvelde[3], Tessa de Block[3], Claude Mambo Muvunyi[1], Jan Jacobs[3], Stijn Deborggraeve[2]

[1]University of Rwanda, [2]KU Leuven, [3]Institute of Tropical Medicine

BACKGROUND

Typhoidal and invasive non-typhoidal *Salmonella* present a large health burden in Asia and Africa. Molecular diagnostics based on the polymerase chain reaction (PCR) have been developed for the detection of *Salmonella* in blood of infected patients but generally show low sensitivity and reproducibility. Targeting the highly abundant 16S ribosomal RNA (rRNA) molecules can increase the sensitivity of molecular detection of *Salmonella* in blood. However, there is no standardized protocol for field applicable blood collection for subsequent bacterial RNA analysis. The PAXgene Blood collection system (PreAnalytix) is currently used for storing up to 2.5 ml blood at -80°C for human RNA analysis but has never been applied to bacteria. Our aim was to investigate the efficiency and biosafety of storing *Salmonella* cells in PAXgene® Blood RNA tubes and to develop a *Salmonella* specific 16S rRNA reverse transcriptase real-time PCR (RT-PCR) for the detection of *Salmonella* in blood samples stored in PAXgene® Blood RNA tubes.

METHODS

Experimental samples were prepared in PAXgene® Blood RNA tubes and PAXgene® Blood DNA tubes containing 2.4 ml healthy human blood spiked with 100µl PBS containing known numbers of *Salmonella* Typhimurium SL1344 cells. The viability of the *Salmonella* bacteria was assessed by microbiological viability assays. Total RNA and DNA were extracted with the *in house* adapted protocols of the PAXgene® Blood RNA Kit and PAXgene® Blood DNA Kit (PreAnalytix) respectively. A *Salmonella* specific 16S rRNA RT-PCR was developed with the SensiFAST™ SYBR® No-ROX One-Step Kit (Bioline) on a Lightcycler 480 instrument (Roche).

RESULTS

Resuspended *Salmonella* pellets after storage in PAXgene tubes did not show growth on LB agar plates indicating deactivation of *Salmonella* by the PAXgene tubes. *Salmonella* 16S rRNA could efficiently be detected at lower detection limit of 1 *Salmonella* cell per 2.5 ml blood compared to 10,000 bacteria per 2.5 ml blood for rDNA detection.

CONCLUSIONS

We showed that PAXgene® Blood RNA tubes are an efficient and safe system to store *Salmonella* for subsequent extraction of total RNA, and we developed a sensitive 16S rRNA RT-PCR assay for the detection of *Salmonella* in blood. The assay is currently being transformed into a TaqMan probe-based RT-PCR assay.

137. Antimicrobial Susceptibility of Azithromycin Among *Salmonella* Typhi and Paratyphi A: A Report From India

Dabet Rynga, Rajni Gaind

VMMC & Safdarjung Hospital

BACKGROUND

Decreased ciprofloxacin susceptibility (DCS) and multidrug resistance among *Salmonella* Typhi and Paratyphi A in endemic areas pose therapeutic challenges. Azithromycin is considered a good option as it is available orally. Guidelines for azithromycin disc diffusion and MIC interpretive criteria for *Salmonella* enterica serovar Typhi were published recently by the Clinical and Laboratory Standards Institute in 2015. No breakpoints have been proposed for S. Paratyphi A.

METHODS

Antimicrobial susceptibility pattern of azithromycin among Salmonella Typhi (n=100), Paratyphi A (n=20) recovered from bloodstream infections from January 2015 to December 2017 were studied using disc diffusion and MIC were determined using E test. Zone sizes were extrapolated against MIC values, and a scatter plot was constructed. Break points ≤32 µg /m and ≥13 mm to a 5µg azithromycin disk was selected as susceptible breakpoint for Paratyphi A,

RESULTS

The MICs against azithromycin in the S. Typhi isolates were normally distributed and ranged between 0.25 µg/ml and 32 µ g/ml, with MIC50 and MIC90 values of 6 µg/ml and 12 µg/ml, respectively. For the S. Paratyphi A isolates, the MICs against azithromycin ranged from 1 µ g/ml to µ 32 µg/ml and the corresponding MIC50 and MIC90 values were 12 µ g/ml and 24 µ g/ml, respectively. We observed that the margin of the zone of inhibition around the azithromycin disc may not be very clear and therefore difficult to interpret and that there was wide variation in the zone sizes for the same MIC value in both serovars. For Salmnella Typhi, very major and major errors were less than 2% and were within the limits described by CLSI. For Paratyphi A the both VME and ME were high and outside the acceptable limits. Resistance to azithromycin among S. Typhi and Paratyphi A was 5% and 10% respectively.

CONCLUSIONS

The data from this study suggest that S. Paratyphi A and S. Typhi cannot be assigned to the same MIC break point or zone diameter criteria. With emergence and spread of fluroquinolone resistance among Salmonella Typhi and Paratyphi A, azithromycin can emerge as a drug of choice for the future treatment and control of enteric fever.

138. Intestinal Perforations From Enteric Fever Among Children and Adults: Data From Prospective Surveillance in Karachi, Pakistan

Muhammad Tahir Yousafzai[1], Saqib Qazi[1], Mohammad Tahir Yousafzai[1], **Nasir Saddal[2],** Ashley Tate[3], Caitlin Barkume[4], Denise Garrett[4], Farah Qamar[1]

[1]Aga Khan University, [2]National Institute of Child Health, [3]Centers for Disease Control and Pervention, [4]Sabin Vaccine Institute

BACKGROUND

Intestinal perforation is the most common complication of severe enteric fever, an important public health problem in South Asia. Surveillance for Enteric fever in Asia Project (SEAP) is a large, multi-center, prospective surveillance study designed to estimate the burden of enteric fever and characterize illness severity, including complications in Bangladesh, Nepal, and Pakistan. We describe intestinal perforations and their outcome from the SEAP surveillance study in Pakistan.

METHODS

Data were collected from hospitalized patients with suspected intestinal perforations due to typhoid from September 2016 to July 2018, from public and private sector hospitals in the SEAP study (National Institute of Child Health (NICH), Jinnah Postgraduate Medical Center (JPMC), Karadar General Hospital (KGH), and Aga Khan University Hospital (AKUH) Karachi). Patients with non-traumatic, terminal ileal, intestinal perforations, with or without blood culture confirmation, were identified and enrolled; those with an alternative diagnosis for the perforation (tuberculosis, and perforated appendix) were excluded. Demographic data, clinical presentation, duration of illness and type of perforation identified on surgery (single or multiple), length of stay, and mortality were noted.

RESULTS

A total of 106 patients were enrolled with a suspected typhoid perforation. The age range of cases enrolled from the pediatric hospital (NICH) was 0-13 years (median=8), for JPMC 12-58 (median=23), and AKUH 14-50 (median=24). Majority (n=76, 72%) were males. The median duration of illness prior to admission was 12 days. The average length of hospital stay was 9 days, and chest and abdominal radiographs revealed pneumoperitonium in 6 of cases. Postoperative complication rate was 25%, and the most common complications were wound infections (n=13, 48%), followed by hemodynamic shock (n=8, 30%). A total of 3 cases were confirmed by blood culture or tissue culture (2 and 1, respectively). There were 8 deaths (mortality rate = 8%).

CONCLUSIONS

There is a high, unrecognized burden of enteric fever related intestinal perforations in Pakistan, leading to morbidity and mortality.

139. Hospitalization of Pediatric Enteric Fever Cases During 2016-2018: Surveillance for Enteric Fever in Asia Project (SEAP), Bangladesh

Shampa Saha[1], Maksuda Islam[1], Afiour Rahman[1], Hafizur Rahman[1], Popy Debnath[1], Caitlin Barkume[2], Denise Garrett[2], Samir K Saha[1,3]

[1]Child Health Research Foundation, [2]Sabin Vaccine Institute, [3]Bangladesh Institute of Child Health

BACKGROUND

Enteric fever remains a significant public health problem in developing countries. We aim to evaluate hospitalization of enteric fever cases visiting pediatric hospitals in Bangladesh.

METHODS

Surveillance for Enteric Fever in Asia (SEAP), a multi-country multi-site prospective cross-sectional study, is underway in two large pediatric hospitals in Dhaka: Dhaka Shishu Hospital and Shishu Shasthya Foundation Hospital. In SEAP, suspected and lab-confirmed enteric fever cases aged <18 years were enrolled if they had blood culture in the study hospitals and gave consent. Blood cultures were obtained from the children at out-patient departments if they lived in the catchment area of the hospitals and visited with >3 days fever, and at in-patient departments if they were diagnosed as enteric fever by clinicians.

RESULTS

During October'16-September'18, a total of 8449 blood cultures were obtained. Of those, 1440 (17%) were positive for Salmonella; 1265 (87.8%) were *S.* Typhi, 172 (11.9%) were *S.* Paratyphi and 3 (0.2%) were non-typhoidal salmonella. Additional 434 *S.* Typhi, 100 *S.* Paratyphi and 2 non-typhoidal salmonella were identified in the hospital laboratories. Of 1976 lab-confirmed enteric fever cases, 675 (34%) were hospitalized. Hospitalization was significantly higher among children aged <5 years (46% Vs. 38%, p=0.004). Median duration of fever at the time of hospitalization was 7 (inter-quartile range=5-9) days. Hospitalization was associated with fever duration >5 days (p=<0.001), abdominal pain (p=<0.001), diarrhea (p=<0.001), vomiting (p=<0.001), jaundice (p=0.03), seizure (p=0.002), cough (p=0.01), leucopenia (p=<0.001) and thrombocytopenia (p=<0.001). Multidrug resistance (resistant to ampicillin, chloramphenicol, and cotrimoxazole) was higher among admitted (19% Vs 15%, p=0.004) cases. No deaths were reported.

CONCLUSIONS

Data showed high rate of hospitalization among pediatric enteric fever cases visiting hospital. This suggests the need for appropriate preventive strategies including introduction of the typhoid conjugate vaccine in Bangladesh.

140. First Characterization of Immunogenic Conjugates of Vi Negative *Salmonella* Typhi O-Specific Polysaccharides With rEPA Protein for Vaccine Development

Muhammad Salman[1], Frank Michael[2], Aamir Ali[3], Moazur Rahman[3], Mazhar Iqbal[3], Abdul Haque[3], Andrew Cox[2]

[1]Abasyn Univserity, [2]National Research Council Canada, [2]National Institute for Biotechnology & Genetic Engg (NIBGE), Pakistan

BACKGROUND

Typhoid fever is one of the major public health problems worldwide. Efficacious typhoid vaccines for young children will significantly reduce the disease burden in developing world. The Vi polysaccharide based conjugate vaccines (Vi-rEPA) against *Salmonella* Typhi Vi positive strains has shown high efficacy but may be ineffective against Vi negative S. Typhi.

METHODS

Salmonella Typhi was fermented followed by purification of OSP from LPS of S. Typhi. In this study, for the first time, we report the synthesis and evaluation of polysaccharide-protein conjugates of Vi negative *S.* Typhi as potential vaccine candidates. Four different conjugates were synthesized using recombinant exoprotein A of *Pseudomonas aeruginosa* (rEPA) and human serum albumin (HSA) as the carrier proteins, using either direct reductive amination or an intermediate linker molecule, adipic acid dihydrazide (ADH). The conjugates were evaluated SDS-PAGE and Western blotting followed by Mice immunization.

RESULTS

Upon the comparison of various conjugates; a significantly higher antibody titer was observed in mice administrated with conjugate-1 (OSP-HSA) ($P = 0.0001$) and conjugate 2 (OSP-rEPA) ($P \leq 0.0001$) as compared to OSP alone. In contrast, the antibody titer elicited by conjugate 3 (OSPADH-HSA) and conjugate 4 (OSPADH-rEPA) were insignificant ($P = 0.1684$ and $P = 0.3794$, respectively). We conclude that reductive amination is the superior method to prepare the S. Typhi OSP glycoconjugate. Moreover, rEPA was a better carrier protein than HSA.

CONCLUSIONS

Thus OSP-rEPA conjugate seems to be efficacious typhoid vaccines candidate, it may be evaluated further and recommended for the clinical trials.

141. Comparative Studies on Molecular Typing Methods and Antimicrobial Resistance for Epidemiological Investigation of *S.* Typhi and *S.* Paratyphi A

Sriparna Samajpati[1], Surojit Das[2], Shanta Dutta[1]

[1]ICMR-National Institute of Cholera and Enteric Diseases, [2]Tata Medical Centre, Kolkata

BACKGROUND

Enteric fever still remains one of major infectious diseases of public health importance globally affecting pediatric age population of developing nations. *Salmonella enterica* serotype Typhi (*S.* Typhi) and Paratyphi (*S.* Paratyphi A) are the major etiological agents of enteric fever.

METHODS

The present study was undertaken to characterize 334 *S.* Typhi and 66 *S.* Paratyphi A strains isolated from blood specimen of clinical typhoid fever cases attending OPD of hospitals in Kolkata during four year study period (2014-2017) with respect to their Antimicrobial resistance (AMR) profiles, AMR genes and molecular subtypes by various methods like, Pulsed-field gel electrophoresis (PFGE); Multilocus variable number of tandem repeat (VNTR) analysis (MLVA) and Clustered regularly short palindromic repeats (CRISPR).

RESULTS

Majority of the isolates were resistant to nalidixic acid Na^R associated with decreased ciprofloxacin susceptibility (DCS) (97.6% for *S.* Typhi and 98.4% for *S.* Paratyphi A). Ciprofloxacin resistance was found in 25.4% of *S.* Typhi strains. A single point mutation in gyrA gene (S83F) was common in Na^RDCS *S.* Typhi/ *S.* Paratyphi A strains. Double mutations in gyrA (S83F and D87N) and single mutation in parC (S80I) gene was responsible for Ci^R *S.* Typhi isolates. MDR, multidrug resistance (resistance to ampicillin, chloramphenicol, cotrimoxazole) and non MDR (resistance to cotrimoxazole and tetracycline or chloramphenicol) were found in 4.19% and 1.49%. No MDR *S.* Paratyphi A was isolated during this period. Molecular subtyping method revealed that, MLVA typing was more discriminatory for both *S.* Typhi and *S.* Paratyphi A isolates (D value, 0.987 and 0.938) than PFGE (D value, 0.886 and 0.789) and CRISPR (D value, 0.073 and 0.029) typing.

CONCLUSIONS

The study shows decline in MDR *S.* Typhi isolates and absent of MDR *S.* Partyphi A isolates, but increase in flouroquinolone resistance among both the isolates in recent years from this region, hence evidence based use of 1st line drug could be suggested as treatment practice for enteric fever patients. The study also shows the usefulness of MLVA typing over PFGE and CRISPR typing for better understanding of the epidemiology of antimicrobial resistance typhoidal *Salmonella*.

142. Antibiotic Usages for Suspected Typhoid Fever in Children Aged Between 6 Months to 14 Years in a Rural Region of Western India

Pravin Sawant[1], Ankita Shrivastava[1], Bharat Chaudhari[1], Sudipto Roy[1], Sonali Sanghavi[1], Sanjay Juvekar[1], Jacob John[2], Ashish Bavdekar[1]

[1]KEM Hospital Research Centre, Pune, [2]Christian Medical College, Vellore

BACKGROUND

A National Surveillance System for Enteric Fever in India has been set up at four sites to estimate the burden of culture confirmed typhoid and paratyphoid fever and explore the risk factors for typhoid transmission in the community and to describe the incidence of acute febrile illness and its associated treatment practices in the community.

METHODS

A community-based cohort of children aged between 6 months and 14 years has been under active surveillance for the past one year in order to detect fever episodes at KEMHRC Vadu, in rural Pune district which is one of the study sites. Fever lasting for three consecutive days and more is defined as suspected Typhoid Fever (STF) which is further investigated for diagnosis of typhoid and paratyphoid. Children with STF receive medical care at their preferred healthcare provider.

RESULTS

Among a cohort of 5962 children, duration of antibiotics use ranges from 0 to 27 days (median 3 days). Out of the total 2369 STF episodes, in almost three-fourth (n=1752) of the episodes antibiotics were being prescribed, in those STF cases 86.8% (n=1521) treated with antibiotics within first two days. And more than one fourth (28.4%, n=497) of the STF episodes were managed with multiple antibiotics. Mean duration from onset of STF to antibiotic initiation and total antibiotic consumption duration were 1.24 days and 3.47 days respectively. There were 12 antibiotic groups initially prescribed to treat STF; the most common among these were oral penicillin groups (51.4%) followed by third-generation cephalosporins (32.4%) and macrolides (7.9%).

CONCLUSIONS

Overuse of antibiotics, specifically, higher-grade antibiotics in treatment of STF for insufficient duration underlines towards silent brewing of anti-biotic resistance in STF cases. This antibiotic use might give rise to serious public health problem among paediatric typhoid cases in the coming years and there is a need to monitor the usage of antibiotics among STF cases.

143. Knowledge, Attitude and Practices of Household Contacts and Neighbors of *Salmonella* Typhi Cases in Relation to Typhoid Fever in Peri-Urban Ghana

Dominic Sawiri-Kanin[1,2], Isaac Osei[1,2], Christina Potter[3], Francis Aminkiah[1,2], Isaac Aguna[1,2], Richard Wamai[4], Ellis Owusu-Dabo[2]

[1]Kumasi Centre for Collaborative Research in Tropical Medicine, [2]Kwame Nkrumah University of Science and Technology (KNUST), [3]John Hopkins Bloomberg School of Public Health, [4]College of Social Sciences and Humanities, Northeastern University

BACKGROUND

Typhoid fever is an enteric, bacterial disease caused by *Salmonella enterica* serotypes *S.typhi* and *S. paratyphi*. Globally, approximately 11-21 million cases are recorded per year, resulting in 128,000 to 161,000 deaths annually. In Ghana, there were 384,704 outpatient cases of typhoid fever in 2016, representing 1.7% of all outpatient visits in the country. However, there is scarcity of data on population-based research focussed on knowledge, attitude, and practices of at risk-groups such as the immediate household contacts and neighbours of a blood culture confirmed *Salmonella typhi* patient. At risk-group focussed research is necessary to enable detection of factors that contribute to the burden of the disease in Ghana and also inform public health intervention programs targeted at controlling the disease.

METHODS

A descriptive cross-sectional survey was conducted among seventy-one (71) participants comprising of 43 immediate household contacts and 28 neighbors of blood culture confirmed *Salmonella typhi* patients who have been recruited into the ongoing Severe Typhoid in Africa (SETA) study in peri-urban setting in southern Ghana. A structured questionnaire covering knowledge, attitude, and practices related to typhoid fever and purposive sampling was used to collect data from the participants. Data was entered in Microsoft Excel and analysis performed using R statistical analysis tool.

RESULTS

Approximately 89% (63/71) of the respondents had heard of typhoid fever. Almost half (31/63) of the participants reported been more likely to be infected with typhoid fever at least once in the span of their lifetime. While prevention-based behaviors such as handwashing with soap and water were reported by more than half of participants, knowledge regarding typhoid fever was often misinformed with incorrect cause attribution such as dirt (18%), mosquitoes (18%), and house flies (14%). Additionally, no significant difference was found between the overall responses of household contacts and neighborhood controls ($p = 0.6$).

CONCLUSIONS

Overall, knowledge, attitude and practices of participants regarding typhoid fever is poor and this could lead to an increased risk of typhoid fever transmission, in particular the household contacts of typhoid fever cases. Intervention programs towards control of typhoid fever in this and similar populations should be targeted towards the most at risk groups.

144. Exploring Effective Therapeutic Options Against Extensively Drug Resistant (XDR) *S.* Typhi Infections

Ghazala Shaheen, Yusra Shafquat, Dania Saeed, Russell Seth Martins, Sadia Shakoor

Aga Khan University

BACKGROUND

In November 2016, an outbreak of ceftriaxone resistant *Salmonella enterica* serovar typhi was identified from blood cultures received from Hyderabad, Pakistan. Although, vaccination against *S.* Typhi is the ideal strategy of elimination of these extensively drug resistant (XDR) strains, accessibility and use of the available conjugate vaccine is limited by various economic and social factors in developing countries. It is important that therapeutic options be explored for effective treatment of XDR *S.* Typhi infection. In this study, we aim to determine treatment options for management of enteric fever caused by XDR *Salmonella* Typhi. .

METHODS

Retrospective analysis of phenotypic resistance profile of 208 XDR S.typhi isolates received from Hyderabad at Clinical Microbiology Laboratory, Aga Khan University, Karachi was performed. Minimum Inhibitory Concentrations (MICs) of ampicillin, ceftazidime, cefepime, ciprofloxacin, levofloxacin, meropenem, ertapenem, and trimethoprim sulfamethoxazole were determined using VITEK®2 AST-GN81 (**B**ioMÃ©rieux, Marcy l'Etoile, France). Imipenem and azithromycin susceptibilities were performed using disk diffusion. Additionally, azithromycin MICs of 40/208 isolates were also determined using Etest. Interpretation of results was done using CLSI M100 Ed27.

RESULTS

All isolates were resistant to ampicillin (MIC_{90} >=32 µg/mL), ceftazidime (MIC_{90} >=64 µg/mL), cefepime (MIC_{90} >=64 µg/mL) and trimethoprim sulfamethoxazole (MIC_{90} >=16/304µg/mL). Similarly, all isolates were resistant to both ciprofloxacin and levofloxacin, with MIC_{50} of 2 µg/mL & MIC_{90} of 4 µg/mLfor both fluoroquinolones. However, all isolates were susceptible to ertapenem (MIC_{90} of <0.5 µg/mL) and meropenem (MIC_{90} 0.3 µg/mL). All isolates were also susceptible to imipenem and azithromycin. The susceptibility results of azithromycin disk and Etest when performed on limited isolates, were consistent and MIC_{90} was 4 µg/mL (n=40).

CONCLUSIONS

Our study shows all isolates were susceptible to azithromycin, ertapenem, meropenem and imipenem and these drugs can be used for treatment of XDR *S.*typhi infections. However ongoing surveillance and monitoring of MDR and XDR *S.*Typhi strains against these antibiotics is essential to identify emerging resistance and to guide future strategies in drug development for treatment of enteric fever.

145. A Detailed Demographic Description of Three Urban Sites With High Typhoid Incidence: The STRATAA Study

Mila Shakya[1], James Meiring[2], Farhana Khanam[3], Buddha Basnyat[1], Melita Gordon[4], Firdausi Qadri[3], John Clemens[3], Andrew Pollard[5]

[1]Oxford University Clinical Research Unit Nepal, [2]Oxford Vaccine Group, [3]icddr,b, [4]Malawi Liverpool Wellcome Trust, [5]Oxford University

BACKGROUND

Infections caused by *Salmonella enterica* serovar Typhi and Paratyphi account for 12 – 21 million cases of febrile illness each year predominantly in countries with poor water and sanitation infrastructure. Here we present a detailed description of three sites from the Strategic Typhoid Alliance across Africa and Asia (STRATAA) study.

METHODS

A demographic census was enumerated within three urban settings in Dhaka (Bangladesh), Blantyre (Malawi), and Lalitpur (Nepal). Age, education and employment were recorded for each individual, with household size and GPS/GIS location documented. Census updates were conducted once in Nepal, twice in Dhaka and full repeat census at two years in all sites with migration recorded. 24 months of passive surveillance was conducted to assess febrile illnesses for enteric fever. Two separate healthcare utilisation and water and sanitation surveys were conducted in 735 selected households at each site to characterise health seeking behaviour and the physical condition of the house, economic descriptors and water and sanitation risk factors.

RESULTS

A total of 26,119, 23,567 and 24,502 households with 110,731, 97,410 and 102,963 individuals were enrolled in Dhaka, Blantyre and Lalitpur respectively. The average household size was 4.2(SD=1.8), 4.4(SD=2.1) and 4.2(SD=2.2) members respectively. The median age was 25 years (IQR:13-37) in Dhaka, 19 years (IQR:9- 31) in Blantyre, and 28 years (IQR:17-42) in Lalitpur. Migration rates were high in all sites. 41%, 24.1% and 54% of the households in Dhaka, Blantyre and Lalitpur respectively had access to their own toilets. 32%, 84% and 13% of the households in Dhaka, Blantyre and Lalitpur respectively used communal drinking water sources. In Blantyre 45% of the population accessed government health facilities for febrile illness, whilst 85% accessed either pharmacy or other forms of self-treatment in Dhaka. In Lalitpur 29.8% of the population accessed private clinics, with a further 42% using pharmacies or self-treatment with antimicrobials.

CONCLUSIONS

These data show the different demographic contexts of three sites with known high rates of enteric fever. Healthcare seeking behaviour is markedly different with high rates of private treatment in both Lalitpur and Dhaka. This will have an impact of the implementation of control strategies and ongoing surveillance of enteric fever.

146. Association of Climatic Factors With Occurrence of *Salmonella* Typhi in Surface Water of Kathmandu, Nepal

Supriya Sharma[1,2], Nisha Rijal[3], Anjana Singh[1]

[1]Central Department of Microbiology, Tribhuvan University, [2]National College affiliated to Tribhuvan University, [3]National Public Health Laboratory

BACKGROUND

Evidences suggest that climatic factors influence transmission of various infectious diseases. This study aims to correlate the association of climatic factors - temperature (maximum and minimum), rainfall and relative humidity with the occurrence of *Salmonella* Typhi in surface water and sediments of Kathmandu, Nepal.

METHODS

This prospective longitudinal study was conducted from April 2015 to March 2016. Triplicates of 1000 ml of surface water and 500 ml of sediment samples were collected on a monthly basis from Bishnumati River (Kalimati) and Bagmati River (Tripureshwor) located at Kathmandu district, Nepal. Each sample was inoculated into Selenite F broth and incubated at 37°C overnight and then subcultured into Xylose Lysine Deoxycholate (XLD) agar. *S.*Typhi was identified based on colony characteristics, Gram's staining and biochemical tests. Monthly data on climatic factors i.e temperature (maximum and minimum), relative humidity and rainfall were accessed from Department of Hydrology and Meteorology, Kathmandu. Collected longitudinal data was entered into SPSS 21.0 and descriptive and inferential statistics calculated. Ethical approval of this research was obtained from Nepal Health Research Council.

RESULTS

*S.*Typhi was isolated throughout the year except in November, December and January from sediment samples whereas only from July to September from water samples. Seasonal variation was associated with the isolation of *S.*Typhi from sediment samples (Spearman correlation(r) =0.637, p=0.035). Rainfall was correlated with isolation of *S.*Typhi from water (r=0.776, p=0.005) and sediment samples (r=-0.776, p=0.005).

CONCLUSIONS

With the exception during winter, *S.*Typhi persists in the environment throughout the year in the sediments of river water. This might pose a risk of outbreak in Kathmandu valley, if suitable climatic conditions occur.

147. Isolation and Antibiogram of *Salmonella* Species From Blood and Clot Cultures From Two Tertiary Care Hospital in Mumbai, India

Jayanthi Shastri, Anuradha De, Sachee Agarwal, Mansvi Pednekar

T.N. Medical Collge & Nair Hospital

BACKGROUND

Enteric fever is endemic in India and in Mumbai. The estimated incidence of culture confirmed typhoid in India is at 377 (178 – 801) per 1,000,000 person years, with the highest incidence in early childhood. Clinical presentation being Fever of Unknown Origin, definitive diagnosis is impossible. Therefore culture based diagnosis is critical as patients can be treated appropriately depending on the antibiogram. Challenges in isolation of *Salmonella species include* inadequate volume of blood collected, emperical use of antibiotics by practitioners.

Hence, a retrospective analysis of data was conducted from two affiliated tertiary care hospitals in Mumbai, India for a period of three years (from November 2015 to October 2018), to determine the percentage of *Salmonella species* isolated and their antibiotic susceptibility among clinically suspected cases of enteric fever.

METHODS

Blood was collected in Tryptic soy broth (TSB) for culture in Automated blood culture system (BACTEC). Clot was lysed with streptokinase and put in 0.5% bile broth. All Salmonella isolates were identified by standard biochemical tests and confirmed by agglutination with specific antisera. Antimicrobial susceptibility was performed by Kirby-Bauer Disc Diffusion Method and MIC was done by E-strip, according to Clinical Laboratory Standards Institute guidelines.

RESULTS

Out of 7064 automated blood cultures and 11,430 clot cultures, 22 (0.31%) and 90 (0.79%) *Salmonella species were isolated* respectively. Among 112 isolates, majority were from the paediatric age group (66.96%). Distribution of *S. typhi* and *S. paratyphi A* were found to be 90.18% and 8.93% respectively.

Nalidixic acid and Ciprofloxacin resistance among isolates was 100% and 49.12% respectively. Ceftiaxone susceptibility was 100%. Chloramphenicol susceptibility was 97.32%. Azithromycin, Co-trimoxazole and Ampicillin susceptibility to *S. Typhi* were 99.11%, 95.54% and 91.07% respectively. All isolates of *S. paratyphi A* were susceptible to Azithromycin.

CONCLUSIONS

Inadvertent use of antibiotics for fevers pose a challenge to the isolation of Salmonella .Clot cultures show better isolation of *Salmonella species*. Ceftriaxone is the preferred drug for treating enteric fever among clinicians in Mumbai. This holds promise in the near future. Azithromycin sensitivity among *Salmonella paratyphi A* is heartening. Continuous monitoring of resistance patterns among Salmonella isolates is crucial for reviewing antibiotic policies by clinicians regularly.

148. Pattern of Antibiotic Susceptibility of *Salmonella enterica* Serovar Paratyphi A in Paediatric Population – Study From India

Bhaskar Shenoy, Archana Mahalimgam, Muhammed Hafis

Manipal Hospitals, Bangalore, India

BACKGROUND

Antibiotic susceptibility of Salmonella Typhi with reduced susceptibility to Ciprofloxacin have been commonly reported across the world. There are not many studies related to antibiotic susceptibility of Salmonella Paratyphi.

METHODS

A retrospective study of 195 culture proven cases of Paratyphi A conducted between 0-18 years over a period of 10 years. Blood culture done by BacT/Alert 3D system and serotypes identification by biochemical tests or by using specific antisera by slide agglutination method. Antimicrobial susceptibility tested by the disc diffusion. MIC of Azithromycin and Ciprofloxacin were determined by using E-strips.MIC of Ciprofloxacin was interpreted as per the revised CLSI breakpoints which came into effect in 2012. Paratyphi Isolates with MIC of ≥ 1 µg/ml for Ciprofloxacin and > 16µg/ml for Azithromycin were considered as resistant. The results were analysed by descriptive univariate analysis.

RESULTS

Out of 858 Salmonella Enterica isolates ,195 were *Salmonella* Paratyphi(22.7%) and all were Paratyphi A. Male to female ratio of 1.48:1,with major incidence between 2-10 years (49.23%), followed by above 10 years(43.1%), 1-2 years(4.61%) and below 1 year(3.07%). All isolates were susceptible to third generation Cephalosporins and Azithromycin. Susceptibility to Ampicillin (97.44%), Chloramphenicol (100%) and Cotrimoxazole (100%) is resurging. Resistance to Nalidixic acid (92.3%) has been increasing. 65.12 % were susceptible to Ciprofloxacin, however 33.84 and 1.02 % cases were intermediate and resistant respectively. No multi drug resistance cases were noted. Increasing trend of MIC observed for Azithromycin (Mean MIC 3.35 in 2014 and 6.47 in 2018), but MIC of Ciprofloxacin showed a reverse trend(Mean MIC of 0.5 in 2014 and 0.38 in 2018).

CONCLUSIONS

Salmonella Enterica serovar Paratyphi A continues to remain susceptible to third generation Cephalosporins. Resurgence of susceptibility to first generation antibiotics like Ampicillin, Chloramphenicol and Cotrimoxazole is noteworthy. Local antibiograms improve the compliance and provide better outcome and reduces the cost in under privileged counties. In view of the increasing MIC of Azithromycin, its use in routine infections has to be restricted. It should be kept as a reserve drug for emerging drug resistant enteric fever in future. Developing a bivalent vaccine to cover paratyphoid is the need of the hour.

149. Burden of Typhoid Fever in Association With Seasonal Trends and Antimicrobial Susceptibility in Tertiary Care Hospital, Kathmandu Nepal

Jeevan Sherchand, Sangita Sharma, Shyam K. Mishra, Hari P. Kattel, Shovita Shrestha Dhakal, Niranjan P Shah, Keshab Parajuli

Institute of Medicine, Tribhuvan University Teaching Hospital, Maharajgunj Medical Campus

BACKGROUND

Background: Typhoid fever caused by *Salmonella* Typhi or *Salmonella* Paratyphi A is one of the major public health problems in Nepal. Moreover, irrational use of antibiotics and increasing trends of drug resistance have increased serious for the treatment. The study was conducted to determine seasonal trends and antimicrobial susceptibility pattern of *Salmonella* Typhi and Paratyphi A isolated from suspected cases of Typhoid fever visiting tertiary care hospital in Nepal.

METHODS

Methods: A total of 4584 suspected cases of typhoid fever who were attending for the treatment in the hospital from October 2017 to September 2018 were enrolled in the study and 172 *Salmonella* isolates were tested for antimicrobial susceptibility test against chloramphenicol, amoxycillin, cotrimoxazole, ciprofloxacin, ceftriaxone and azithromycin according to CLSI guideline of microbiology. Information on patient's history along with demographic information and seasonality were obtained.

RESULTS

Results: Of the total 4584 blood culture from suspected cases of typhoid fever- 172 cases (3.75%) *Salmonella* were isolated in which *S.* Typhi 161 (93.6%) and Paratyphi A 11 (6.4%) were found. A maximum number of cases were found between March and June among 20 to 30 years of age. Among the tested antimicrobial, *S.* Typhi was susceptible to chloramphenicol and ceftriaxone 100%, followed by cotrimoxazole 98%, amoxycillin 92%, azithromycin 89%, whereas, the least susceptible antibiotic was ciprofloxacin 27.9%. Regarding *S.* Paratyphi A most of the tested antibiotics found more than 90% susceptible except ciprofloxacin (28%).

CONCLUSIONS

Conclusion: In the study, the most common etiological agent for typhoid fever is *Salmonella* Typhi causing the majority of cases from March to June. The antimicrobial susceptibility test of *S.* Typhi and Paratyphi A found highly susceptible (> 89%) to most of the antibiotics except ciprofloxacin. Hence the study identified that ciprofloxacin is not recommended for treatment.

150. Sampling to Detect *Salmonella* Typhi Within Samoan Concrete Septic Tanks Serving Households of Typhoid Fever Cases - A New Use for Moore Swabs

Michael Sikorski[1], Paulo Pemita[2], Siaosi Tupua[2], Susan Ballard[3], Robert Thomsen[2], Take Naseri[2], Sharon Tennant[1], Myron Levine[1]

[1]University of Maryland School of Medicine, [2]Samoa Ministry of Health, [3]Microbiological Diagnostic Unit Public Health Laboratory

BACKGROUND

Endemic typhoid fever in Samoa exhibits no seasonality and occurs often where households have potable water and concrete septic tanks. Some acute cases likely derive from short-cycle transmission of *Salmonella* Typhi from asymptomatic chronic carriers. Environmental bacteriology using Moore swabs to filter/concentrate pathogens from sewage effluents has successfully detected chronic carriers of *S.* Typhi and Paratyphi (United Kingdom, California, Chile); however, detection in septic tanks has not yet been investigated. In Samoa, where 87.3% of household latrines connect to a septic tank, the feasibility of sampling household septic tanks of acute typhoid cases with Moore swabs was undertaken in July/August, 2018.

METHODS

Households of confirmed typhoid cases were visited. If an in-ground Samoan septic tank (sealed cement box with or without a cement bottom) was found, a 10-cm diameter hole was created in the top. Three Moore swabs (15x120 cm lengths of cotton gauze folded into 15 cm2 pads and tied to 300 cm of fishing line) were placed into the septic tank. After 72 hours, swabs were transferred into 300 mL of selenite-F broth and the septic tank was re-sealed with cement. Broths were incubated at 37°C in a microbiology laboratory re-furbished within the Ministry of Health to culture Moore swabs. Broth was sub-cultured (24 and 48 hours) onto *Salmonella-Shigella* and bismuth-sulfite agars. Triple-sugar-iron agar slants were inoculated with suspicious colonies; those exhibiting characteristic biochemical patterns were confirmed by API.

RESULTS

Households of 5 confirmed typhoid cases were visited; three were served by accessible concrete septic tanks. Bacteria recovered included colonies suspect for *Salmonella* (but not Typhi), *Citrobacter*, *Klebsiella*, and *E. coli*.

CONCLUSIONS

We established that it was logistically feasible to access cement-sealed septic tanks in Samoa with the help of a construction artisan and to place, retrieve, and culture septic swabs using classical bacteriologic techniques. Hereafter, PCR methods will also be used. Limitations and challenges to the use of Moore swab septic surveillance were identified including saturation of the Selenite enrichment broth with septic contents. Septic tank surveillance will be incorporated into a new Samoa Typhoid Fever Surveillance Initiative beginning January 2019.

151 . Phase I Study to Assess Safety and Immunogenicity of Vi-DT Vaccine Compared to Vi Vaccine in Healthy Filipino Adults and Children

Sushant Sahastrabuddhe[1], **Arijit Sil[1],** Maria Rosario Capeding[2], Anh Wartel[1], Ji Hwa Ryu[3], Hun Kim[3], Yun Chon[1], Jae Seung Yang[1]

[1]International Vaccine Institute, [2]Research Institute of Tropical Medicine, [3]SK Bioscience

BACKGROUND

As the currently licensed typhoid vaccines have limitations and cannot be administered in children less than 2 years of age, the International vaccine Institute developed a typhoid conjugate vaccine (Vi-Polysaccharide conjugated to diphtheria toxoid (Vi-DT)) which was transferred to SK Chemicals in Korea. After completing the preclinical study phase I clinical trial was conducted in the Philippines.

METHODS

In this randomized, observer-blinded Phase I study to assess the safety and immunogenicity of Vi-DT compared to Vi-Polysaccharide vaccine, 2-45-year old participants (divided in 3 age cohorts) were randomized between Test (Vi-DT) and Comparator (Vi-Polysaccharide) vaccine administered at 0 and 4 weeks. The objectives were to evaluate the safety and immunogenicity (anti-Vi IgG ELISA and serum bactericidal antibody, SBA) of 25 µg of Vi-DT comparatively to Vi-Polysaccharide (Typhim Vi®, Sanofi Pasteur) vaccine.

RESULTS

48 participants in each age cohort for a total of 144 participants were enrolled and randomized to Vi-DT and Comparator equally. No SAE was reported in either group. No subject was discontinued from the study due to AE. All solicited and unsolicited AEs were mild or moderate in both groups with the exception of a 4-year old girl in Test group with severe (grade 3) fever that resolved without sequela. All subjects (100%) in Test group showed seroconversion after 1st and 2nd doses while 97.1% and 97.2%, respectively in Comparator group. Vi-DT showed 4-fold higher GMT vs. Comparator. No further increase of GMT was detected after the 2nd dose. SBA seroconversion rate in Test group was higher than Comparator group after first dose (71% vs. 52.17%) and second dose (70.4% vs. 51.4%). SBA GMT showed similar pattern post first and second doses. Anti-DT responses post first dose in the test group were higher, 26-fold rise compared to baseline value, while a 0.93-rise in the Comparator group.

CONCLUSIONS

The results of this first-in-human Phase I trial of Vi-DT show that the vaccine is safe, generally well-tolerated and immunogenic in participants aged 2-45 years. These results allow pursuing the clinical development of Vi-DT in children 6 to 23 months of age.

152. Phase II Study to Assess the Safety, Reactogenicity and Immunogenicity of Vi-DT Vaccine in 6-23-Month Old Healthy Filipino Infants and Toddlers

Sushant Sahastrabuddhe[1], **Arijit Sil[1],** Maria Rosario Capeding[2], Anh Wartel[1], Ji Hwa Ryu[3], Hun Kim[3], Yun Chon[1], Jae Seung Yang[1]

[1]International Vaccine Institute, [2]Research Institute of Tropical Medicine, [3]SK Bioscience

BACKGROUND

After the encouraging results from the phase I study, wherein the vaccine was found to be safe, generally well-tolerated and immunogenic in participants aged 2-45 years, we planned for conduct of the phase II study. The phase II study of Vi-DT was planned in children 6 to 23 months of age at the same site of the phase I study.

METHODS

Our Phase II study is Randomized, Dose-scheduling, Observer-Blinded Study to Assess the Safety, Reactogenicity and Immunogenicity of Vi-DT Conjugate Vaccine in 6-23-Month old Healthy Filipino Infants and Toddlers. The study has a primary objective of safety of Vi-DT and comparison of anti-Vi seroconversion rate 4 weeks post dose 1 between test and comparator group. Total sample size is planned to be 285 and the participants will be divided in 3 groups with two receiving test vaccine and one placebo. The participants in the single dose arm of test vaccine will receive a booster at the end of 2 years.

RESULTS

After the initial approvals from PFDA and two IRBs (site and IVI), the site initiation visit was completed in February 2018. However, because of the Dengue vaccine introduction fallout in the Philippines, enrollment started in April 2018 and completed in July 2018. As per planning 285 participants were enrolled. No safety concerns so far. Following Source data verification, resolution of the entire queries data base has been locked for interim analysis. Both pre dose and 1 month post dose serum samples have been shifted to IVI and the anti Vi IgG and MMR analysis is under process.

CONCLUSIONS

This trial faced lot of challenges because of the Dengvaxia fallout in the Philippines, Measles outbreak in the community, and typhoons at the end of enrollment period. In spite of these issues, the site and IVi have been able to manage to complete the enrollment, without much delay and now the long-term follow-up (upto 24 months) is ongoing.

153. Phase 2 Randomized, Double-Blind, Controlled Safety & Immunogenicity Trial of Typhoid Conjugate Vaccine in Children <2 in Burkina Faso: Study Design

Matthew Laurens[1], **Sodiomon Sirima[2],** Mohamadou Siribie[2], Alfred Tiono[2], Alphonse Ouedraogo[2], Yuanyuan Liang[1], Karen Kotloff[1], Kathleen Neuzil[1]

[1]University of Maryland School of Medicine, [2]Groupe de Recherche Action en Santé

BACKGROUND

Recently, a single-dose typhoid conjugate vaccine that allows infants as young as six months old to be vaccinated was pre-qualified by the World Health Organization. This Vi-based conjugate vaccine demonstrated robust immunogenicity after one dose in infants and young children in India with no safety signal. The first study of this vaccine in Africa is being conducted by the Typhoid Vaccine Acceleration Consortium in Malawi. The World Health Organization Strategic Advisory Group of Experts recommends studies of Vi-typhoid conjugate vaccine co-administered with routine childhood vaccines in typhoid-endemic countries. The Burkina Faso immunization schedule includes yellow fever vaccine at 9 months and meningococcal A conjugate vaccine at 15 months in addition to measles-rubella vaccine at both 9 and 15 months.

METHODS

The Typhoid Vaccine Acceleration Consortium is planning to conduct a randomized, controlled, phase 2 trial of Vi-typhoid conjugate vaccine co-administration with vaccinations routinely given at 9 and 15 months of age in Burkina Faso. The overall aim is to assess the safety and immunogenicity of the vaccine when co-administered with yellow fever vaccine at 9 months of age and with meningococcal A conjugate vaccine at 15 months of age. A total of 250 participants (100 infants aged 9-11 months and 150 children aged 15-23 months) will be enrolled and followed for six months after vaccination. Blood draws will occur at 0 and 28 days. Reactogenicity data will be monitored for the first seven days and adverse events will be monitored through six months post-vaccination.

RESULTS

The study is anticipated to start at the end of 2018.

CONCLUSIONS

This study is only the second in Africa and first in West Africa for a Vi-based conjugate vaccine. Co-administration testing of Vi-typhoid conjugate vaccine with routine vaccinations provides safety and immunogenicity data to national policy makers.

154. Vi-DT Typhoid Conjugate Vaccine Development Strategy and Update at PT Bio Farma

Arijit Sil[1], **Novilia Sjafri Bachtiar[2],** Sushant Sahastrabuddhe[1], Anh Wartel[1], Adriansjah Azhari[2], Mita Pushpita[2], Rini Mulia Sari[2], Erman Tritama[2]

[1]International Vaccine Institute, [2]PT Biofarma

BACKGROUND

As the currently licensed typhoid vaccines have limitations and cannot be administered in children below 2 years, IVI developed a typhoid conjugate vaccine (Vi-Polysaccharide conjugated to diphtheria toxoid (Vi-DT)) which was transferred to Bio Farma in Indonesia. After completing the preclinical study phase I clinical trial was conducted and phase II trial is ongoing in Jakarta.

METHODS

Following toxstudy, a phase I study was conducted in 100 adults and children in Jakarta, Indonesia. Phase I study had Vi polysaccharide vaccine as the comparator. Phase I was study was planned to assess the safety of the product in adult and Children. After the phase I, a phase II study was planned in 600 adults, children and infants. Phase I and II were conducted by Cipto Mangunkusumo Hospital/Department of Child Health, School of Medicine, University of Indonesia, Jakarta.

RESULTS

Phase I study has been completed and safety of Vi-DT in children and adult has been established. Phase I manuscript has been submitted to an International Journal. Phase II clinical study enrollment has been started in Infant as well as Adult cohort and recruitment expected to be finished by end of Jan 2019. As of 26th October, there were 159 infants, 13 children, and 175 adults enrolled in the study across the 2 sites. Draft protocol for Phase III study and site selection is going on. IVI is in constant touch with PT Bio Farma for technical support.

CONCLUSIONS

This clinical development is going on under Bio Farma's lead. Recently there were issues around acceptability of non-halal vaccines in Indonesia and other Islamic countries. Bio Farma is working closely with the regulatory agency and halal certifying bodies in Indonesia to comply with these requirements. This might have huge impact on the acceptability of vaccines in other Islamic countries as well.

155. Blood Culture Volumes Collected as Part of *Salmonella* Typhi Surveillance Within a Clinical Vaccine Trial in Nepal

Nicola Smith[1], Dikshya Pant[2], Mila Shakya[2], Merryn Voysey[1], Buddha Basnyat[2], Andrew Pollard[1], TyVAC Study Team Nepal[2]

[1]Oxford Vaccine Group, [2]Oxford University Clinical Research Unit Nepal

BACKGROUND

TyVAC-Nepal is an ongoing double-blind randomised controlled trial taking place in Lalitpur, Nepal, in which we aim to determine the efficacy of a typhoid conjugate vaccine. Passive surveillance will continue until April 2020 (two years post-vaccination) to ascertain the incidence of blood culture confirmed typhoid fever among participants. Study "fever clinics" have been established both in the hospital and community; parents of children presenting with either a reported fever of at least 2 days or a measured fever of ≥38°C provide consent for blood culture. The sensitivity of blood culture for detecting infection with *Salmonella* Typhi is dependent on sample volume; the study plan stipulates a 3-4ml target.

METHODS

To estimate blood culture volumes, a system for weighing blood cultures has been established, initially in the hospital-based fever clinic. Each culture bottle is pre-weighed, and the weight recorded on the bottle label. Immediately after inoculation with participant blood the bottle, together with its cap, is re-weighed using the same calibrated scales. The pre- and post-weight are recorded. The blood weight is calculated for each participant, adjusted into a volume, and matched with participant information using the ID number and study database.

RESULTS

A total of 1222 blood cultures were collected between February and October 2018, of which 1069 (87.5%) were taken in the hospital clinic, and of these 852 (79.7%) were weighed and accurately recorded. Volumes ranged from 0.45ml to 8.31ml (mean, 2.59ml; standard deviation 1.10ml). 238 (27.0%) cultures were in the target range of 3-4ml, and 585 (68.7%) samples were less than 3ml.

There were no significant volume differences between samples collected from differing age groups (p-value 0.78), mean volumes are: age <2 years, 2.65ml; ≥2 to <5 years, 2.60ml; ≥5 to <10 years, 2.64ml; ≥10 years, 2.60ml.

Most cultures were reported as "no growth" (804, 94.9%), 20 (2.6%) were positive for *S.* Typhi (mean volume 2.73ml, range 1.16-7.10ml), and 17 (2.0%) contained likely contaminants.

CONCLUSIONS

There is scope for improvement in the volume of blood collected for culture. However, age of participant is not a significant hindrance to volume collected, and contamination rates remain low.

156. A Novel Vaccine Candidate for Non-Typhoidal *Salmonella*

Akosierere Sokairibo, Aaron White, Sumudu Perera, Will Deck, Sam Attah-Poku, Shirley Lam

University of Saskatchewan

BACKGROUND

Gastroenteritis caused by Non-typhoidal Salmonella (NTS) is one of the most common foodborne diseases worldwide. Recently, NTS serovars that typically cause self-limiting gastroenteritis, have been shown to cause systemic infections, referred to as invasive NTS (iNTS) diseases. We have characterized a surface-associated polysaccharide that is conserved in pathogenic Salmonella strains, and cross-reactive between the most common serovars associated with iNTS: Salmonella serovars Typhimurium and Enteritidis.

METHODS

We used random and targeted mutagenesis to generate a Salmonella strain that produces high levels of the capsule antigen, and have established an optimal purification protocol. We performed an immunization trial in mice with the capsule alone and capsule conjugated to carrier proteins.

RESULTS

Targeted mutagenesis was used to mutate a repressor, whose deletion increased expression for the capsule biosynthesis operon by 100-fold. Random mutagenesis in the high capsule expressing strain was used to generate an isolate with 166 fold increased capsule production. The immunization trial showed that the antigen can induce an immune response when administered alone, and when conjugated to a carrier protein.

CONCLUSIONS

Our results indicates that the polysaccharide capsule can induce an immune response in mice, and this response can be increased by conjugating the capsule to a carrier protein. Future challenge experiments will allow us assess the level of protection against NTS isolates: Typhimurium and Enteritidis. Studies have shown that the presence of naturally acquired antibodies against NTS corresponds with a reduced risk of iNTS disease. Hence we hypothesize that protective immune responses induced by our antigen will also provide protection against iNTS isolates.

157. Independent Pathways Leading to Impaired Biofilm Formation Suggests Environmental Niche Specialization in Invasive *Salmonella* Strains

Aaron White[1], Keith MacKenzie[2], Yejun Wang[3], Patrick Musicha[4], Elizabeth Hansen[5], Melissa Palmer[5], Nicholas Feasey[6], **Akosierere Sokaribo[5]**

[1]Vaccine and Infectious Disease Organization, [2] University of Regina, [3] Shenzhen University, [4] University of Oxford, [5] University of Saskatchewan, [6] Liverpool School of Tropical Medicine

BACKGROUND

There is an established correlation between biofilm formation and the ability of Salmonella strains to colonize and replicate within the intestines of multiple host species. In contrast, host-restricted Salmonella strains, such as S. Typhi and Paratyphi have lost the ability to form biofilms. We hypothesized that invasive nontyphoidal Salmonella strains in sub-Saharan Africa would have impaired biofilm formation, since these strains also have evidence of genome degradation and host-adaptation.

METHODS

We investigated biofilm formation in two NTS strains that caused invasive disease in Malawian children, S. Typhimurium D23580 and S. Enteritidis D7795, and compared them to a panel of NTS strains associated with enterocolitis, as well as S. Typhi strains. Analysis and comparisons were done using a mixture of phenotypic tests, gene expression assays, sequence analysis and bioinformatics.

RESULTS

We identified a single promoter SNP that shuts off biofilm formation completely in S. Enteritidis D7795 and found that this SNP was conserved throughout this clade of isolates going back 50-80 years. For S. Typhimurium D23580, we identified several other important SNPs that were conserved in this lineage and contribute to biofilm impairment. Finally, we identified the plausible reason for biofilm loss in S. Typhi, which is also conserved through these isolates.

CONCLUSIONS

Our results indicate that biofilm deficiency has been selected since the first divergence of the invasive African isolates. We hypothesize that invasive NTS isolates have undergone environmental niche specialization and are becoming human-adapted with less reliance on environmental survival, as compared to enterocolitis-causing isolates. The independent, convergent pathways leading to biofilm loss suggests that similar selection pressures could be acting on all invasive Salmonella isolates.

158. Drinking Water and Sanitation in an Urban Community in India

Manikandan Srinivasan, Kulandaipalayam Natarajan Sindhu, Sathyapriya Subramaniam, Jacob John, Gagandeep Kang

Christian Medical College, Vellore

BACKGROUND

In 2015, WHO reported that 1.9 billion people had access only to contaminated water and 2.9 billion people did not have access to improved sanitation. This study is a situational analysis on drinking water and sanitation status of an urban community in India.

METHODS

This study describes the existing drinking water facilities and sanitation practices of an urban community of Vellore, where a cohort of 5956 children are being followed up under the Surveillance for Enteric Fever in India (SEFI) study. Data collection was done through a semi-structured questionnaire administered by trained field research assistants (FRA). Data on drainage of toilets was completed based on the observations made by FRA.

RESULTS

Among the 5956 children in the cohort, the majority 5147 (86.4%) use public distribution system as their source of drinking water and supply is intermittent. Of 1454 drinking water samples were tested during 2017 and 2018, and 1047 (72%) samples had coliform counts greater than 10,000/100 ml. In 2018, the observed median (range) of contamination rates in January-March, April-June and July-September were 80.9% (46.7% - 100%), 92.8% (70% - 100%) and 100% (70.6% - 100%) respectively. It can be inferred that contamination with coliforms was higher during drier seasons (April-June) and monsoon (July-September), when compared to winter (January-March). High water contamination rates were associated with poor residual chlorine. Regarding sanitation, families of 433 children (7%) had no toilets and no access to public toilets. Of 5135 children who had toilets (either exclusive for their family or shared with neighbouring households), 780 (15%) had their toilets connected directly into open drains.

CONCLUSIONS

Approximately 8 in 10 children in urban Vellore drink water from a heavily contaminated public source. Nearly 22% of children do not have access to improved sanitation. Thus, access to safe water and improved sanitation has to be accelerated to reduce the burden of feco-orally transmitted diseases.

159. Examining the Epidemiology, Drug Resistance and Transmission of Typhoid Fever in Fiji Using Bacterial Genomics

Richard Strugnell[1], Mark Davies[1,2], Aaron Jenkins[3], Adam Jenney[1,2,3], Ben Howden[1,2], John Crump[4], Kim Mulholland[5]

[1]University of Melbourne, [2]Fiji Typhoid Taskforce, [3]Edith Cowan University, [4]University of Otago, [7]MCRI RCH Melbourne

BACKGROUND

Typhoid fever is endemic in Fiji, like many other Pacific countries. The disease prevalence, demonstrated through serosurveys, is considerably higher than the number of reported cases suggesting a significant burden of undiagnosed infection. An enhanced understanding of the genetics of *S.* Typhi isolates will inform research on this undiagnosed disease. We investigated isolates from Fiji collected during 2012-2017 and tested hypotheses concerning the relatedness of Fijian typhoid isolates to global typhoid fever, transmission and common source outbreaks, and emerging drug resistance.

METHODS

S. Typhi isolates from Fijian patients diagnosed with typhoid fever were sent to the MDU at the Peter Doherty Institute, University of Melbourne where genome data was obtained through Illumina sequencing. This data was analysed using the Nullarbor pipeline and the phylogeography interrogated using high resolution genome wide polymorphisms and patient/sample spatial data.

RESULTS

We demonstrated that there are two major genotypes of *S.* Typhi circulating in Fiji, defined as 4.2.1 and 4.2.2 according to the Genotyphi classification framework; there was one isolate that was a member of the global and increasingly resistant H58 phylogroup of *S.*Typhi. The Fijian H58 *S.* Typhi was imported from India by a patient returning from surgery. There were no differences in the patterns of transmission of the two major phylogroups that suggested a phenotypic advantage, and the clades were disseminated throughout the region. SNP typing was used to show that focal outbreaks were common source. The same bacteria were identified in different regions of Fiji which suggested spread by either active cases, or carriers. The analysis identified genotypic resistance to naladixic acid in two isolates, which was confirmed as phenotypic resistance to ciprofloxacin.

CONCLUSIONS

The data suggest that Fiji, which is endemic for *S.* Typhi infection, is home to two major evolving genotypes of *S.* Typhi, which are different from the bacteria infecting much of the rest of the world, and especially South Asia and Africa. The genomic analyses confirmed transmission from common sources and will be useful in identifying carriers and emerging drug resistant lineages, and will assist in identifying where the large burden of infection resides.

160. Determination of Fever Defervescence Periods of Ceftriaxone Treated Enteric Fever in Children

P. Sulochana Putli Bai, S. Balasubramanian, Surekha Surendranathan, **S. Senthilnathan**

The CHILDS Trust Medical Research Foundation, Kanchi Kamakoti CHILDS Trust Hospital

BACKGROUND

Enteric fever is a common infection caused by Salmonella Typhi and Salmonella Paratyphi species. It is prevalent among children living in developing countries. Ceftriaxone is a third-generation cephalosporin and is a broad – spectrum antibiotic. It is highly effective against Salmonella species. In this study, we determine and compare the defervescence period of ceftriaxone treated enteric fever in children to previous studies, to help identify the efficacy of the drug.

METHODOLOGY

A retrospective and descriptive study was carried out from December 2017 to September 2018 in a paediatric population (<18 years) in Kanchi Kamakoti CHILDS Trust Hospital, Chennai, India. This study included 46 patients who were culture positive for Salmonella Typhi (39) and Salmonella Paratyphi A (7). The defervescence period of Ceftriaxone was determined along with high grade fever temperatures to check its influence on antibiotic therapy.

RESULTS

All Salmonella Typhi isolates (100%) and all Salmonella Paratyphi A isolates (100%) were susceptible to Ceftriaxone. No episodes of complications, relapses and mortality. The clinical cures occurred in 100% of the patients treated with ceftriaxone. Among the 46 patients enrolled in the study, 35 (76.1%) were treated with ceftriaxone. The mean defervescence period is **3.6 days** with a range of 2 to 6 days.28 (60.9%) had high grade fever, i.e. Patients with temperature of 38°C and more, had a mean defervescence period of **4.1 days.** Patients with a low-grade fever were 18(39.1%) and had a mean defervescence period of **3.9 days**.

CONCLUSION

In our study, we conclude that the defervescence period of ceftriaxone for the treatment of enteric fever in a paediatric population is 3.6 days. In comparison to previous studies, the defervescence period has been reduced significantly. The patients presenting with high grade fever have a longer defervescence period than the patients with low grade fever. The importance of blood culture is highlighted over serological tests, as they provide information on appropriate antibiotic usage leading to a shorter defervescence period, especially in primary health care centres. The results of this study will provide useful information to the clinicians on appropriate usage of the drugs and for providing cost-effective treatment.

161. Relationship of Prior Antibiotic Use, Blood Volume and Defervescence Period With Time to Positivity in Blood Culture of Patients With Enteric Fever

P. Sulochana Putli Bai, Balasubramanian S, **Surekha Surendranathan**, Senthilnathan S, Akshya Vanamali

Kanchi Kamakoti Childs Trust Hospital

BACKGROUND

Time to Positivity (TTP) of blood cultures of patients with Enteric fever, can be associated with the severity of infection. This study compares the TTP of patients who were treated with antibiotics prior to blood culture with those who were not.The volume of the blood taken between the two study groups were also analysed.The defervescence periods between rapid TTP and slow TTP are compared to add emphasis on prognosis.

METHODS

A retrospective and descriptive study was carried out from December 2017 to September 2018 in a paediatric population (<18 years) in KKCTH, India. A total of 66 patients,who were culture positive for *Salmonella* Typhi or *Salmonella* Paratyphi A,were enrolled in the study.Of the 66,18 were treated with prior antibiotics before the blood culture was taken and 48 did not receive any treatment.The mean TTP for the two study groups were calculated by retrieving the TTP data from BactAlert.A cut-off of 10 hours TTP was taken to analyse the defervescence period.The volume of blood drawn was inferred from the difference between Post-inocular and Pre-inocular weights of the blood culture bottles and was compared to TTPs.

RESULTS

Among the 66 patients,patients with an antibiotic history had a mean TTP of 15.08 hours and patients without an antibiotic history had a mean TTP of 15.29 hours.All the blood cultures in our study turned positive before 24 hours.The number of patients with a TTP of <10 hours was 6 who had an average defervescence period of 3.3 days. Similarly, 60 patients had >10 hours TTP with a mean defervescence period of 2.7 days. The average blood drawn weight for <10 TTP was 64.18 gm and for >10 TTP was 64.23 gm.

CONCLUSIONS

In our study, we conclude that there is insignificant difference between the TTPs of patients who were previously treated with antibiotics and those who were not.The defervescence period was lower with patients with >10 TTP when compared to the other group. The difference between blood drawn weight in patients who had <10 TTP and >10 TTP was negligible.These conclusions may provide useful prognostic and diagnostic information to the physicians treating Enteric fever in a paediatric population.

162. Effect of Live Oral Attenuated Typhoid Vaccine, Ty21a, on Systemic and Terminal Ileum Mucosal CD4+ T Memory Responses in Humans

Jayaum Booth[1], Eric Goldberg[2], Seema Patil[2], Robin Barnes[1], Bruce Greenwald[2], **Marcelo B. Sztein[4]**

[1]Center for Vaccine Development, School of Medicine University of Maryland, [2]Department of Medicine, University of Maryland School of Medicine, [3]Department of Pediatrics, School of Medicine University of Maryland

BACKGROUND

Our current understanding of CD4+ T cell mediated immunity (CMI) elicited by the oral live attenuated typhoid vaccine Ty21a is primarily derived from studies using peripheral blood. Very limited data is available regarding mucosal immunity particularly on the induction of CD4+ T M responses to *S.* Typhi in the human terminal ileum (TI) mucosa (favored site of infection for *S.* Typhi) following Ty21a immunization.

METHODS

Using multiparametric flow cytometry, we examined the effect of Ty21a immunization on TI lamina propria mononuclear cells (LPMC) and peripheral blood CD4+ T memory (T_M) subsets in Ty21a-vaccinated and unvaccinated volunteers undergoing routine colonoscopy. *S.* Typhi-responsive CD4+ TM were determined from the two groups following stimulation with (i) autologous target cells infected with or without wt *S.* Typhi and (ii) *S.* Typhi antigens (e.g., Ty21a homogenate).

RESULTS

Interestingly, we observed significant increases in the frequencies of LPMC CD4+ T cells following Ty21a-immunization, restricted to the T-effector/memory (T_{EM})-CD45RA+ (T_{EMRA}) subset. Importantly, Ty21a-immunization elicited *S.* Typhi responsive LPMC CD4+ T cells in all major T_M subsets (interferon (IFN)γ and interleukin (IL)-17A in T effector/memory -T_{EM}-; IFNγ and macrophage inflammatory protein (MIP)-1β in T central/memory -T_{CM}-; and IL-2 in T_{EMRA}). Subsequently, we analyzed LPMC *S.* Typhi responsive CD4+ T cells in depth for multifunctional (**MF**) effectors. We found that LPMC CD4+ T_{EM} responses were mostly **MF**, except for those cells exhibiting the characteristics associated with IL-17A responses. We noted that CD4+ T_{EM} *S.* Typhi-specific IFNγ **MF**, TNFα **S**, MIP1β **MF** and IL-17A **MF** were similarly elicited by stimulation with either targets or soluble antigens following Ty21a-immunization. In contrast, the potential to be cytotoxic (CD107 expression; which showed significant

increases with soluble antigen) and production of IL-2 (which exhibited significant increases with infected targets) seems to be dependent on the type of stimulation. Finally, we compared mucosal to systemic responses and observed that LPMC CD4+ *S.* Typhi-specific responses were unique and distinct from their systemic counterparts.

CONCLUSIONS

This study provides the first demonstration of *S.* Typhi-specific CD4+ T_M responses in the human terminal ileum mucosa and provides valuable information about the generation of mucosal immune responses following oral Ty21a-immunization.

163. Manipulation of *Salmonella* Typhi Gene Expression Impacts Innate Cell Responses in the Human Intestinal Mucosa

Rosangela Salerno-Goncalves[1], James E. Galen1[1], Myron M. Levine[1], Alessio Fasano[2], **Marcelo B. Sztein[1]**

[1]Center for Vaccine Development and Global Health, [2]Massachusetts General Hospital for Children

BACKGROUND

Although immunity induced by typhoid fever is moderated and short-lived, typhoid vaccination with the attenuated Ty21a oral vaccine generates long-lasting protection rates reaching up to 92%. Thus, there are important differences on how wild-type *Salmonella* and typhoid vaccine strains stimulate host immunity. We hypothesize that vaccine strains with different mutations might affect gut inflammation and intestinal permeability by different mechanisms.

METHODS

To test this hypothesis, we used an *in vitro* organotypic model of the human intestinal mucosa composed of human intestinal epithelial cells, lymphocytes/monocytes, endothelial cells, and fibroblasts. We also used six *Salmonella enterica* serovar Typhi (*S.* Typhi) strains: the licensed Ty21a oral vaccine, four typhoid vaccine candidates (i.e., CVD 908, CVD 909, CVD 910, and CVD 915) and the wild-type Ty2 strain.

RESULTS

We found that genetically engineered *S.* Typhi vaccine strains elicit differential host changes not only in the intestinal permeability and secretion of inflammatory cytokines, but also in the phenotype and activation pathways of innate cells. These changes were distinct from those elicited by the parent wild-type *S.* Typhi and depended on the genetic manipulation.

CONCLUSIONS

In sum, these results emphasize the importance of carefully selecting specific manipulations of the *Salmonella* genome in the development of typhoid vaccines.

164. Emerging Antibiotic Co-Resistance in Invasive Salmonellosis: A Need for Clinical Studies, Adapted Treatment Guidelines and Harmonized Policy Documents

Bieke Tack[1], Sandra Van Puyvelde[1], Marie-France Phoba[2], Brecht Ingelbeen[1], Stijn Deborggraeve[1], Octavie Lunguya[2], Jan Jacobs[1]

[1]Institute of Tropical Medicine, [3]National Institute for Biomedical Research (INRB)

BACKGROUND

In the light of the rising antibiotic resistance in typhoidal *Salmonella* (TS) and invasive non-typhoidal *Salmonella* (iNTS) infections, antibiotic resistance surveillance and antibiotic treatment guidelines are needed.

METHODS

We assessed published literature and supranational documents for guidelines about antibiotic resistance testing and antibiotic treatment of TS and iNTS infections from 2010 onwards. Documents about antibiotic susceptibility testing included those issued the U.S. Clinical Laboratory Standards Institute and the European Committee on Antimicrobial Susceptibility Testing. Patient management guidelines included those published by the Word Health Organization (WHO): Pocket Book of Hospital care for children (2016), Hospital Care for Adolescents and Adults (2011), Model List of Essential Medicines (EML) (2017), List of Critically Important Antimicrobials (CIA) for Human Medicine (2016).

RESULTS

Historically, antibiotic susceptibility testing guidelines focused on TS and over time adapted the interpretative criteria and terminology for fluoroquinolone susceptibility. Interpretative criteria and definitions (such as decreased ciprofloxacin susceptibility (DCS)) were gradually extended to extra-intestinal iNTS. The definition of Multidrug Resistance (MDR) in *Salmonella* differs from MDR in other Gram negative bacteria, and there is no consensus about acronyms to convey other combinations of co-resistance, such as "XDR" (X=extensive) and "PDR" (pan-drug-resistance) in other Gram negative bacteria. Validated antibiotic treatment guidelines for TS infections comprise ciprofloxacin (first-line) and ceftriaxone or azithromycin (second line), but there are few guidelines for antibiotic treatment of iNTS infection. Ceftriaxone, ciprofloxacin and azithromycin are as such listed in the WHO CIA and EML documents as "watch group" antibiotics, but TS infections are not listed among their treatment indications.

CONCLUSIONS

The successive changes in interpretative criteria for fluoroquinolone resistance makes monitoring over time difficult. Given the differences in patient profile, clinical presentation and antibiotic resistance patterns (iNTS compared to TS: more MDR, less DCS, more ceftriaxone-resistance), TS treatment guidelines cannot be extended to iNTS infections. Dedicated observational studies and clinical studies are needed to establish iNTS treatment guidelines, including the switch from intravenous to oral regimens. The use of convened acronyms, and updating and harmonizing policy documents are recommended.

165. Invasive Non-Typhoidal *Salmonella* Infections in the Democratic Republic of the Congo, a 10 Year Surveillance

Bieke Tack[1], Marie-France Phoba[2], Lisette Kalonji[2], Liselotte Hardy[1], Barbara Barbé[1], Octavie Lunguya[2], Jan Jacobs[1]

[1]Institute of Tropical Medicine, [2]National Institute for Biomedical Research (INRB)

BACKGROUND

Non-typhoidal *Salmonella* (NTS) is a major cause of bloodstream infections in DRC. This study presents the occurrence and antimicrobial susceptibility of NTS bloodstream infections in a hospital-based microbiological surveillance from 2015-2017, compared to previous periods (2007-2010, 2010-2014).

METHODS

Blood cultures were collected in hospital-admitted patients suspected of bloodstream infection.

RESULTS

NTS were the most frequently isolated pathogens of bloodstream infection with 6.8% (954/13381) and 45.4% (954/1642) of suspected and culture-confirmed bloodstream infection episodes respectively. The number of NTS bloodstream infections has significantly increased (2007-2010: 3.0%, 20.9%; 2011-2014: 6.0%, 40.0%; both p<0.001). *Salmonella* Enteritidis peaked (50.5% of NTS; 2007-2010: 18.5%, difference p<0.001) in 2010-2014, the increasing number of NTS was driven by *Salmonella* Typhimurium (61.6% (588/954) and *Salmonella* Enteritidis 36.2% (346/954); difference 2011-2014: p<0.001). *Salmonella* Typhimurium variant Copenhagen represented 36.0% of *Salmonella* Typhimurium (210/ 583) and augmented yearly (27.7%, 34.8%, 45.9%; p=0.002). NTS bloodstream infections occurred perennially, but peaked during the rainy season. The majority of NTS were isolated from children <2 years (p50=15 months (range: 0m-76y); 54% < 2 years, 83% < 5 years). Prehospital antibiotics were given in 24.4% of bloodstream infections without pathogen isolation, 27.5% culture-confirmed infections and 25.5% NTS infections. Multidrug resistance (co-resistance to ampicillin, co-trimoxazole and chloramphenicol) was found in 87.6% (n=797), ceftriaxone-resistance 15.16% (n=138), decreased ciprofloxacin susceptibility in 7.1% (n=67) and azithromycin-resistance in 14.4% (n=131) (2007-2010: 46.8%, no data for ceftriaxone: 2.7% cefotaxime-resistance, 5.4%, 3.6% and 2011-2014: 85.4%, 6.5%, 2.2%, 6.5% respectively; all p<0.001). Multidrug resistance and decreased ciprofloxacin susceptibility were more frequent in *Salmonella* Typhimurium (90.3% versus 83.9% and 9.6% versus 2.3% in *Salmonella* Enteritidis, p<0.001). Resistance to ceftriaxone and azithromycin only occurred in *Salmonella* Typhimurium (24.3% and 23.0%). Co-resistance to ceftriaxone and azithromycin was found in 126, ceftriaxone resistance and decreased ciprofloxacin susceptibility in 6 and co-resistance to ceftriaxone and azithromycin with decreased ciprofloxacin susceptibility in 2 *Salmonella* Typhimurium.

CONCLUSIONS

Non-typhoidal *Salmonella* were the most frequent cause of bloodstream infections, especially in young children. The emergence of antibiotic resistance to second-line antibiotics and co-resistance to multiple second-line antibiotics is alarming and highlights the importance of microbiological surveillance and antibiotic stewardship.

166. Lessons Learned From Typhoid Outbreaks in Nepal: Integrating an Outbreak Warning System Into Typhoid Population Surveillance

Dipesh Tamrakar[1], Krista Vaidya[1], Prabinraj Shakya[1], Jivan Shakya[1], Kristen Aiemjoy[2], Caryn Bern[3], Jason Andrews[2], Alexander Yu[2]

[1]Dhulikel Hospital, Kathmandu University Hospital, [2]Division of Infectious Diseases and Geographic Medicine, Stanford University, [3]Department of Epidemiology and Biostatistics, University of California San Francisco

BACKGROUND

Typhoid outbreaks pose serious public health threats. Early detection of outbreaks allows for control of outbreaks and investigation of causes for future preventative efforts. While many existing typhoid surveillance systems collect the data necessary to identify outbreaks, most are primarily set up to determine population disease. Outbreaks detection requires both vigilant monitoring of data and expedient analysis, which are challenging especially in resource constrained settings. We share experiences from two recent outbreaks in Nepal and then describe plans for a simple, integrated automated warning system to leverage our ongoing typhoid surveillance system.

METHODS

We compared the characteristics of two outbreaks that occurred in Nepal in 2018 and reviewed weekly case reports at the ward level between 2016-2018. We identified key attributes and the resolution needed from those outbreaks to design an automated dashboard for future outbreak detection.

RESULTS

In March 2018, an outbreak in Kathmandu affected 76 cases across 4 wards, over 7 weeks; an outbreak in Dhulikhel in August 2018 affected 19 people in 1 municipality over 4 weeks. The Kathmandu outbreak was not detected until the outbreak was starting to wane; by the time an investigation could be coordinated, the outbreak had ended. The Dhulikhel outbreak took place close to our main research facility and was recognized early, allowing for a full investigation into possible causes and notification of government health authorities. In both outbreaks, geographically aggregated weekly average of new cases represented an over three-fold weekly increase in cases compared to the weekly average in the previous month and over the same time period in the prior year. A system that calculated and compared average weekly cases by ward would have detected both outbreaks by week 2 of the outbreak.

CONCLUSIONS

Using information gathered through our existing typhoid surveillance system about two recent outbreaks in Nepal, we are planning an automated system to analyze data at a high resolution, generate real-time reports, and push notifications at pre-specified warning thresholds. This notification system

leverages data already being collected and through automation, allows for the monitoring and early notification of possible outbreaks so that investigation and public health response can occur.

167. Analysis of Isolates From Bangladesh Highlights Multiple Ways to Carry Resistance Genes in *Salmonella* Typhi

Nicholas Costa Barroso Lima[1], **Arif Mohammad Tanmoy[2],** Emilie Westeel[3], Luiz Gonzaga de Paula Almeida[4], Hubert P Endtz[3], Samir K Saha[5], Ana Tereza Ribeiro de Vasconcelos[4], Florence Komurian-Pradel[3]

[1]Departamento de Bioquímica e Biologia Molecular, Universidade Federal do Ceará, [2]Department of Medical Microbiology & Infectious Diseases, Erasmus University Medical Center, [3]Fondation Mérieux – Laboratoire des Pathogènes Emergents, [4]Laboratório Nacional de Computação Científica, [5]Child Health Research Foundation, Bangladesh Institute of Child Health, Dhaka Shishu Hospital

BACKGROUND

Typhoid fever, caused by *Salmonella* Typhi, follows a fecal-oral transmission route and is a major global public health concern, especially in developing countries like Bangladesh. The increasing emergence of antimicrobial resistance (AMR) is a serious issue; the list of treatments for typhoid fever is ever-decreasing. In addition to IncHI1-type plasmids, *Salmonella* genomic island (SGI) 11 has been reported to carry AMR genes. Although reports suggest a recent reduction in multidrug resistance (MDR) in the Indian subcontinent, the corresponding genomic changes in the background are unknown.

METHODS

Here, we assembled and annotated complete closed chromosomes and plasmids for 73 *S.* Typhi isolates using short-length Illumina reads. *S.* Typhi had an open pan-genome, and the core genome was smaller than previously reported. Considering AMR genes, we identified five variants of SGI11, including the previously reported reference sequence.

RESULTS

Five plasmids were identified, including the new plasmids pK91 and pK43; pK43 and pHCM2 were not related to AMR. The pHCM1, pPRJEB21992 and pK91 plasmids carried AMR genes and, along with the SGI11 variants, were responsible for resistance phenotypes. pK91 also contained *qnr* genes, conferred high ciprofloxacin resistance and was related to the H58-sublineage Bdq, which shows the same phenotype. The presence of plasmids (pHCM1 and pK91) and SGI11 were linked to two H58-lineages, Ia and Bd.

CONCLUSIONS

Loss of plasmids and integration of resistance genes in genomic islands could contribute to the fitness advantage of lineage Ia isolates. Such events may explain why lineage Ia is globally widespread, while the Bd lineage is locally restricted. Further studies are required to understand how these *S.* Typhi AMR elements spread and generate new variants. Preventive measures such as vaccination programs should also be considered in endemic countries; such initiatives could potentially reduce the spread of AMR.

168. Typhoid Fever Surveillance in Africa Program (TSAP): Characteristics of Febrile Illnesses Among Children in Butajira, South-Central Ethiopia

Ursula Panzner[1], **Mekonnen Teferi[2],** Mulualem Desta[3], Biruk Yeshitela[2], Tigist Beyene[2], Abraham Aseffa[2], Ursula Panzner[1], Florian Marks[1]

[1]International Vaccine Institute, [2]Armauer Hansen Research Institute, [3]Science and Technology Information Center

BACKGROUND

Febrile illnesses including typhoid fever remains challenging for diagnosis in areas where diagnostic infrastructures are sparse. Patient management from poor diagnosis may result in disease recurrence, deterioration and potentially death. This study aimed at looking into characteristics of acute febrile children in Butajira, Ethiopia to identify potential attributes for patient diagnosis and management.

METHODS

Children ≤15 years were approached for participation during a surveillance study from January 2012 to January 2014. Upon enrollment at a primary/secondary healthcare facility, an aerobic blood culture using 1-3mL blood, malaria microscopy and complete blood count were performed. Microbiological, biochemical, species/sub-species and antimicrobial susceptibility identification were undertaken on cultures yielding growth. A scheme for classifying children as having malaria, acute febrile illness (AFI), acute respiratory tract infection (ARTI), gastrointestinal infection (GI), or urinary tract infection (UTI) was developed. A community survey collected socio-economic, behavioral and hygiene/sanitation-related data. Frequencies, Z-scores for assessing malnutrition, incidences and multivariate logistic regression analyses were computed.

RESULTS

A total of 513 children were recruited. Children were categorized primarily as ARTI (49.7%, 255/513) followed by AFI (25.7%, 132/513), malaria (13.5%, 69/513) and GI (11.1%, 57/513). Hospitalization was low (4.1%, 21/513) as were stunting (0.8%, 4/513), underweight (0.2%, 1/513) and wasting (0.2%, 1/513). Blood cultures detected few pathogens (1.6%, 8/513) related mainly to respiratory and gastrointestinal infections that include E coli and S typhi among others. The malaria prevalence (13.5%, 69/513) including the detection of *Plasmodium vivax* and *falciparum* parasites confirms the initial presumptive diagnosis. The community survey conducted among 559 households (urban: 32.2%, 180/559, rural: 67.8%, 379/559) revealed most household heads had no formal school education (77.1%, 431/559). Rural families reported utilizing pumped (68.3%, 259/379;37.5%, 142/379) and surface water (24.5, 93/379;25.9%, 98/379) for drinking and had low participation in the Health Extension Program.

CONCLUSIONS

The fever origin remains unclear for most children. The case classification scheme applied may be considered as a comprehensive guideline for healthcare personnel to help a presumptive diagnosis, especially when blood culture findings are very limited. A definite diagnosis will require more procedures, including laboratory investigations, to implement appropriate management of febrile illness in children.

169. Assessing the Impact of a Vi-Polysaccharide Conjugate Vaccine in Preventing Typhoid in Nepalese Children – Protocol for a Randomised Control Trial

Katherine Theiss-Nyland[1], Mila Shakya[2], Rachel Colin-Jones[1], Merryn Voysey[1], Shrijana Shrestha[3], Buddha Basnyat[4], Andrew J Pollard[1], The Study Team TyVAC[5]

[1]Oxford Vaccine Group, University of Oxford, [2]Oxford University Clinical research Unit – Nepal, [3]Patan Academy of Health Sciences – Nepal, [4]Oxford University Clinical Research Unit - Nepal, [5]TyVAC consortium

BACKGROUND

Enteric fever is estimated to affect 11-20 million people worldwide each year. Morbidity and mortality from enteric fever primarily occurs in lower income countries, with children under 5 years of age experiencing a significant portion of the burden. Over the last few decades, control of enteric fever has focused primarily on improved water and sanitation, with available vaccines unsuitable for children, and primarily used by travellers. A new typhoid conjugate vaccine (Vi-TCV), prequalified by the WHO, and highly immunogenic in children under 5 has the potential to reduce typhoid burden in endemic countries.

METHODS

This study is a double-blinded, randomised controlled trial with a two-year follow-up to assess the protective impact of the Vi-TCV vaccine, compared with a control vaccine, in children from 9 months to 16 years of age. The primary outcome of interest is the reduction in culture confirmed typhoid cases attributable to Vi-TCV. Approximately 20,000 children living in the Lalitpur district within Kathmandu valley, will be enrolled in the study, and followed to measure both safety and efficacy data, which will include adverse events, hospitalisations, antibiotic use, and fever frequency.

RESULTS

The complete results of this study will be available after the two year follow-up of all participants is completed. Ethics and Dissemination: Both the intervention and control vaccines are WHO prequalified vaccines, which provide a health benefit to all participants. Children have been chosen to participate because they bear a substantial burden of both typhoid morbidity and mortality in this population. The results of this study will be disseminated through a series of published articles. The findings will also be made available to the participants and the broader community, as well as local stakeholders, within Nepal

CONCLUSIONS

This is the first large-scale individually randomised controlled trial of Vi-TCV in children in an endemic setting, and will provide new data on Vi-TCV field efficacy. With Vi-TCV introduction being considered in high burden countries, this study will support important policy decisions.

170. Assessing the Impact of a Vi-PS Conjugate Vaccine in Preventing Typhoid in Bangladeshi Children – Protocol for a Cluster Randomised Controlled Trial

Katherine Theiss-Nyland[1], Firdausi Qadri[2], Rachel Colin-Jones[1], Farhana Khanam[2], K Zaman[2], Andrew J Pollard[1], John D Clemens[3], The study team TyVAC[4]

[1]Oxford Vaccine Group, University of Oxford, [2]International Centre for Diarrhoeal Disease Research – Bangladesh, [3]International Centre for Diarrhoeal Disease Research - Bangladesh, [4]TyVAC consortium

BACKGROUND

Typhoid fever illnesses are responsible for greater than 100,000 deaths worldwide each year. In Bangladesh, typhoid fever is endemic, with incidence rates between 292-395 per 100,000 annually. While considerable effort has been made to improve access to clean water and sanitation services in in the country, there is still a significant typhoid annual typhoid burden, particularly affecting children. A typhoid conjugate vaccine (Vi-TCV) was recently prequalified by WHO and recommended for use, and offers the potential to greatly reduce typhoid burden in Bangladesh.

METHODS

This study is a double-blind cluster-randomised controlled trial of Vi-TCV in a geographically defined area in Dhaka, Bangladesh. At least 32,500 children from 9 months to <16 years of age will be vaccinated and followed for 2 years to assess the effectiveness and safety of Vi-TCV in a real-world setting. All cluster residents will also be followed to measure the indirect effect of Vi-TCV in this community.

RESULTS

The full results of this study will be available when the study has been completed after two years of follow-up. This protocol has been approved by the icddr,b research review and the ethical review committees and informed written consent and assent will be obtained before enrolment. Vi-TCV has been shown to be safe and effective in previous smaller-scale studies. The results of this study will be shared through a series of peer-reviewed journal articles. The findings will also be disseminated to local government and stakeholders within the community and the population within which the study was conducted.

CONCLUSIONS

This trial is the largest and the only cluster randomised control trial of Vi-TCV ever conducted, and will describe the effectiveness of Vi-TCV in an endemic population. The results of this trial may provide important evidence to support introductions of TCV in countries with a high burden of typhoid.

171. The Utility of Real Time PCR for Detection of *Salmonella* Typhi in Suspected Enteric Perforation Cases: A Study From a Hospital in North India

Shavi Nagpal[1], Dhruva Ghosh[1], Aroma Oberoi[1], Sarah Valson[1], **Maria Thomas[1],** Navneet Chaudhary[1], Vishal Michael[2], Shraddha Engles[1]

[1]Christian Medical College, Ludhiana, [2]Christian Medical College, Vellore

BACKGROUND

Typhoid fever, has continued to be a public health problem in India. One of the most serious complications of typhoid fever is perforation of the small bowel. Although perforation can occur early in the febrile phase of typhoid fever, it is more commonly seen during or after the second week of illness and usually occurs in the terminal ileum, near the ileocecal junction, in the centre of an ulcer.

Many attempts have been made to develop PCR-based assays to detect bacterial DNA but very few of these approaches have been instituted in clinical settings mainly due to the difficulty in validating tests when using real-life specimens, in which a low bacterial load is present.

In this project we attempted to isolate and identify S. Typhi microbiologically using various diagnostic modalities including Real time PCR.

METHODS

The present study was carried out on clinical samples received from patients with a suspected diagnosis of enteric small bowel perforation who underwent surgery.

Blood samples from patients with suspected enteric small bowel perforation were collected and sent to microbiology laboratory for Blood culture, Widal test and IgM ELISA. Whereas to detect Salmonella Typhi DNA using Real Time PCR, tissue sample was taken from the perforation edge.

RESULTS

Clinical samples were obtained from 27 suspected cases of enteric small bowel perforation.

Only one case of Salmonella *typhi* was isolated by blood culture.

The total number of samples which had titres indicative of Typhoid fever were 11.

Twelve samples were reported as indicative of presence of IgM antibody towards S.typhi.

Real time PCR was performed on DNA prepared from perforation biopsy samples (21/27), the assay demonstrated S.typhi specific amplification on six compared to no amplification seen on blood samples.

CONCLUSIONS

The molecular method for the detection of invasive salmonella serovars in biopsy specimens using Real Time PCR appears to be a useful addition to the current conventional diagnostic methods.

PCR for S.typhi DNA on biopsy specimens shows high sensitivity and is a rapid diagnostic test, and can be used with low pathogen load. We recommend that multiple diagnostic methodologies must be employed to define a "positive" sample.

172. Implementing the Research Electronic Data Capture (REDCap) System in Support of Research in Low and Middle Income Countries: The TyVAC Experience

Kathleen Tracy[1], Yama Farooq[2], Olga Mazur[2], Bhola Prasad Koirala[3], Prasanta Kumar Biswas[4], Clemens Masesa[5]

[1]University of Maryland School of Medicine, [2]University of Oxford, [3]Nepal Family Development Foundation, [4]International Centre for Diarrhoeal Disease Research, Bangladesh, [5]Malawi-Liverpool-Wellcome Trust

BACKGROUND

This paper describes the implementation of Research Electronic Data Capture (REDCap) systems in support of typhoid vaccine clinical trials in three low and middle income countries conducted by the Typhoid Vaccine Acceleration Consortium (TyVAC). The objective is to highlight advantages and challenges encountered using electronic data capture systems to support research in low and middle income countries.

METHODS

REDCap was implemented under two different scenarios (i.e., central and distributed implementations). Key features and tools built into REDCap were used to facilitate recruitment, data capture and management, and data quality.

RESULTS

Use of REDCap allowed near real-time access to all study data and the ability to continuously monitor study activities and milestones. More than 80,000 children were enrolled across the three trials. Major advantages of REDCap included: ease of system implementation and case report form, real-time data access, improved data quality, flexible online/offline capture capabilities, and time and cost savings. Challenges included performance issues related to internet connectivity speed and stability, device management, and enforcement of data validations.

CONCLUSIONS

Use of REDCap to support research trials in low and middle income countries has numerous, significant advantages over traditional paper-based data capture methods. Challenges are manageable with training and technical assistance.

173. Antibiotic Resistance and Transmission of *Salmonella* Isolated From Pig Slaughterhouses to Retails Markets in Hanoi, Vietnam

Thi Quy Duong Truong[1], Stijn Deborggraeve[2], Pierre Dorny[2], Thi Ngoc Pham[1]

[1]National Institute of Veterinary Research, [2]Institute of Tropical Medicine

BACKGROUND

Salmonella is one of the most important pathogens causing illness in human, and transmission through. Contaminated pork is a common source of transmission. The aim of this study is to determine the prevalence, antibiotic resistance levels and transmission events of *Salmonella* in pork from pig slaughterhouses to retail markets in Hanoi, Vietnam.

METHODS

Salmonella strains were isolated from feces, carcass swabs and pork samples of 43 pigs in 12 family slaughterhouses and retail markets in Hanoi, Vietnam, during 10 visits from June to November 2017. Serotypes were determined by slide agglutination test for O and H antigens. Antibiotics susceptibility testing was performed by the disk diffusion method (12 antibiotics) and microdilution method (colistin). Colistin resistance due to the mcr1 gene was determined by PCR. The genetic relationship between the isolated *Salmonella* strains was determined by pulsed field gel electrophoresis (PFGE) using the restriction enzyme Xba I.

RESULTS

Salmonella prevalence in carcass swabs, feces and pork samples were 23.3% (10/43), 34.9% (15/43) and 32.6% (14/43), respectively. Ten different *Salmonella* serovars were identified in a total of 39 *Salmonella* isolates. *S.* Typhimurium, which is the main serovar causing salmonellosis in human, was the most commonly identified (n=19), followed by *S.* Derby (n=7) and *S.* Weltevreden (n=4). *Salmonella* isolates showed high resistance to antibiotics with 20 isolates (51%) showing multidrug resistance, defined as co-resistance to the first line antibiotics ampicillin, chloramphenicol and trimethoprim/sulfamethoxazole. Interestingly, 35 isolates (90%) showed full or intermediate resistance to ciprofloxacin and 28 (72%) resistance to colistin. There was no mcr1 gene detected in 28 colistin resistant strains and resistance may be due to other mcr genes. PFGE analysis of the 19 *S.* Typhimurium, 7 *S.* Derby, 4 *S.* Weltevreden strains showed that the *Salmonella* transmission probably occurs at the slaughterhouses.

CONCLUSIONS

This study shows that the prevalence of antibiotic resistant *Salmonella* in the pork supply chain in Hanoi is high and may be a risk for transmission to human

174. Genomic Insights From *Salmonella* Bloodstream Infections Among Young African Children Identified During the MAL055 RTS,S/AS01 *Salmonella* Ancillary Study

Sandra Van Puyvelde[1], Samuel Kariuki[2], Simon Kariuki[2], Calman A. MacLennan[3], Maxim Agnanji[4]

[1]Institute of Tropical Medicine, [2]Kenya Medical Research Institute (KEMRI), [3]Oxford University, [4]Clinical Trials Partnership Committee

BACKGROUND

Invasive *Salmonella* disease forms a large disease burden in sub-Saharan Africa, especially among young children. The aim of this study was to explore the genomic variability among invasive *Salmonella* isolates from different sites in sub-Saharan Africa participating in the phase 3 RTS,S/AS01 malaria vaccine trial-MAL055 (NCT20866619).

METHODS

Children in the MAL055 study admitted to hospital with fever between 2009 and 2014 in 11 sites across sub-Saharan Africa underwent a blood-culture investigation for potential bacteremia using a standardized protocol. *Salmonella* isolates were analyzed by Illumina whole-genome sequencing with subsequent phylogenetic analysis, determination of antimicrobial resistance (AMR) determinants and spatiotemporal mapping using the MicroReact tool.

RESULTS

A total of 174 *Salmonella* Typhimurium, 69 *Salmonella* Enteritidis and 150 *Salmonella* Typhi isolates were whole genome sequenced. A phylogenetic analysis in context of publicly available sequences shows clustering of isolates within the East (Kenya, Tanzania) and West (Ghana, Burkina Faso) Africa. Among the three serovars, clusters of isolates were identified harboring genetic determinants for multidrug resistance (MDR), extended spectrum beta-lactamase (ESBL) production and fluoroquinolone (FQ) resistance.

CONCLUSIONS

Invasive *Salmonella* isolates from across sub-Saharan Africa are characterized by heterogeneity and spatial clustering, and a high degree of AMR determinants.

175. Two Non-H58 *Salmonella* Typhi Lineages From the Democratic Republic of the Congo Show Decreased Ciprofloxacin Susceptibility

Sandra Van Puyvelde[1], Octavie Lunguya[2], Zoe Dyson[3], Liselotte Hardy[1], Gordon Dougan[3], Jan Jacobs[1], Stijn Deborggraeve[1]

[1]Institute of Tropical Medicine, [2]National Institute for Biomedical Research, [3]University of Cambridge

BACKGROUND

*Salmonella*Typhi forms a large burden in the Democratic Republic of the Congo (DRC), and fluoroquinolone antibiotics

are currently recommended for the treatment. Resistance against fluoroquinolones in *Salmonella*was listed as a high priority by the World Health Organisation in 2017. Full resistance to fluoroquinolones is rare but decreased ciprofloxacin susceptibility (DCS) is increasingly being reported and is associated with treatment failure. Whereas DCS *Salmonella*Typhi is highly reported from Asia and East Africa linked to the success of lineage H58, the situation is less well clear for Central Africa.

METHODS

We have whole genome sequenced 96 DCS SalmonellaTyphi isolates that originate from ongoing bloodstream surveillance in the DRC, isolated between from 2007 and 2017 from different provinces of the DRC. From the same regions and years we have whole genome sequenced an additional 61 non-DCS SalmonellaTyphi to provide genomic context to the phylogenetic analysis.

RESULTS

A bioinformatics analysis shows the presence of two non-H58 DCS SalmonellaTyphi lineages from the DRC. These lineages have GenoTyphi type 2.5.1 and are associated respectivaly a D87G and a S83F substitution in GyrA. The D87G lineage is constrained to Kisantu in western DRC, contains isolates from 2014 onwards and is associated with variable multidrug resistance (MDR) levels. The S83F lineage contains predominantly isolates from Kisantu but is also identified in other provinces of the DRC. Strains of this lineage were isolated since 2009 onwards and show a more homogeneous distribution of MDR genes. Combined DCS and MDR isolates mostly form single cases within the SalmonellaTyphi population. One DCS isolate from DRC was part of lineage H58.

CONCLUSIONS

Whereas the majority of the DCS SalmonellaTyphi cases in the world make part of lineage H58, our data show that DCS SalmonellaTyphi from the DRC fall predominantly in GenoTyphi type 2.5.1. These are the first non-H58 clonal DCS SalmonellaTyphi lines, emerging from the DRC. Further surveillance is needed to map the success and spread of these lineages.

176. An Eighteen Year Retrospective Analysis of *Salmonella* Typhi, *Salmonella* Paratyphi and Invasive Non-Typhoidal *Salmonella* Isolated From Southern India

Balaji Veeraraghavan, Shalini Anandan, Jobin John Jacob, Agila Kumari Pragasam, Jacob John, Gagandeep Kang

Christian Medical College, Vellore

BACKGROUND

Invasive infections caused by *Salmonella enterica* serovar Typhi, Paratyphi A and invasive Non-typhoidal salmonella (iNTS) continues to inflict major disease burdens in India. The typhoidal serovars routinely cause severe systemic diseases while iNTS typically associated with self-limiting gastroenteritis in humans. Population based studies of such invasive bloodstream infections is essential to understand the disease burden for effective management.

METHODS

The current study has assessed the incidence of *Salmonella* from blood culture performed in a Southern Indian region along with a perspective on its AMR profiles and serovar distribution from a period between 2001 – 2018. Blood samples collected from patients admitted to Christian Medical College and Hospital, Vellore were included. *Salmonella* serovars were identified as per standard protocols and antimicrobial susceptibility profile was determined by disk diffusion method

RESULTS

Salmonella enterica accounted for 0.6% of all the blood cultures performed from this tertiary care hospital. Among the 3611 *Salmonella* isolates obtained, *S.* Typhi, *S.*Paratyphi and iNTS constitutes 69%, 19% and 12% respectively. We have observed a gradual decline in trend of *S.* Typhi and *S.* Paratyphi while a slow but continuous increase in the number of iNTS isolates over the years. Antibiotic resistance against first-line agents has decreased from 45% to 5% during the study period. However, an alarming finding of increased rates of fluoroquinolones non-susceptibility in *S.*Typhi and *S.* Paratyphi was observed. Increase in resistance to cephalosporins has been particularly noted in iNTS. The incidence of MDR *S.*Typhi isolates has been reported to significantly decline from 43% to 1%, whereas a slight increase in the prevalence of MDR iNTS isolates were observed

CONCLUSIONS

This study represents the changing trend of invasive Salmonellosis close to two decades from a Southern Indian region. Although there was a decreasing incidence of MDR in typhoidal serovars, increasing cephalosporin resistance in iNTS serovars is a cause of concern, as typhoid like manifestations has been recently identified among certain iNTS serovars. Monitoring of any such changing trend across Indian sub-continent would aid in the development and implementation of vaccine and public health strategies

177. Antimicrobial Susceptibility of Invasive Nontyphoidal *Salmonella* in a Rural and Urban Setting in Kenya, 2007-2017

Jennifer Verani[1], Arthur Odoyo[2], Herine Odiembo[2], Newton Wamola[2], Clayton Onyango[3], Bonventure Juma[3], Godfrey Bigogo[2], Population-Based Infectious Disease Surveillance (PBIDS) Investigator Group

[1]Centers for Disease Control and Prevention, [2]Kenya Medical Research Institute -- Centre for Global Health Research, [3]Centers for Disease Control and Prevention -- Division of Global Health Protection

BACKGROUND

Nontyphoidal *Salmonella* (NTS) is a major cause of invasive bacterial disease in sub-Saharan Africa. Increasing antibiotic resistance among NTS is an important public health threat, since resistant infections are more difficult to treat and can increase healthcare costs. We examined antimicrobial susceptibility patterns of invasive NTS isolates from two sites in Kenya over an 11-year period.

METHODS

We analyzed data from 2007 to 2017 from the Population-Based Infectious Disease Surveillance system (PBIDS). PBIDS monitors the health of ~25,000 persons in each of two sites: Kibera (Nairobi urban informal settlement) and Asembo (rural western Kenya, malaria-endemic). PBIDS participants receive free medical care at a centrally located health facility; those meeting case definitions for acute febrile illness or pneumonia undergo blood culture. *Salmonella* is isolated using standard microbiologic techniques after incubation in an automated machine, with serotyping by *Salmonella* antisera and/or genomic sequencing, and antimicrobial susceptibility testing (AST) using Kirby-Bauer disc diffusion.

RESULTS

Overall, 273 NTS were isolated in Asembo and 107 in Kibera; 252 (92%) and 82 (77%) respectively underwent AST. The prevalence of antimicrobial resistance in NTS isolates from Asembo and Kibera were: ampicillin 90%, 77%; chloramphenicol 83%, 74%; trimethoprim-sulfamethoxazole 83%, 78%; ceftriaxone 7%, 10%; and ciprofloxacin 1%, 2%There were no clear trends over time. Ceftriaxone resistance was first detected in Asembo in 2009 (1/36 tested; prevalence 3%), and subsequently observed in all years except 2010 and 2017, with highest prevalence in 2014 (5/9 tested; 56%). In Kibera, ceftriaxone resistance was also first noted in 2009 (1/13 tested; 8%) and observed in all subsequent years except 2012 and 2016 (in 2017 no iNTS cases were detected); highest resistance prevalence was in 2015 (2/2 tested; 100%). Among 25 ceftriaxone-resistant isolates from both sites, 3 were also resistant (and 6 intermediate) to ciprofloxacin.

CONCLUSIONS

Resistance to antibiotics previously used to treat invasive NTS disease (trimethoprim-sulfamethoxazole, chloramphenicol, and ampicillin) was high, and ceftriaxone resistance was relatively common – consistent with findings from other African settings. Strains resistant to both ceftriaxone and ciprofloxacin pose an important threat and highlight the importance of understanding NTS transmission and developing effective prevention measures, including vaccines.

178. Characteristics of Fever Cases Who Are Blood Cultured and Those Who Are Missed When Presenting to Passive Surveillance Fever Clinics: TyVAC-Nepal

Merryn Voysey[1], Nicola Smith[1], Dikshya Pant[2], Mila Shakya[2], Buddha Basnyat[2], Andrew J Pollard[1], TyVAC Study Team[1]

[1]University of Oxford, [2]Oxford University Clinical Research Unit - Nepal

BACKGROUND

In late 2017 and early 2018, 20,019 children aged 9 months to 15 years in Lalitpur, Nepal, were vaccinated with either typhoid conjugate vaccine or capsular group A meningococcal vaccine as part of the TyVAC-Nepal clinical trial. Enhanced passive surveillance for typhoid fever is ongoing for trial participants in one tertiary hospital and 15 community clinics.

METHODS

Participants in TyVAC-Nepal are eligible for blood cultures when they present to clinic reporting 2 or more days of fever or a current temperature of at least 38 degrees. We assessed the clinical characteristics of eligible fever cases presenting to clinic in the first six months of surveillance and compared those who did and did not receive a blood culture.

RESULTS

There were 1135 eligible fever presentations, of which 806 had a blood culture. A clinical suspicion of typhoid was one of the strongest predictors of a blood culture; 83% of those with suspected typhoid had a blood culture compared with 67% of those without ($p<0.0001$). A suspected upper respiratory tract infection decreased the probability of blood culture ($p=0.0008$), whereas suspected lower respiratory tract infection did not ($p=0.9$). Suspected urinary tract infections increased blood culture rates ($p<0.0001$). Those with three or more days of fever had blood cultures 78% of the time compared with 66% for those with less than 3 days. Younger children were less likely to be cultured. There was no difference between males and females.

Suspected typhoid was also strongly associated with blood culture positivity with 16 out of 24 blood culture-positive cases having a clinical suspicion of typhoid initially. Of the 8 cases of blood culture positive typhoid fever that initially were not suspected as typhoid, 3 were suspected upper respiratory tract infection, 1 was suspected viral illness, 1 acute tonsillitis, and 1 acute gastroenteritis.

The number of days of fever and age were also significantly associated with blood culture positivity.

CONCLUSIONS

When adjusting incidence estimates in typhoid surveillance programmes to account for under-detection of cases, the difference in the probability of typhoid in unmeasured populations and those with blood cultures needs to be evaluated.

179. The Design and Analysis of Seroefficacy Studies for Typhoid Conjugate Vaccines: A Simulation Study

Merryn Voysey[1], Xinxue Liu[1], Virginia Pitzer[2], Andrew Pollard[1]

[1]University of Oxford, [2]Yale School of Public Health

BACKGROUND

Demonstrating efficacy of new Vi-conjugate typhoid vaccines is challenging due to the cost of field trials requiring tens of thousands of participants, and the lack of functional assays or correlates of protection. The current gold standard for typhoid diagnosis in clinical trials is culture of Salmonella Typhi from blood. However, incidence of blood culture-confirmed typhoid fever is low owing to the poor sensitivity of culture tests, self-treatment with antibiotics, or missed cases due to attendance at non-study clinical facilities. New trial designs that use serologically-defined typhoid infections (seroefficacy trials) rather than blood culture positivity as a study endpoint may be useful to assess efficacy using small trials.

METHODS

Immunogenicity trial participants in endemic settings will be naturally exposed to Salmonella Typhi during trial follow-up, particularly where disease incidence is high. The detection of a Vi-antibody response to natural exposure can be used to estimate the incidence of clinical or subclinical infection if blood samples are taken from participants at appropriate times.

We developed a model for Vi-IgG antibody response to a Vi-vaccine, decay over time, and natural boosting due to endemic exposures. From this we simulated clinical trials in which two blood samples were taken during follow-up, and the relative risk of serologically-defined typhoid infection (seroefficacy) was computed. We aimed to determine if seroefficacy trial designs could substantially reduce sample sizes compared with trials using blood-culture-confirmed cases; if case detection was higher in seroefficacy trials; and the optimal timing of sample collection.

RESULTS

The majority (>90%) of blood-culture-positive typhoid cases remain unobserved in surveillance studies. In contrast, underdetection in simulated seroefficacy trials of equivalent vaccines was as little as 26%, and estimates of the relative risk of typhoid infection were unbiased. For simulated trials of non-equivalent vaccines, relative risks were slightly inflated by at least 5% depending on sample collection times. Seroefficacy trials required as few as 460 participants per arm, compared with 10,000 per arm for trials using blood-culture-confirmed cases.

CONCLUSIONS

Seroefficacy trials can establish the efficacy of new conjugate vaccines using small trials enrolling hundreds rather than thousands of participants, and without the need for resource-intensive typhoid fever surveillance programmes.

180. A Review of the Economic Evidence of Typhoid Fever and Typhoid Vaccines

Dagna Constenla[1], Karuna Luthra[2], **Elizabeth Watts[1],** Frédéric Debellut[3], Clint Pecenka[3], Naor Bar-Zeev[1]

[1]Johns Hopkins University, [2]Gavi, the Vaccine Alliance, [3]PATH

BACKGROUND

Typhoid places a substantial economic burden on low and middle-income countries.We performed a literature review and critical overview of typhoid-related economic issues to inform vaccine introduction.

METHODS

We searched four literature databases covering 2000-2017 to identify typhoid-related cost of illness studies (COIs), cost of delivery studies, cost-effectiveness analyses (CEA), and demand forecast (DF) studies. Manual bibliographic searches of reviews revealed studies in grey literature. Planned studies were identified in conference proceedings and through partner organization outreach.

RESULTS

We identified 29 published, unpublished and planned studies. PublishedCOI studies revealed substantial burden in Asia with hospitalization costs alone ranging from $159 to $636 in India, but there was less evidence for Africa. Cost of delivery studies are unpublished, but one study found that $671,000 government investment would avert $60,000 in public treatment costs. CEA evidence was limited but found targeted vaccination programs cost-effective.

CONCLUSIONS

This review revealed economic evidence for vaccine introduction can be enhanced. Countries considering vaccine introduction should have access to relevant economic evidence to aid in decision making and planning. Planned studies will fill many of the existing gaps in the literature.

181. Prevalence and Antimicrobial Resistance Profile of Non-Typhoidal *Salmonella* in Pigs in Kenya and Malawi

Catherine Wilson, Caisey Pulford, Gina Pinchbeck, Melita Gordon, Paul Wigley, Eric Fevre

University of Liverpool

BACKGROUND

Non-typhoidal *Salmonella* has a huge disease burden in humans and is one of the commonest food-borne pathogens. There is suspicion that human-to-human transmission may not be the sole route of ST313 spread and that zoonotic transmission may occur.

Free-range pig production is common in rural Kenya and Malawi, increasing the contact between humans and pigs and hence risk of transmission of non-typhoidal *Salmonella*. The prevalence of non-typhoidal *Salmonella* in sub-Saharan Africa pig populations has not yet been described.

The aim of this work was to determine and compare prevalence, strains and diversity of non-typhoidal *Salmonella* in pig samples collected at post mortem from 3 slaughter house sites; 2 rural (Busia, Kenya and the Chikwawa Valley, Malawi) and 1 urban (Nairobi, Kenya).

METHODS

Faecal and mesenteric lymph node samples were collected from pigs at slaughter (Busia=267, Nairobi=306 and Chikwawa Valley=65), 2016-2017. Microbiological and molecular analyses were performed including selective culture and antigen serotyping, and 151 isolates of non-typhoidal *Salmonella* were gained as an output of whole genome sequencing (Busia=71,Nairobi=48,Chikwawa=31,location unknown=1).

RESULTS

A variety of zoonotic serovars of non-typhoidal *Salmonella* were detected at each site, and multiple isolates were detected in some pigs. The prevalence of carriage of non-typhoidal *Salmonella* by pigs in Nairobi was found to be 10.8% (95% CI 7.3-14.3%), Busia 16.9%(95% CI 12.4-21.3%) and Chikwawa 29.2%(95% CI 18.2-40.3%). One isolate of *Salmonella* Typhimurium ST313 was identified in the mesenteric lymph of a pig slaughtered in Nairobi which was found to be lineage 1 ST313, fully susceptible to all antibiotics

tested. Six isolates of *Salmonella* Typhimurium ST19 were also detected in pigs at slaughter in Nairobi.

Three multi-drug resistant isolates were detected in pigs slaughtered in Busia, one multi-drug resistant isolate from a pig originating in Chikwawa. 22.2% of non-typhoidal *Salmonella* isolates from Busia(CI 7.9-30.3%) and 20.0% from Nairobi(CI 8.3-31.7%) were resistant to 1-2 antimicrobials.

CONCLUSIONS

Pigs at slaughter in all study sites carry a variety of non-typhoidal *Salmonella* serovars including multi-drug resistant phenotypes. There is the potential for zoonotic transmission of non-typhoidal *Salmonella* between pigs and humans in Kenya and Malawi and the transfer of antimicrobial resistance determinants between these species should be considered.

182. Comparison of Anti-Vi IgG Responses Between Two Clinical Studies of Typhoid Vi Conjugate Vaccines (Vi-DT Vs Typbar-TCV)

Jae Seung Yang[1], Eun Young Lee[1], Deok-Ryun Kim[1], Ju Yeon Park[1], Manki Song[1], Sushant Sahastrabuddhe[1], Hun Kim[2], Yun Chon[1]

[1]International Vaccine Institute, [2]SK Bioscience

BACKGROUND

Salmonella enterica serova Typhi (*S.* Typhi) is a causative agent for typhoid fever in developing countries. Although clinical studies for various typhoid conjugate vaccines (TCVs) have been done, it could not compare the immune responses of vaccines due to lack of harmonization of the ELSIA assay. Recently, Tybar-TCV was prequalified by WHO and recommended for vaccination in endemic areas.

METHODS

Forty eight serum samples were selected based on anti-Vi IgG levels and age cohort from recent Vi-DT phase 1 study. The anti-Vi IgG titers of these sera were also determined by Vacczyme ELISA, used in the Typbar-TCV phase 3 study, to find correlation between in-house and Vacczyme ELISAs. The Vacczyme ELISA's geometric mean titer (GMT) values in the Vi-DT phase I study were predicted using a multiple linear regression model.

RESULTS

A good correlation between two assays was observed when anti-Vi IgG titer was determined based on the U.S. reference reagent Vi $IgG_{R1,\ 2011}$ (Spearman correlation coefficient (r) = 0.951, $P < 0.001$) or Vacczyme ELISA's calibrator (r = 0.950, $P < 0.001$). The similar anti-Vi IgG GMT were observed as 9.3 (95% CI: 5.9 to 14.9) vs 10.4 (95% CI: 9.6 to 11.3) at baseline and 1628 (95% CI: 1291 to 2051) vs 1293 (95% CI: 1153 to 1449) after vaccination of Vi-DT and Typbar-TCV vaccines, respectively.

CONCLUSIONS

This is the first estimate of anti-Vi IgG between two different clinical studies of TCVs. This approach enables to compare the antibody responses among TCVs under development and would be helpful to facilitate licensing of new TCVs.

183. Multipronged Surveillance Activities for Identification of *S.* Typhi Patients in Hyderabad: Experience From XDR Typhoid Outbreak Setting in Pakistan

Mohammad Tahir Yousafzai, Sultan Karim, Amber Kashif, Anayat Baig, Hina Iqbal, Najeeb Rehman, Farah Qamar

Aga Khan University

BACKGROUND

Hyderabad city in Pakistan is facing the world largest outbreak of Ceftriaxone resistant extensive drug resistant (XDR) typhoid. The first case of XDR typhoid was identified on November 30, 2016 by the clinical laboratory of Aga Khan University in Hyderabad. Outbreak investigation and control activities were initiated by Aga Khan University in collaboration with ministry of health Sindh during December 2016. Surveillance with door-to-door mass immunization with typhoid conjugate vaccine is still continued in the high risk areas of Hyderabad. Here we report surveillance methodology and burden of typhoid (including XDR) identified through surveillance.

METHODS

Three different approaches were used for the identification of XDR typhoid cases. 1) Sentinel based active surveillance in hospitals, 2) identification of cases from the household and neighborhood contacts of the confirmed cases, and 3) identification of cases from laboratory network in Hyderabad. Patients with fever for 3 or more days during the last 7 days, without any other focus of infection were considered as suspected cases of typhoid and were confirmed with blood culture and sensitivity testing. Surveillance was further enhanced by including rural health centers, basic health units and private practitioners since the beginning of door-to-door mass vaccination.

RESULTS

During Nov 30 2016 - June 30 2018, a total of 1569 cases of salmonella typhi were identified from the two sub-districts (Latifabad and Qasimabad) of Hyderabad. Out of total 944 (60%) were resistant to Ceftriaxone and the rest were sensitive. There were 1304 cases of typhoid identified before the initiation of mass immunization (January 30, 2018). Out of 1304, 751 (57.5%) were resistant to Ceftriaxone. Only 264 cases were identified after the beginning of mass immunization (Feb 01, 2018 to June 30, 2018). There were 193/264(73%) resistant to Ceftriaxone. Most of the cases before the initiation of mass immunization were children aged 10 years and below however the incidence of cases significantly decreased among children after the mass immunization.

CONCLUSIONS

The cases of culture proven typhoid has substantially decreased after the TCV campaign among children aged 10 years and below. Proportion of XDR as compared to sensitive cases of typhoid has increased during the last 4 months.

184. Typhoid Fever in Malaysia: An Overview of Trend From 1987 to 2017

Mohd Hanif Zailani, A'aishah Senin

Disease Control Division, Ministry of Health Malaysia

BACKGROUND

Typhoid fever is a food and water borne disease, which is endemic mainly in developing countries. Crumps JA et al., 2004 estimated that the typhoid incidence in South East Asia Region was >100 case per 100,000 per year, which was classified as high. This study described the overviews on the current situation of typhoid fever in Malaysia and previous documented estimation.

METHODS

A cross sectional study using secondary data obtained from the National Infectious Diseases Surveillance System was conducted from 1 to 30 September 2018. Only case with culture positive for *Salmonella typhi* were registered in this surveillance system and included in this study.

RESULTS

From 1987 to 2017, the incidence of typhoid fever in Malaysia had markedly declined from 17.9 to 0.6/100,000 populations. The mortality rate had also declined from 0.41/100,000 populations in 1987 to 0.01/100,000 populations in 2017. Typhoid cases were highest among the age group of 5 – 19 years (49.8%) followed age group of, 20 to 60 years (37.2%). Annually, higher incidence was recorded in the state of Kelantan which is located at east coast of peninsular Malaysia. Similar to other states in Malaysia, Kelantan had also experienced of marked reduction in typhoid incidence from 21.7/100,000 populations in 1990 to 1.4/100,000 populations in 2017.

CONCLUSIONS

Comparing to the incidence classification documented by Crumps JA et al., 2004, Malaysia has rapidly transformed from moderately endemic to low endemic for typhoid fever. Typhoid fever was found to be sporadic where the incidence was relatively low and confined to few areas. This dramatic improvement showed that Malaysia has obtained a remarkable achievement in public health particularly in the prevention and control of the disease.

185. The Role of SPI-2 Effectors in *Salmonella* Typhi Pathogenesis

Parisa Zangoui, Linda J. Kenney

Mechanobiology Institute, National University of Singapore

BACKGROUND

Human-restricted *Salmonella* Typhi is the causative agent of typhoid fever. In the process of host restriction, *Salmonella* Typhi has undergone a major genome reduction compared to its close relative *Salmonella* Typhimurium. *S.* Typhi can also exist in an asymptomatic carrier state, presumably as biofilms on gallstones in the gall bladder. Understanding how *S.* Typhi exists inside cells and causes systemic infection is not presently understood. In *S.* Typhimurium, two type three secretion systems drive uptake (encoded on *Salmonella* pathogenicity island 1 or SPI-1) and survival in the vacuole (*Salmonella* pathogenicity island 2 or SPI-2). Our laboratory has focused on SPI-2. The transcriptional regulator that drives the expression of the SPI-2 secretory system and its secreted effectors is SsrB. It is also important for maintaining the intracellular lifestyle of *S.* Typhi. One of the principal effectors causing endosomal tubulation is SseJ, but in *S.* Typhi, SseJ is a pseudogene.

METHODS

We used super-resolution microscopy to image intracellular *S.* Typhi, comparing wildtype and *ssrB* null strains.

RESULTS

Our results indicate that *ssrB* is essential for intracellular survival and endosomal tubulation occurs in the absence of *sseJ*. Supported by NIH AI123640 and an RCE in Mechanobiology from the Singapore Ministry of Education.

186. Development of a Low-Cost Digital Nucleic Acid Amplification Test Platform Using Hydrogel Beads for Environmental Surveillance of *Salmonella* Typhi

Yanzhe Zhu, Xiao Huang, Xingyu Lin, Jing Li, Michael Hoffmann

California Institute of Technology

BACKGROUND

Environmental surveillance of fecal-oral transmitted typhoidal *Salmonella* is essential for targeted sanitation interventions, vaccine distribution planning, and effectiveness assessment. Using microfluidic compartmentalization and Poisson statistics, recent developments in digital nucleic acid amplification test (dNAAT) allows absolute quantification of pathogen DNA without calibration required in qPCR. However, the application of dNAAT for environmental surveillance of *Salmonella* Typhi is challenging due to technical and financial barriers. Here we report a simple and cost-effective hydrogel beads-based dNAAT platform which demonstrated successful quantification of *Salmonella* Typhi in spiked environmental waters.

METHODS

We designed a simple droplet generation device composed of a 1.5-mL tube and a bent needle. Biocompatible fluorinated oil was added in the tube and aqueous loop-mediated isothermal amplification (LAMP) reagent was loaded in the needle Luer-lock. Water-in-oil droplets were produced by centrifugation with a standard lab centrifuge. Droplets were characterized with various needle sizes and centrifugation speeds. The reagent recipe was optimized with polyethylene glycol (PEG) hydrogel precursors, which polymerize droplets into beads within minutes. The droplets/beads were incubated at 65°C for 1 hour. After reaction, the fluorescence of droplets/beads were analyzed to calculate target concentration by Poisson distribution. The platform was challenged with pond water and wastewater spiked with *Salmonella* Typhi DNA.

RESULTS

Our device was capable of producing size-tunable monodispersed droplets. The smallest droplets generated were 115 ± 9 µm in diameter and the best monodispersed ones were 175 ± 7 µm. During 1-hour heating required for LAMP assay, aqueous droplets were susceptible to merging, leading to 22 µm increase in size standard deviation and less droplets qualified for target quantification. The addition of hydrogel showed negligible merging and thus provide more reliable quantification. The optimized hydrogel beads quantified DNA in buffer with a dynamic range of 0.5-3000 copies/µL. With spiked environmental waters, LAMP with hydrogel beads demonstrated higher amplification efficiency and more accurate quantification than aqueous droplets, likely due to restricted diffusion of environmental inhibitors in hydrogel matrix.

CONCLUSIONS

We have developed a hydrogel beads dNAAT platform with a device made from off-the-shelf components (less than $0.1/unit), that promises potential application in environmental surveillance of *Salmonella* Typhi in resource-limited setting.

LOCAL INFORMATION

Conference Registration

The registration desk is located in the foyer outside Grand Ballroom on Floor G of the hotel.

Registration Operating Hours:

Tuesday March 26, 2019 – 7:30-18:30
Wednesday March 27, 2019 – 8:00-17:30
Thursday March 28, 2019 – 8:30-17:30

Name Badges

Each delegate registered for the conference will receive a name badge at the registration desk. This badge will be your official pass and must be worn to obtain entry to all sessions, poster presentations and all social functions. Certain activities such as the Lunchtime Workshops are only available to those who have pre-registered.

Poster Presentations

We encourage all attendees to visit the wide array of posters on display in Fansipan Ballroom.

Mobile Phones

As a courtesy to fellow delegates and speakers, please ensure your mobile phones are switched off during conference sessions.

Refreshments

Morning and afternoon coffee breaks will be served in the foyer and Fansipan Ballroom. Lunch will be served in the JW Café and adjoining areas.

Special Dietary Requirements

If you have notified the conference organizers of any special dietary requirements, please be advised that this information has been supplied to the venue. Please make yourself known to the catering staff during meal breaks.

Airport Transfers

Noi Bai International Airport is located 30 km from JW Marriott Hanoi hotel. Travel by car costs approximately VND400,000 each way and takes approximately 45 minutes to 1 hour depending on traffic.

Recommended taxi services:
Mai Linh, Noi Bai or Taxi Group

Credit Cards

Cash is the main form of transactions in Vietnam, though credit cards are accepted in many restaurants, hotels and shops in Vietnam's big cities. Visa, Master Card, JBC and American Express are the most common credit cards honored in Vietnam.

For credit card transactions, you may be charged an addition 3-4 percent per transaction.

Bank Facilities

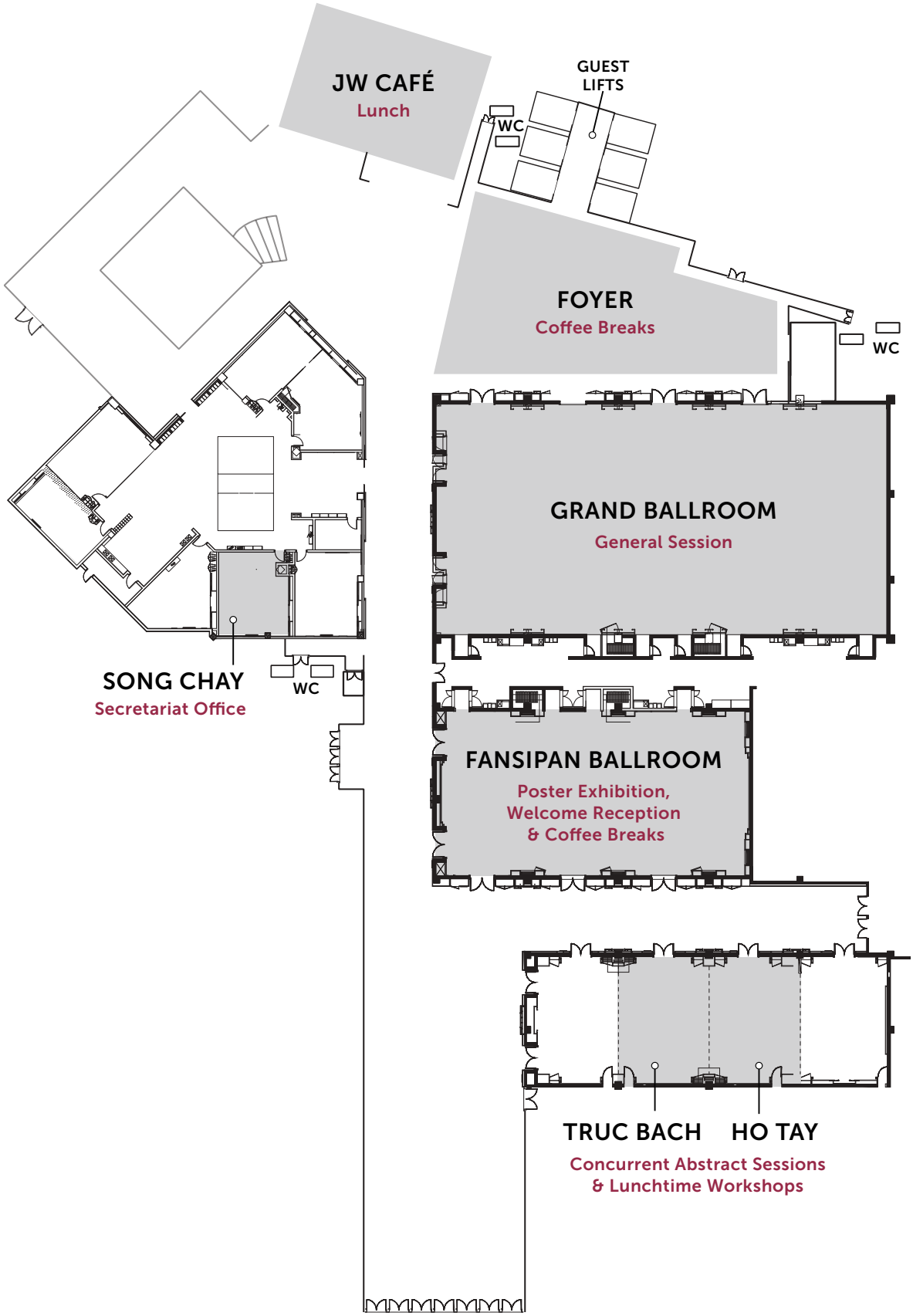
An ATM is location on Floor L of the hotel near the French Grill Restaurant. Foreign Currency can be exchanged at the front desk.

Wireless Access

Those staying at the JW Marriott should use their guest room credentials to access the Wi-Fi.

Those not staying at JW Marriott can connect to:

Network: JWMarriott_CONFERENCE
Password: jwmeetings


JW CAFÉ
Lunch
GUEST LIFTS
WC
FOYER
Coffee Breaks
WC
GRAND BALLROOM
General Session
SONG CHAY
Secretariat Office
WC
FANSIPAN BALLROOM
Poster Exhibition,
Welcome Reception
& Coffee Breaks
TRUC BACH
HO TAY
Concurrent Abstract Sessions
& Lunchtime Workshops

Basic Vietnamese Phrases

Hello = Xin Chao (*Sin chow*)

How are you? = Ban Khoe Khong (*Ban Kwe Khom*)

Thank you = Cam on (*Kahm uhn*)

Sorry = Xin Loi (*Sin Loy*)

Goodbye = Tam Biet (*Tarm Byeet*)

Can you speak English? = Ban noi tieng Anh duoc khong? (*Banh noi thien an durkh khom?*)

Where is the taxi rank? = Taxis o dau? (*Taxis urh dauh?*)

Where is the ATM? = May rut tien ATM o dau? (*May root tien ATM urn dole?*)

Go to the airport = Di san bay (*Di sun bay*)

Downtown = Trung Tam thanh pho (*Trumh tam tan fo*)

Station = Ga

Bus stop = Tram xe bus (*Tram seh butt*)

Where? = O dau? (*Uh dow?*)

How much? = Bao nhieu? (*Baow nyew?*)

Too expensive = Mac Qua (Mac wa)

Can you reduce the price? = Giam gia duoc khong? (*Zam za duoc khom?*)

Excuse me (to waitress) = Chi oi

Excuse me (to waiter) = Anh oi

What is it? = Cai gi vay? (*Kai zi vai?*)

The bill please = Tinh Tien (*Din ting*)

May I have the menu = Cho toi cai menu duoc khong (*Cho toy khai menu duuc khom*)

I am allergic to peanut = To di ung voi dau phong (*Doi yi ung voy dau fong*)

I cannot eat pork = Toi khong an duoc thit heo (*Toi khom an duo tit hehll*)

I am vegetarian = Toi an chay (*Toi an chayh*)

I need to see a doctor = Toi can gap bac si (*Toy can gap back szi*)

I need to go to the hospital = Toi can di benh vien (*Toy can di ben vien*)

Call the police = Goi canh sat (*Goi gang sack*)

Help me = Cuu toi voi (*Coo toy vuyh*)

SABIN VACCINE INSTITUTE

COALITION AGAINST TYPHOID