10th INTERNATIONAL CONFERENCE ON TYPHOID & OTHER INVASIVE SALMONELLOSES

April 4–6, 2017 | Kampala, Uganda

BILL & MELINDA GATES *foundation*

COALITION AGAINST TYPHOID

SABIN VACCINE INSTITUTE

THE WORLD NEEDS ACTION ON TYPHOID — BUILDING EVIDENCE AND REFINING STRATEGIES

The Coalition against Typhoid, housed at the Sabin Vaccine Institute, welcomes you to the 10th International Conference on Typhoid and Other Invasive Salmonelloses. We are pleased to provide a forum for more than 300 researchers, policy makers, immunization managers and advocates to come together to share the latest developments and best strategies to reduce the burden of typhoid, paratyphoid and nontyphoidal salmonelloses (NTS) on communities around the world.

The conference theme, "From Evidence to Action," is timely as we prepare for the introduction of new typhoid conjugate vaccines. The research, evidence and ideas shared this week in Kampala will provide the foundation for global action against typhoid, paratyphoid and NTS.

Together, we will review crucial developments to reduce the global burden of these diseases, including results from major surveillance projects in Africa and Asia, the potential of human infection models and strategies for countering antibiotic resistance. The program will also highlight outbreak control methods, exciting innovations in diagnostics, water, sanitation and hygiene strategies for prevention, and policy measures aimed at accelerating the implementation of these interventions.

The coming availability of a new generation of typhoid conjugate vaccines makes this a pivotal moment for global action on typhoid. These promising new vaccines offer important advantages over prior vaccines, including longer duration of protection, the ability to protect young children, and the potential for administration with other vaccines in routine immunization of infants. As *Salmonella* bacteria become increasingly resistant to available antibiotic treatments, conjugate vaccines have the potential to dramatically reduce the burden of typhoid around the world and consequently help to prevent the occurrence of antibiotic resistance. Working together to share research and generate evidence to shape solutions is more important than ever.

We thank you for joining us and extend our gratitude to the Bill & Melinda Gates Foundation for their generous support of this conference, the world's only conference devoted to typhoid and other invasive salmonelloses. In addition, we would like to thank the Ministry of Health of the Republic of Uganda for their assistance and hospitality. We look forward to three days of discussion, debate and forging new partnerships in the fight against typhoid.

Sincerely,

Denise Garrett, MD, MSc
Vice President, Typhoid Programs
Sabin Vaccine Institute
Director, Coalition against Typhoid

Bruce Gellin, MD, MPH
President, Global Immunization
Sabin Vaccine Institute

Amy Finan
Chief Executive Officer
Sabin Vaccine Institute

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Eric Mintz Centers for Disease Control and Prevention

Kathy Neuzil University of Maryland School of Medicine

Andrew Pollard University of Oxford

Samir Saha Child Health Research Foundation

Dipika Sur Translational Health Science and Technology Institute

ABSTRACT REVIEW PANEL

Jason Andrews Stanford University

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Virginia Pitzer Yale School of Public Health

Firdausi Qadri International Centre for Diarrhoeal Disease and Research, Bangladesh

Farah Qamar Aga Khan University

Jeff Stanaway Institute for Health Metrics and Evaluation

AGENDA

TUESDAY, APRIL 4		
08:30 – 08:35	Welcome Remarks	Bruce Gellin, Sabin Vaccine Institute
08:35 – 08:40	Conference Opening	Denise Garrett, Sabin Vaccine Institute
08:40 – 10:10	**Body of Evidence: Updates on Global Disease Burden** PLENARY SESSION MODERATED BY: Thomas Cherian (World Health Organization) & Melita Gordon (University of Liverpool)	
08:40 – 08:55	Looking to the Future: Control of Typhoid in the Next Decade	Anita Zaidi, Bill & Melinda Gates Foundation
08:55 – 09:10	Progress in Typhoid Fever Epidemiology	John Crump, University of Otago
09:10 – 09:25	Incidence, Presentation and Outcomes of *Salmonella* Bacteraemia Among Young Children in Sub-Saharan Africa: MAL055 RTS,S-AS01 *Salmonella* Ancillary Study	Cal MacLennan on behalf of the MAL055 RTS,S-AS01 *Salmonella* Ancillary Study
09:25 – 09:40	Enteric Fever Among Outbreaks in Africa: Same Old Foe but Emerging New Challenges in Management	Sam Kariuki, Kenya Medical Research Institute
09:40 – 09:55	Clades of *Salmonella* Associated with Epidemics of Invasive *Salmonella* Disease	Nick Feasey, Liverpool School of Tropical Medicine
09:55 – 10:10	QUESTIONS AND DISCUSSION	
10:10 – 10:30	Coffee Break and Posters	
10:30 – 12:30	**The Devil you Know: Diagnosing and Detecting Enteric Fever** ORAL ABSTRACT SESSION MODERATED BY: Gagandeep Kang (Christian Medical College, Vellore) & Hubert Endtz (Fondation Mérieux)	
10:30 – 10:45	Evaluation of a New Real-Time PCR to Identify *S.* Typhi, *S.* Paratyphi A and *S.* spp. from Patients with Fever in Bangladesh	Stephane Pouzol, Fondation Mérieux
10:45 – 11:00	Identification of a New Serodiagnostic Signature of Acute Typhoid Fever Using *Salmonella* Proteome Arrays	Thomas Darton, University of Oxford
11:00 – 11:15	Antigen Discovery for Improved Diagnosis of Invasive Salmonellosis by Targeted Proteomics	Sara Saleh, Institute of Tropical Medicine, Antwerp
11:15 – 11:30	Carriage of *Salmonella* Typhi Among Vendors in Two Kampala Markets	Mark Bumano, Makerere University College of Health Sciences
11:30 – 11:45	Typhoid Outbreak Caused by Drinks Made from Contaminated Underground Water Sources in Kampala, Uganda, January-March, 2015	David Oguttu, Uganda Public Health Fellowship Program
11:45 – 12:00	*Salmonella* Typhi Bloodstream Infections Among Infants and Children, Korogwe District Hospital, Tanzania	John Lusingu, National Institute for Medical Research
12:00 – 12:15	Typhoid Fever in Santiago, Chile: Modern Insights Where Historical Data Meet Mathematical Modeling	Jillian Gauld, Institute for Disease Modeling
12:15 – 12:30	*Salmonella* Typhi Bactericidal Antibody Activity is a Correlate of Disease Severity, but Not Protection Against Typhoid Fever	Andrew Pollard, University of Oxford
12:30 – 13:30	Lunch and Posters	

13:30 – 15:00	**The Right Shot: Vaccine Session I** ORAL ABSTRACT SESSION MODERATED BY: John Clemens (International Centre for Diarrhoeal Disease Research, Bangladesh) & Laura Martin (GSK Vaccines Institute for Global Health)	
13:30 – 13:45	Creating a Sustainable Vaccine Landscape: Overcoming Barriers to Vaccine Development and Speed to Market	Vinita Vishwanarayan, Clinton Health Access Initiative
13:45 – 14:00	Comparison of Strategies and Thresholds for the Vi Conjugate Vaccine Against Typhoid Fever: A Cost-Effectiveness Modeling Study	Nathan Lo, Stanford University
14:00 – 14:15	Development of New Generation Monovalent Typhoid Conjugate Vaccine: Vi-CRM_{197}	Akshay Goel, Biological E
14:15 – 14:30	Live Oral Typhoid Vaccine Ty21a Elicited Cross-Reactive Multifunctional IL-17A Producing T Cell Responses Against *Salmonella enterica* Serovars In Humans	Rezwanul Wahid, University of Maryland School of Medicine
14:30 – 14:45	Exploring *S.* Typhi-Specific HLA-E-Restricted Immune Responses in Pediatric and Adult Ty21a Recipients Using Mass Cytometry	Mark Rudolph, University of Maryland School of Medicine
14:45 – 15:00	Whole Genome Sequence Analysis of *Salmonella* Typhi Isolated in Thailand Before and After the Introduction of a National Immunisation Program	Zoe Dyson, University of Melbourne
15:00 – 15:30	Coffee Break and Posters	
15:30 – 17:45	**Spotlight on Africa and Asia: Enteric Fever Surveillance** SYMPOSIUM SESSION CHAIRED BY: Robert Breiman (Emory University) & Megan Carey (Bill & Melinda Gates Foundation)	
15:30 – 15:45	Epidemiology and Disease Burden of Typhoid Fever and iNTS Disease in Sub-Saharan Africa	Florian Marks, International Vaccine Institute
15:45 – 16:00	The Severe Typhoid Fever Surveillance in Africa (SETA) Program: An Overview	Justin Im, International Vaccine Institute
16:00 – 16:15	SETA: The First Data from the Six African Sites	Se Eun Park, International Vaccine Institute
16:15 – 16:30	African Risk Factor Prediction Model and Implications for Vaccination Strategies	Jong-Hoon Kim, International Vaccine Institute
16:30 – 16:45	At a Glance: The Surveillance for Enteric Fever in Asia Project (SEAP)	Denise Garrett, Coalition against Typhoid, Sabin Vaccine Institute
16:45 – 17:00	Approaches to Community Surveys for Typhoid Burden Estimation: Experience from SEAP	Alexander Yu, Stanford University
17:00 – 17:15	*Salmonella* Typhi and Paratyphi in Bangladesh and Their Antimicrobial Resistance	Samir Saha, Child Health Research Foundation
17:15 – 17:30	Looking Back While Moving Forward with Enteric Fever Surveillance in Pakistan	Farah Qamar, Aga Khan University
17:30 – 17:45	A Retrospective Review of Existing Hospital-Based Data on Enteric Fever in India	Dipika Sur, Translational Health Science and Technology Institute
17:45 – 18:00	Break	
18:00 – 19:30	**Reception with Featured Remarks from Honorable Dr. Jane Aceng, Minister of Health, Uganda**	

WEDNESDAY, APRIL 5		
08:30 – 10:00	**Staying One Step Ahead: Prevention and Control** PLENARY SESSION MODERATED BY: Jan Jacobs (Institute of Tropical Medicine Antwerp) & Buddha Basnyat (Oxford University Clinical Research Unit-Nepal)	
08:30 – 08:45	**Development and Challenges in Developing a Sensitive Diagnostic Test for Typhoid Fever**	Firdausi Qadri, International Centre for Diarrhoeal Disease and Research, Bangladesh
08:45 – 09:00	**Vaccine and non-Vaccine Measures for Prevention and Control of Typhoid Fever**	Eric Mintz, Centers for Disease Control and Prevention
09:00 – 09:15	**Gaps in Knowledge in Therapeutics and Treatment**	Chris Parry, Liverpool School of Tropical Medicine
09:15 – 09:30	**The SaniPath Approach to Fecal Exposure Assessment and Application to Typhoid Transmission**	Christine Moe, Emory University
09:30 – 09:45	**A Broad-Spectrum Vaccine to Prevent Invasive *Salmonella* Disease in Sub-Saharan Africa**	Myron Levine, University of Maryland School of Medicine
09:45 – 10:00	QUESTIONS AND DISCUSSION	
10:00 – 10:30	**Coffee Break and Posters**	
10:30 – 12:30	**Crush the Resistance: Antimicrobial Resistance Session** ORAL ABSTRACT SESSION MODERATED BY: Ken Simiyu (University of Maryland School of Medicine) & Gordon Dougan (Wellcome Trust Sanger Institute)	
10:30 – 10:45	**Antibiogram Pattern, Mechanism of Fluoroquinolone Resistance and Seasonality of *Salmonella* Serotypes in a North Indian Tertiary Care Hospital**	Rajni Gaind, Vardhman Mahavir Medical College & Safdarjung Hospital
10:45 – 11:00	**The Impact of Antimicrobial Treatment on Pathogen Behavior at the Subpopulation Level During Invasive *Salmonella* Infections**	Pietro Mastroeni, University of Cambridge
11:00 – 11:15	**Changing Trends in Antibiograms of *Salmonella enterica* in Pediatric Population — A Hospital Based Study**	Bhaskar Shenoy, Manipal Hospital, Bangalore, India
11:15 – 11:30	**Health Outcomes from Multidrug-Resistant *Salmonella* in High-Income Countries: A Systematic Review**	Andrea Parisi, The Australian National University
11:30 – 11:45	**Multidrug Resistant Non-Typhoidal *Salmonella* Hotspots as Targets for Vaccine Use in Management**	Sam Kariuki, Kenya Medical Research Institute
11:45 – 12:00	**Whole Genome Sequencing for Identification, Drug Resistance, Detection and Epidemiology of *Salmonella*: A Revolution in Public Health Microbiology**	Satheesh Nair, Public Health England
12:00 – 12:15	**Emergence of a New *Salmonella* Typhimurium ST313 Lineage in D.R. Congo with Increased Antibiotic Resistance and Indications for Further Host Adaptation**	Sandra Van Puyvelde, Institute of Tropical Medicine Antwerp
12:15 – 12:30	**Antimicrobial Pre-Treatment and Blood Culture Positivity Rates for *S.* Typhi, iNTS and Other Invasive Bacterial Pathogens**	Ondari D. Mogeni, International Vaccine Institute
12:30 – 13:30	**Lunch and Posters**	

13:30 – 15:00	**The Right Shot: Vaccine Session II** ORAL ABSTRACT SESSION MODERATED BY: Chisomo Msefula (University of Malawi) & Rob Heyderman (University College London)	
13:30 – 13:45	Pre-clinical Immunogenicity of Typhoid (Vi-CRM_{197}), Paratyphoid (O:2- CRM_{197}) and Bivalent (Vi-CRM_{197}+O:2- CRM_{197}) Conjugate Vaccine	Ravi P.N. Mishra, Biological E
13:45 – 14:00	Development of a Sustainable and Effective Vaccine Against Invasive Non-Typhoidal Salmonellosis (iNTS) in Africa	Gianluca Breghi, Fondazione Achille Sclavo
14:00 – 14:15	Development of a Vaccine Based on GMMA Against Invasive Non-Typhoidal *Salmonella* Disease in Sub-Saharan Africa	Oliver Koeberling, GSK Vaccines Institute for Global Health
14:15 – 14:30	*S.* Typhimurium Core-OPS (COPS) Glycoconjugate with the Homologous Serovar Phase 1 Flagellin as a Vaccine to Prevent Invasive *S.* Typhimurium Infections in Sub-Saharan Africa	Raphael Simon, University of Maryland School of Medicine
14:30 – 14:45	Measurement of LPS Specific IgA and IgG Avidity Maturation in Vivotif Vaccinees and Naturally Infected Typhoid Patients in Bangladesh	Farhana Khanam, International Centre for Diarrhoeal Disease and Research, Bangladesh
14:45 – 15:00	Forecasting Typhoid Conjugate Vaccine Introduction and Demand in Typhoid-Endemic Low- and Middle-Income Countries	Enusa Ramani, International Vaccine Institute
15:00 – 15:30	Coffee Break	
15:30 – 17:30	***Salmonella* Controlled Human Infection Models — Insights, Opportunities and Challenges** SYMPOSIUM SESSION CHAIRED BY: Thomas Darton (University of Sheffield) & Andrew Pollard (University of Oxford)	
15:30 – 15:35	*Salmonella* Challenge Studies — Introduction and Historical Perspective	Andrew Pollard, University of Oxford
15:35 – 15:50	Assessment of the Efficacy of a Vi-Tetanus Toxoid Conjugate Vaccine Using a Controlled Human Infection Model of *Salmonella* Typhi	Celina Jin, University of Oxford
15:50 – 16:05	Investigating Immunity to Typhoid and Paratyphoid Fever — The Response to Re-Challenge in a Controlled Human Infection Model	Malick Gibani, University of Oxford
16:05 – 16:20	Identifying Correlates of Protection — Systemic Immune Responses to *Salmonella* Typhi and Paratyphi A Infection	Giorgio Napolitani, University of Oxford
16:20 – 16:35	Mucosal Immune Responses to *Salmonella* Typhi and Paratyphi A Infection	Lorena Preciado-Llanes, University of Oxford
16:35 – 16:50	Comparative Analysis of Molecular Immune Profiles and Disease Pathogenesis in Typhoid and Paratyphoid Fever	Christoph Blohmke, University of Oxford & Jennifer Hill, University of Oxford
16:50 – 17:05	Recent Advances in the Identification of Immunological Correlates of Protection in a Human *S.* Typhi Challenge Model	Marcelo Sztein, University of Maryland School of Medicine
17:05 – 17:20	Towards Human Challenge with NTS	Cal MacLennan, University of Oxford
17:20 – 17:30	QUESTIONS AND DISCUSSION	
17:30 – 19:30	**#TakeOnTyphoid with TyVAC: Reception to Launch the New Typhoid Vaccine Acceleration Consortium**	

THURSDAY, APRIL 6		
08:30 – 10:45	**The Next Generation: Typhoid Conjugate Vaccine** PLENARY SESSION MODERATED BY: Joachim Hombach (World Health Organization) & Vittal Mogasale (International Vaccine Institute)	
08:30 – 08:50	**Overview on Vaccine Pipeline: Current Status and Future Plans**	Sushant Sahastrabuddhe, International Vaccine Institute
08:50 – 09:05	**Introduction of Typhoid Conjugate Vaccines: Opportunities and Challenges**	Kathy Neuzil, University of Maryland School of Medicine
09:05 – 09:20	**Development of a Bivalent *Salmonella* Typhi and Paratyphi A MAPS Vaccine**	Rick Malley, Boston Children's Hospital/ Harvard Medical School
09:20 – 09:35	**Cost-Effectiveness of Typhoid Conjugate Vaccine Strategies Across Five Settings in Africa and Asia**	Virginia Pitzer, Yale School of Public Health
09:35 – 10:05	**TYPBAR-TCV: A Clinical Development Review**	Krishna Mohan, Bharat Biotech
10:05 – 10:20	**First Planned Public Sector Introduction of a Typhoid Conjugate Vaccine in Navi Mumbai, India**	Jason Andrews, Stanford University
10:20 – 10:45	QUESTIONS AND DISCUSSION	
10:45 – 11:15	**Coffee Break and Posters**	
11:15 – 12:45	**Global Trends in Typhoid Fever: Determinants and Implications for Policy** SYMPOSIUM SESSION CHAIRED BY: Zulfiqar Bhutta (Aga Khan University) & Kathy Neuzil (University of Maryland School of Medicine)	
11:15 – 11:25	**Short Overview and Provenance of the Study**	Zulfiqar Bhutta, Aga Khan University
11:25 – 11:40	**Global Review and Epidemiology**	Daina Als, SickKids Centre for Global Child Health
11:40 – 11:50	**Additional Trend Data from Global Burden of Disease Study**	Jeff Stanaway, Institute for Health Metrics and Evaluation
11:50 – 12:00	**Country Case Study: Chile**	Catterina Ferreccio, Escuela de Medicina Pontificia Universidad Católica de Chile
12:00 – 12:10	**Country Case Study: Pakistan**	Jai K. Das, Aga Khan University
12:10 – 12:20	**Country Case Study: Thailand**	Amruta Radhakrishnan, The Hospital for Sick Children
12:20 – 12:30	**Country Case Study: Nigeria**	Kabiru Olusegun Akinyemi, Lagos State University
12:30 – 12:45	QUESTIONS AND DISCUSSION	
12:45 – 13:45	**Lunch and Posters**	

13:45 – 15:45	**What's New, Doc? Late Breaker Abstracts** MODERATED BY: Isaac Bogoch (University of Toronto) & Richard Strugnell (University of Melbourne)	
13:45 – 14:00	Virulence of Invasive *Salmonella* Typhimurium ST313 in Animal Infection Models	Ellen Higginson, University of Maryland School of Medicine
14:00 – 14:15	Average Treatment Cost for Typhoid Fever and Average Vaccine Delivery Cost per Dose for Each of the 54 GAVI-Eligible Countries	Joke Bilcke, University of Antwerp
14:15 – 14:30	Outbreak Investigation and Assessment of Risk Factors of Ceftriaxone Resistant *S.* Typhi from Hyderabad, Pakistan	Tahir Yousufzai, Aga Khan University
14:30 – 14:45	*Salmonella enterica* Serovars Isolated from Stool of Children Enrolled in the Global Enteric Multicenter Study in Africa	Irene Kasumba, University of Maryland School of Medicine
14:45 – 15:00	Leveraging the WHO-Coordinated IB-VPD Surveillance Platform for Enteric Fever Surveillance: Lessons from Bangladesh	Senjuti Saha, Child Health Research Foundation
15:00 – 15:15	A Case-Control Investigation into the Household Distribution of Invasive *Salmonellae* in Blantyre, Malawi	Melita Gordon, University of Liverpool
15:15 – 15:30	Knowledge, Attitudes and Practices Related to Typhoid Fever: The Case of Glen View Suburb, City of Harare, 2016	Kudzai Masunda, City of Harare Health Department
15:30 – 15:45	Spatial and Temporal Patterns of Typhoid and Paratyphoid Fever Outbreaks: A Worldwide Systematic Review, 1990-2016	Vittal Mogasale, International Vaccine Institute
15:45 – 16:15	**Coffee Break**	
16:15 – 17:30	**Mission Possible: From Evidence to Action** PLENARY SESSION MODERATED BY: Bruce Gellin (Sabin Vaccine Institute) & Narendra K. Arora (International Clinical Epidemiology Network)	
16:15 – 16:30	Global Typhoid Control in the Context of the Sustainable Development Goals: Pragmatism or Utopia?	Zulfiqar Bhutta, Aga Khan University
16:30 – 16:45	Considerations for Revised Global Typhoid Vaccination Policy and Strategies	Adwoa Bentsi-Enchill, World Health Organization
16:45 – 17:00	Breaking Good: Making Science Great Again	Robert Breiman, Emory University
17:00 – 17:20	QUESTIONS AND DISCUSSION	
17:20 – 17:25	Closing Remarks	Bruce Gellin, Sabin Vaccine Institute
17:25 – 17:30	Adjourn	Denise Garrett, Sabin Vaccine Institute

PROGRAM

TUESDAY

» TUESDAY, APRIL 4

8:30 WELCOME REMARKS

BRUCE GELLIN, *Sabin Vaccine Institute*

Dr. Bruce Gellin, MD MPH, is President, Global Immunization at the Sabin Vaccine Institute. Dr. Gellin previously served as the Deputy Assistant Secretary for Health and Director of the National Vaccine Program Office at the U.S. Department of Health and Human Service (HHS), where he was the principal advisor to the Assistant Secretary for Health on vaccine and immunization programs and policies. Dr. Gellin also represented HHS as a technical and policy advisor to the World Health Organization with a focus on influenza and vaccine hesitancy and as a contributor to the Decade of Vaccines Collaboration and the Global Action Vaccine Action Plan (GVAP). Dr. Gellin earned an MPH in epidemiology from the Columbia University Mailman School of Public Health, is a graduate of Weill Cornell Medical College, and was a Morehead Scholar at the University of North Carolina at Chapel Hill and previously worked at CDC and NIH. Dr. Gellin achieved board certification in internal medicine and infectious diseases and serves as a peer reviewer for over a dozen medical journals.

8:35 CONFERENCE OPENING

DENISE GARRETT, *Sabin Vaccine Institute*

Denise Garrett, MD, MSc, 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.

BODY OF EVIDENCE: UPDATES ON GLOBAL DISEASE BURDEN

8:40–10:10 PLENARY SESSION

MODERATORS

THOMAS CHERIAN, *World Health Organization*

Dr. Cherian is the Coordinator for the Expanded Programme on Immunization in the Department of Immunization, Vaccines and Biologicals at the World Health Organization (WHO), Geneva. Prior to this, he was the Coordinator for Implementation Research in the Initiative for Vaccine Research at WHO in Geneva. He also holds the position of Senior Associate in the Department of International Health at the Johns Hopkins Bloomberg School of Public Health, Baltimore, USA. Before joining WHO, Dr. Cherian was Professor of Paediatrics at the Christian Medical College in Vellore, India, where he did his medical training as well as his post graduate training in Paediatrics. Subsequently, he did a three-year fellowship in Paediatric Infectious Diseases at the Johns Hopkins University School of Medicine, Baltimore. Dr. Cherian has authored or co-authored over 130 scientific articles and book chapters. His main research interests have been related to acute respiratory infections in children. His research has contributed to the case management protocols for acute respiratory infections in children and for policy development for the use of Pneumococcal and Hib vaccines worldwide.

MELITA GORDON, *University of Liverpool*

Melita Gordon is a clinical scientist with 18 years track-record working on invasive typhoidal and non-typhoidal *Salmonella* disease in Malawi and UK. She has worked in Malawi for 20 years, to describe the clinical features, epidemiology, host inflammatory and immune response, and the clinical pathogenesis of invasive *Salmonella* disease, using experimental medicine, genomic, cellular, molecular, transcriptomic and modelling approaches. Genomic studies of invasive strains of *Salmonella* have demonstrated newly emerged invasive pathovars of several serovars in Africa, which have spread transcontinentally, and which show multidrug resistance and evidence of recent adaptation to unique niches in Africa. Melita 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 Malawi where her research group addresses the epidemiology, genomics, diagnostics, transmission, antimicrobial resistance and vaccinology of typhoid and non-typhoidal invasive *Salmonella* disease, and to train local and international scientists and clinicians.

PRESENTATIONS

8:40 LOOKING TO THE FUTURE: CONTROL OF TYPHOID IN THE NEXT DECADE

ANITA ZAIDI, *Bill & Melinda Gates Foundation*

Anita Zaidi is the Director of the Enteric and Diarrheal Diseases (EDD) program at the Bill and Melinda Gates Foundation. The EDD team is focused on eliminating diarrheal diseases mortality and significantly reducing the adverse consequences of diarrheal and enteric infections on children's health in low and middle-income countries. Anita has a multi-disciplinary training background and professional expertise in pediatrics, clinical microbiology, infectious diseases in children, and tropical public health. Her research has focused on vaccine-preventable illnesses and newborn infections in resource-limited settings, publishing more than a 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 Karachi, Pakistan. 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.

8:55 PROGRESS IN TYPHOID FEVER EPIDEMIOLOGY

JOHN A. CRUMP, *University of Otago*

John Crump, MB ChB, MD, DTM&H, FRACP, FRCPA, FRCP, is McKinlay Professor of Global Health and Co-Director of the Centre for International Health at the University of Otago, Dunedin; Adjunct Professor of Medicine, Pathology, and Global Health at Duke University; and a Guest Researcher with the US Centers for Disease Control and Prevention. 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.

9:10 INCIDENCE, PRESENTATION AND OUTCOMES OF *SALMONELLA* BACTERAEMIA AMONG YOUNG CHILDREN IN SUB-SAHARAN AFRICA: MAL055 RTS, S-AS01 *SALMONELLA* ANCILLARY STUDY

CAL MacLENNAN, *MAL055 RTS, S-AS01 Salmonella Ancillary Study*

Cal MacLennan is a clinician scientist currently spending a year with the Enteric and Diarrheal Diseases team at the Bill and Melinda Gates Foundation. He qualified in medicine and then obtained his doctorate from Oxford. As a junior doctor, Cal developed an interest in infectious disease immunology which led him to work in Kenya and then Malawi, investigating immunity to invasive *Salmonella* disease. These studies continued at the University of Birmingham, UK, prior to Cal becoming Head of Exploratory Programme at the Novartis Vaccines Institute for Global Health in 2010. There, his programme developed new vaccines against *Salmonella*, *Shigella* and meningococcus. Following a sabbatical at the Wellcome Trust Sanger Institute, he returned to Oxford in 2015 as a Senior Clinical Fellow at the Jenner Institute. *Salmonella* immunology continues to be a main focus of Cal's research with ongoing projects in Africa. He is an honorary consultant immunologist at Oxford University Hospitals NHS Foundation Trust, a member of visiting faculty at the Sanger Institute and Professor of Vaccine Immunology at the University of Birmingham.

9:25 ENTERIC FEVER AMONG OUTBREAKS IN AFRICA: SAME OLD FOE BUT EMERGING NEW CHALLENGES IN MANAGEMENT

SAM KARIUKI, *Kenya Medical Research Institute*

Sam Kariuki, PhD, is Chief Research Scientist and Director, Centre for Microbiology Research at KEMRI in Nairobi and a Wellcome Trust Sanger Institute International Fellow. He is visiting Professor of Tropical Microbiology, Nuffield Department of Medicine, University of Oxford, UK. He is Co-ordinator of Medical Microbiology postgraduate course, Institute of Tropical Medicine and Infectious Diseases, KEMRI. He has research interest in the epidemiology and antimicrobial resistance of enteric bacterial pathogens, including invasive non-typhoidal salmonellosis (NTS) and typhoid fever, *Shigella* spp., *Vibrio cholerae* and *Escherichia coli*. He is Chair, Global Antimicrobial Resistance Partnership (GARP)-Kenya chapter and in 2014-16, led the initiative for development of the Situational Analysis on AMR in Kenya culminating in the National Action Plan Draft document. He has authored/co-authored over 130 papers in peer-reviewed journals and three text books on Antimicrobial resistance and Food Safety.

9:40 CLADES OF *SALMONELLA* ASSOCIATED WITH EPIDEMICS OF INVASIVE *SALMONELLA* DISEASE

NICK FEASEY, *Liverpool School of Tropical Medicine*

Nick Feasey is a clinical microbiologist and senior lecturer based both at the Liverpool School of Tropical Medicine and the Malawi Liverpool Wellcome Trust Clinical Research Programme in Blantyre, Malawi. His research is focused on the surveillance and management of bacterial bloodstream infection and identifying environmental reservoirs of Salmonellae associated with invasive disease.

9:55 QUESTIONS AND DISCUSSION

Coffee Break and Posters
10:10 – 10:30

TUESDAY

TUESDAY

THE DEVIL YOU KNOW: DIAGNOSING AND DETECTING ENTERIC FEVER

10:30 – 12:30 ORAL ABSTRACT SESSION

MODERATORS

GAGANDEEP KANG,
Christian Medical College, Vellore

Gagandeep Kang, MD, PhD, FRCPath, FAAM, FASc, FNASc, FNA, FFPH, is Professor of Microbiology at the Christian Medical College (CMC) in Vellore, India, currently on sabbatical as the Executive Director, Translational Health Science Technology Institute, an autonomous institute of the Department of Biotechnology. She works on enteric infections in children, particularly on transmission and immune responses, in order to design effective interventions. Current studies include active hospital and community based surveillance and clinical trials of new and existing vaccines, with use of molecular based assays to study the diversity of pathogens and the immune response of children with viral and parasitic enteric infections.

HUBERT P. ENDTZ, *Fondation Mérieux*

Professor Hubert Endtz is the Scientific Director of Fondation Mérieux. Professor Endtz is a microbiologist with a broad, international background. Most recently, he has been Head of Research and Development and deputy Chairman of the Department of Medical Microbiology & Infectious Diseases. He still holds the chair in Tropical Bacteriology at Erasmus University in Rotterdam. Prior to that, he held leadership positions at the International Centre for Diarrheal Disease Research, Bangladesh (ICDDR,B), where he directed the Centre for Food and Waterborne Diseases and the Laboratory Sciences Division from 2007-2012. He continues to be involved with ICDDR,B as an Associate Scientist. He holds MD 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 Institut Pasteur in Paris. His main research interests include diarrheal and respiratory diseases in low-income countries; the pathogenesis of Guillain-Barre syndrome and antecedent infections; and antimicrobial resistance. He is the author of over 165 peer-reviewed scientific publications.

PRESENTATIONS

10:30 EVALUATION OF A NEW REAL-TIME PCR TO IDENTIFY *S.* TYPHI, *S.* PARATYPHI A AND *S.* SPP FROM PATIENTS WITH FEVER IN BANGLADESH

STEPHANE POUZOL, *Fondation Mérieux, Lyon, France*

Stephane Pouzol[1], Arif Tanmoy[2], Dilruba Ahmed[3], Abdullah Brooks[3], Thomas Benet[4], Laetitia Fabre[5], François-Xavier Weill[5], Bill Carman[6], Firdausi Qadri[3], Samir Saha[2], Hubert Endtz[1,7]

[1]Fondation Mérieux, Lyon, France; [2]CHRF, Dhaka, Bangladesh; [3]ICDDR,B, Dhaka, Bangladesh; [4]UCBL1, Lyon, France; [5]Pasteur Institute, Paris, France; [6]Fast Track Diagnostics, Luxembourg; [7]Erasmus MC, The Netherlands

BACKGROUND

Enteric fever is a severe illness caused by *Salmonella* Typhi or *Salmonella* Paratyphi A or B. Routine diagnosis in endemic regions is done by blood culture or Widal test. However, low sensitivity of both tests is a serious limitation and highlights the need for the development of alternative diagnosis.

METHOD

Based on a pre-enrichment step combined with a real-time multiplex polymerase chain reaction, we developed a method to identify *S.* Typhi, *S.* Paratyphi A and *S.* spp. directly from 2-3 ml of whole blood. After *in vitro* optimization with *Salmonella* spiked whole blood, we evaluated the assay in an enteric fever endemic population (temperature ≥ 38°C) in Dhaka, Bangladesh (n=685) and in healthy volunteers (n=45).

RESULTS

The molecular probe set was first validated *in vitro* and had a high level of sensitivity of 1 and 10 genome copies/reaction for *S.* Typhi and *S.* Paratyphi A strains, respectively. One CFU/sample was detected by mixing a blood sample with an equal volume of tryptone soya broth containing 5.0% (w/v) ox bile and further subjected to suitable DNA extraction method. Out of the 685 blood samples, 99 were positive by blood culture and 164 with the assay. Interestingly, Ct values of both *S.* Typhi and *S.* Paratyphi A were significantly different ($p<0.01$) in positive and negative blood culture samples (ΔCt = -4.7 and -5.1 respectively). Considering true positive as having a positive blood culture or qPCR test, sensitivity of qPCR assay was 92.9% while it dropped to 56.1% for blood culture. All 45 healthy controls remained negative. We did not observe any cross-reactions between *Salmonella* species, indicating a high level of specificity.

CONCLUSION

We developed a sensitive method to identify the two major *Salmonella* serovars that cause enteric fever. A new evaluation is underway in sub-Saharian Africa where *S.* Paratyphi A is known to be more prevalent.

10:45 IDENTIFICATION OF A NEW SERODIAGNOSTIC SIGNATURE OF ACUTE TYPHOID FEVER USING *SALMONELLA* PROTEOME ARRAYS

THOMAS DARTON, *University of Oxford; The University of Sheffield*

Thomas C. Darton[1,2,3], Stephen Baker[2], Arlo Randall[4], Krista Trappl[4], Sabina Dongol[5], Abhilasha Karkey[5], Douglas Molina[4], Claire S. Waddington[1], Claire Jones[1], Jozelyn Pablo[4], Chris Hung[4], Andy Teng[4], Adam Shandling[4], Tim Le[4], Cassidy Walker[4], Michael Carter[1,5], Jason Andrews[6], Buddha Basnyat[5], Andrew J. Pollard[1], Christoph J. Blohmke[1]

[1]Oxford Vaccine Group, Centre for Clinical Vaccinology and Tropical Medicine, Department of Paediatrics, University of Oxford and the National Institute for Health Research Oxford Biomedical Research Centre, Oxford, United Kingdom; [2]The Hospital for Tropical Diseases, Wellcome Trust Major Overseas Programme, Oxford University Clinical Research Unit, Ho Chi Minh City, Vietnam; [3]Department of Infection, Immunity and Cardiovascular Disease, The University of Sheffield, Sheffield, United Kingdom; [4]Antigen Discovery Inc., Irvine, California, United States of America; [5]Oxford University Clinical Research Unit, Patan Academy of Health Sciences, Kathmandu, Nepal; [6]Division of Infectious Diseases and Geographic Medicine, University of Stanford, United States of America

BACKGROUND

Effective rapid diagnostic tests for typhoid fever are needed to optimise patient management, assess infection incidence and reduce inappropriate antimicrobial use. Here we model the longitudinal humoral antibody response to acute typhoid fever in recently performed controlled human in studies and validate a diagnostic signature in samples from an endemic setting.

METHODS

Using a *Salmonella* protein microarray containing 4288 ORFs expressed by *E. coli*, we measured IgM/IgA/IgG responses in 41 participants challenged with wild type *S.* Typhi until 90 days after challenge (60% infection rate). After down-selection, a 250-feature array incorporating purified proteins (lipopolysaccharide, flagellin), Vi polysaccharide and markers for dengue and *P. falciparum* infection, was used to confirm responses seen in a second cohort of 30 challenged participants (66% infection rate). Final selection of diagnostic antigen/antibody responses was optimised using machine learning methods and validated in cohorts of 150 typhoid patients, 50 healthy controls and 50 non-*S.* Typhi bacteraemic febrile controls from an endemic setting (Kathmandu, Nepal).

RESULTS

Broad, heterogeneous antibody responses were seen after challenge in participants developing typhoid infection. Antibody, and in particular IgM/IgA responses, were seen as early as 96 hours after diagnosis (defined as fever and/or bacteraemia). A panel of 31 antigen/antibody combinations in addition to LPS, flagellin and Vi polysaccharide were chosen for validation; acute and longer durability responses were confirmed in those diagnosed with infection, including hlyE and ompA. Detailed data regarding the humoral responses seen during acute infection and convalescence will be presented, together with the results of computational classification approaches and endemic setting validation.

CONCLUSIONS

New diagnostic tests for typhoid, in particular tests which may be multiplexed for rapid diagnosis of febrile individuals, are urgently needed. The identification and investigation of responses in a controlled human infection models provides a unique opportunity to interrogate novel diagnostics for enteric fever.

11:00 ANTIGEN DISCOVERY FOR IMPROVED DIAGNOSIS OF INVASIVE SALMONELLOSIS BY TARGETED PROTEOMICS

SARA SALEH, *Institute of Tropical Medicine, Antwerp*

Sara Saleh[1,2,3], An Staes[2,3], Sandra Van Puyvelde[1], Laura Kuijpers[4], Barbara Barbé[4], Jan Jacobs[4] , Kris Gevaert[2,3], Stijn Deborggraeve[1]

[1]Department of Biomedical Sciences, Institute of Tropical Medicine, Antwerp, Belgium; [2]VIB Medical Biotechnology Center, B-9000 Ghent, Belgium; [3]Department of Biochemistry, Ghent University, B-9000 Ghent, Belgium; [4]Department of Clinical Sciences, Institute of Tropical Medicine, Antwerp, Belgium

BACKGROUND

With an estimated 20 million typhoid cases and an even higher number of non-typhoid cases, the health burden caused by blood infections with *Salmonella* is huge. Currently no single diagnostic test for invasive salmonellosis is available that reaches satisfactory accuracy. Therefore, there is an urgent need for a sensitive, specific and rapid diagnostic test for invasive salmonellosis. In this work, we have applied shotgun proteomics to discover novel candidate antigens, followed by a targeted proteomics approach to validate the candidate antigens.

METHODS

The proteomes of five clinical isolates and one reference strain per *Salmonella* serovar Typhi, Paratyphi A, Typhimurium and Enteritidis were analyzed in duplicate. Candidate antigens were identified and their diagnostic potential was assessed using a targeted proteomics approach based on Multiple Reaction Monitoring (MRM). MRM allows accurate quantification of proteins in samples through spiking with exogenous isotope labeled proteotypic peptides.

RESULTS

In total, 1222 proteins were detected over the four *Salmonella* serovars. Downstream analysis identified 24 novel candidate antigens that are either unique for *Salmonella* or for one of the serovars. We designed and synthesized 93 proteotypic peptides as representatives for the candidate antigens. Sixty-eight proteotypic peptides survived the MRM optimization assays and were used to validate the candidate antigens in *in vitro* cultured *Salmonella* strains as well as in non-target Gram negative and Gram positive bacteria. We are currently validating the candidate antigens with MRM in blood specimens from patients with invasive salmonellosis and other bacterial bloodstream infections.

CONCLUSION

We have applied shotgun and targeted proteomics to identify novel candidate antigens for the diagnosis of invasive salmonellosis. The best candidate antigens will be used to develop an antigen-based rapid diagnostic test for invasive salmonellosis.

11:15 CARRIAGE OF *SALMONELLA* TYPHI AMONG VENDORS IN TWO KAMPALA MARKETS

MARK BUMANO, *Makerere University College of Health Sciences*

Mark Bumano[1], C.F. Najjuka[1], Steven Aisu[2], Henry Kajumbula[2]

[1]Department of Medical Microbiology, Makerere University; [2]Central Public Health Laboratories, Uganda Ministry of Health

BACKGROUND

Typhoid fever affects nearly 27 million people with 200,000 deaths globally every year. Chronic gall bladder carriage of *S.* Typhi could initiate sporadic cases and major typhoid outbreaks. Kampala city suffered a large typhoid outbreak involving 10,230 cases during 2015. Many cases were vendors at Nakasero Market found in the city center. We therefore set out to estimate the prevalence of *S.* Typhi carriage in stool of vendors at two markets in Kampala city.

METHODS

This was a descriptive cross-sectional study involving vendors at two markets in Kampala City. Nakasero Market, sampled in July 2016, is found in the central business district of the city, while Kalerwe market, sampled in September 2016, is located about 3km from the city centre. Following ethical clearance from the Makerere University School of biomedical science, demographic data and stool samples were gathered from the participants. Stool was cultured onto selenite F broth and XLD agar for isolation of *Salmonella*. Identification was done using biochemical tests and by typing antisera.

RESULTS

Of the 778 participants, 7 (0.9%) were positive for *S.* Typhi in stool. These included 3 (0.7%) of the 427 participants from Nakasero market and 4 (1.1%) of the 351 participants from Kalerwe market.

CONCLUSIONS

S. Typhi carriage exists among market vendors in Kampala with a prevalence comparable to that found in studies in other parts of sub-Saharan Africa. We recommend strengthening of hygiene in the markets to control transmission at work and studies to establish relatedness of the carriage strains to the recent outbreak strains.

11:30 TYPHOID OUTBREAK CAUSED BY DRINKS MADE FROM CONTAMINATED UNDERGROUND WATER SOURCES IN KAMPALA, UGANDA, JANUARY-MARCH, 2015

DAVID OGUTTU, *Uganda Public Health Fellowship Program, Field Epidemiology Track*

BACKGROUND

On 6 February 2015, the Ministry of Health of Uganda was notified of a "strange disease" that had killed several people and more were ill with similar symptoms. We investigated this disease to identify the cause and mode of transmission.

METHODS

We defined a suspected case as a person working in Kampala with onset of fever ≥5 days since 1 January 2015 plus ≥2 of the following: abdominal pain, nausea/vomiting, diarrhea, constipation, jaundice, mental confusion; a probable case had a positive TUBEX test and a confirmed case was one whose blood-culture was positive for *Salmonella* Typhi. We found cases by visiting affected communities and reviewing line-lists at the free treatment centers. In a case-control study we compared food/water exposures of 33 case-patients and 78 control-persons frequency-matched by work-place and sex. We tested blood and environmental samples for pathogen-identification.

RESULTS

By 3 March, we had identified 1483 suspected (including 322 probable, eight confirmed) cases. Initial 63 case-patients had fever (100%), abdominal pain (68%), diarrhea (51%), nausea/vomiting (32%) and constipation (22%). The epidemic curve indicated continuous common-source exposure. Twenty-six percent (7/31) of case-patients and 2.6% (2/78) of control-persons usually drank locally-made drink "Kaveera" (ORM-H=8.9; 95% CI=1.6-49); 55% (18/33) of case-patients and 19% (15/78) of control-persons drank locally-made "passion fruit juice" (ORM-H=4.6; 95% CI: 1.9-11). No foods were associated with illness. Local drink-makers routinely extracted water from underground sources without chlorination to make drinks. Eight blood specimens were blood-culture positive for *Salmonella* Typhi; samples of locally made drinks and underground water all had heavy fecal contamination.

CONCLUSION

This was a typhoid outbreak caused by consumption of drinks made from contaminated underground water. We recommended sealing off all underground water sources and supplying free chlorinated water to affected areas.

11:45 *SALMONELLA* TYPHI BLOODSTREAM INFECTIONS AMONG INFANTS AND CHILDREN, KOROGWE DISTRICT HOSPITAL, TANZANIA

JOHN LUSINGU, *National Institute for Medical Research*

Omari Abdul[1], Bruno Mmbando[1], Coline Mahende[1], Samwel Gesase[1], Anangisye Malabeja[1], Denise Dekker[2], Lorenz von Seidelein[2], Thor Theander[3], Myriam Bruls[4], Christine Swysen[4], Andrea Reijman[5], Dyan Belonje[5], Barbara Savarese[6], John Lusingu[1,3]

[1]National Institute for Medical Research, Tanga Centre, Tanga, Tanzania; [2]London, School of Hygiene & Tropical Medicine, London, UK; [3]University of Copenhagen, Copenhagen, Denmark; [4]Glaxo SmithKline Vaccine, Rixensart, Belgium; [5]Clinical Laboratory Services, South Africa; [6]The PATH-Malaria Vaccine Initiative, Washington DC, USA

BACKGROUND

Understanding the age distribution of typhoid fever is essential for typhoid conjugate vaccine policy. However, there are few data on prevalence of *Salmonella* Typhi bloodstream infections by age among infants and children in African countries. We sought to describe the prevalence of *Salmonella* Typhi bloodstream infections by age at a district hospital in northeastern Tanzania.

METHODS

Infants and children aged one month to five years admitted at Korogwe District Hospital with temperature ≥37.5ºC from 2008 to 2012 were enrolled. After obtaining demographic and clinical information blood was collected for culture in a continuously monitored blood culture instrument. Organisms were identified by conventional methods and antimicrobial susceptibility was done by Kirby Bauer's disc diffusion method.

RESULTS

We enrolled 3,224 participants. Of participants, 1478 (45.8%) were female, the median (range) age was 1.2 (0.1 –5.2) years, and 291 (9.0%) had a pathogen isolated from blood culture. Of bloodstream infections, 128 (44.0%) were *Salmonella*, 54 (18.6%) were *Streptococcus pneumoniae*, 27 (9.3%) *Haemophilus influenzae* and 24 (8.2%) *Escherichia coli.* Of *Salmonella*, 89 (69.5%) were *Salmonella* Typhi and the remainder were nontyphoidal *Salmonella*. Patients with *Salmonella* Typhi were younger (median age 1.6 years: range: 0.2 – 3.5) than those with non-typhoidal Salmonellae (2.8 years, interquartile range: 0.2 – 4.6) (p<0.001). Of *Salmonella* Typhi isolates, 66 (88.0%) were resistant to ampicillin, 66 (82.5%) to chloramphenicol, and 72 (92.3%) to trimethoprim-sulfamethoxazole, 4 (5.4%) to ciprofloxacin, and 8 (11.1%) to ceftriaxone.

CONCLUSIONS

Salmonella Typhi predominated and was most common among children <2 years of age. Isolates were often multi-drug resistant. In northeastern Tanzania typhoid is common in infants and young children, suggesting that typhoid conjugate vaccine may best be included in routine infant vaccine schedules.

12:00 TYPHOID FEVER IN SANTIAGO, CHILE: MODERN INSIGHTS WHERE HISTORICAL DATA MEET MATHEMATICAL MODELING

JILLIAN GAULD, *Institute for Disease Modeling*

Jillian Gauld[1], Dennis Chao[1], Hao Hu[1], Myron Levine[2]

[1]Institute for Disease Modeling, Seattle, USA; [2]University of Maryland, Baltimore, USA

BACKGROUND

The mechanisms of typhoid transmission remain largely unknown in most modern-day settings. Although the disease is broadly correlated with a lack of clean drinking water and sanitation, Santiago, Chile had nearly universal access to treated drinking water and widespread sewage coverage, yet had high endemic levels of typhoid in the 1970s. Prior to vaccination and other interventions in the early 1980s, high resolution data were collected to shed light on cases, chronic carriers and mechanisms of disease transmission, data that are rarely available in combination in modern settings.

METHODS AND RESULTS

An individual-based mathematical model was developed to capture the mechanisms of transmission, immunity and seasonality of typhoid. The historical data were then used to fit the model to the Santiago site. The model was then applied to understand unknowns within the historical site, and how they may impact projections of vaccination or environmental interventions both within the Santiago context and modern-day intervention settings.

CONCLUSIONS

Investigating historical sites where typhoid has been successfully controlled can provide valuable insight for modern intervention planning. By understanding the significance of unknowns that remain within a site where we understand the burden of chronic carriers, mechanisms of transmission and incidence, we are more prepared to quantify potential risks for control planning we may face in modern settings.

12:15 *SALMONELLA* TYPHI BACTERICIDAL ANTIBODY ACTIVITY IS A CORRELATE OF DISEASE SEVERITY, BUT NOT PROTECTION AGAINST TYPHOID FEVER

ANDREW POLLARD, *University of Oxford*

Helene B. Juel, Helena Thomaides-Brears, Elizabeth Jones, Claire Jones, Christoph Blohmke, Sonu Shrestha, Thomas C Darton, Andrew J. Pollard

Oxford Vaccine Group, Department of Paediatrics, University of Oxford and the NIHR Oxford Biomedical Research Centre, United Kingdom

BACKGROUND

Several new vaccines against typhoid fever are currently in development, but immune correlates of protection remain elusive. This study investigated the humoral immune responses to oral vaccination and infection with *Salmonella* Typhi as possible correlates of protection in a controlled human infection model.

METHODS

Ninety-nine participants received the live oral vaccines Ty21a or M01ZH09 or placebo, and one month later ingested 10^4 CFU *Salmonella* Typhi. Typhoid fever was diagnosed by positive blood culture and/or fever, and the vaccine efficacy was 35% for Ty21a and 14% for M01ZH09. Bactericidal activity of serum was assessed with an optimised serum bactericidal assay using antibody-depleted human complement. Antibodies in serum against LPS, H, HlyE, CdtB, PilL and Vi were quantified with ELISA, antibody-secreting cells against LPS, H and Vi with ELISpot, and cytokine plasma levels with Luminex.

RESULTS

Serum bactericidal antibody titre was significantly increased after vaccination with M01ZH09, but not Ty21a. Neither bactericidal titre nor any of the antibody levels nor number of antibody-secreting cells measured correlated with protection from typhoid fever. However, bactericidal titre correlated with decreased disease severity, including delay in onset of disease, reduced symptom severity, and reduced levels of circulating inflammatory cytokines. Bactericidal antibodies were found to be mainly anti-LPS and of various isotypes.

CONCLUSION

Although the humoral immune response likely plays an important role in protection from typhoid fever, a central role for antibodies directed against the antigens assessed in this study and previously considered important in immunity is not supported. The lack of a relationship between bactericidal antibodies and protection is an important observation with implications for vaccine development. Evaluation of new, particularly LPS-based, vaccines against typhoid and paratyphoid fever should not rely on immunogenicity data alone, but be supported by efficacy testing.

Lunch and Posters
12:30 – 13:30

THE RIGHT SHOT: VACCINE SESSION 1
13:30 – 15:00 ORAL ABSTRACT SESSION

MODERATORS

JOHN CLEMENS, *International Centre for Diarrhoeal Disease Research, Bangladesh*

Professor 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. His work on bacterial enteric pathogens has included studies on salmonellosis, shigellosis, cholera, and ETEC. A graduate of Stanford (BS) and Yale (MD) 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. 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. In 1999, he became the first Director-General of the International Vaccine Institute. In 2011 became the Founding Director of a new Center for Global Infectious Diseases at UCLA. Since 2013, Dr Clemens is the Executive Director of the International Centre for Diarrheal Disease Research. Dr. Clemens is the author of over 300 peer-reviewed publications and the recipient of the 2010 Sabin Gold Medal.

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 consisting of vaccines targeting Typhoid and Paratyphoid A fevers, Shigellosis and invasive non-typhoidal Salmonella. 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 activities through early clinical development and subsequent out licensing for commercialization and WHO prequalification. She is the principle investigator on grants from the Wellcome Trust (Paratyphoid A vaccines) and Bill & Melinda Gates Foundation (Shigellosis) to demonstrate proof of concept in humans. Prior to joining NVGH, 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).

PRESENTATIONS

13:30 CREATING A SUSTAINABLE VACCINE LANDSCAPE: OVERCOMING BARRIERS TO VACCINE DEVELOPMENT AND SPEED TO MARKET

VINITA VISHWANARAYAN,
Clinton Health Access Initiative

BACKGROUND

Currently, typhoid causes 21 million cases and ~150,000 deaths per year, of which 20-40% of cases and ~20% of deaths occur in children <5 years. Limited disease burden awareness, diagnostic challenges and absence of a suitable vaccine have constrained the ability to address this high-risk population. The vaccine supply landscape is promising yet uncertain, with one licensed Typhoid Conjugate Vaccine (TCV) candidate that can be administered to children <2 years. Previous Gavi VIS funding decision was postponed because no suitable TCV vaccine candidate was available. Suppliers face several barriers in bringing their vaccines to market, including clinical development risks, limited funding, demand uncertainty and downward pricing pressures. Suppliers need to make investment decisions based on limited information to estimate highest returns and probability of success. De-risked vaccine development and accelerated speed to market can be achieved by building certainty around the potential return and feasibility of bringing a vaccine candidate to market.

METHODS

- Developed balanced portfolio to manage supplier capabilities with market demands and de-risk product development
- Analyzed existing vaccine landscape and consulted with experts to identify the favorable product profile for target markets (LMICs, Gavi, PAHO, MICs, HICs)
- Identified variables and key macro and micro drivers of potential demand for TCV
- Developed sustainable pricing and commercial strategy to support healthy markets and deliver supplier value

RESULTS

Developed framework to help suppliers manage their product development risks and accelerate speed to market by matching supplier strengths with market needs.

CONCLUSIONS

A healthy supply of a TCV vaccine that meets underserved populations can be achieved by helping suppliers identify and mitigate key risks and uncertainties that could otherwise hinder vaccine development and speed to market.

13:45 COMPARISON OF STRATEGIES AND THRESHOLDS FOR THE VI CONJUGATE VACCINE AGAINST TYPHOID FEVER: A COST-EFFECTIVENESS MODELING STUDY

NATHAN LO, *Stanford University*

Nathan C. Lo[1,2], Ribhav Gupta[1], and Jason R. Andrews[1]

[1]Division of Infectious Diseases and Geographic Medicine, Stanford University School of Medicine, Stanford, CA, USA; [2]Division of Epidemiology, Stanford University School of Medicine, Stanford, CA, USA

BACKGROUND

Typhoid fever remains a major public health problem globally. While new Vi conjugate vaccines hold promise for averting disease, optimal programmatic delivery strategies remain unclear. We modeled typhoid transmission dynamics, outcomes, and vaccine program costs to identify epidemiologic conditions under which Vi conjugate vaccines would be cost-effective.

METHODS

We developed a dynamic, age-structured transmission and cost-effectiveness model that simulates vaccination strategies with a typhoid Vi conjugate vaccine. We simulated a 10-year vaccination program at 85% coverage through: (i) routine immunization of infants (ages <1) via the Expanded Program on Immunization (EPI); and (ii) one-time catch-up campaign in school-aged children (ages 5-15) plus EPI. We tested incidence rates from 25-500 cases per 100,000 people. We simulated a range of biologic and epidemiologic uncertainty to address limitations in understanding of typhoid transmission. Case fatality rate was estimated at 1%. Direct vaccination costs were estimated at US$2.50 per dose, including production and delivery. The incremental cost-effectiveness ratio (ICER) was calculated in 2016 US$ per disability-adjusted life year (DALY) averted, with a base case comparison of no vaccination. We defined strategies as highly cost-effective if the ICER was less than the per capita income for a World Bank-designated low-income country (US$1,035).

RESULTS

Vi-conjugate typhoid vaccine was highly cost-effective by routine immunization through EPI in settings with an incidence above 40 cases per 100,000, and for the combined strategy (EPI plus a one-time catch-up campaign) in settings with an incidence above 75 cases per 100,000. The incidence threshold was highly sensitive to the typhoid-related case fatality rate, which contributed the majority of disease burden.

CONCLUSION

Typhoid Vi conjugate vaccines would be highly cost-effective in low-income countries even in medium incidence settings (40 per 100,000). These results are highly sensitive to case fatality rates, underscoring the need for additional data in an era of rising antimicrobial resistance.

14:00 DEVELOPMENT OF NEW GENERATION MONOVALENT TYPHOID CONJUGATE VACCINE: Vi-CRM$_{197}$

AKSHAY GOEL, *Biological E. Limited, Hyderabad, Telangana, India*

BACKGROUND

Typhoid fever caused by *Salmonella enterica* serovar Typhi is a major cause of morbidity and mortality, particularly among children and adolescents in developing world. A safe, efficacious and affordable vaccine against enteric fever, especially for young children, would make a major impact on disease burden in developing countries. The Vi antigenic polysaccharide is considered to be a major antigen involved in typhoid pathogenesis, thus can be targeted by vaccine.

METHODS

Biological E, based in Hyderabad, India, has been involved in development and clinical manufacturing of a monovalent Typhoid Conjugate vaccine using the technology provided by GVGH (GSK Vaccines Institute for Global Health).

RESULTS

The vaccine development program has crossed several development stages and is ready for clinical evaluation (1Q17) in India. The presentation will provide an overview of the current status of the vaccine development program including process development, analytics, and preclinical immunogenicity.

14:15 LIVE ORAL TYPHOID VACCINE TY21A ELICITED CROSS-REACTIVE MULTIFUNCTIONAL IL-17A PRODUCING T CELL RESPONSES AGAINST *SALMONELLA ENTERICA* SEROVARS IN HUMANS

REZWANUL WAHID, *University of Maryland School of Medicine*

Rezwanul Wahid, Stephanie Fresnay, Myron M. Levine, Marcelo B. Sztein

Institute of Global Health and Center for Vaccine Development, University of Maryland School of Medicine, Baltimore, Maryland, USA

BACKGROUND

Interleukin-17A producing (IL-17A+) T cells are likely to play a critical role in protecting humans against intracellular organisms, including *Salmonella* spp., the causative agents of enteric fevers. Therefore, we investigated the induction of *Salmonella* (*S.* Typhi, *S.* Paratyphi A and B)-responsive IL-17A+ CD4+ and CD8+ T-cells in volunteers immunized with the oral typhoid vaccine Ty21a.

METHODS

Peripheral blood mononuclear cells (PBMC) from volunteers (n=8) were collected before and 42 and/or 84 days after immunization. Using multi-parametric flow-cytometry we studied vaccine-elicited *Salmonella*-specific memory/effector T cells that produced IL-17A+ alone (Single+) or simultaneously with other cytokines, e.g., interferon-γ, tumor necrosis factor-α, IL-2, macrophage inflammatory protein-1β and/or expression of cytotoxicity marker CD107a (multifunctional cells: MF).

RESULTS

PBMC obtained from 6 out of 8 (75%) immunized volunteers, showed a post-vaccination increase in IL-17A producing CD4+ T effector-memory (TEM:CD45RA-CD62L-) following stimulation with *S.* Typhi-infected targets. Similar cross-reactive responses against *S.* Paratyphi A- and B-infected targets were observed in 38% and 63% of volunteers respectively. Moreover, *S.* Typhi- and *S.* Paratyphi B- but not *S.* Paratyphi A-specific MF IL-17A+ CD4+ T_{EM} cells showed a strong trend to be higher than the corresponding Single+ cells. In contrast, *Salmonella*-infected target-responsive T_{EM} or RA positive T_{EM} (T_{EMRA}: CD45+CD62L-) CD8+ T cell subsets from 38% of the same volunteers showed similar increases of IL17A+ MF cells. Further characterization of *Salmonella*-specific IL17A+ CD4+ T_{EM} cells revealed that 65-70% of MF cells produced three or more cytokines or expressed CD107a.

CONCLUSIONS

Immunization with Ty21a predominantly induces CD4+ MF Th17 helper cells, which are likely an important component of vaccine-induced protective cell-mediated immune responses. These observations detailing the vaccine-elicited immune responses in humans will advance the development of more effective vaccines against *S.* Typhi as well as novel vaccines against *S.* Paratyphi A and B infection.

14:30 EXPLORING *S.* TYPHI-SPECIFIC HLA-E-RESTRICTED IMMUNE RESPONSES IN PEDIATRIC AND ADULT TY21A RECIPIENTS USING MASS CYTOMETRY

MARK RUDOLPH, *University of Maryland School of Medicine*

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

Institute of Global Health and Center for Vaccine Development, University of Maryland School of Medicine, Baltimore, Maryland, USA

BACKGROUND

Salmonella enterica serovar Typhi (*S.* Typhi) is associated with significant morbidity among school-aged children. Ty21a, the licensed oral live-attenuated vaccine against *S.* Typhi, induces cell-mediated immune (CMI) responses in approximately two-thirds of adult recipients. However, despite the burden of typhoid disease in this population, there has been little exploration into pediatric responses to Ty21a vaccination. HLA-E is a non-polymorphic, non-classical major histocompatibility complex (MHC) class 1b molecule that has been shown to present bacterial chaperonins, and the related mitochondrial heat-shock proteins, to cytotoxic T lymphocytes. We have previously identified HLA-E restricted, *S.* Typhi-specific, CMI responses in adult volunteers.

METHODS

Peripheral blood mononuclear cells (PBMC) were collected from children between the ages of 6 and 17, pre- and 14-42 days post-vaccination with Ty21a. Following stimulation of PBMC isolated from older children (16-17) with a *S.* Typhi infected, HLA-E-restricted cell line we utilized the novel technology and instrumentation of mass cytometry, to simultaneously measure 36 parameters on a per-cell basis.

RESULTS

We identified similar percentages of T cell subsets (CD3+, CD4+, and CD8+) and memory populations (T naïve, T central memory, T effector memory, and T effector memory expressing CD45RA) both at baseline and post-vaccination in older children and adults. We also measured post-vaccination *S.* Typhi-specific, HLA-E restricted responses over baseline. We found similar percentages of CMI "responders" in both age groups.

CONCLUSIONS

These data, in conjunction with ongoing autologous *S.* Typhi antigen presentation experiments, aim to improve age-dependent vaccine strategies, and inform critical immune measurements for age de-escalation studies to evaluate future generations of typhoid vaccines.

14:45 WHOLE GENOME SEQUENCE ANALYSIS OF *SALMONELLA* TYPHI ISOLATED IN THAILAND BEFORE AND AFTER THE INTRODUCTION OF A NATIONAL IMMUNISATION PROGRAM

ZOE DYSON, *University of Melbourne*

Zoe A. Dyson[1,2], Duy Pham Thanh[3], Ladaporn Bodhidatta[4], Carl Jeffries Mason[4], Maia A. Rabaa[3,5], Phat Voong Vinh[3], Tuyen Ha Thanh[3], Guy E. Thwaites[3,5], Stephen Baker[3,5,6] and Kathryn E. Holt[1,2]

[1]Centre for Systems Genomics, University of Melbourne, Parkville, Victoria 3052, Australia; [2]Department of Biochemistry and Molecular Biology, Bio21 Molecular Science and Biotechnology Institute, University of Melbourne, Parkville, Victoria 3010, Australia; [3]The Hospital for Tropical Diseases, Wellcome Trust Major Overseas Programme, Oxford University Clinical Research Unit, Ho Chi Minh City, Vietnam; [4]Department of Enteric Diseases, Armed Forces Research Institute of Medical Sciences, Bangkok, Thailand; [5]Centre for Tropical Medicine and Global Health, Oxford University, Oxford, United Kingdom; [6]The London School of Hygiene and Tropical Medicine, London, United Kingdom

BACKGROUND

Vaccines against the typhoid agent *Salmonella* Typhi are commonly used by travellers, but less so by residents of endemic areas. A sustained outbreak of typhoid fever occurred in Thailand in the 1970s, peaking in 1975-1976. In response to this the government of Thailand initiated an immunisation program using a locally produced heat/phenol-inactivated vaccine in 1977.

METHODS

We conducted whole genome sequencing as well as comparative genomic analysis to examine the population structure of 44 *S.* Typhi collected from Thai hospitals both before and after the immunisation program over 19 years (1973-1992) by inferring maximum likelihood phylogenetic trees using chromosomal SNPs.

RESULTS

The 44 *S.* Typhi examined were highly diverse, including 10 distinct genotypes, and the majority of *S.* Typhi genotypes observed prior to the immunisation program were not observed following it. Comparisons with a global collection of ~2,000 *S.* Typhi revealed that post-vaccine era isolates were genetically more closely related to *S.* Typhi isolated from neighbouring countries than to earlier Thai isolates, providing no evidence for the local persistence of endemic *S.* Typhi following the national immunisation program.

CONCLUSIONS

The vaccination program was highly effective in eliminating endemic genotypes of *S.* Typhi present in Thailand before the introduction of the vaccine. Later cases of typhoid following the introduction of the vaccine appear to have been caused by the occasional importation of common genotypes from neighbouring Vietnam, Laos and Cambodia. These data provide support for the proposal that large-scale typhoid immunisation programs in endemic areas could result in lasting local disease elimination, however, larger prospective studies are needed to test this directly.

Coffee Break and Posters
15:00 – 15:30

SPOTLIGHT ON AFRICA AND ASIA: ENTERIC FEVER SURVEILLANCE

15:30 – 17:45 SYMPOSIUM SESSION

Salmonella infections are a major cause of global morbidity and mortality. The best described invasive *Salmonella* serovars are Typhi (*S.* Typhi), which causes typhoid fever and Paratyphi A, B, and C, which cause paratyphoid fever. Other *Salmonella* serovars, known as non-typhoidal *Salmonella* (NTS), generally cause self-limiting diarrhea, but can cause systemic infections in susceptible individuals, referred to as invasive NTS (iNTS). Globally, typhoid and iNTS disease are estimated to cause 21.7 and 3.4 million illnesses, and 217,000 and 681,000 deaths annually, respectively.

There are several data gaps in sub-Saharan Africa and Asia and the International Vaccine Institute (IVI) and Sabin Vaccine Institute have subsequently, with support of the Bill & Melinda Gates Foundation, instituted the Severe Typhoid in Africa (SETA) program and the Surveillance for Enteric Fever in Asia Project (SEAP) to examine the burden and severity of invasive *Salmonella* infections. The two projects assess the immune responses to natural typhoid, paratyphoid and iNTS infection over a 1-year follow-up period, estimate the prevalence of *S.* Typhi, *S.* Paratyphi and NTS carriers among immediate household members of positive *Salmonella* cases. Furthermore, SETA and SEAP assess the public and private expenditures for treatment and productivity losses associated with disease due to typhoid, paratyphoid and iNTS infections. This symposium will present the first results from SETA and SEAP.

ORGANIZERS

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.

DENISE GARRETT, *Coalition against Typhoid, Sabin Vaccine Institute*

Denise Garrett, MD, MSc, 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.

CO-CHAIRS

ROBERT BREIMAN, *Emory University*

Dr. Breiman is Director of the Emory Global Health Institute (EGHI) where he oversees the strategy of engaging a wide array of disciplines and interests at Emory with the goal of integrated, innovative, and impactful contributions towards addressing challenging problems affecting health. Dr. Breiman is the PI for projects on rotavirus, typhoid fever, and pneumococcal disease. He is also the Co-PI for the Child Health and Mortality Prevention Surveillance (CHAMPS) Network which is aimed at characterizing and preventing childhood mortality in Sub-Saharan Africa and South Asia. Before joining Emory, Dr. Breiman was at the CDC for 26 years, most recently based at CDC-Kenya. Prior to Kenya, Dr. Breiman was Director of the Health Systems and Infectious Diseases Division and Head, Programme on Infectious Diseases and Vaccine Sciences at the International Center for Diarrheal Disease Research, Bangladesh (ICDDR,B). He was previously Director of the National Vaccine Program Office, and Chief of the Epidemiology Section of the Respiratory Diseases Branch. He is Board Certified in Internal Medicine and Infectious Diseases, a Fellow of the Infectious Diseases Society of America, and a member of American Society of Epidemiology, American Society of Tropical Medicine and Hygiene (Chair of Pneumonia and TB scientific committee), and American Society of Microbiology.

MEGAN CAREY, *Bill & Melinda 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 had training in 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. 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.

PRESENTATIONS

15:30 EPIDEMIOLOGY AND DISEASE BURDEN OF TYPHOID FEVER AND INTS DISEASE IN SUB-SAHARAN AFRICA

FLORIAN MARKS, *International Vaccine Institute*

See bio above

15:45 THE SEVERE TYPHOID FEVER SURVEILLANCE IN AFRICA (SETA) PROGRAM: AN OVERVIEW

JUSTIN IM, *International Vaccine Institute*

Justin has a background in human physiology and immunology and earned an MSc in Epidemiology at the London School of Hygiene and Tropical Medicine. Having started his career at the International Vaccine Institute in 2011, Justin has been involved in typhoid fever surveillance in the sub-Saharan African region as part of a series of multi-country studies. Through these programs, a network of sentinel sites in over 10 African countries where blood-culture surveillance to detect invasive bacterial pathogens causing febrile illness has been established. Current surveillance studies serve as a platform for characterizing the severity of typhoid fever, describing antimicrobial susceptibility patterns of bacterial strains, investigating immunological markers of acute cases and chronic carriers, and measuring the economic impact of disease. Additionally, Justin has worked in disease surveillance for Japanese Encephalitis in the Philippines and cholera disease surveillance following vaccination in Malawi.

16:00 SETA: THE FIRST DATA FROM THE SIX AFRICAN SITES

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 providing support for the coordination of a standardized, multi-country disease burden epidemiology study on severe typhoid in Africa. These studies address a wide scope of research questions including antimicrobial resistant characteristics of bacterial strains, natural history of infection with an investigation on host immune response and chronic carriers, and socio-economic burden of disease. Se Eun is also working on the disease surveillance for cholera in Mozambique, and is currently pursuing her DPhil in Clinical Medicine with Oxford University Clinical Research Unit, focusing on epidemiology including phylogenetic surveillance and infectious diseases.

16:15 AFRICAN RISK FACTOR PREDICTION MODEL AND IMPLICATIONS FOR VACCINATION STRATEGIES

JONG-HOON KIM, *International Vaccine Institute*

Jong-Hoon Kim, PhD, is a theoretical epidemiologist who specializes in modeling infection transmission. Dr. Kim completed a PhD in epidemiology from The University of Michigan, Ann Arbor, in 2010. His doctoral study was on the impact of sexual network structure on the transmission of Human Immunodeficiency Virus using mathematical and computer models. From 2010 to 2011, he investigated the dynamics of transmission and evolution of the poliovirus at Kid Risk, Inc., formerly Kids Risk project at Harvard School of Public Health, Harvard University, again using the modeling technique. Since then, he has studied various infectious diseases including cholera, typhoid, hepatitis E, and Middle East Respiratory Syndrome at the International Vaccine Institute in Seoul, Korea, using various statistical and mathematical modeling techniques.

TUESDAY

16:30 AT A GLANCE: THE SURVEILLANCE FOR ENTERIC FEVER IN ASIA PROJECT (SEAP)

DENISE GARRETT, *Coalition against Typhoid, Sabin Vaccine Institute*

See bio above

16:45 APPROACHES TO COMMUNITY SURVEYS FOR TYPHOID BURDEN ESTIMATION: EXPERIENCE FROM SEAP

ALEXANDER YU, *Stanford University*

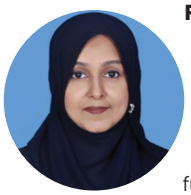
Alexander Yu is currently a fellow in Infectious Diseases at Stanford University and is interested in the interface between infectious diseases and the environment, with a focus on developing practical interventions to problems facing populations in low-income settings. He completed his residency training at Massachusetts General Hospital in Internal Medicine and earned his MD from Texas Tech University and MPH at the Harvard School of Public Health.

17:00 *SALMONELLA* TYPHI AND PARATYPHI IN BANGLADESH AND THEIR ANTIMICROBIAL RESISTANCE

SAMIR SAHA, *Child Health Research Foundation*

Dr. Samir 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. Dr. Saha is also an associate of the Department of International Health at Johns Hopkins University and adjunct scientist at International Centre for Diarrhoeal and Research, Bangladesh (ICDDR,B). Dr. Saha is currently a member of the National Committee for Immunization Policies of the Government of Bangladesh. He is also a member of WHO Technical Working Group for Vaccine Preventable Diseases surveillance network and Pneumococcus Awareness Council of Experts (PACE). Dr. Saha has published more than 100 papers in peer-reviewed journals, mostly relating to childhood pneumonia and meningitis. He is now conducting several multi-site and multi-country research projects on infectious disease supported by different international funding organizations. Dr. Saha earned his MSc. from The University of Dhaka in Bangladesh in 1983, and his PhD from the Institute of Medical Sciences of Banaras Hindu University, Varanasi, India, in 1989.

17:15 LOOKING BACK WHILE MOVING FORWARD WITH ENTERIC FEVER SURVEILLANCE IN PAKISTAN



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.

17:30 A RETROSPECTIVE REVIEW OF EXISTING HOSPITAL-BASED DATA ON ENTERIC FEVER IN INDIA

DIPIKA SUR, *Translational Health Science and Technology Institute*

Dipika Sur is a consultant for the Translational Health Science and Technology Institute in India with a research interest in enteric diseases. Her background encompasses cholera and typhoid vaccine trials, micronutrient supplementation, probiotics, anthelminthic administration, disease burden studies and others, working with institutes and universities around the world. She has received the Fogarty fellowship and is the author of 129 publications. Additionally, she is a member of a number of committees for the World Health Organization, including the SAGE working group on cholera and typhoid vaccines.

Break
17:45 – 18:00

Reception
18:00 – 19:30

FEATURED REMARKS FROM HONORABLE **DR. JANE ACENG,** MINISTER OF HEALTH, UGANDA

Dr. Jane Ruth Aceng was appointed as the Minister of Health Uganda in June 2016. She holds a Bachelor's degree in Medicine (MBChB), MMED (Paediatrics), Masters in Public Health and a Diploma in Public Administration and Management (ongoing). She is a Paediatrics expert and is currently at the level of Senior Consultant Paediatrics. Dr. Aceng has vast experience both as a manager and a practicing medical personnel, which she accumulated while serving in various capacities as: Medical Officer, Senior Medical Officer, Medical Officer Special Grade, Medical Superintendent, Consultant Paediatrician, Senior Consultant Paediatrician, Hospital Director and the Director General, Health Services, Ministry of Health Uganda.

» WEDNESDAY, APRIL 5

STAYING ONE STEP AHEAD: PREVENTION AND CONTROL

8:30 – 10:00 PLENARY SESSION

MODERATORS

JAN JACOBS, *Institute of Tropical Medicine Antwerp*

Jan Jacobs, MD, worked at the University Hospital of Maastricht (diagnostic microbiology and infection control) from 1990 to 2005. Since 2006, I am appointed at the Institute of Tropical Medicine (ITM). I am involved in patient care (diagnostic laboratory of the travel clinic of ITM), teaching (Hospital Infection Prevention and Control and Laboratory Practicals) and in oversea capacity building projects about microbiological surveillance of invasive diseases and antibiotic resistance/infection control. I am (co)-promoter of ITM projects in the Democratic Republic of the Congo, Burkina Faso, Benin and Cambodia. My main research focuses on tropical bacteriology, with projects addressing invasive salmonellosis, clinical bacteriology and antibiotic resistance. In addition, I am performing operational research in quality of *in-vitro* diagnostics in low resource settings and act as technical advisor for the World Health Organization's Prequalification of Diagnostics Program and the Expert Review Panel for Diagnostics. My unit has extensive expertise in implementing clinical bacteriology, microbiological surveillance projects (bloodstream infections in sub-Saharan Africa) and biobanking.

BUDDHA BASNYAT, *Oxford University Clinical Research Unit-Nepal*

Buddha Basnyat is a medical doctor practicing medicine in Kathmandu, Nepal. His research interests are infectious disease and high altitude medicine both of which are in ample supply in Nepal. He has published widely in both these fields in well-known medical journals and written chapters with co- authors in the latest standard medical textbooks (for example, Harrison's textbook of internal medicine Oxford textbook of medicine and Manson's Tropical Diseases). He has over 200 publications in peer-reviewed journals. He is the Director for the Oxford University Clinical Research Unit\Nepal and is also the Medical Director for the Nepal International Clinic (a travel medicine clinic) and The Himalayan Rescue Association (dealing with high altitude medical problems). In all these institutions one of his primary interest is to encourage young people to do research. He also works at Patan Hospital as a consultant in the internal medicine department and is a Professor of Medicine and Physiology at the Patan Academy of Health Sciences.

PRESENTATIONS

8:30 DEVELOPMENT AND CHALLENGES IN DEVELOPING A SENSITIVE DIAGNOSTIC TEST FOR TYPHOID FEVER

FIRDAUSI QADRI, *International Centre for Diarrhoeal Disease and Research, Bangladesh*

Dr. Firdausi Qadri is the Senior Director, Infectious Diseases Division, and leads the Mucosal Immunology and Vaccinology Laboratory at the International Centre for Diarrhoeal Disease Research, Bangladesh (icddr,b). She and her team have made significant contributions to the field of enteric diseases and to understanding mucosal immune responses to natural infection and vaccination with oral vaccines. She has made extensive efforts in developing strategies for immunization against infectious diseases that are main bacterial causes of morbidity and mortality in Bangladesh. She has contributed to the development of diagnostics suitable for detection of *V. cholerae*, ETEC, *S.* Typhi/*S.* Paratyphi and *H. pylori* using high throughput immunological and molecular biological techniques. The work has led to many innovative field studies in endemic urban settings in Bangladesh on oral cholera vaccine and on oral ETEC vaccine, with plans to test typhoid vaccines in these settings. The diagnostic tests are being evaluated in sentinel site surveillance for enteric diseases to gauge the real burden of disease to plan a disease control program. The ultimate aim is to pave the way for introducing much needed vaccines to prevent major bacterial causes of enteric diseases and decrease the disease burden.

8:45 VACCINE AND NON-VACCINE MEASURES FOR PREVENTION AND CONTROL OF TYPHOID FEVER

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 at Harlem Hospital in 1987, and received a Masters in Public Health from Columbia University in 1989. That year he joined 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 150 scientific publications on topics including typhoid and paratyphoid fever, cholera, dysentery, and new technologies to make safe drinking water, safe sanitation and better hygiene more accessible, affordable, and sustainable in developing countries.

9:00 GAPS IN KNOWLEDGE IN THERAPEUTICS AND TREATMENT

CHRIS PARRY, *Liverpool School of Tropical Medicine*

Chris Parry is a Clinical Microbiologist at the Liverpool Clinical Laboratories, Aintree University Hospital and the Walton Centre, Liverpool, UK, an 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 qualified in Natural Sciences and Medicine from Cambridge University and trained in in Internal

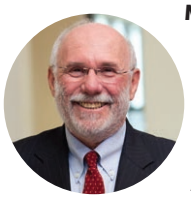
Medicine, Infectious Diseases, Clinical Microbiology and Tropical Medicine in the UK and Malawi. His PhD from the Open University, UK addressed the antibiotic treatment of typhoid fever in Vietnam. In the last thirty year's he has worked in the Oxford University South-East Asia Tropical Network and at Liverpool and Nagasaki Universities on research studies in Vietnam, Cambodia, Bangladesh, the Philippines, Nepal, and Fiji. His current research interests concern the epidemiology, diagnosis and management of severe bacterial infections, including typhoid fever.

9:15 THE SANIPATH APPROACH TO FECAL EXPOSURE ASSESSMENT AND APPLICATION TO TYPHOID TRANSMISSION

CHRISTINE 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. Her field research in Bangladesh, Bolivia, Cambodia, China, El Salvador, 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 served on the US Environmental Protection Agency Science Advisory Board and chaired a National Research Council Committee to advise USAID on Grand Challenges in International Development. She has been a consultant for the World Health Organization and the Bill and Melinda Gates Foundation. She has received the World Bank Development Marketplace Infrastructure award and the NSF Food Safety Leadership award. Dr. Moe has a BA in Biology from Swarthmore College and MS and PhD in Environmental Sciences from the University of North Carolina at Chapel Hill.

9:30 A BROAD-SPECTRUM VACCINE TO PREVENT INVASIVE *SALMONELLA* DISEASE IN SUB-SAHARAN AFRICA



MYRON M. LEVINE, *University of Maryland School of Medicine*

Myron M. Levine, MD, DTPH, 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 629 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 (to be awarded May 18, 2017), and is a member of the National Academy of Medicine, USA.

9:45 QUESTIONS AND DISCUSSION

Coffee Break and Posters
10:00 – 10:30

CRUSH THE RESISTANCE: ANTIMICROBIAL RESISTANCE SESSION
10:30 – 12:30 ORAL ABSTRACT SESSION

MODERATORS

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. 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. Before joining Grand Challenges Canada, Dr. Simiyu provided marketing research and business development expertise to the Kenyan government and worked as a consultant for the International Organization for Migration (IOM) in Washington, DC. 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.

GORDON DOUGAN, *Wellcome Trust Sanger Institute*

Professor Dougan is a group leader at The Wellcome Trust Sanger Institute (WTSI) and a Professor in the Department of Medicine at Cambridge University. He also holds adjunct professorships at the Universities of Monash and Melbourne. His personal research team studies enteric pathogens with a strong emphasis on pathogenic mechanisms, genomics and immunology. 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 PhD 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 and is an expert in vaccinology.

PRESENTATIONS

10:30 ANTIBIOGRAM PATTERN, MECHANISM OF FLUOROQUINOLONE RESISTANCE AND SEASONALITY OF *SALMONELLA* SEROTYPES IN A NORTH INDIAN TERTIARY CARE HOSPITAL

RAJNI GAIND, *Vardhman Mahavir Medical College & Safdarjung Hospital*

Geetarani Purohit, Ruchi Gupta, Rajni Gaind

Vardhman Mahavir Medical College & Safdarjung Hospital

BACKGROUND

Enteric fever is a global public health problem, especially in developing countries. Monitoring of antimicrobial resistance is important, as in endemic areas most patients are treated empirically before microbiological results are available. This study examined the antibiogram pattern, mechanism of fluoroquinolone resistance and seasonal distribution of *Salmonella* Typhi isolated over a 10-year period (2004-2013) from enteric fever cases presenting at a tertiary care centre in New Delhi, India.

METHODS

Blood cultures received in the Bacteriology Laboratory from patients with suspected enteric fever were processed by standard procedures and the *Salmonella* spp. isolates were identified with specific antisera and standard biochemical tests. Antimicrobial susceptibility testing was carried out by a standard disc diffusion method and the minimum inhibitory concentration (MIC) of ciprofloxacin, nalidixic acid, ceftriazone and Azithromycin and was determined by E test. DHPLC was performed for detection of mutations in QRDR region of *gyr*A, *gyr*B, *par*C and *par*e. Role of permeability changes and plasmid mediated quinolone resistance was also investigated.

RESULTS

Salmonella Typhi was the predominant serotype among 664 *Salmonella* spp. isolated during the study period followed by *S.* Paratyphi A. The maximum number of enteric fever cases occurred during April–June (dry season) followed by July–September (monsoon season). There was a decrease in multidrug-resistant (MDR) *S.* Typhi from 27.9% in 2004 to 14% in 2013. There was also a dramatic increase in nalidixic acid-resistant (NAR) isolates and these isolates showed decreased ciprofloxacin susceptibility (DCS). High level fluoroquinolone resistance (CIP-R) increased from 3% to 18% from 2004 to 2013 respectively. Three diverse Fluoroquinlone resistance phenotypes were observed i.e. NAR –DCS, NAS –DCS and CIP-R. Mutations in *gyr*A/*gyr*B and/or *par*C were associated with distinct resistance phenotype. All isolates were susceptible to third-generation cephalosporins. MIC 50 and MIC 90 was 6 and 12 µg/ml and 0.064 and 0.125 µg/ml for azithromycin and ceftriazone respectively. Azithromycin resistance was observed although rare.

CONCLUSIONS

Knowledge of the seasonal distribution and antibiotic resistance pattern of *S.* Typhi in endemic regions is helpful in the delineation of appropriate control measures required for prevention of enteric fever.

10:45 THE IMPACT OF ANTIMICROBIAL TREATMENT ON PATHOGEN BEHAVIOR AT THE SUBPOPULATION LEVEL DURING INVASIVE *SALMONELLA* INFECTIONS

PIETRO MASTROENI, *University of Cambridge*

Omar Rossi, Richard Dybowski, Oliver Restif, Duncan Maskell, Andrew Grant, Pietro Mastroeni

University of Cambridge, United Kingdom

BACKGROUND

Central to the understanding of antimicrobial treatment is the need to capture the fundamental impact of antibiotics on disease dynamics *in vivo.* Antimicrobial therapy does not always result in rapid and complete resolution of *Salmonella* infections, which can persist chronically and relapse upon cessation of the treatment, especially in immune-deficient individuals. The aim of our work was to study the reciprocal interactions between antimicrobial pressure, pathogen growth rates, between-organ spread, and heterogeneity in the bacterial population structure during invasive *Salmonella* infections.

METHODS

We used different sets of Isogenic Tagged Strains (ITS) of serovar Typhimurium in separate infections, each set having a different growth rate and ability to spread from cell to cell. We monitored the within- and between-organ fluctuations of the ITS subpopulation structure in the spleen, liver, blood and mesenteric lymph nodes (MLN) of mice before, during and after the cessation of treatment with ampicillin or ciprofloxacin. This was done using a sequencing-based approach combined with a novel method for Bayesian bottleneck analysis.

RESULTS

Our work revealed correlations between bacterial growth rates *in vivo* and treatment efficacy in all organs except for MLN where bacterial loads remained largely unaffected by the administration of either drug. Antibiotic pressure did not change the heterogeneity of the ITS population structure during treatment, thus not substantially selecting for some subpopulations over others. Chronic and relapsing infections arose evenly from the persistence of multiple subpopulations of *Salmonella*.

CONCLUSIONS

The presence of persisters causing relapse or chronicity of the infection is not due to stochastic "jackpot" events and occurs in bacterial strains with different growth and spread rates. The ITS population structure of MLN was different from that of the spleen and liver. Thus, MLN represent a compartmentalized site, not affected by bacteraemia, less susceptible to antibiotic treatment, but still prone to post-treatment relapse.

11:00 CHANGING TRENDS IN ANTIBIOGRAMS OF *SALMONELLA ENTERICA* IN PEDIATRIC POPULATION — A HOSPITAL BASED STUDY

BHASKAR SHENOY, *Manipal Hospital, Bangalore, India*

Shenoy B.[1],Prasad K.[2], Selvi A.[2], Joshi S.[3], Adhikary R.[3], Archana M.[2]

[1]Division of Pediatric infectious diseases, Department of Pediatrics, Manipal Hospital, Bangalore, India; [2]Department of Pediatrics, Manipal Hospital, Bangalore, India; [3]Department of Microbiology, Manipal Hospital, Bangalore, India

BACKGROUND

Enteric fever is a major public health problem in tropical countries including India. There have been reports of changing antibiogram and age wise incidence. The objectives of this study were to analyze the antibiotic sensitivity pattern of culture positive enteric

fever and to evaluate the prevalence, changing trends in antibiotic resistance and demographic profile.

METHODS

It is a retrospective study of case records of 826 children in the age group of 0-18 years diagnosed with culture proven enteric fever at Manipal hospital, Bangalore, India, between November 2008 and June 2016. Inclusion criteria — Presence of clinical signs & symptoms compatible with enteric fever and isolation of *S.* Typhi or *S.* Paratyphi from blood. Blood culture was done by BacT/Alert 3D system and serotypes were identified by biochemical tests or Vitek method. Susceptibility to antimicrobial drugs was tested by the disc diffusion according to Kirby Bauer method. Exclusion criteria — Diagnosis based only on clinical and serologic grounds.

RESULTS

There were 630 *S. enterica* serovar Typhi (76.2%) and 196 serovar Paratyphi A strains (23.7%) among the 826 enteric fever children. 9% of the cases were below two years of age. Typhoid was predominantly seen in males (57.02%) and 2-10 yrs of age (52.4%). All strains were susceptible to third generation cephalosporins. Susceptibility to ampicillin (98.66%), chloramphenicol (98.1%) and cotrimoxazole (97.7%) is resurging. Three cases (0.36%) of azithromycin resistance was documented. Resistance to nalidixic acid (91.2%) has been increasing.

CONCLUSIONS

S. Typhi continues to remain susceptible to third generation cephalosporins. Resurgence of susceptibility to first generation antibiotics is noteworthy, thus local antibiograms improve patient care, and reduce the treatment cost in developing countries, hence improving the compliance. Also ceftriaxone and azithromycin can be reserved for the future use. In view of a high prevalence of typhoid and paratyphoid fever in children, it may be advisable to strengthen vaccination at an early age and develop a bivalent vaccine to cover paratyphoid also.

11:15 HEALTH OUTCOMES FROM MULTIDRUG-RESISTANT *SALMONELLA* IN HIGH-INCOME COUNTRIES: A SYSTEMATIC REVIEW

ANDREA PARISI, *The Australian National University*

Andrea Parisi[1], Samantha Vilkins[1], John. A. Crump[2], Benjamin P. Howden[3], Darren Gray1, Kathryn Glass[1], Martyn Kirk[1]

[1]Research School of Population Health, Australian National University, Canberra, Australia; [2]Centre for International Health, University of Otago, Dunedin, New Zealand; [3]Department of Microbiology and Immunology, University of Melbourne, Victoria, Australia

BACKGROUND

Salmonella is a leading cause of foodborne enterocolitis worldwide. Non-typhoidal Salmonella (NTS) infections that are multi-drug resistant (MDR) (non-susceptible to ≥1 agent in ≥3 antimicrobial categories) may result in more severe outcomes, although these effects have not been systematically examined. We conducted a systematic review to examine impacts of MDR NTS on health in high-income settings.

METHODS

We systematically reviewed the literature from scientific databases, including PubMed, Scopus and grey literature sources, using PRISMA guidelines. We searched for data from case-control studies, outbreaks, reports and theses, imposing no language restriction. We included only publications from January 1990 to September 2016 from high income countries as classified by World Bank. We extracted data from papers on duration of illness, hospitalisation rates, morbidity and mortality for MDR and non-MDR NTS strains.

RESULTS

After removing duplicates, the initial search revealed 4261 articles. After further screening, we identified 312 relevant titles and of these included 16 articles in the final review. NTS serotypes differed among the reported countries (Denmark, USA, Canada, Taiwan, Hong Kong), but serotype Typhimurium and Enteritidis were among the most often reported as MDR pathogens. *Salmonella* infections that were MDR were associated with higher mortality and morbidity (higher risk for an invasive disease), excess hospitalizations and longer hospitalization periods.

CONCLUSIONS

MDR NTS infections are a serious public health concern. With the emergence of MDR Salmonella strains in the high-income countries, it is crucial to restrict the use of antimicrobials both in animals and humans, and intervene to prevent foodborne infections.

11:30 MULTIDRUG RESISTANT NON-TYPHOIDAL *SALMONELLA* HOTSPOTS AS TARGETS FOR VACCINE USE IN MANAGEMENT

SAM KARIUKI, *Kenya Medical Research Institute*

Samuel Kariuki[1], Robert S. Onsare[1], Mohamed Ali[2], John Clemens[3], Gordon Dougan[4]

[1]Centre for Microbiology Research, KEMRI; [2]John Hopkins University, USA; [3]International Centre for Diarrheal Diseases Research, Dhaka, Bangladesh; [4]Wellcome Trust Sanger Institute, Cambridge, United Kingdom

BACKGROUND

In Kenya, invasive non-typhoidal *Salmonella* (iNTS) disease causes severe bacteremic illness among adults with HIV and among children especially under five years of age co-infected with HIV, malaria, sickle cell disease, or with severe malnutrition. Incidence in children ranging from 166-568 cases per 100,000 persons per year. iNTS disease has mainly been associated with two serovars; *Salmonella* enterica serotype Typhimurium and serotype Enteritidis, together constituting close to 87% of all serotypes isolated from cases. While it is certain that immunosuppression is a major risk factor for iNTS disease in both adults and young children, we do not know how these serotypes are distributed in endemic areas of disease.

METHODS

In a three year period 2013-2015, we carried out surveillance for iNTS in a DSS site in an informal settlement 20 km East of Nairobi, with a population of 150,000. We used GPS to map hotspots of disease in children < 5y of age reporting to three outpatient health facilities in the community. Antimicrobial susceptibility profiles of isolates were determined for commonly available antimicrobials and related to usage patterns in the community. Patients were followed to their homes to investigate environmental and socioeconomic risk factors of disease.

RESULTS

A total of 365 iNTS isolates were mapped onto GPS points depicting hotspots of disease occurrence close to one health centre and around major water points. The prevalence of multidrug resistance in iNTS strains was 75% resistance to three or more commonly used antimicrobials. We observed an emergence of ceftriaxone resistant strains (encoded by CTX-M-15 genes on a large 300kb plasmids) also showing reduced susceptibility to flouroquinolones.

CONCLUSION

As most cases present with non-specific febrile illness with no laboratory confirmed aetiology, empiric treatment of iNTS disease is a major challenge in Kenya. Treatment with antimicrobials remains the mainstay of management for iNTS disease and with reduced choices of antimicrobials available, it is prudent that alternative methods, including vaccination, be considered for hotspots identified in the endemic areas.

11:45 WHOLE GENOME SEQUENCING FOR ROUTINE IDENTIFICATION, DRUG RESISTANCE, DETECTION AND EPIDEMIOLOGY OF *SALMONELLA*: A REVOLUTION IN PUBLIC HEALTH MICROBIOLOGY

SATHEESH NAIR, *Public Health England*

BACKGROUND

Salmonella is a major human pathogen and a global public health burden. There is also genuine concern from the threat of emerging multidrug resistant (MDR) *Salmonella.* As part of the public health action to control *Salmonella,* all isolates (c.10,000 a year) from human infections in England and Wales are sent to the *Salmonella* Reference Service (SRS), Gatrointestinal Bacteria Reference Unit (GBRU) at Public Health England (PHE). GBRU has an on-going programme of evaluating emerging whole genome sequencing (WGS) technologies to assess their potential value in improving routine microbiology.

METHODS

Sequence data derived from WGS by Illumina HiSeq for c.7000 *Salmonella i*solates between 2014 -2015 was used to generate MLST for serovar identification, detection of known acquired resistance genes and single nucleotide polymorphisms (SNP) analysis for typing.

RESULTS

1. ***Salmonella* identification:** A WGS approach using a bioinformatics pipeline has been developed to extract MLST directly from the sequence data such that a serovar can be inferred. Here we provide an insight into the genetic population structure of all *Salmonella* serovars in England and Wales during a 12 month period. *S.* Enteritidis and *S.*Typhimurium were the predominant serovars, with a significant number of S. Typhi and S. Paratyphi A isolates.

2. **Detection of antimicrobial resistance (AMR):** The use of an in-house AMR pipeline for drug resistance detection and characterisation of resistance mechanisms/regions that were previously challenging to define. WGS was used to determine the prevalence of azithromycin in a U.K population of non-typhoidal *Salmonella* (NTS) and the detection of a novel Salmonella Azithromycin Resistance Genomic Island in *Salmonella* Blockley. A cause of concern as azithromycin is being used as the drug of choice for enteric fever and invasive NTS treatment in many parts of the world.

3. **Typing:** High resolution typing based on SNP typing for detection and surveillance of outbreaks (e.g *S.* Enteritidis) as well as the detection of emerging pathogens (e.g *S.*Typhimurium ST313).

CONCLUSIONS

WGS is revolutionising and transforming 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. As of 1 April 2015 WGS has been adopted for routine use in SRS.

12:00 EMERGENCE OF A NEW *SALMONELLA* TYPHIMURIUM ST313 LINEAGE IN D.R. CONGO WITH INCREASED ANTIBIOTIC RESISTANCE AND INDICATIONS FOR FURTHER HOST ADAPTATION

SANDRA VAN PUYVELDE, *Institute of Tropical Medicine Antwerp*

Sandra Van Puyvelde[1], Eva Heinz[2], Tessa de Block[1], Barbara Barbé[1], Laura Kuijpers[1,4], Derek Pickard[2], Simon Clare[2], Octavie Lunguya[3], Marie-France Phoba[3], Lili Kalonji Mbuyi[3], Jan Jacobs[1,4], Gordon Dougan[2], Stijn Deborggraeve[1]

[1]Institute of Tropical Medicine Antwerp; [2]The Wellcome Trust Sanger Institute, Hinxton, Cambridge, United Kingdom; [3]National Institute for Biomedical Research, Kinshasa, Democratic Republic of the Congo; [4]Department of Microbiology and Immunology, KU Leuven, Belgium

BACKGROUND

A largely underestimated cause of bacterial bloodstream infections in sub-Saharan Africa is *Salmonella* Typhimurium. The *Salmonella* Typhimurium strains that are dominant in Africa (sequence type ST313) have already undergone genomic changes, causing specialization towards the human host. This is further complicated by a dramatic spread of antibiotic resistance, urging the need for using last-resort antibiotics such as azithromycin. In the Democratic Republic (D.R.) of Congo, the majority of *Salmonella* Typhimurium from blood are now multi-drug resistant (MDR). However, from 2013 onwards, strains with additional extended-spectrum beta-lactamase (ESBL) activity and co-resistance against azithromycin have emerged. In this study, we aimed at unraveling the phylogenetic and biological characteristics of these emerging, highly resistant *Salmonella* Typhimurium strains, within the African epidemiological context.

METHODS

A collection of 49 *Salmonella* Typhimurium strains was subjected to whole-genome sequencing. These strains were isolated from blood during microbiological surveillance in D.R. Congo between 2013 and 2015. Thirty-eight resistant strains showing MDR, ESBL and azithromycin resistance and 11 controls showing MDR but no ESBL or azithromycin resistance were analyzed in the context of 181 previously published *Salmonella* Typhimurium genomes from Africa.

RESULTS

A phylogenetic analysis revealed that the strains with additional azithromycin resistance and ESBL activity form a new Typhimurium lineage in Africa, which was not observed for previously published outbreaks. All strains in this new lineage have acquired a large mobile genetic element carrying multiple antibiotic resistance genes, which has been inserted in the chromosome. Importantly, this insertion caused a loss of the flagellin gene *fljB*, involved in bacterial motility and invasion. In addition, we observed mutations causing potential loss-of-function in proteins that are important for virulence.

CONCLUSIONS

Our findings suggest the recent emergence of a new invasive *Salmonella* Typhimurium lineage in the D.R. Congo, with increased antibiotic resistance and further adaptation to the human host.

12:15 ANTIMICROBIAL PRE-TREATMENT AND BLOOD CULTURE POSITIVITY RATES FOR *S.* TYPHI, INTS AND OTHER INVASIVE BACTERIAL PATHOGENS

ONDARI D. MOGENI, *International Vaccine Institute*

Gi Deok Pak[1], Trevor Toy[1], Ligia Maria Cruz Espinoza[1], Abdramane Soura Bassiahi[2], Abraham Aseffa[3], Aissatou Niang[4], Amy Gassama Sow[4,5], Ralf Krumkamp[6], Arvinda Sooka[7], Christian G. Meyer[8,9], Eric D. Mintz[10], Frank Konings[1,11], Heidi Schütt-Gerowitt[1,12], Henintsoa Rabezanahary[13], Jean Philibert Rakotondrainiarivelo[13], Joel M. Montgomery[14], John D. Clemens[1,15], John A. Crump[16-18], Julian Hertz[16,17], Jürgen May[6], Karen H. Keddy[7], Hyon Jin Jeon[1], Hye Jin Seo[1], Nimako Sarpong[19], Nagla Gasmelseed[20], Mekonnen Teferi[3], Morten Bjerregaard-Andersen[21], Ondari Mogeni[1], Muna El Tayeb Ahmed[20], Raphael Rakotozandrindrainy[13], Robert F. Breiman[14,22], Peter Aaby[21], Thomas F. Wierzba[1,23], Yun Chon[1], Justin Im[1], Se Eun Park[1], Ursula Panzner[1], Stephen Baker[24], Yaw Adu-Sarkodie[19], Florian Marks[1]

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BACKGROUND

Typhoid Fever (TF) is caused by *Salmonella* enterica serovar Typhi and is a vaccine preventable. It occurs in a many developing countries, particularly in sub-Saharan Africa and Asia. The diagnosis of TF requires the identification of *Salmonella* Typhi (*S.* Typhi) bacteria through blood culture, which requires at least 3-5 days. Hence, patients commonly treat themselves with antibiotics prior to the establishment of a final diagnosis. In the course of the Typhoid Fever Surveillance in Africa Program (TSAP), the antibiotic pretreatment was recorded. Here we investigate the effect of antibiotic pre-treatment on invasive bloodstream infections caused by *S.* Typhi and non-typhoidal *Salmonella* spp. compared to other invasive bacterial pathogens.

METHODS

Between 2010 and 2014, the TSAP collected blood cultures of febrile patients presenting at 13 health facilities in 10 sub-Saharan African countries, namely Guinea Bissau, Ghana, Senegal, Burkina Faso, Ethiopia, Sudan, Tanzania, Kenya, Madagascar and South Africa. Patients with objective fever of ≥37.5°C regardless of age were recruited. Clinical information including antibiotic pre-treatment information was collected by the clinicians on paper at enrolment.

RESULTS

Twelve percent of enrolled participants reported antibiotic pre-treatment (2,534/21,179); 4,0% of enrolled patients harboured a bacterial pathogen in their bloodstream (854/21,179). Among these, 192 *S.* Typhi and 135 iNTS isolates were identified; 36 and 14 patients with *S.* Typhi and iNTS bacteremia, respectively, reported antibiotic pre-treatment. Antibiotic pre-treatment affected *S.* Typhi less than other bacteria (OR: 1.71; 95% [CI] 1.19 - 2.46; p=.004). This effect could not be shown in the iNTS group (OR: 0.85; [CI] 0.49 - 1.48; p=.567). Similar findings could be seen in a country stratification model that will be presented.

CONCLUSION

Antibiotic pre-treatment appears to have reduced effect on *S.* Typhi bacteria. We surmise that patients infected with *S.* Typhi are exerting more severe symptoms than those infected with other pathogens; hence they are treated earlier and more often with antibiotics. This might result in *S.* Typhi being more resistant to commonly used antibiotics. Other possible scenarios will be discussed.

Lunch and Posters
12:30 – 13:30

THE RIGHT SHOT: VACCINE SESSION II
13:30 – 15:00 ORAL ABSTRACT SESSION

MODERATORS

CHISOMO MSEFULA, *University of Malawi*

Chisomo Msefula is a Research Scientist and Senior Lecturer at the College of Medicine, University of Malawi, in Blantyre Malawi. His research focus has largely been on describing the molecular epidemiology of invasive nontyphoidal Salmonella in Malawi and sub-Saharan Africa. Recently the scope of work has expanded to include typhoid fever following the epidemic increase of Salmonella Typhi isolation at Queen Elizabeth Central Hospital (QECH) in Blantyre. Collective achievements have been the description of the invasive S. Typhimurium strain sequence type ST313 in sub-Saharan Africa (SSA) and recently the identification of S. Typhi haplotype H58 as the epidemic strain in SSA and Malawi. He is also developing a PCR technique to diagnose invasive Salmonella in blood to improve case ascertainment at QECH, in Blantyre.

ROB HEYDERMAN, *University College London*

Rob Heyderman is a clinician scientist with skills and experience that bridge clinical practice and fundamental understanding of the mechanisms of infectious disease. He moved to University College London (UCL) two years ago after directing the highly succesful Malawi-Liverpool-Wellcome Trust Programme (MLW) for eight years. His UK and Africa-based research continues to focus on the endothelial biology & coagulopathy of severe infection; the microbial and immunological basis of severe infection by mucosal pathogens and their prevention through vaccination; regulation of host inflammation; and the diagnosis and management of meningitis and sepsis. Heyderman is a Professor of Infectious Diseases & International Health, Division of Infection and Immunity at University College London.

PRESENTATIONS

13:30 PRE-CLINICAL IMMUNOGENICITY OF TYPHOID (VI-CRM_{197}), PARATYPHOID (O:2- CRM_{197}) AND BIVALENT (VI-CRM_{197}+O:2- CRM_{197}) CONJUGATE VACCINE

RAVI P.N. MISHRA, *Biological E*

Ravi P.N. Mishra, Ravishankar P. Yadav and Akshay Goel*

Biological E. Limited, Hyderabad, Telangana, India

BACKGROUND

Typhoid and paratyphoid fever (enteric fever) are major causes of morbidity and mortality, particularly among children and adolescents in the developing world. A safe, efficacious and affordable vaccine against enteric fever, especially for young children, would make a major impact on disease burden in developing countries. *Salmonella enterica* serovar Typhi was believed to cause most enteric fever episodes, but several recent reports have shown an increasing incidence of *S.* Paratyphi A, encouraging the development of a bivalent vaccine to protect against both serovars, especially considering that at present there is no vaccine against *S.* Paratyphi A. The Vi and O:2 capsular polysaccharide are considered as major antigen that can be targeted by vaccine.

METHODS

Using the core technology provided by GVGH (GSK Vaccines Institute for Global Health), we have developed a monovalent vaccine for each of the antigenic polysaccharide by covalent coupling of CRM_{197} carrier protein with Vi and O:2 generating Vi-CRM_{197} and O:2-CRM_{197} conjugate vaccine, respectively. The immunogenicity of these conjugate vaccines was evaluated in mice and rabbit models. The specific antibody response against Vi and O:2 was assessed by ELISA, following subcutaneous injection of Vi-CRM_{197}, O:2-CRM_{197} and Bivalent vaccine.

RESULTS

The data suggests that immunization with glycoconjugates elicited a robust α-Vi IgG response and α-O:2 IgG response in animals when immunized with Vi-CRM_{197} and O:2-CRM_{197} vaccine, respectively. Furthermore, the groups immunized with Bivalent vaccine also elicited both Vi and O:2-specific serum IgG titers and no interference between Vi and O:2 IgG was seen. A booster response was seen in all the groups immunized with conjugates following second dose of vaccine. The IgG response in conjugate was found to be significantly higher than the groups immunized with unconjugated Vi and O:2 respectively.

CONCLUSIONS

These data confirm the immunogenicity of Vi-CRM_{197} and O:2-CRM_{197} in mice and rabbit models, thus strengthening the suitability of Vi-CRM_{197} and Bivalent as a promising vaccine candidate against *Salmonella* Typhi and Paratyphi A. This new generation of conjugate vaccine opens up a new era for enteric fever prevention and elimination.

13:45 DEVELOPMENT OF A SUSTAINABLE AND EFFECTIVE VACCINE AGAINST INVASIVE NONTYPHOIDAL SALMONELLOSIS (INTS) IN AFRICA

GIANLUCA BREGHI, *Fondazione Achille Sclavo*

Magini, Spadafina, S-AFRIVAC Consortium and Breghi

Fondazione Achille Sclavo, Siena, Italy

BACKGROUND

iNTS is a major cause of bloodstream infection in sub-Saharan Africa, where it is fatal among children <5 years and HIV patients, and often associated with malaria, anaemia and malnutrition. iNTS is difficult to diagnose and recently several reports have documented an increasing emergence of antimicrobial-resistant iNTS isolates (Crump JA et al 2015, CMR). Nevertheless, the disease kills very rapidly, with an estimated 20% case fatality rate (Ao TT et al 2015, EID). No vaccine is currently available, but its development is crucially needed.

METHODS

A vaccine has been designed with developing countries in mind to be very immunogenic, safe, high quality, affordable and with a simple production process. Indeed, to formulate the new vaccine for iNTS a novel delivery strategy, named "Generalized Modules for Membrane Antigens", is used. The new technology is self-adjuvanting, as antigens are delivered in their native conformations (Tennant SM et al 2016, Vaccine).

RESULTS

To allow the generation of a sustainable vaccine against iNTS, in September 2016 a novel project named S-AFRIVAC started with the support of the Toscana Regional Government, Italy. The project main objectives are to:

- Refine the burden of iNTS disease, aggregating the sparse knowledge
- Help the progress of a new vaccine to clinical trials, evaluating the immunological response in preclinical models
- Produce a GMP batch of the vaccine for next clinical trials
- Study the vaccine sustainability use in low- and middle-income countries

CONCLUSION

iNTS is a serious cause of morbidity and mortality in Africa and vaccine development is high priority. The major goal of S-AFRIVAC is to develop for and provide to Africa population the first vaccine against iNTS, within the next eight to 10 years.

14:00 DEVELOPMENT OF A VACCINE BASED ON GMMA AGAINST INVASIVE NONTYPHOIDAL *SALMONELLA* DISEASE IN SUB-SAHARAN AFRICA

OLIVER KOEBERLING, *GSK Vaccines Institute for Global Health*

Oliver Koeberling[1], Anna Maria Colucci1, Luigi Sollai[1], Ivan Pisoni[1], Carlo Giannelli[1], Vito di Cioccio[1], Audino Podda[1], Joachim Auerbach[1], Martina Carducci[1], Francesca Necchi[1], Omar Rossi[2], Luisa Lanzilao[1], Maria-Grazia Aruta[1], Simona Rondini[1], Allan J Saul[1], Laura B Martin[1]

[1]GSK Vaccines Institute for Global Health, Siena, Italy; [2]University of Cambridge, Department of Veterinary Medicine, Cambridge, UK

BACKGROUND

Invasive non-typhoidal *Salmonella* disease (iNTS), is an important emerging, neglected and poverty-related disease in sub-Saharan Africa. At highest risk of iNTS are young children and immunocompromised individuals of all ages. *Salmonella enterica* serovars Typhimurium and Enteritidis account for >90% of iNTS cases. iNTS is one of the leading causes of bacteremia with 20% case fatality rate, difficult early diagnosis and wide spread multidrug resistance collectively advocate for the urgent development of a vaccine against iNTS.

METHODS

GSK Vaccines Institute for Global Health (GVGH) has developed a vaccine against iNTS based on an innovative technology platform called Generalized Module for Membrane Antigens (GMMA). These outer membrane blebs are isolated from the supernatant of strains genetically engineered to release high amounts of GMMA and to

have a modified lipopolysaccharide. The vaccine primarily targets the surface polysaccharide O-antigen (OAg) present on the two most prevalent invasive African *Salmonella* strains (O:4,5 and O:9 on Typhimurium and Enteritidis, respectively).

RESULTS

By testing cytokine release from human peripheral blood mononuclear cells, the GMMA have been shown to induce reduced levels of IL-6 secretion compared to GMMA with unmodified LPS and similar levels to the detoxified *Shigella sonnei* GMMA, which were well tolerated in clinical trials. In immunized mice, Typhimurium and Enteritidis GMMA induced high levels of serotype specific anti-OAg antibodies with bactericidal activity against Typhimurium and Enteritidis isolates. We have developed a simple and robust GMMA production process with high yields, making the iNTS vaccine affordable to manufacture and deliver. A clinical path forward has been established to demonstrate the safety and immunogenicity of this vaccine in young children of sub-Saharan Africa, the target population.

CONCLUSION

Thus, GVGH's iNTS-GMMA vaccine is a promising approach for protecting young children against invasive non-typhoidal *Salmonella* disease in sub-Saharan Africa with the potential to save many lives.

WEDNESDAY

14:15 *S.* TYPHIMURIUM CORE-OPS (COPS) GLYCOCONJUGATE WITH THE HOMOLOGOUS SEROVAR PHASE 1 FLAGELLIN AS A VACCINE TO PREVENT INVASIVE *S.* TYPHIMURIUM INFECTIONS IN SUB-SAHARAN AFRICA

RAPHAEL SIMON, *University of Maryland School of Medicine*

Scott M. Baliban[1], Girish Ramachandran[1], Brittany Curtis[1], Rachel S. Laufer[1], John Van Druff[2], Ellen E. Higginson[1], Sharon M. Tennant[1], Andrew Lees[2], Myron M. Levine[1], Raphael Simon[1]

[1]*Center for Vaccine Development, Institute for Global Health, University of Maryland School of Medicine, Baltimore, MD, USA;* [2]*Fina Biosolutions, Rockville, MD, USA*

BACKGROUND

Invasive infections with non-typhoidal *Salmonella* (NTS) serovars Typhimurium (STm) and Enteritidis (SE) are widespread in infants and young children in sub-Saharan Africa where death occurs in 15 – 30% of cases. There are presently no available human NTS vaccines. NTS O polysaccharides (OPS) and flagellin proteins are virulence factors and protective antigens in animal models. We previously documented that SE COPS conjugated to SE phase 1 flagellin (FliC) was immunogenic and protected mice against fatal infection with a Malian SE blood isolate. We report here preclinical development and optimization of a comparable STm COPS:FliC vaccine.

METHODS

Lattice conjugates were generated by chemically linking COPS at random hydroxyls to adipic acid dihydrazide modified FliC with cyanylation chemistry. Sun-type conjugates were produced by derivatization of the COPS reducing end with an aminooxy thiol linker followed by conjugation to maleimide modified FliC with thioether chemistry. CD-1 mice were immunized at 0, 28 and 56 days with PBS, 2.5 mcg of STm FliC, or 2.5 mcg of COPS:FliC, and challenged at day 84 with high or low LD100 levels of Malian *S.* Typhimurium blood isolate D65. Sera obtained before immunization and 21 days after the final dose were assessed for anti-COPS and anti-FliC IgG levels by ELISA.

RESULTS

Conjugates synthesized by end-linkage with thio-ether chemistry retained higher levels of COPS O-acetyls, induced higher levels of anti-COPS IgG (GMT = 144,452 versus 186 ELISA Units), and were more protective against STm challenge (95-100% vaccine efficacy [VE] versus 30-43% VE) relative to lattice conjugates. Immunization with STm FliC alone provided 30% protection against infection with monophasic D65 mutants expressing FliC or phase 2 flagellin FljB.

CONCLUSIONS

An immunogenic and protective STm COPS:FliC vaccine candidate was identified that could be co-formulated with an SE COPS:FliC component as a bivalent NTS vaccine for use in sub-Saharan Africa.

14:30 MEASUREMENT OF LPS SPECIFIC IGA AND IGG AVIDITY MATURATION IN VIVOTIF VACCINEES AND NATURALLY INFECTED TYPHOID PATIENTS IN BANGLADESH

FARHANA KHANAM, *International Centre for Diarrhoeal Disease and Research, Bangladesh*

Farhana Khanam, Md. Abu Sayeed, Faisal Bin Rashed, Sadia Isfat, Taufiqur R. Bhuiyan, Firdausi Qadri

Centre for Vaccine Sciences, International Centre for Diarrhoeal Disease Research, Bangladesh (icddr,b), Dhaka, Bangladesh

BACKGROUND

Typhoid fever caused by *Salmonella enterica* serotype Typhi is a potentially life-threatening systemic disease. High prevalence rates of typhoid fever have been reported in the resource limited regions of the world, with children under five years of age being the largest target. The antibody avidity maturation in patients with typhoid fever or in individuals following oral typhoid vaccination has not been reported to date.

METHODS

We measured lipopolysaccharide (LPS) specific immunoglobulin G (IgG) and IgA avidity maturation in naturally infected Bangladeshi typhoid fever patients of all age groups as well as individuals aged below five years after immunization with liquid formulation of Vivotif vaccine. We assessed the antibody avidity responses at acute stage in patients or prior to vaccination in vaccinees and then in follow-up at day seven and then at day 21.

RESULTS

Both patients and vaccinees mounted LPS-specific IgG and IgA antibodies of high avidity. After vaccination IgA and IgG antibodies with significantly higher avidity are induced in the vaccinees that lasted throughout the study period of 21 days. The patients with an age below five years showed a higher IgA avidity index in the first two study day points, followed by a decrease at day 21. We compared the avidity response in patients of different age groups (young children: below five years old; older children: 6-17 years old and adults: above 18 years old). Adults showed significantly higher antibody avidity indices than young and older children at day 7 for LPS-specific IgG; whereas for IgA avidity indices the patients of all age group had similar responses at all study days.

CONCLUSIONS

This is the first demonstration of antibody avidity response in typhoid fever patients and the findings also suggest that the liquid formulation of Vivotif vaccine induces the antibody avidity in children under five years of age.

14:45 FORECASTING TYPHOID CONJUGATE VACCINE INTRODUCTION AND DEMAND IN TYPHOID ENDEMIC LOW AND MIDDLE COUNTRIES

ENUSA RAMANI, *International Vaccine Institute*

Enusa Ramani, Vittal Mogasale, Il-Yeon Park, Jung-Seok Lee

Policy and Economic Research Department, International Vaccine Institute, Seoul, South Korea

BACKGROUND

At least one typhoid conjugate vaccine (TCV) is expected to acquire WHO prequalification soon, which will allow its use in many low- and middle-income countries where typhoid is endemic. At this juncture, a policy and planning process to build necessary resources and finances for the introduction of TCV is necessary. It is critical to know what would be the expected vaccine demand in the future so that vaccine supply can be matched. In this paper, we estimate TCV demand using a mixed quantitative and qualitative method.

METHODS

We quantitatively forecast introduction dates for countries based on typhoid disease burden, history of past vaccine introduction, capacity of the underlying immunization system and experience in typhoid research; and then qualitatively adjusted it based on opinions from typhoid experts. Finally, we quantitatively estimate vaccine demand by year for defined vaccination strategies assuming coverage levels of measles-containing vaccine in typhoid-endemic countries. We present an optimistic and a slow vaccine introduction scenario.

RESULTS

In the optimistic scenario, we forecast 17 countries introducing TCV by 2024 while in the slow introduction scenario we forecast 5 countries introducing TCV by 2024. If a vaccine is targeted to high-risk populations only, the routine vaccine demand peaks between 40 and 65 million doses per year. If the whole population is targeted, the vaccine demand will increase to 100 million to 160 million per year.

CONCLUSIONS

In conclusion, our demand forecast project is an upper-limit estimate of vaccine demand, with actual demand depending on country priorities, vaccine introduction, vaccination strategies, Gavi financing, cost and overall product profile. Given the potential role of TCV in disease control, policy makers, donors and financing bodies at the global, regional and country level should consider working towards setting up capacity to produce sufficient quantity of vaccine, early WHO prequalification, continued Gavi financing support and developing policy support.

Coffee Break
15:00 – 15:30

SALMONELLA CONTROLLED HUMAN INFECTION MODELS: INSIGHTS, OPPORTUNITIES AND CHALLENGES

15:30 – 17:30 SYMPOSIUM SESSION

Controlled human infection models (CHIM) for typhoid fever have been in existence for over sixty years and offer the potential to better understand the nature of host-pathogen interactions, as well as providing a platform to test novel vaccine, diagnostic and therapeutic candidates. A programme of typhoid and paratyphoid challenge studies has been undertaken at the University of Oxford since 2010 and, thus far, such models have been applied to test the efficacy of oral and parenteral typhoid vaccine candidates and to evaluate diagnostic approaches. Longitudinal sample collection allows detailed profiling of the clinical, microbiological and immunological response to infection before, during and after the onset of typhoid and paratyphoid fever, including analysis of samples not obtainable in the field. Collectively, lessons learned from these studies could be applied to accelerate testing of a new generation of vaccines, diagnostics and therapeutics.

In this symposium, we will present rapidly emerging data from human challenge models for typhoid and paratyphoid fever. In particular, we will present data from a vaccine efficacy study utilizing the typhoid challenge model, comparing the response to challenge in a group of healthy volunteers vaccinated with a Vi-conjugate vaccine compared with Vi-polysaccharide and control vaccines. These data could directly inform future decisions regarding the development of oral or subunit vaccines and the deployment and support for Vi-conjugate vaccines in endemic settings. In addition, we will also present results generated from challenge/re-challenge studies and present data outlining possible mechanisms of systemic and mucosal immunity to *Salmonella* Typhi and Paratyphi A infection. We will present data generated from the application of a systems biology approach to better understand the response to vaccination and infection in the context of this model. Finally, we will discuss the potential application, utility and role of CHIM for Non-Typhoidal *Salmonella* infections.

ORGANIZERS

MALICK GIBANI, *University of Oxford*

Dr. Gibani studied medicine at the University of Oxford and graduated in 2010. After continuing his training in general medicine at a variety of London hospitals, he joined the Oxford Vaccine Group in 2014 to work on a range of vaccine trials for Ebola virus, meningococcal disease and typhoidal *Salmonella*. He is currently undertaking a DPhil focusing on the use of Salmonella controlled human infection models to better understand infection-derived immunity to *Salmonella* Typhi and Paratyphi infection, as well as studying the role of typhoid toxin in the pathogenesis of typhoid fever.

ANDREW POLLARD, *University of Oxford*

Andrew Pollard, FRCPCH PhD FMedSci, is Professor of Paediatric Infection and Immunity at the University of Oxford since 2001. 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, leads a project on burden and transmission of typhoid, and co-leads typhoid vaccine impact studies at these sites. He has supervised 23 PhD students and his publications include over 300 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 the World Health Organization's Strategic Advisory Group of Experts (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.

CO-CHAIRS

THOMAS DARTON, *University of Sheffield*

Tom completed his DPhil with the Oxford Vaccine Group in 2014 in which he helped to establish controlled human infection models (CHIM) of *Salmonella* Typhi and Paratyphi A. With a fellowship in Translational Medicine, his principle interests were in the application of the CHIM to discovery, development and evaluation of new diagnostics, vaccines and therapeutics. In addition to working on CHIM in Oxford, Tom has performed studies of typhoid diagnostics in Nepal and is now part of the Strategic Typhoid Alliance across Africa and Asia consortium. Tom is currently an NIHR Academic Clinical Lecturer in Infectious Diseases and Medical Microbiology at the University of Sheffield and is based at the Oxford University Clinical Research Unit in Ho Chi Minh City in Viet Nam.

ANDREW POLLARD, *University of Oxford*

See bio above

PRESENTATIONS

15:30 *SALMONELLA* CHALLENGE STUDIES – INTRODUCTION AND HISTORICAL PERSPECTIVE

ANDREW POLLARD, *University of Oxford*

See bio above

15:35 ASSESSMENT OF THE EFFICACY OF A VI-TETANUS TOXOID CONJUGATE VACCINE USING A CONTROLLED HUMAN INFECTION MODEL OF *SALMONELLA* TYPHI

CELINA JIN, *University of Oxford*

Celina obtained her medical degree at the University of Melbourne, Australia, in 2009 and has since spent four years working as an adult physician trainee at the Royal Melbourne Hospital. She is currently a third year DPhil student researching typhoid vaccines and B cell responses following vaccination and typhoid infection at the University of Oxford.

15:50 INVESTIGATING IMMUNITY TO TYPHOID AND PARATYPHOID FEVER — THE RESPONSE TO RE-CHALLENGE IN A CONTROLLED HUMAN INFECTION MODEL

MALICK GIBANI, *University of Oxford*

See bio above

16:05 IDENTIFYING CORRELATES OF PROTECTION — SYSTEMIC IMMUNE RESPONSES TO *SALMONELLA* TYPHI AND PARATYPHI A INFECTION

GIORGIO NAPOLITANI, *University of Oxford*

Giorgio Napolitani graduated in Biology at the University of Padua (Italy) with a Diploma Thesis on the molecular mechanisms of action of Helicobacter pylori VacA and Bacillus anthracis LF toxins. After a PhD at the University of Siena/Novartis Vaccines (Italy) on the molecular pathways controlling innate immune responses of human Dendritic Cells to Lipopolysaccharide he joined Professor Lanzavecchia Laboratory at the Institute of Research in Biomedicine in Bellinzona (Switzerland) where he showed how distinct immune sensor for microbial invasion can synergy to elicit potent Th1 immune responses, and provided the first characterization of the phenotype and specificity of human Il-17 producing CD4 T cells. Giorgio Napolitani currently works in the laboratory of Professor Cerundolo, within the University of Oxford MRC Human Immunology Unit where he focuses on the characterization of human innate and adaptive immune responses in cancer, vaccination and infection.

16:20 MUCOSAL IMMUNE RESPONSES TO *SALMONELLA* TYPHI AND PARATYPHI A INFECTION

LORENA PRECIADO-LLANES, *University of Oxford*

Dr. Lorena Preciado-Llanes is a postdoctoral researcher at the University of Oxford. She is based in the Weatherall Institute of Molecular Medicine, within the Simmons lab. After obtaining her medical degree, Lorena undertook a Masters and PhD in infection and immunity. Her research interests include innate and adaptive immune responses against invasive and non-invasive bacteria, as well as the effects of bacterial infection on the intestinal microbiome. Further projects also incorporate the use of single cell RNAseq to characterise rare mucosal T cells. In collaboration with the Oxford Vaccine Group and the Cerundolo Lab, Lorena investigates gut mucosal T cell antigen responses against Typhoidal *Salmonella* in a controlled human infection model. Her project will be extended into the clinical field in Malawi (Gordon Lab), where she hopes to validate the findings of her research.

16:35 COMPARATIVE ANALYSIS OF MOLECULAR IMMUNE PROFILES AND DISEASE PATHOGENESIS IN TYPHOID AND PARATYPHOID FEVER

CHRISTOPH BLOHMKE, *University of Oxford*

Christoph is Senior Research Associate at the Oxford Vaccine Group (OVG) with an interest in investigating the host's immune responses to enteric fever and diagnostic biomarker discovery. Prior to joining OVG, he completed an MSc in Medical Biochemistry at the University of Amsterdam and received a PhD in Experimental Medicine from the University of British Columbia, Canada. During his PhD he gained extensive experience in respiratory immunology and host pathogen interactions focusing on the discovery of novel targets for anti-inflammatory therapy in patients suffering from lung infections (P. aeruginosa, B. cenocepacia). At OVG Christoph focuses on computational analyses of datasets derived from the enteric fever challenge model and samples collected in the field.

JENNIFER HILL, *University of Oxford*

Jennifer Hill is a post-doctoral researcher at Oxford Vaccine Group (OVG) and has a keen interest in immunological responses to vaccination and infection with typhoid. Using samples from human typhoid challenge studies at OVG she is currently investigating responses of natural killer (NK) cells and a potential role for NK cells in vaccine-mediated protection. Other areas of interest include measuring the early innate response to exposure to typhoid, and understanding how properties of the Fc region of antibodies induced in typhoid vaccination influence protection. Jennifer completed her PhD in the lab of Professor Gordon Dougan at the Wellcome Trust Sanger institute in 2015. During her time in Cambridge she combined transcriptomic and proteomic approaches to explore changes in the intestinal mucosa in non-typhoidal *Salmonella* infection using a mouse model.

16:50 RECENT ADVANCES IN THE IDENTIFICATION OF IMMUNOLOGICAL CORRELATES OF PROTECTION IN A HUMAN *S.* TYPHI CHALLENGE MODEL

MARCELO SZTEIN, *University of Maryland School of Medicine*

Dr. Sztein is Professor of Pediatrics, Medicine and Microbiology and Immunology at the University of Maryland. In addition, Dr. Sztein is Associate Director for Immunologic Research, Leader of the Immunology Group and Chief of the Cellular Immunology Section and Flow Cytometry Core Laboratory at the prestigious Center for Vaccine Development. Dr. Sztein is an accomplished investigator in the area of immunology of infectious diseases. He has published 196 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*, hepatitis B, *P. falciparum*, influenza, *F. tularensis* and Ebola. Dr. Sztein has over 33 years of experience in performing flow cytometric studies, including mass cytometry. He directs a multidisciplinary center, part of NIAID's CCHI network, that studies the interplay between Mucosal Immunity, Vaccines and Microbiota.

17:05 TOWARDS HUMAN CHALLENGE WITH NTS

CAL MacLENNAN, *University of Oxford*

Cal MacLennan is a clinician scientist currently spending a year with the Enteric and Diarrheal Diseases team at the Bill and Melinda Gates Foundation. He qualified in medicine and then obtained his doctorate from Oxford. As a junior doctor, Cal developed an interest in infectious disease immunology which led him to work in Kenya and then Malawi, investigating immunity to invasive *Salmonella* disease. These studies continued at the University of Birmingham, UK, prior to Cal becoming Head of Exploratory Programme at the Novartis Vaccines Institute for Global Health in 2010. There, his programme developed new vaccines against *Salmonella*, *Shigella* and meningococcus. Following a sabbatical at the Wellcome Trust Sanger Institute, he returned to Oxford in 2015 as a Senior Clinical Fellow at the Jenner Institute. *Salmonella* immunology continues to be a main focus of Cal's research with ongoing projects in Africa. He is an honorary consultant immunologist at Oxford University Hospitals NHS Foundation Trust, a member of visiting faculty at the Sanger Institute and Professor of Vaccine Immunology at the University of Birmingham.

17:20 QUESTIONS AND DISCUSSION

TyVAC Reception
17:30 – 19:30

#TAKEONTYPHOID WITH TYVAC: RECEPTION TO LAUNCH THE NEW TYPHOID VACCINE ACCELERATION CONSORTIUM

» THURSDAY, APRIL 6

THE NEXT GENERATION: TYPHOID CONJUGATE VACCINE

8:30 – 10:45 PLENARY SESSION

MODERATORS

JOACHIM HOMBACH,
World Health Organization

Dr. Joachim Hombach is Senior Adviser at the Intiative for Vaccine Research of the Department of Immunisation, Vaccines and Biologicals of WHO. In this function he is responsible for research to support the development of global immunization policies. He also serves as WHO focal point for the R&D agenda of the Global Vaccine Action Plan. In former managerial positions at WHO, he served as interim Head of the Initiative for Vaccine Research, and Coordinator in charge of policy & strategy and implementation research. He also served as focal point for the flavivirus vaccine portfolio, with particular emphasis on dengue and Japanese encephalitis vaccines. Before joining WHO, Joachim Hombach's career focused on vaccine research and implementation policy, with emphasis on vaccines for the developing world. In this context, he had assignments as Director of vaccine policy at GlaxoSmithKline Biologicals S.A., and as Scientific Officer with the European Commission. In the latter function, he was seminal in setting up the European and Developing Countries Clinical Trials Partnership. Joachim Hombach's career started as a researcher in molecular and cellular immunology at the University of Zürich, Switzerland and the Max-Planck Institute for Immunology in Freiburg, Germany. He holds a PhD from the University of Cologne, Germany, as well as a Master of Public Health from Johns Hopkins University, Baltimore, USA.

VITTAL MOGASALE,
International Vaccine Institute

Vittal Mogasale, MBBS, MPH, PhD is Head, Policy and Economic Research Department at International Vaccine Institute. He has over 17 years of experience in the control of infectious diseases and immunization programs in developing countries. His current work focusses on Health Economics and Policy Research for evidence based decision making at global and country levels. Dr. Mogasale has obtained his Medical Degree from Manipal University, India; international Masters in Public Health from Hebrew University, Israel and Doctor of Philosophy from University of Queensland, Australia.

PRESENTATIONS

8:30 OVERVIEW ON VACCINE PIPELINE: CURRENT STATUS AND FUTURE PLANS

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 7 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.

8:50 INTRODUCTION OF TYPHOID CONJUGATE VACCINES: OPPORTUNITIES AND CHALLENGES

KATHY NEUZIL, *University of Maryland School of Medicine*

Dr. Neuzil is an internationally recognized research scientist and advocate in Vaccinology. Dr. Neuzil is Professor of Medicine and Pediatrics, and director, Center for Vaccine Development at the University of Maryland School of Medicine. She is deputy director of the Institute for Global Health. Throughout her career, she has conducted clinical and epidemiologic studies on vaccine-preventable diseases, including notable work on influenza and rotavirus, which have informed domestic and international vaccine policy. Currently, Dr. Neuzil directs TyVAC, the Typhoid Vaccine Acceleration Consortium, with a goal to accelerate the introduction of typhoid conjugate vaccines into low-resource countries. From 2005-2015, Dr. Neuzil held leadership positions at PATH, a nonprofit global health organization. Dr. Neuzil's research capabilities are complemented by 20 years of involvement in domestic and international policy, including membership on the Centers for Disease Control's Advisory Committee on Immunization Practices. She has served as a technical advisor to the World Health Organization on diarrheal diseases, maternal immunization and vaccine safety. Dr. Neuzil has contributed more than 160 scientific publications on vaccines and infectious diseases.

9:05 DEVELOPMENT OF A BIVALENT *SALMONELLA* TYPHI AND PARATYPHI A MAPS VACCINE

RICK MALLEY, *Boston Children's Hospital/ Harvard Medical School*

Rick Malley, MD, began his education at the Ecole Active Bilingue in Paris, France, getting his Baccalaureate in 1982. He received his B.A. from Yale University, his MD from Tufts University in 1990, and pediatric infectious diseases and emergency medicine training at Boston Children's Hospital. Dr. Malley is the Kenneth McIntosh Chair in Pediatric Infectious Diseases at Children's and Professor of Pediatrics at Harvard Medical School. Dr. Malley runs a research laboratory with funding from NIH, PATH, BMGF, focusing on vaccine development for pneumococcus, *Staphylococcus aureus*, *Salmonella* Typhi and Paratyphi, and *Mycobacterium tuberculosis*. In collaboration with PATH and the BMGF, Dr. Malley led an international effort for the development of a whole-cell pneumococcal vaccine for developing countries. A Phase II trial of the whole cell vaccine in toddlers is ongoing in Kenya. In 2014, Dr. Malley and collaborators started Affinivax, a biotechnology

company seed-funded by BMGF and based on a novel technology called MAPS (Multiple Antigen Presentating System) to develop vaccines for developing countries. *Streptococcus pneumoniae* is the lead target being developed at Affinivax.

9:20 COST-EFFECTIVENESS OF TYPHOID CONJUGATE VACCINE STRATEGIES ACROSS FIVE SETTINGS IN AFRICA AND ASIA

VIRGINIA PITZER, *Yale School of Public Health*

Virginia Pitzer, ScD, is an Assistant Professor in the Department of Epidemiology of Microbial Diseases at Yale School of Public Health. She received her ScD 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 enteric 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.

9:35 TYPBAR-TCV: A CLINICAL DEVELOPMENT REVIEW

KRISHNA MOHAN,
Bharat Biotech International Ltd.

Dr. Krishna Mohan obtained his PhD in Chemical Physics from the Indian Institute of Science, Bangalore and subsequently carried out Post-doctoral work in the United States, the United Kingdom and Japan. This included the prestigious Cavendish Laboratory at the University of Cambridge. He has published more than 100 papers in various peer reviewed, international journals. Currently, Dr. Mohan is designated as the Executive Director of Bharat Biotech International Ltd., an organization with strong focus on novel vaccines and new biological entities. His current work involves working with teams developing vaccines for various infectious diseases such as Rotavirus, Japanese Encephalitis, Typhoid and H1N1.

10:05 FIRST PLANNED PUBLIC SECTOR INTRODUCTION OF A TYPHOID CONJUGATE VACCINE IN NAVI MUMBAI, INDIA

JASON ANDREWS, *Stanford University on behalf of Kashmira Date, Centers for Disease Control and Prevention*

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.

10:20 QUESTIONS AND DISCUSSION

Coffee Break and Posters
10:45 – 11:15

GLOBAL TRENDS IN TYPHOID FEVER: DETERMINANTS AND IMPLICATIONS FOR POLICY

11:15 – 12:45 SYMPOSIUM SESSION

Typhoid fever clearly remains a significant health burden in low- and middle-income countries (LMICs). Despite the availability of more recent global data on enteric fevers, additional longitudinal research is needed in many regions, particularly Africa, Latin America, and other LMICs. Critically, population-based data on risk factors including: safe water, adequate sanitation, appropriate personal and food hygiene, and vaccination are needed to attribute changes in disease burden and priority setting for the prevention and control of typhoid fever. Currently, two safe and effective typhoid vaccines are licensed and marketed internationally. Globally, there has been no comprehensive longitudinal study of typhoid and its association with known risk factors and a critical debate is currently underway on the best way to allocate resources to combat typhoid: water, sanitation and hygiene (WASH) interventions, the new VI-conjugate vaccine, or some combination of the two (and in what proportions).

Detailed country level analysis and collaborative work is necessary to understand trends in the burden and distribution of typhoid and determinants. This work has successfully brought global collaborators together to address, and analyze the trends of this disease. The objective of this symposium is to foster further discussion on the future of combatting this enteric disease. Our teams have objectively evaluated factors which may have been associated with changes in observed incidence of typhoid over time through i) a global systematic review, specific to typhoid, and ii) through case studies in select countries with available information on typhoid at the national or large representative sub-national level.

Having undertaken this large and comprehensive body of work we have addressed a key question on the relationship of general development and contextual group-level factors (WASH, education, wealth) with burden of typhoid over time using objective mixed methods. Our work identified the causes, and regional factors that contribute to this ongoing burden, to distill opportunities for priority setting for research and interventions to tackle the global burden of typhoid and inform global policy. In particular the eight country case studies undertaken represent comprehensive in-depth assessments at national or sub-national level of culture proven typhoid trends over the last two decades.

ORGANIZER

ZULFIQAR BHUTTA, *Aga Khan University*

Dr. Zulfiqar A. Bhutta is the Founding Director of the Centre of Excellence in Women and Child Health at the Aga Khan University; the Inaugural Robert Harding Chair in Global Child Health, Co-Director, and Director of Research at The Hospital for Sick Children, Toronto; and Chairman of The Coalition of Centres in Global Child Health. Dr. Bhutta also holds adjunct professorships at several leading Universities globally including the Schools of Public Health at Johns Hopkins University, Harvard University, Tufts University, the

University of Alberta and the London School of Hygiene & Tropical Medicine. Dr. Bhutta was educated at the University of Peshawar (MBBS) and obtained his PhD from the Karolinska Institute, Sweden. He is a Fellow of the Royal College of Physicians (Edinburgh and London), the Royal College of Pediatrics and Child Health (London), American Academy of Pediatrics and the Pakistan Academy of Sciences. He has been associated with the Aga Khan University since 1986 and heads a large research team working on issues of maternal, newborn and child survival and nutrition regionally and globally.

CO-CHAIRS

ZULFIQAR BHUTTA, *Aga Khan University*

See bio above

KATHY NEUZIL, *University of Maryland School of Medicine*

Dr. Neuzil is an internationally recognized research scientist and advocate in Vaccinology. Dr. Neuzil is Professor of Medicine and Pediatrics, and director, Center for Vaccine Development at the University of Maryland School of Medicine. She is deputy director of the Institute for Global Health. Throughout her career, she has conducted clinical and epidemiologic studies on vaccine-preventable diseases, including notable work on influenza and rotavirus, which have informed domestic and international vaccine policy. Currently, Dr. Neuzil directs TyVAC, the Typhoid Vaccine Acceleration Consortium, with a goal to accelerate the introduction of typhoid conjugate vaccines into low resource countries. From 2005-2015, Dr. Neuzil held leadership positions at PATH, a nonprofit global health organization. Dr. Neuzil's research capabilities are complimented by 20 years of involvement in domestic and international policy, including membership on the Centers for Disease Control's Advisory Committee on Immunization Practices. She has served as a technical advisor to the World Health Organization on diarrheal diseases, maternal immunization and vaccine safety. Dr. Neuzil has contributed more than 160 scientific publications on vaccines and infectious diseases.

PRESENTATIONS

11:15 SHORT OVERVIEW AND PROVENANCE OF THE STUDY

ZULFIQAR BHUTTA, *Aga Khan University*

See bio above

11:25 GLOBAL REVIEW AND EPIDEMIOLOGY

DAINA ALS, *Tackling Typhoid (T2) Project, The Hospital for Sick Children*

Daina is a research assistant at the Centre for Global Child Health at The Hospital for Sick Children. She has worked on various projects supporting Professor Zulfiqar Bhutta since the summer of 2014. Over the past two years, she has been working on a systematic review looking at the trends in typhoid globally as well as in the local contexts of eight endemic countries. Her interest in public health stems from the desire to have an impact on the health of individuals around the world in resource poor settings. The work done at the Centre has the potential to bring about policy change and improve the health care resources in those settings. She loves the work that she does and hopes that one day it will translate into visible change in the world.

11:40 ADDITIONAL TREND DATA FROM GLOBAL BURDEN OF DISEASE STUDY

JEFF STANAWAY, *Institute for Health Metrics and Evaluation*

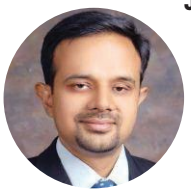
Jeff Stanaway, PhD, MPH, is Assistant Professor at the Institute for Health Metrics and Evaluation (IHME) at the University of Washington. He is part of the research team for the landmark Global Burden of Disease and Geospatial Analysis. In this role, he models morbidity and mortality from enteric and neglected tropical diseases. His research focuses on macro-epidemiology with a special interest in understanding connections between the physical environment (e.g., climate and land cover) and the spatiotemporal distribution of disease and how these connections may inform surveillance and research. Dr. Stanaway received his PhD in Epidemiology from the University of Washington and his MPH from the University of Arizona.

11:50 COUNTRY CASE STUDY: CHILE

CATTERINA FERRECCIO, *Escuela de Medicina Pontificia Universidad Católica de Chile*

Catterina Ferreccio, MD, MPH, is a Full Professor and Director of the Masters in Epidemiology Program, Department of Public Health, School of Medicine, Pontificia Universidad Católica de Chile (UC). Her area of interests include prevention and control of cancers associated to infectious and environmental causes in Chile. Since 2014, Ferreccio is the Deputy Director Advanced Center for Chronic Diseases (ACCDiS). From 1990 to date, she is a Professor of Public Health, School of Medicine, UC. Prior, she was a Regional Consultant at PAHO in Washington DC, conducting operational research on cervical cancer in Peru, Chile and El Salvador. Ferreccio is a member of the WHO country study group on Burden of Foodborne Diseases and the Advisory Committee of Immunization in Chile. From 1989 to 2000, she served as President of the Chilean Society of Epidemiology. Her research has been published in 145 in peer review journals.

12:00 COUNTRY CASE STUDY: PAKISTAN



JAI K. DAS, *Aga Khan University*

Dr. Jai K. Das works as an Assistant Professor for the Division of Women and Child Health at the Aga Khan University, Karachi. He holds a bachelor's in medicine and has done his residency in pediatric surgery. He is currently pursuing his PhD in population and public health. He is currently Pakistan's site director for the Cochrane Collaboration and coordinator for the Maternal Child Link on the Global Health Network. His research interests include interventions to address maternal and child nutrition and infections. He is the author of more than 70 international peer-reviewed papers and contributed to more than 10 book chapters. He has a strong academic acumen and involved in teaching at both undergraduate and postgraduate level and actively conducts research training workshops. His interests are related to the use of evidence in policy and programs, including estimates of burden of disease, the development of research capacity and the strengthening of public health.

12:10 COUNTRY CASE STUDY: THAILAND

AMRUTA RADHAKRISHNAN, *Centre for Global Child Health at the Hospital for Sick Children*

Amruta Radhakrishnan is a researcher working at the Centre for Global Child Health at the Hospital for Sick Children in Toronto, Canada. She completed her undergraduate studies in Life Science at McMaster University, Canada, after which she obtained a Master's degree in Public Health from the University of Edinburgh, UK. Since 2015, she has been a part of the Typhoid team at the Centre for Global Child Health led by Dr. Zulfiqar Bhutta. Their work looks at global trends in Typhoidal Salmonella and aims to shed light on what existing interventions are best suited to curb transmission in endemic settings. She is interested in infectious diseases and their transmission, particularly in low- and middle-income settings, and hopes that their findings can guide policy makers and impact the large scale management and delivery of interventions.

12:20 COUNTRY CASE STUDY: NIGERIA

KABIRU OLUSEGUN AKINYEMI,
Lagos State University

Dr. Akinyemi, PhD, FAvH, FRSPH, is a Professor of Microbiology, Infectious Diseases, Molecular Epidemiology and Antimicrobial Resistance Surveillance at Lagos State University (LASU), Ojo, Lagos, Nigeria. Dr. Akinyemi received B.Sc Microbiology (21) from LASU in 1990 and M.Sc Microbiology, University of Lagos (Unilag) Akoka, in 1992. In 1997, he focused on the studies of multiple drug resistance in Salmonella enterica serovar Typhi at the College of Medicine, Unilag, Idi-Araba to obtain Ph.D in Medical Microbiology in 2001. He did postdoctoral research on phage typing and molecular epidemiology of Salmonella isolates at Universitat Hohenheim, Stuttgart, Germany. Dr. Akinyemi had professional Certificates in molecular immunology, and Vaccinology from Universities of Ibadan and Ghana in collaboration with the World Health Organization in 2003 and 2007 respectively. He began his academic career as an Assistant Lecturer in LASU in 1995 and became the first Alumnus staff to attain the status of Professor in 2011. Dr. Akinyemi has received several awards including the Distinguished Alumni Award. He is an Alexander von Humboldt Fellow and a Royal Society for Public Health Fellow. He has participated in local and international research collaborations with over fifty publications.

12:30 QUESTIONS AND DISCUSSION

Lunch and Posters
12:45 – 13:45

WHAT'S NEW, DOC?
LATE BREAKER ABSTRACTS
13:45 – 15:45 ORAL ABSTRACT SESSION

MODERATORS

ISAAC BOGOCH, *University of Toronto*

Dr. Isaac Bogoch is an Assistant Professor at the University of Toronto in the Department of Medicine, and is an Infectious Diseases consultant and General Internist at the Toronto General Hospital. He completed medical school and Internal Medicine residency training at the University of Toronto and then specialized in Infectious Diseases at the Harvard Partners program. He holds a Masters Degree in Clinical Epidemiology from the Harvard School of Public Health, and has completed fellowships in both Tropical Infectious Diseases and HIV care. Dr. Bogoch divides his clinical and research time between Toronto and several countries in Africa and Asia. He collaborates with a team that models the spread of emerging infectious diseases, and studies innovative and simple diagnostic solutions to improve the quality of medical care in resource-constrained settings.

RICHARD STRUGNELL, *University of Melbourne*

Richard's long term interests are in assessing the role of innate immune responses, especially innate secretory antibodies, and adaptive cellular responses in host defense against bacterial pathogens, predominantly Klebsiella pneumoniae and Salmonella typhimurium. This largely animal model-based work has now moved into human field studies of Salmonella infection, in Fiji where they are working to map the incidence of typhoid, and trying to understand the risk factors, using a combination of social science and genomics. Part of this work will include testing novel antigens, identified in murine studies of Salmonella infection, as immunodiagnostics, in collaboration with the Fijian Ministry of Health.

PRESENTATIONS

13:45 VIRULENCE OF INVASIVE *SALMONELLA* TYPHIMURIUM ST313 IN ANIMAL INFECTION MODELS

ELLEN HIGGINSON, University of Maryland School of Medicine

Ellen E. Higginson[1,2†], Girish Ramachandran[1,2†], Aruna Panda[3†], Eugene Ateh[3], Michael M. Lipsky[3], Sunil Sen[1,2], Courtney A. Matson[1,2], Jasnehta Permala-Booth[1,2], Louis J. DeTolla[3], Sharon M. Tennant[1,2*]

[1]Center for Vaccine Development and Institute for Global Health, [2]Department of Medicine, 3Department of Pathology, Program of Comparative Medicine, University of Maryland School of Medicine, Baltimore, MD, USA

[†]co-first authors

BACKGROUND

Salmonella Typhimurium sequence type (ST) 313 produces septicemia in infants in sub-Saharan Africa. Although there are known genetic and phenotypic differences between ST313 strains and the global, gastroenteritis-causing ST19 strains, conflicting data about the *in vivo* virulence of ST313 strains have been reported. To resolve these differences, we investigated the pathogenesis of clinical *Salmonella* Typhimurium ST313 and ST19 strains, isolated from the blood of infants in Mali, in murine and rhesus macaque infection models.

METHODS

The intraperitoneal and peroral 50% lethal dose (LD_{50}) was determined for three clinical *Salmonella* Typhimurium ST19 and ST313 strains in BALB/c and CD-1 mice. For dissemination studies, mice were administered 10^9 CFU perorally, and bacterial burden in the spleen, liver and blood was determined at 3, 24, 48 or 168 h post-challenge. Indian rhesus macaques (RM; 3 per group) were infected orogastrically with 3×10^9 CFU of one ST19 and one ST313 strain. Animals were monitored for clinical symptoms and samples taken to determine bacterial burden and pathology.

RESULTS

The LD_{50} values for ST19- and ST313-infected mice were not significantly different. However, ST313-infected mice had significantly higher bacterial numbers in blood at 24 h post-infection than ST19-infected mice. ST19-infected RM had moderate-to-severe diarrhea from days 3 to 7 post-challenge, while ST313-infected monkeys showed no-to-mild diarrhea. ST19-infected monkeys also had significantly higher stool counts on days 3 and 4 than ST313-infected RM. There was no significant difference in bacterial burden or pathology.

CONCLUSIONS

Our data suggest that *Salmonella* Typhimurium ST313 invasiveness may be investigated by using a 24 h infection model in mice. The RM experiment results are consistent with reports from the field, suggesting that ST313 strains do not cause diarrhea. This is an excellent model for further investigation of ST313 pathogenesis.

14:00 AVERAGE TREATMENT COST FOR TYPHOID FEVER AND AVERAGE VACCINE DELIVERY COST PER DOSE FOR EACH OF THE 54 GAVI-ELIGIBLE COUNTRIES

JOKE BILCKE, *University of Antwerp*

Joke Bilcke[1], Marina Antillon[2], David Paltiel[2], Viginia Pitzer[2]

[1]University of Antwerp, [2]Yale School of Public Health

BACKGROUND

WHO, GAVI and countries with substantial typhoid incidence need to decide whether and how to implement vaccination strategies using typhoid conjugate vaccines. We aim to perform a cost-effectiveness analysis for 54 GAVI-eligible countries, along with value of information analysis to help set priorities for future research. For this, we estimated the average treatment cost for typhoid fever for each of these countries and the vaccine delivery cost per dose, as well as the uncertainty around these estimates.

METHODS

Literature was reviewed and global databases were searched (WHO-CHOICE) for costs (health care provider perspective) of treating typhoid fever (unit cost for an inpatient and outpatient visit, unit cost for medication, unit cost for lab tests, length of stay in the hospital, number of consultations per outpatient), and routine immunization (cost per dose for vaccine delivery, including start-up and ongoing costs)). For each cost item, an uncertainty distribution was specified reflecting the strength of the information available for that cost item. Costs are presented in 2016US$.

RESULTS

Average treatment cost ranges for a hospitalised case from \$19 $\pm$ 7 (Pakistan) to \$221 $\pm$ 110 (India) and for an outpatient from \$1.0 $\pm$ 0.4 (Tanzania) to \$24.8 $\pm$ 17.6 (Nigeria). Costs for Pakistan, India and Tanzania are based on primary level country data whereas cost estimates for all other countries are based on WHO-CHOICE estimates and data from other countries. Average delivery cost per dose for implementing typhoid vaccines in a routine immunization program ranges from \$1.0 $\pm$ 0.5 (Western Pacific countries) to \$4.9 $\pm$ 2.5 (European countries), of which 60 $\pm$ 12% are ongoing costs.

DISCUSSION

These estimates can be used directly to inform health economic evaluations of typhoid vaccination strategies. The estimated uncertainty ranges are crucial for value of information analysis, to determine the type of data most needed to inform decision-making.

14:15 OUTBREAK INVESTIGATION AND ASSESSMENT OF RISK FACTORS OF CEFTRIAXONE RESISTANT *S.* TYPHI FROM HYDERABAD, PAKISTAN

TAHIR YOUSUFZAI, *Aga Khan University*

Farah Naz Qamar[1], Khalid Saleem[1], Sadia Shakoor[1], Tahir Yousufzai[1], Momin Kazi[1], Heeramani Lohana[1], Ayub Khan[1], Denise Garrett[2], Farrukh Raza[1]

[1]Aga Khan University; [2]Sabin Vaccine Institute

INTRODUCTION

Antimicrobial resistance has been increasing health problem worldwide particularly in developing countries. Increased mortality and morbidity has been caused due to multiple outbreaks by multidrug resistant typhoid fever. The Aga Khan University Hospital clinical laboratory reported outbreak of ceftriaxone resistant typhoid fever due to S. typhi in 38 cases of residents from Hyderabad, Pakistan. An outbreak investigation was carried out to identify possible source of transmission and institute control measures.

METHODOLOGY

A matched case control study was conducted in Hyderabad (talukas Latifabad and Qasimabad), Pakistan. Cases were identified through field, hospital, and laboratory surveillance. A case was defined as a resident of Hyderabad with a positive blood culture for ceftriaxone resistant S. typhi from 28th November 2016 to 15th February 2017, identified from Aga Khan Laboratory surveillance data on typhoid fever. A suspected case was defined as a resident of Hyderabad with $\geq$ 3 days of fever with no laboratory confirmation. A control was

defined as resident of Hyderabad who had been otherwise healthy four weeks before the interview. Cases and controls were matched 1:4 on neighborhood and age. A questionnaire was administered to study participants to identify risk factors for contracting typhoid, including geographical location through generation of a case 'spot map'. Venous blood specimens were drawn from suspected cases. Water samples were collected for microbiological analysis.

RESULTS

A total 190 subjects, 38 cases (32 from laboratory data, one from field survey and five from sentinel hospitals) and 152 matched controls were enrolled in the study. Median age of cases was 4 years; 74 % were ≤ 5 years of age. Males constituted 55 % of the cases. In a conditional logistic regression model, taking antimicrobials in the 2 weeks preceding the onset of symptoms (OR = 3.7, 95% CI 1.50 – 9.1, AR = 61%) and contact with person diagnosed with typhoid in last 4 weeks (OR = 14.4, 95 % CI 3.02 – 68.75, AR = 70 %) were independently associated with ceftriaxone resistant S. typhi fever. All the isolates were resistant to first line drugs (ampicillin, chloramphenicol and cotrimoxazole) as well as fluoroquinolones and cephalosporins (cefixime, ceftriaxone). However, these isolates were sensitive to Imipenem / Meropenem and Azithromycin. Twenty cases required intravenous therapy with meropenem and remaining were treated with oral Azithromycin. There was no mortality in this cohort.

CONCLUSION

This investigation revealed a large outbreak of Ceftriaxone resistant S. typhi, first of its kind from Hyderabad, Pakistan. Contact with typhoid patient, previous use of antibiotics and faulty sewerage line were implicated as cause of this outbreak. Community education on personal hygiene and drinking safe drinking water, improving WASH factors and mass vaccination of at risk population are important measures for the control of the outbreak.

14:30 *SALMONELLA ENTERICA* SEROVARS ISOLATED FROM STOOL OF CHILDREN ENROLLED IN THE GLOBAL ENTERIC MULTICENTER STUDY IN AFRICA

IRENE KASUMBA, *University of Maryland School of Medicine*

I.N. Kasumba[1], S. Sen[1], N. Sayed[1], J. Permala-Booth[1], B. Tamboura[2], J.B. Ochieng[3], M. Antonio[4], I. Mandomando5, D. Saha[4], Q. Bassat[5,6], P.L. Alonso[5,6], R. Omore[3], M.J. Hossain[4], S. Sow[2], J.O. Oundo[3], R.F. Breiman[3], J.P. Nataro[1], K.L. Kotloff[1], M.M. Levine[1], Sharon M. Tennant[1]

[1]Center for Vaccine Development, University of Maryland School of Medicine, Baltimore, MD, USA; [2]Centre pour le Developpement des Vaccins, Bamako, Mali; [3]Kenya Medical Research Institute/Center for Global Health Research (KEMRI-CGHR), Kisumu, Kenya; [4]Medical Research Council Unit, the Gambia; [5]Centro de Investigacao em Saude da Manhiça, Maputo, Mozambique; [6]Barcelona Institute for Global Health (ISGlobal), Barcelona, Spain

BACKGROUND

The Global Enteric Multicenter Study (GEMS) determined the etiological agents of moderate-to-severe diarrhea (MSD) in children under the age of five years in four countries in Africa and three countries in Asia. *Salmonella* was not strongly associated with MSD. However, non-typhoidal *Salmonella* (NTS) infections are an important cause of septicemia in infants in Africa. Here, we present the NTS serovars isolated from stool during GEMS at African sites.

METHODS

Salmonella spp. identified in Kenya, Mali, The Gambia and Mozambique were shipped to the Center for Vaccine Development in Baltimore for complete identification of serovars using antisera and biochemical tests. We tested 181 African *Salmonella* isolates, of which 101 were from cases and 80 were from controls. Multiplex PCR was employed to confirm agglutination results and determine *Salmonella* Typhimurium sequence types. We also tested sensitivity to selected antibiotics by the Kirby Bauer disk diffusion method.

RESULTS

Of the 181 *Salmonella enterica* strains, 138, 35, 2 and 6 were from Kenya, The Gambia, Mozambique and Mali, respectively. 38.7% were *S.* Typhimurium, 9.4% were *S.* Virchow, 6.6% were *S.* Newport, 6.6 % were *S.* Enteritidis, 5.5% were *S.* Heidelberg, 3.9% were *S.* Paratyphi B Java, 1.7 % were *S.* Hissar, 1.1% were *S.* Wingrove, *S.* Aberdeen, or *S.* Bovismorbificans, 0.6% were *S.* Muenster, *S.* Bsilla, *S.* Larochelle, *S.* Eastbourne or *S.* Muenchen, 8.3% were other *Salmonella* serovars and 13.3% were non-typable. Antibiotic resistance of *S.* Typhimurium was 94.7% for ampicillin and trimethoprim-sulfamethoxazole, and 76.3% and 7.9% for chloramphenicol and gentamicin, respectively. 89.6% of tested *S.* Typhimurium strains were ST313.

CONCLUSIONS

The most common *Salmonella* serovar that was isolated in GEMS was *S.* Typhimurium. Although *S.* Typhimurium ST313 has been associated with invasive disease in sub-Saharan Africa, we determined that it was isolated from the stools of children in this region too.

14:45 LEVERAGING THE WHO-COORDINATED IB-VPD SURVEILLANCE PLATFORM FOR ENTERIC FEVER SURVEILLANCE: LESSONS FROM BANGLADESH

SENJUTI SAHA, *Child Health Research Foundation*

Senjuti Saha[1], Maksuda Islam[1], Mohammad J Uddin[1], Shampa Saha[1], Rajib C Das[1], Abdullah H Baqui[2], Mathuram Shantosham[3], Robert E Black[2], Samir K Saha[1,4]

[1]Child Health Research Foundation, Department of Microbiology, Dhaka Shishu Hospital, Dhaka, Bangladesh; [2]Department of International Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, United States of America; [3]Center for American Indian Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, United States of America; [4]Bangladesh Institute of Child Health, Dhaka Shishu Hospital, Dhaka, Bangladesh

BACKGROUND

Lack of surveillances and accurate data impede evidence-based decisions on treatment and prevention of *Salmonella* Typhi and Paratyphi, causative agents of enteric fever. The WHO coordinates a global Invasive Bacterial–Vaccine Preventable Diseases (IB-VPD) surveillance network to monitor pneumonia, meningitis and sepsis, but not enteric fever. We evaluated the practicability of integrating enteric fever surveillance into the IB-VPD surveillance in Bangladesh.

METHODS

Between January 2012 and December 2016, in Dhaka Shishu and Shishu Shasthya Foundation hospitals, 2-59 months-old children admitted with suspected pneumonia, sepsis or meningitis were enrolled in the "original" IB-VPD surveillance. Inclusion criteria for possible enteric fever, ≥102°F for ≥3 days, were used for "expanded" surveillance. Blood culture was performed on enrolled cases. If *S.* Typhi/Paratyphi were isolated from blood of a non-enrolled case, it (irrespective of age) was retrospectively-enrolled.

RESULTS

In the "original" surveillance, of 5,185 enrolled cases, 3.3% were culture-positive; 50% of them were *S.* Typhi and 5.2% *S.* Paratyphi A. In the "expanded" surveillance, of 1,699 cases, 22% were culture positive; 85% (305/358) were *S.* Typhi, 12% (44/358) *S.* Paratyphi A.

Through laboratory surveillance, 263 *S.* Typhi and 48 *S.* Paratyphi A cases were retrospectively-enrolled; 28 (9%) were 2-59m and 283 (91%) were ≥60m. Hence, combined surveillances missed 6% (28/471) of 2-59m enteric fever cases. No differences in seasonality and antimicrobial susceptibility were seen between 2-59m (N=471) and ≤60m (N=283) cases.

CONCLUSIONS

By broadening the inclusion criteria of IB-VPD surveillance, we increased isolation of *S.* Typhi/Paratyphi A from 19 to 151/year. Integrated surveillance captured 94% of enteric fever cases in 2-59m children. As no differences in seasonality and susceptibility patterns were seen between 2-59m and ≥60m cases, disease patterns in all age groups may be assumed to be similar and data from combined IB-VPD platforms can be used to guide intervention policies for all. We recommend addition of enteric fever surveillance to WHO IB-VPD platforms.

15:00 A CASE-CONTROL INVESTIGATION INTO THE HOUSEHOLD DISTRIBUTION OF INVASIVE *SALMONELLAE* IN BLANTYRE, MALAWI

MELITA GORDON, *University of Liverpool*

Reenesh Prakash[1,2], Leonard Koolman[1,2], Franziska Olgermoeller[1,3], Rose Nkhata[1], Brigitte Denis[1], Jay Hinton[2], Sian Jones[2], Martin Cormican, Robert S Heyderman, Chisomo Msefula1,[4], Nicholas A Feasey[3], Melita A Gordon[2,4]

[1]Malawi Liverpool Wellcome Trust Clinical Research Programme, [2]University of Liverpool, [3]Liverpool School of Tropical Medicine, [4]University of Malawi, College of Medicine

BACKGROUND

Typhoid fever and invasive non-typhoidal Salmonella (iNTS) disease are frequent causes of hospital admission and mortality in Malawi. Knowledge of environmental reservoirs and routes of transmission are needed to inform prevention strategies.

METHODS

Sixty index cases with Salmonella BSI (26 iNTS, 34 S. Typhi; 21 adults, 39 children) presenting to Queen Elizabeth Hospital were recruited. A microbiological survey of the index-case household and a randomly selected control household (bottle spin, 100 yards) was conducted, comprising stool from household members, stool or rectal swabs from domestic animals, boot-sock sampling of the living environment, and food and water samples. Samples were cultured using non-selective broth-enrichment followed by selenite culture and plating on XLD. Identified *Salmonella* isolates underwent whole genome sequencing to determine relatedness with the index case.

RESULTS

1,510 samples were collected within 2 weeks of illness (802 from 60 case households, 708 from 60 control households), including 491 from human stool (273 from case households, 218 from control households) and 92 from domestic animals (49 from case households and 43 from control households). There were 49 (3.2%) *S. enterica* isolates (19 [2.4%] from case households, 30 [4.2%] from control households). For 2 iNTS (ST313 *S.* Typhimurium) index cases (1 child, 1 adult), corresponding matched isolates were found among household members (2 adults). No ST313 isolates were isolated from control household members. Domestic animal and environmental samples from all households yielded a wide range of serovars not found in human invasive disease in Blantyre. *S.* Typhi was not isolated from any household contact or control samples.

CONCLUSIONS

A wide range of *Salmonellae* not linked to invasive disease were isolated within case and control households. Two matched *S.* Typhimurium ST313 isolates between iNTS cases and household members are in keeping with human-to human-transmission. There were no matched iNTS isolates among domestic animals.

15:15 KNOWLEDGE, ATTITUDES AND PRACTICES RELATED TO TYPHOID FEVER: THE CASE OF GLEN VIEW SUBURB, CITY OF HARARE, 2016

KUDZAI MASUNDA, *City of Harare Health Department*

Bara HT, Makoni AC, Masunda KPE, Vere M, Makwara IP, Manyara J, Mukeredzi I, Chonzi P, Moetsabi T

City of Harare Health Department, Zimbabwe

BACKGROUND

Harare has had Typhoid fever outbreaks since 2010. In 2016 there were 1,169 reported cases from January to June, and 70 were confirmed through blood and stool cultures. Knowledge, attitudes and practices (KAPs) regarding typhoid are central to understand transmission and improve control of typhoid. Glen View suburb has been at the epicenter of typhoid outbreaks. This study was undertaken to evaluate the KAPs of typhoid fever among Glen View residents and to assess preferred information, education and behavior change communications.

METHODS

A descriptive cross-sectional KAP survey was conducted in the high density suburb of Glen View, Harare, Zimbabwe. Interviewer-administered questionnaires and an observation checklist were used to collect quantitative data on knowledge of typhoid transmission and prevention and sanitation practices from a random sampling of Glenview residents. Focus Group Discussions (FGDs) were conducted with men, women, food vendors and home industry workers for in depth qualitative data. Epi Info ™ 7.2.0.1. was used for data collection and analysis was done using Stata 13© Statacorp LP, College Station. Data from FGDs were summarised using Atlas.ti7© and Microsoft Excel®.

RESULTS

625 questionnaires were analysed while 65 persons participated in the FGDs. Knowledge assessment showed only 33% of the respondents had adequate knowledge of typhoid. Similar analysis showed that attitudes towards perceived risks, severity and benefits were also poor as only 15% of respondents were aware of risks and severity of typhoid. Only 44% of respondents reported proper practices on water storage and treatment, sanitation and hygiene.

CONCLUSION

This study demonstrated that the majority of the respondents had low levels of knowledge, and poor attitudes and practices around typhoid in Glen View. The study findings call for reviewing of the health education messages that are going to the public aimed at positively influencing preventive behaviours against typhoid fever and any other food borne diseases.

15:30 SPATIAL AND TEMPORAL PATTERNS OF TYPHOID AND PARATYPHOID FEVER OUTBREAKS: A WORLDWIDE SYSTEMATIC REVIEW, 1990–2016

VITTAL MOGASALE, *International Vaccine Institute*

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

[1]International Vaccine Institute, Seoul, South Korea; [2]Imperial College London, London, United Kingdom

BACKGROUND

Mapping spatial and temporal pattern of enteric fever outbreaks enhances the comprehensiveness of disease burden necessary for policy decisions.

METHODS

We conducted a systematic review of enteric fever outbreak data from PUBMED, EMBASE, ProMED-mail and GIDEON databases from January 1st 1990 to December 31st 2016 and classified them by time, place, diagnostic methods and drug susceptibility to develop spatial maps. If an author reported the occurrence of enteric fever as an outbreak in the manuscript, we included it in our analysis.

RESULTS

There were 168,770 cases in 266 identified outbreaks. The size of outbreak ranged from one to 42,564. Fifty-one percent of outbreaks occurred in Asia, 17% in Africa and 14% in Oceania, and the rest in other regions. Only 35% outbreaks specified confirmation by blood culture, and 71 outbreaks reported drug susceptibility, of which 55% were multi-drug resistant. Paratyphoid outbreaks were less common compared to typhoid (20 vs. 244), although more prevalent in Asia than Africa. Risk factors were multi-factorial with contaminated water being the main factor.

CONCLUSIONS

This review highlights geographical locations where urgent attention is needed for enteric fever control and calls for global action to control typhoid fever including use of vaccines.

Coffee Break and Posters
15:45 – 16:15

MISSION POSSIBLE: FROM EVIDENCE TO ACTION

16:15 – 17:30 PLENARY SESSION

MODERATORS

BRUCE GELLIN, *Sabin Vaccine Institute*

Dr. Bruce Gellin, MD MPH, is President, Global Immunization at the Sabin Vaccine Institute. Dr. Gellin previously served as the Deputy Assistant Secretary for Health and Director of the National Vaccine Program Office at the U.S. Department of Health and Human Service (HHS), where he was the principal advisor to the Assistant Secretary for Health on vaccine and immunization programs and policies. Dr. Gellin also represented HHS as a technical and policy advisor to the World Health Organization with a focus on influenza and vaccine hesitancy and as a contributor to the Decade of Vaccines Collaboration and the Global Action Vaccine Action Plan (GVAP). Dr. Gellin earned an MPH in epidemiology from the Columbia University Mailman School of Public Health, is a graduate of Weill Cornell Medical College, and was a Morehead Scholar at the University of North Carolina at Chapel Hill and previously worked at CDC and NIH. Dr. Gellin achieved board certification in internal medicine and infectious diseases and serves as a peer reviewer for over a dozen medical journals.

NARENDRA K. ARORA, *The INCLEN Trust International, New Delhi*

Dr. Narendra Arora is the Executive Director of The INCLEN Trust International, a renowned organization focused on fostering research and training to address health challenges particularly in low- and middle-income countries. Prior, he worked as a faculty member at the All India Institute of Medical Sciences, New Delhi, and as a Professor of Pediatrics Gastroenterology, Hepatology & Nutrition. Dr. Arora has made major contributions to the immunization sector at both national and global levels. Throughout his professional career, his research, teaching and clinical care actions have consistently contributed to the immunization of children in India. Dr. Arora has provided leadership to several national policy making bodies and is Chairman of the National Certification Committee for Polio Eradication and the National Verification Committee for Measles, Rubella and CRS. Dr. Arora has also served on the WHO-SAGE from 2010 to 2016 and has been chair of three SAGE working groups. Dr. Arora has contributed to the development of training and health education tools for primary health care, and is the recipient of various awards and distinctions for his academic excellence and research endeavors.

PRESENTATIONS

16:15 GLOBAL TYPHOID CONTROL IN THE CONTEXT OF THE SUSTAINABLE DEVELOPMENT GOALS: PRAGMATISM OR UTOPIA?

ZULFIQAR BHUTTA, *Aga Khan University*

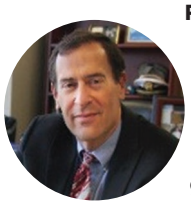
Dr. Zulfiqar A. Bhutta is the Founding Director of the Centre of Excellence in Women and Child Health at the Aga Khan University; the Inaugural Robert Harding Chair in Global Child Health, Co-Director, and Director of Research at The Hospital for Sick Children, Toronto; and Chairman of The Coalition of Centres in Global Child Health. Dr. Bhutta also holds adjunct professorships at several leading Universities globally including the Schools of Public Health at Johns Hopkins University, Harvard University, Tufts University, the University of Alberta and the London School of Hygiene & Tropical Medicine. Dr. Bhutta was educated at the University of Peshawar (MBBS) and obtained his PhD from the Karolinska Institute, Sweden. He is a Fellow of the Royal College of Physicians (Edinburgh and London), the Royal College of Pediatrics and Child Health (London), American Academy of Pediatrics and the Pakistan Academy of Sciences. He has been associated with the Aga Khan University since 1986 and heads a large research team working on issues of maternal, newborn and child survival and nutrition regionally and globally.

16:30 CONSIDERATIONS FOR REVISED GLOBAL TYPHOID VACCINATION POLICY AND STRATEGIES

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 (WHO), Geneva where she currently leads WHO's activities to update the global policy on typhoid vaccine use and to support national level decision-making for typhoid conjugate vaccine introduction in endemic countries. Dr Bentsi-Enchill's previous work in the WHO focused on immunization safety and she has over 15 years of experience in international health including 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.

16:45 BREAKING GOOD: MAKING SCIENCE GREAT AGAIN



ROBERT BREIMAN, *Emory University*

Dr. Breiman is Director of the Emory Global Health Institute (EGHI) where he oversees the strategy of engaging a wide array of disciplines and interests at Emory with the goal of integrated, innovative, and impactful contributions towards addressing challenging problems affecting health. Dr. Breiman is the PI for projects on rotavirus, typhoid fever, and pneumococcal disease. He is also the Co-PI for the Child Health and Mortality Prevention Surveillance (CHAMPS) Network which is aimed at characterizing and preventing childhood mortality in Sub-Saharan Africa and South Asia. Before joining Emory, Dr. Breiman was at the CDC for 26 years, most recently based at CDC-Kenya. Prior to Kenya, Dr. Breiman was Director of the Health Systems and Infectious Diseases Division and Head, Programme on Infectious Diseases and Vaccine Sciences at the International Center for Diarrheal Disease Research, Bangladesh (ICDDR,B). He was previously Director of the National Vaccine Program Office, and Chief of the Epidemiology Section of the Respiratory Diseases Branch. He is Board Certified in Internal Medicine and Infectious Diseases, a Fellow of the Infectious Diseases Society of America, and a member of American Society of Epidemiology, American Society of Tropical Medicine and Hygiene (Chair of Pneumonia and TB scientific committee), and American Society of Microbiology.

17:00 QUESTIONS AND DISCUSSION

17:20 CLOSING REMARKS

BRUCE GELLIN, *Sabin Vaccine Institute*

17:25 ADJOURN

DENISE GARRETT, *Sabin Vaccine Institute*

POSTER ABSTRACTS

1	Acheampong, Godfred	Multi-drug Resistance Profile of *Salmonella* Typhi Causing Bacteremia in Rural Ghana
2	Adogo, Lillian	Prevalence of *Salmonella* Typhi Among Pregnant Women in Niger State
3	Ahmed, Saly	Using McFarland Tube Densitometer in Pulse Field Gel Electrophoresis Molecular Subtyping Protocol of Salmonella Species, Egypt
4	Antillon, Marina	The Burden of Typhoid Fever in Low- and Middle-Income Countries: A Meta-Regression Approach
5	Antillon, Marina	Relationship between Blood Volume and Diagnostic Sensitivity of Blood Culture for Typhoid Fever: A Systematic Review and Meta-Regression Study
6	Anyanwu, Lofty-John	Typhoid Intestinal Perforation: Analysis of the Outcome of Surgical Treatment in Kano, Nigeria
7	Appiah, Grace	*Salmonella* Bacteremia in Hospitalized Ugandan Children with Febrile Illness
8	Argimón, Silvia	WGSA.net: A Flexible Global Resource for Genomic Predictions of Antimicrobial Resistance and Surveillance of *Salmonella* Typhi
9	Aulicino, Anna	Temporal Transcriptomic Profile of the Human MoDC Response to Invasive non-Typhoidal *Salmonella*
10	Barbé, Barbara	*Salmonella* Typhi Producing CTX-M-15 Extended Spectrum β-Lactamase in the Democratic Republic of the Congo
11	Barton, Amber	Changes in the Human Blood Transcriptome 12 Hours after Typhoid Challenge
12	Bello, Rebecca	Problem of Poor Water Supply and Prevalence of Enteric Fever in Wukari Area of Taraba State in Nigeria
13	Bhuyan, Golam Sarower	Nationwide Surveillance of Typhoid Fever in Both Hospital- and Community-Based Clinical Settings of Bangladesh Using ELISA-Based Rapid Diagnosis Method (TPTest)
14	Blohmke, Christoph	Typhoid and Paratyphoid Fever — Comparative Analysis of Molecular Immune Profiles and Disease Pathogenesis
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49	Mogasale, Vittal	The Quality of Life and Long-Term Socio-Economic Impact of Typhoid Fever Complications in Africa: A Multi-Country Study
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54	Murphy, Jennifer	An Environmental Survey of Drinking Water in Kampala, Uganda, During a Typhoid Fever Outbreak
55	Nkeza, Awung	The Susceptibility Pattern of *Salmonella* Species to Commonly Used Antibiotics in the Bamenda District Health Area, Cameroon
56	Nobela, Nélio	Non-Typhoidal *Salmonella* Mixed Infections Among Children with Bacteraemia Admitted to the Manhiça District Hospital
57	Nsimire, Juliet	Antimicrobial Susceptibility and Resistance Patterns of *Salmonella* Typhi During the 2015 Typhoid Outbreak in Kampala, Uganda
58	Nyirenda, Tonney	Loss of Protective Humoral and Cellular Immunity to Invasive Nontyphoidal *Salmonella* during Plasmodium falciparum Malaria Infection in Malawian Children
59	Odoch, Terence	Potential Threats from Antibiotic Resistant Strains of Non-Typhoidal *Salmonella* from Chicken Farms in Uganda
60	Owusu, Michael	Typhoid Perforation Associated with Extended Spectrum β-Lactamase Producing Bacteria
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64	Preciado-Llanes, Lorena	Investigating Gut Cellular Immunity in a Controlled Human Infection Model of Typhoid Fever

65	Purohit, Geetarani	Molecular Epidemiology of Quinolone Resistant *Salmonella* Typhi and *Salmonella* Paratyphi A from India
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70	Raymond, Meriel	Investigating Humoral Immunity to Paratyphoid Fever in a Human Challenge Model of Infection
71	Reuben, Rine	Epidemiological Studies of Typhoid Fever in Pregnant Women in a Community in Central Nigeria
72	Rijal, Nisha	Can Treatment of Enteric Fever Still Rely on Fluoroquinolones?
73	Saad, Neil	Drivers of Typhoid Fever Transmission in Kathmandu, Nepal: A Mathematical Modelling Study
74	Saad, Neil	Seasonal Dynamics of Typhoid and Paratyphoid Fever
75	Samajpati, Sriparna	Studies on Antimicrobial Resistance and Molecular Subtyping of *Salmonella* Typhi Isolates from Kolkata During 2014-2015
76	Sarkar, Kaushik	Changing Pattern of Resistance to Antimicrobials in Patients of Enteric Fever in India in Three Decades: A Systematic Review
77	Satyal, Deepa	Revival of Conventional First Line Drugs in *Salmonella enterica* Clinical Isolates: Assessment of MICs for Therapeutic Antimicrobials in Enteric Fever Cases from Nepal
78	Shaheen, Ghazala	Evaluation of Direct Susceptibility Testing by Disk Diffusion of *Salmonella* Typhi and *Salmonella* Paratyphi from Blood Culture
79	Shaheen, Ghazala	Laboratory Detection of Typhoidal Salmonellae in Urine Cultures in a Typhoid Endemic Setting
80	Shakya, Mila	Surveillance of Three Large Cohorts for Typhoid Fever: the Strategic Typhoid Alliance across Africa and Asia
81	Shenoy, Bhaskar	Enteric with Twist- A Case of Enteric Fever with Multiple Complications
82	Shenoy, Bhaskar	Study of Azithromycin Sensitivity Pattern of *Salmonella enterica* in Pediatric Population
83	Sooka, Arvinda	Evaluation of *In Vitro* Synergy Testing of South African Invasive *Salmonella* Typhi Isolates Using the Liofilchem® MTS Application System
84	Soubal, Jean Pierre	Preclinical Evaluation of a *Salmonella* Typhi Polysaccharide Vi-Diphtheria Toxoid (VI-DT) Conjugate Vaccine Candidate Against Typhoid Fever
85	Soubal, Jean Pierre	Selection of Polysaccharide Length, Conjugation Procedure and Carrier Protein for Vi Polysaccharide Conjugate Obtaining
86	Tanmoy, Arif Mohammad	A NGS Approach to Characterize Drug Resistance of *Salmonella enterica* serovar Typhi
87	Tanmoy, Arif Mohammad	Enteric Fever and Household Water Supply: Detection of *Salmonella enterica* Serovar Typhi and Paratyphi in the Supply Water of Urban Dhaka, Bangladesh
88	Teshome, Samuel	A Randomized, Observer-Blinded, Phase I Study to Assess the Safety and Immunogenicity of Vi-DT Conjugate Vaccine Compared to Vi-Polysaccharide (Typhim Vi®, Sanofi Pasteur) Typhoid Vaccine in Healthy Filipino Adults and Children
89	Thindwa, Deus	Electronic Data Capture for Large Scale Typhoid Surveillance, Household Contact Tracing, and Health Utilization Survey: Strategic Typhoid Alliance across Africa and Asia
90	Thomas, Kate	Investigating the Contribution of Food Animals to Human Non-Typhoidal *Salmonella* Disease in East Africa
91	Toy, Trevor	Variations of Invasive *Salmonella* Infections by Population Size in Asante Akim North Municipal, Ghana
92	Uche, Ifeanyi	A Systematic Review of the Incidence, Risk Factors and Case Fatality Rates of Invasive Nontyphoidal *Salmonella* (iNTS) Disease in Africa (1966 to 2014)
93	Wahid, Rezwanul	Cell-Mediated Immune Responses Elicited in Volunteers Immunized with the Novel Live Oral *Salmonella enterica* Serovar Paratyphi A Vaccine Strain CVD1902
94	Watson, Conall	A Cross-Sectional Seroepidemiological Survey for Typhoid Fever in Fiji
95	Yu, Alexander	Estimating Case Fatality Rate of Blood Culture Confirmed Typhoid Fever in Dhaka, Bangladesh

1. MULTI-DRUG RESISTANCE PROFILE OF *SALMONELLA* TYPHI CAUSING BACTEREMIA IN RURAL GHANA

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BACKGROUND

S. Typhi remains a big problem in West and Sub-Saharan Africa. The lack of incidence studies has made it difficult to monitor the progress of the disease and resistance pattern of the organism. The emergence of multi-drug resistant (MDR) strains of *S*. Typhi has increased treatment cost greatly, making it difficult for less developed countries like Ghana to afford, and as such likelihood of increasing mortality rate as a result of multi-drug resistant *S*. Typhi-causing bacteremia.

METHODS

This is a cross-sectional study in newly recruited cases of patients attending the Agogo Government Hospital in Asante-Akyem North District, Ghana, between 1 May, 2016, and 1 November, 2016. Patients arriving at the hospital with symptoms of Salmonellosis were recruited if consented to participate in the study. Venous blood were collected and inoculated directly into a blood culture vial. Biochemical (using API 20E) and Serological investigations were performed on suspected isolates. Susceptibility to Ampicillin, Amoxiclav, Ceftriaxone, Trimethoprim/Sulfamethoxazole, Ciprofloxacin, Gentamicin, Tetracycline, Chloramphenicol, Ceftazidime, Cefotaxime and Nalidixic acid was tested on Mueller Hinton Agar using the KirbyBauer disc diffusion method. Isolates resistant to Ampicillin, Chloramphenicol and Trimethoprim/Sulfamethoxazole were considered MDR.

RESULTS

Of the total number of 400 blood culture samples received, 14 (3.5%) *Salmonella* Typhi were isolated, of which 9 (64.3%) and 5 (35.7%) were males and females respectively. 6 (42.9%) of the isolated serovar Typhi were MDR. This was higher in males than in females. The mean age of individuals with MDR strains was 6.5yrs. Ceftriaxone, Ceftazidime, Cefotaxime and Gentamicin recorded the highest susceptibility while high resistance was recorded for Trimethoprim/Sulfamethoxazole. Resistance in Ampicillin, Chloramphenicol, and Trimethoprim/Sulfamethoxazole alone was 28.5%, 42.8% and 57.1% respectively.

CONCLUSION

MDR remains a threat in Rural Ghana. Great care and intensive surveillance need to be established to monitor SXT resistance rate before it gets out of hand.

2. PREVALENCE OF *SALMONELLA* TYPHI AMONG PREGNANT WOMEN IN NIGER STATE

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BACKGROUND

Typhoid fever is a global infection and it constitutes serious sources of morbidities and mortalities in Nigeria. Special concern arises as soon as pregnancy is complicated by *S.* Typhi. Diverse severe outcomes and morbidity connected with typhoid fever in pregnancy include maternal mortality, premature labor, spontaneous abortion and infection of the fetus. This study aims to determine the seroprevalence of *Salmonella* Typhi among pregnant women in Niger State. The objectives of the study were to determine the agglutinin titre levels among the women, to determine the effect of gestation period, age and water supply in relation to the incidence of the infection.

METHODS

This study was carried out among pregnant women receiving antenatal care in nine General Hospitals, in Niger State between July 2013 and March 2014 and a cross-sectional study design was utilized. Questionnaires were issued to obtain demographic information. Two milliliters of blood sample was collected from each pregnant woman and centrifuged at 1,500 rpm for 5 minutes. Widal test was used to detect the antibody titers in sera. A titre of 1:80 and above was considered significant.

RESULTS

Nine hundred pregnant women were examined from the three zones of the state, out of which 610 (67.8%) were infected. Prevalence of *Salmonella* Typhi in relation to age group shows that women between the ages of 35–44 had the highest rate of infection (71.8%). Those within the age group of 25-34, 15-24 also had a prevalence of 68.1% and 66.7% respectively. The relationship between typhoid fever infection and age group was statistically significant ($P = < 0.05$). Prevalence of *Salmonella* Typhi in relation to gestation period shows that pregnant women in their third trimester had the highest infection rate (71.5%) while those in their first and second trimester had a prevalence of 66.1%, 65.5% respectively. The relationship between typhoid fever infection and gestation period was statistically insignificant ($P = > 0.05$). The highest percentage (69.9%) of significant titre of antibodies to *Salmonella* was detected among subjects who utilize borehole water while the least was detected among subjects who utilize tap water. There was a significance relationship between *Salmonella* Typhi infection and water supply ($P < 0.05$).

CONCLUSION

The prevalence of *Salmonella* Typhi among pregnant women in this study is quite high and alarming and can adversely influence maternal-fetal outcome if left untreated.

3. USING McFARLAND TUBE DENSITOMETER IN PULSE FIELD GEL ELECTROPHORESIS MOLECULAR SUBTYPING PROTOCOL OF *SALMONELLA* SPECIES, EGYPT

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BACKGROUND

Pulsed Field gel electrophoresis (PFGE) helps in monitoring and matching trends and patterns of *Salmonella* serotypes. Adjustment of Cell suspension (CS) concentration is an important step in PFGE protocol. In 2013, Egyptian PULSENET Lab had an old Microscan Turbidity Meter device, its maintenance, tubes source and measuring unit were unknown. This study was conducted for replacing the Dade Microscan Turbidity Meter device and tubes with Tube densitometer device measuring McFarland standard units and cheaper available screw capped tubes.

METHODS

In 2014-2015 a study was conducted in PULSENET lab - Central Public Laboratory Health, Egypt. During *Salmonella* PFGE run, CS of *Salmonella* isolates were prepared, the Dade Microscan Turbidity Meter was used to adjust the turbidity of CS at range 0.4-0.6 in specific Falcon tube (2054), then CS was placed in screw capped sterile glass tubes to measure the equivalent McFarland units

using calibrated densitometer device. The mean of the adjusted McFarland readings was used to prepare CS of *Salmonella* and *Shigella* certification strains. PFGE runs were performed according to the CDC Standardized Laboratory Protocol for Molecular Subtyping for *Salmonella* and *Shigella* serotypes, August 2009.

RESULTS

37 readings from Tube densitometer device were obtained, mean (4.4 McFarland) and Standard deviation was 0.85. PFGE runs were performed for *Salmonella* and *Shigella* certification strains, cell suspensions were adjusted at 4.4 ± 0.85 McFarland. The PFGE tiffs had clear lanes, the bands are all crisp and distinct they are all easily marked, no ghost bands and no background, means proper CS concentration adjustments and successively passed the CDC certification evaluation.

CONCLUSIONS

PFGE protocol of *Salmonella* fingerprinting techniques, McFarland Tube Densitometer device can be used for preparation of CS concentrations at 4.4 ± 0.85 McFarland, using cheap and available ordinary clear sterile tubes.

4. THE BURDEN OF TYPHOID FEVER IN LOW- AND MIDDLE-INCOME COUNTRIES: A META-REGRESSION APPROACH

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BACKGROUND

Upcoming vaccination efforts against typhoid fever require an assessment of the baseline burden of disease in countries at risk. There are no typhoid incidence data from most low- and middle-income countries (LMICs), so model-based estimates offer insights for decision-makers in the absence of readily available data.

METHODS

We developed a mixed-effects model fit to data from 29 population-based studies of typhoid incidence. We tested the contribution of economic and environmental indices for predicting typhoid incidence using a stochastic search variable selection algorithm. We performed out-of-sample validation to assess the predictive performance of the model.

RESULTS

We estimated that 26.5 million cases of typhoid fever occur each year in LMICs (95% credible interval: 9.9-51.4 million). Central Africa was predicted to experience the highest incidence of typhoid, followed by select countries in Central, South, and Southeast Asia. Incidence typically peaked in the 2-5 year old age group. Models incorporating widely available economic and environmental indicators were found to describe incidence better than null models.

CONCLUSIONS

Recent estimates of typhoid burden may under-estimate the number of cases and magnitude of uncertainty in typhoid incidence. Our analysis permits prediction of overall as well as age-specific incidence of typhoid fever in LMICs, and incorporates uncertainty around the model structure and estimates of the predictors. Future studies are needed to further validate and refine model predictions and better understand year-to-year variation in cases.

5. RELATIONSHIP BETWEEN BLOOD VOLUME AND DIAGNOSTIC SENSITIVITY OF BLOOD CULTURE FOR TYPHOID FEVER: A SYSTEMATIC REVIEW AND META-REGRESSION STUDY

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BACKGROUND

Blood culture is the standard approach for diagnosing typhoid fever in epidemiologic studies. We performed a meta-analysis to quantify the relationship between the amount of a suspected typhoid patient's blood inoculated into media and blood culture sensitivity for typhoid fever, a relationship that has been postulated but whose functional form has never been determined.

METHODS

A systematic literature review was performed to identify all studies that report the sensitivity of blood culture in bone-marrow culture-confirmed cases of typhoid fever (which is the current gold standard). We fit a meta-regression model to account for between-study heterogeneity and accommodating for repeated measures within some of the studies.

RESULTS

The studies included in our analyses were representative of the patient populations in contemporaneous typhoid-endemic countries. A meta-regression model showed that across the studies, blood volume inoculation had a significant effect on culture sensitivity, even after inclusion of study-level random effects. During secondary analysis, we determined that the prevalence of antimicrobial use prior to seeking care and the time before diagnostic testing was unlikely to bias our results.

CONCLUSIONS

The relationship between the amount of blood inoculated into growth media and blood culture sensitivity should be rigorously taken into account in the interpretation of typhoid fever incidence studies and the evaluation of next-generation typhoid fever diagnostics.

6. TYPHOID INTESTINAL PERFORATION: ANALYSIS OF THE OUTCOME OF SURGICAL TREATMENT IN KANO, NIGERIA

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BACKGROUND

Intestinal perforation is a serious complication of typhoid fever with high case fatality rates in developing countries. This study aims to determine the factors associated with an adverse clinical outcome among patients managed for typhoid intestinal perforation (TIP) in our hospital.

METHODS

We retrospectively reviewed the records of all patients presenting to our General surgery unit (adult surgical unit) with TIP between January 2012 and December 2015. The patients were categorized based on postoperative outcome status and patient related variables were compared analysed for predictors of outcome, using the chi-square test. Significance was assigned to a p-value <0.05.

RESULTS

There were 50 patients who had surgery for TIP during the study period, but only the records of 47 patients could be retrieved for analysis. Of these, 32 (68.1%) were males, and 15 (31.9%) females. The male/female ratio was 2.13:1. Their ages ranged from 13 years to 55 years with a median of 17 years. A single intestinal perforation was seen in 87.2% (41/47), while 12.8% (6/47) had two or more. The mortality rate was 8.5% (4/47). The occurrence of a post-operative faecal fistula, was significantly (p=0.016) associated with a post-operative mortality. A peritoneal aspirate volume >1000mls was significantly associated with having a post-operative faecal fistula (p=0.011), and post-operative mortality (p=0.002). Number of intestinal perforations was not significantly associated with an adverse outcome (p>0.05).

CONCLUSION

Post-operative faecal fistula adversely affected the outcome of the patients in our series. A proactive approach and supportive care is recommended in patients with TIP.

7. *SALMONELLA* BACTEREMIA IN HOSPITALIZED UGANDAN CHILDREN WITH FEBRILE ILLNESS

Grace D. Appiah[1], Arthur Mpimbaza[2], Ruth Kigozi[2], Asadu Sserwanga[2], James Kapisi[2], Catherine Maiteki[2], Moses R. Kamya[3], Mohammed Lamorde[4], Richard Walwema[4], Franklin Kizito[4], Gilbert Aniku[5], Jane Frances Nanteza[6], Abner Tagoola[7], Jeff N. Borchert[8], Matthew Mikoleit[8], Paul S. Mead[9], Kiersten Kugeler[9], Henry M. Kajumbula[10], Molly Freeman[11], Eric Mintz[1]

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BACKGROUND

Salmonella is a known cause of acute febrile illness (AFI) among children in sub-Saharan Africa; however its contribution to bacterial blood stream infections is poorly defined due to limited diagnostic capacity. To address this gap and to inform accurate patient diagnosis and treatment, improved AFI surveillance and expanded diagnostic testing is needed.

METHODS

The Uganda AFI project conducts sentinel surveillance for causes of AFI in children <1 to 16 years old hospitalized at six regional hospitals. We evaluated preliminary demographic data, blood culture and antimicrobial susceptibility results from children hospitalized with a history of fever or documented temperature ≥38ºC at the first three sentinel AFI sites during the first three months of this ongoing surveillance project (July 2-September 30, 2016).

RESULTS

Blood cultures were performed on 498 (19%) of 2,624 children hospitalized with a history of fever. Overall, 445 (89%) yielded no growth; 12 (2%) yielded a likely contaminant, and 25 (5%) yielded a pathogen, including 11 (2%) *Salmonella* isolates. Among the *Salmonella* isolates, 10 were serogroup D, of which at least three were identified as *S.* Typhi: one was serogroup B. *Salmonella* isolates were resistant to ampicillin (90%), cotrimoxazole (45%), ciprofloxacin (9%) and ceftriaxone (9%).

Three (30%) of the children whose blood cultures yielded *Salmonella* had a positive malaria RDT (2), or a positive blood smear (1), and one had a negative malaria RDT and blood smear. The majority (90%) of *Salmonella* isolates were identified from the site with the highest malaria transmission intensity.

CONCLUSIONS

Salmonella are an important cause of bacteremia in children hospitalized with fever, even among those with a positive malaria RDT or blood smear. To improve detection and treatment, sentinel AFI surveillance will continue to characterize the serotypes of *Salmonella* causing bacteremia and their associated drug resistance patterns.

8. WGSA.NET: A FLEXIBLE GLOBAL RESOURCE FOR GENOMIC PREDICTIONS OF ANTIMICROBIAL RESISTANCE AND SURVEILLANCE OF *SALMONELLA* TYPHI

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BACKGROUND

Whole genome sequencing has the ability to transform the way in which we manage the emergence of microbes that pose a direct threat to human health, in real time. However, there is a need for tools to make microbial genome data broadly and rapidly accessible to those who are not expert in genomics, thus linking the genome sciences to public health utility globally. The treatment of typhoid is being compromised by the emergence of strains with resistance to multiple antibiotics (MDR), including those currently used for treatment. The emergence of MDR typhoid has been driven by the global spread of an MDR *Salmonella* Typhi lineage known as H58 or haplotype 4.3.1. Thus, typhoid represents an exemplar of how MDR is threatening treatment at a global level.

METHODS

We have developed WGSA.net, a web application that maps over 2,400 *S.* Typhi public genomes onto geographical space and predicts their antimicrobial resistance profile, with the ability to add new data rapidly. Users can analyse their own genomes or browse existing public collections.

RESULTS

WGSA performs two essential tasks for surveillance and epidemiological investigations of *S.* Typhi, i.e., i) placing isolates into lineages and the recently established genotyping scheme,

identifying their closest relatives and linking to their geographic distribution, and ii) detecting the presence of genes and mutations associated with antimicrobial resistance, a fundamental phenotype to assess the risk that the isolates pose to public health. Over 50 percent of the genome data currently available in WGSA belongs to the MDR lineage H58.

CONCLUSIONS

The data made easily accessible in WGSA can help the local investigator rapidly identify the potential source of their isolate and to predict likely resistance phenotype. This approach could be used to underpin the surveillance of typhoid and MDR, both locally and globally.

9. TEMPORAL TRANSCRIPTOMIC PROFILE OF THE HUMAN MODC RESPONSE TO INVASIVE NON-TYPHOIDAL *SALMONELLA*

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BACKGROUND

Salmonella Typhimurium is generally responsible for localized, self-limiting gastroenteritis in humans. However, the multi-drug resistant *S.* Typhimurium ST313 pathovar has emerged across sub-Saharan Africa as a major cause of lethal bacteremia in children and HIV-infected adults. The isolate D23580 is a representative blood-stream clinical isolate from a Malawian child, and demonstrates genome degradation resembling that of the human restricted pathogen *S.* Typhi.

Dendritic cells (DCs) play an essential role in the initiation and establishment of antigen-specific immune responses. Modulation of DC functions by *Salmonella* has been reported as a mechanism to avoid adaptive immunity. Studies aimed at elucidating the interaction between invasive *Salmonella* and human DCs yielded important insights, yet they are limited by population-level measurements that mask fundamental differences among individual cells.

METHOD

We combined single cell RNA-seq technology with fluorescent labelling of bacteria to monitor gene expression variation among otherwise seemingly identical cells with regard to the infection phenotype. We quantified the early time course of gene expression induced by *S.* Typhimurium LT2 or D23580 infection in 373 human monocyte-derived dendritic cells.

RESULTS

A core set of genes showing consistent expression profiles in response to both strains was identified. The "core response" was type-I interferon driven, involving the NF-kB signalling pathway with concomitant chemokine production. Most of the genes associated with the "core response" were grouped into distinct modules characterized by different temporal heterogeneity profiles. A direct comparison identified several differentially expressed genes clustering in biological pathways, including antigen presentation and proteolytic processes that may elucidate the mechanisms adopted by invasive *Salmonella* to evade or hijack the host immune system.

CONCLUSION

To our knowledge, this is the first single-cell study carried out in human DCs to provide new insights into the molecular contest at the *Salmonella*-host interface and suggest new areas of research to understand the mechanisms of invasive *Salmonella* disease.

10. *SALMONELLA* TYPHI PRODUCING CTX-M-15 EXTENDED SPECTRUM β-LACTAMASE IN THE DEMOCRATIC REPUBLIC OF THE CONGO

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BACKGROUND

Salmonella Typhi is one of the leading causes of bloodstream infections in the Democratic Republic of the Congo (DRC). We report a CTX-M-15 producing *Salmonella* Typhi from DRC concomitantly showing decreased ciprofloxacin susceptibility (DCS).

METHODS

On November 24, 2015, a 6-year old boy presented at a health center in Kwango Province in DRC with a 3-day history of fever, abdominal pain and vomiting. A blood culture was taken, followed by serotyping and antibiotic susceptibility testing by disk diffusion. ESBL screening was performed with clavulanic acid inhibition testing and confirmed by PCR. DCS screening was performed using pefloxacin and nalidixic acid disks, and confirmed by ciprofloxacin E-test and identification of mutations in the quinolone resistance-determining regions (QRDR). The genome of the isolate was sequenced on Illumina HiSeq 2500. Phylogenetic analysis was performed by mapping the genome together with a global collection of 1,832 *Salmonella* Typhi against the CT18 reference genome.

RESULTS

The blood isolate, identified as *Salmonella* Typhi, showed resistance to ampicillin, trimethoprimsulfamethoxazole, aztreonam and cephalosporins. A CTX-M-15 gene was encoded on a mobile insertion element ISEcp1 showing high similarities to the Klebsiella *pneumoniae* plasmid pKP12226. The isolate was resistant to pefloxacin and nalidixic acid, had a ciprofloxacin MIC-value of 0.38 mg/L and a Ser83Phe substitution in the *gyrA* gene. Acquired antibiotic resistance genes against aminoglycosides (*Aac6-iaa*), sulfonamides (*Sull*), trimethoprim (*Dfr*A7) and ampicillin (*TEM-1D*) were detected. Phylogenetic analysis showed that the isolate did not belong to the dominant H58 clade.

CONCLUSION

The finding of an ESBL producing *Salmonella* Typhi in DRC is of great concern, especially since the CTXM-15 gene was found on a mobile element. In addition to the high prevalence of MDR and DCS among *Salmonella* Typhi isolates, therapeutic options for this pathogen are decreasing further. Continuous surveillance and appropriate use of azithromycin are imperative.

11. CHANGES IN THE HUMAN BLOOD TRANSCRIPTOME 12 HOURS AFTER TYPHOID CHALLENGE

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BACKGROUND

Typhoid fever is a serious systemic infection with a poorly understood pathogenesis. Using a recently developed controlled human infection model of enteric fever, we have identified a novel, previously unreported early cytokine signal 12 hours after challenge, potentially reflecting mucosal host-pathogen interactions.

METHODS

Gene expression was measured using RNA extracted from the peripheral blood of 19 adults immediately before and 12 hours after challenge with *S.* Typhi in sodium bicarbonate solution. The R package limma was used to generate a linear model incorporating dose and gender as potential confounding factors. Gene set enrichment analysis (GSEA) against blood transcriptional modules (BTMs) was then used to interpret transcriptional profiles in a biological context.

RESULTS

Overall, 1,073 genes were significantly upregulated and 521 downregulated (BH<0.05, FC>1.25). GSEA identified gene modules associated with neutrophils, toll-like receptor signalling, monocytes and dendritic cells as overrepresented after challenge. Those associated with the adaptive immune response were significantly underrepresented. These observations were consistent between participants, and occurred irrespective of subsequent diagnosis of overt clinical disease. Performing GSEA on genes ranked by differential expression between those who were diagnosed and those who stayed well following challenge highlighted several differences on the modular level.

CONCLUSIONS

For the first time, evidence of an early innate response, which may influence the outcome of infection, has been observed in *S.* typhi challenge participants who did not go on to develop clinical typhoid fever. Analysis of the blood gene expression at this early time point after challenge indicated significant perturbation of the transcriptome, potentially discriminatory of subsequent clinical disease. Furthermore, BTMs representing neutrophils could play a previously under-appreciated role in host-pathogen interactions with *S.* Typhi.

12. PROBLEM OF POOR WATER SUPPLY AND PREVALENCE OF ENTERIC FEVER IN WUKARI AREA OF TARABA STATE IN NIGERIA

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BACKGROUND

Clean, potable water is a major deficiency of Wukari Local Government Area of Taraba state, Nigeria. Located 7.88° N, 9.78E°, the arid nature of the area makes access to potable water difficult.

METHODS

This study examined the state of enteric fever cases in four major hospitals over a period of January to August of 2016 in the area. Only patients reporting with symptoms suggestive of enteric fevers after clinical examination were subjected to laboratory diagnosis using Widal test technique. A total of 1340 male and 1523 female patients were examined over the study period. Survey of the study area was also carried out to assess the acute shortage of water in the area.

RESULTS

Results of the study revealed a total of 825 (61.6%) and 915 (60.1%) positive cases for typhoid fever in males and females respectively with all the study hospitals showing 60% or more cases from the study population over the period. The acute situation of water shortage and poor environmental hygiene in the study area forces the populace to resort to unsafe and untreated water sources for domestic uses as reflected in the pictures from the area.

CONCLUSIONS

The results of the study clearly highlight the problem that due to poor water availability and quality enteric fever is endemic in the study area. There is therefore the need for urgent intervention in terms of provision of safe drinking water, proper environmental sanitation and protection as well as provision of standard laboratories for adequate diagnostic procedures to monitor the prevalence and provide proper data about the state of enteric fever in the study area for remedial measures.

13. NATIONWIDE SURVEILLANCE OF TYPHOID FEVER IN BOTH HOSPITAL- AND COMMUNITY-BASED CLINICAL SETTINGS OF BANGLADESH USING ELISA-BASED RAPID DIAGNOSIS METHOD (TPTEST)

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BACKGROUND

Typhoid fever continue to be significant causes of illness and death, particularly in developing countries where unhygienic food, water and poor sanitation provide thriving conditions for typhoid-causing organisms. The versatile manifestations of typhoid fever make it a true diagnostic challenge. Although widely acceptable, the conventional blood culture can't depict the true burden of typhoid fever because of its major shortcomings like poor sensitivity, requirement of large volume of blood and preadministration of antibiotics. Antibiotics are used empirically which impedes blood culture. This study intends to delineate the epidemiology of typhoid fever in both hospital- and community-based clinical settings of Bangladesh, using ELISA-based rapid typhoid detection method (TPTest) which is free of all the drawbacks of culture method.

METHODS

In this study, blood specimens were collected from 10 hospitals, spread all over the Bangladesh and three community-based clinical settings of Dhaka. Specimens were collected both in culture bottle to perform blood culture and heparinized tube to carry out TPTest. The antimicrobial susceptibility test of the isolated organisms was done by disc diffusion method.

RESULTS

Over the one-year span of study period, a total number of 2036 specimens of suspected typhoid fever from 10 hospitals were tested, where 2.85% were culture positive and 26.03% were positive for TPTest. Among 266 specimens collected from three community settings, 16.5% and 34% were positive for blood culture and TPTest, respectively. Although the specimens from hospitalized patient were collected before any hospital administration of antibiotics, whether the patients took any dose before hospital admission was not recorded, which may have reflected in blood culture result of two different settings. Among the total isolated (103) *Salmonella* Typhi and Paratyphi, 18 (17.5%) were *Salmonella* Paratyphi. The antimicrobial susceptibility test result reveals that all the isolated organisms were resistant to Nalidixic acid where 21%, 13% and 9% were resistant to Cotrimoxazole, Ciprofloxacin and Azithromycin, respectively.

CONCLUSIONS

The TPTest is a more sensitive method and highly suitable for countries where antibiotics are used unrestrainedly, to diagnose and determine the true burden of typhoid fever as the conventional one fails adequately.

14. TYPHOID AND PARATYPHOID FEVER – COMPARATIVE ANALYSIS OF MOLECULAR IMMUNE PROFILES AND DISEASE PATHOGENESIS

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BACKGROUND

Enteric fever caused by *S.* Typhi and Paratyphi A affects millions of humans every year. While *S.* Typhi predominates globally, *S.* Paratyphi is increasingly recognised in endemic areas. Little is known about the host response to *S.* Paratyphi A or whether it differs from those to *S.* Typhi.

METHODS

In a human challenge model of paratyphoid infection, clinical data and samples were collected before and after challenge to study molecular response profiles and cellular immune responses. Using computational analyses we dissected longitudinal transcriptional responses and related these to clinical and molecular metadata. Incorporating data from our previous typhoid challenged participants we further sought to identify pathogen-specific molecular patterns.

RESULTS

Computational analysis of whole blood transcriptomes showed dynamic regulation of gene expression as early as 12 hours after *S.* Paratyphi A ingestion. These response patterns were similar to those seen with typhoid, with early responses occurring independently of the subsequent disease profile, characterized by strong IFN-related signatures, and cytokine signalling highlighting IFN-γ, CXCL10 and TNF-α activity. Interestingly, marked differences during acute infection were observed in clinical and microbiological outcomes; these could be related to subtle differences at the transcriptional level during acute disease. Other similarities with typhoid responses include the significant dysregulation of transcriptional signatures seven days after *S.* Paratyphi A challenge seen in participants not developing infection. Computational analyses identified several non-diagnosed participants with strong transcriptional signatures consistent with enteric fever indicating that, while remaining clinical and microbiologically inconspicuous, these individuals had responses triggered by systemic pathogen exposure.

CONCLUSIONS

This is the first detailed description of the molecular events leading up to acute paratyphoid fever. While overall similarities were observed at the molecular level, detailed computational analysis has yielded insights into how subtle variations may result in differences of clinical phenotype during acute disease.

15. ASSOCIATION BETWEEN TYPHOID FEVER AND CLIMATOLOGICAL FACTORS IN MEKNES PROVINCE, MOROCCO, BASED ON PARTIAL LEAST SQUARES APPROACH

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BACKGROUND

In spite of all efforts deployed by health officers to control typhoid fever, Meknes stills the most severely affected province in Morocco. Various factors may explain this trend, including climatological and environmental ones. Therefore, this study was carried out in Meknes province and aims to understand the impact of climatological factors on the typhoid temporal variability, and to highlight the relationship between climatological and environmental factors in this case, over the period 2004-2013.

METHODS

Due to non-normal distribution of our input data, Spearman correlation was used. In order to point out the relevant periods of the year where the infection by *Salmonella* Typhi was strongly correlated to climate conditions, namely air temperature and rainfall, a new statistical approach was used, Partial Least Squares.

RESULTS

The results reveal a temporal periodicity of typhoid recorded cases, and the presence of significant positive correlation between the studied factors and the typhoid cases ($P<0.01$). Partial Least Squares regression showed two relevant periods where the number of typhoid recorded cases increased, in coincidence with rise of air temperature and decrease of rainfall. The first period started from the end of March to the beginning of June, while the second one extended from the beginning of August to the end of October. In fact, the need for water for irrigation is higher during these two periods, which are characterized by water scarcity. The wastewater reuse in irrigation is a common practice during the hot season, which may explain this typhoid temporal variability.

CONCLUSIONS

This study identified some climatological and environmental determinants of typhoid fever in Meknes Province, which currently exhibits the highest incidence in Morocco. This knowledge can be used to design intervention measures to reduce and hopefully eradicate the disease in this area.

16. RISK FACTORS ASSOCIATED WITH TYPHOID INTESTINAL PERFORATIONS DURING A LARGE OUTBREAK OF TYPHOID FEVER: KAMPALA UGANDA; 2015

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BACKGROUND

Between January and June, 2015, a large typhoid outbreak occurred in Kampala, causing 10,230 suspected infections. We conducted a study to evaluate typhoid intestinal perforation (TIP) during the outbreak, and to assess risk factors for TIP.

METHODS

We defined TIP case as a physician-diagnosed typhoid patient with nontraumatic terminal ileum perforation. We reviewed medical records from January 2013-December 2015 at five major hospitals in Kampala which performed surgeries. In a case-control study, we compared potential risk factors for TIP among cases and controls; controls were those with typhoid diagnosis by TUBEX, culture, or physician but with no TIP, matched to cases by age, sex and residence. We used conditional logistic regression to assess risk factors and control for confounding.

RESULTS

Of the 88 TIP cases identified, 77% (68/88) occurred during the outbreak period. TIPs sharply increased in January and peaked in March, coinciding with the outbreak period. Compared with 29% (13/45) of cases and 63% (86/137) of controls who sought treatment within three days of onset, 42% (19/45) of TIP cases and 32% (44/137) of controls sought treatment after four to nine days (ORadj=3.0, 95% CI=1.3-6.3); 29% (13/45) of cases and 5.1% (7/137) of controls sought treatment after ≥10 days (OR_{adj}=12, 95%CI=4.1-37). Additionally, 57% (26/46) of cases and 31% (43/137) of controls had self-medication (OR_{adj}=2.9, 95%CI=1.4-6.2); 36% (25/39) of cases and 18% (116/142) of controls had not heard about typhoid (OR_{adj}=2.5, 95%CI=1.1-5.5); and 59% (23/39) of cases and 25% (35/142) of controls had not heard about the typhoid outbreak in Kampala (OR_{adj}=4.9, 95%CI=2.0-12).

CONCLUSION

TIP was associated with delay in seeking treatment, self-medication, and being uninformed of the typhoid outbreak in Kampala. We recommended active community case finding for early and appropriate treatment, health education about typhoid fever and TIPs and raising awareness among physicians about risk of perforation during future typhoid outbreaks.

17. EARLIEST EVIDENCE OF MULTIDRUG ANTIBIOTIC RESISTANT NON-TYPHOIDAL *SALMONELLA* SPP. (iNTS) IN UGANDA: FINDINGS FROM CLINICAL SPECIMENS AT MAKERERE UNIVERSITY CLINICAL MICROBIOLOGY LABORATORY

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BACKGROUND

Invasive non-typhoidal *Salmonella* (iNTS) is an emerging blood-stream infection. Prevalence of iNTS is high in settings with high HIV, malnutrition and malaria burden. It is also likely a contributor to emerging antibiotic resistance. In Uganda, the Ministry of Health has paid attention to typhoid surveillance, however little attention has been placed on surveillance of other *Salmonella* subtypes; therefore the burden of iNTS is unknown. As such, the incidence and the extent of antibiotic resistance of iNTS infections could be under-reported despite concomitant high prevalence of the risk factors. In this study we established the prevalence of iNTS and the associated antibiotic-resistance among the clinical specimens collected at Makerere University Clinical Microbiology laboratory.

METHOD

We analyzed data from all clinical specimens collected at Makerere University Clinical Microbiology laboratory between August 2012 and July 2016. We extracted sample results that were positive for *Salmonella* spp. and further analyzed for the various serotypes and drug resistance.

RESULTS

Of 2,784 specimens, 2.1% (59/2784) were positive for *Salmonella* spp. Of the specimens that were positive: 41% (24/59) were typhoidal species, 17% (10/59) were iNTS and 42% (25/59) were not serotyped. All the iNTS were isolated from blood. Drug resistance was highest for Ampicillin; 68% among typhoidal species, 77.7% among iNTS and 30% untyped *Salmonella* spp. This was followed by co-trimoxazole, chloramphenicol and nalidixic acid. Of the iNTS, 70% were resistant to two or more antibiotics.

CONCLUSION

A high prevalence of iNTS is recorded. A majority of the samples positive for iNTS were resistant to commonly used antibiotics underscoring an emerging public health phenomenon. A big proportion of non-serotyped *Salmonella* spp. may represent an underestimation of iNTS prevalence in this study. We recommend sentinel iNTS surveillance to monitor resistance patterns and incidence trends.

18. UTILITY OF SEROLOGICAL TESTS IN ACHIEVING ACCURATE LABORATORY DIAGNOSIS OF TYPHOID FEVER: A SYSTEMATIC REVIEW OF TUBEX® TF CLINICAL PERFORMANCE

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BACKGROUND

Laboratory tests play an integral role in the diagnosis of typhoid fever infection. New technologies for diagnosing typhoid fever have been developed. However, much of these technologies are rarely used due to either the requirement of sophisticated laboratory facilities and trained personnel, or because of limited sensitivity and specificity. Due to these limitations, the serological tests continue to be the major laboratory applications for the diagnosis of typhoid fever. Among the serological tests, TUBEX® TF was proven useful in diagnosing typhoid infection, provided proper clinical correlation is observed. This systematic review evaluates the usefulness of serological tests such as TUBEX® TF as an alternative to the Widal test.

METHODS

Different articles were reviewed for relevance. The articles were evaluated in terms of methodology focusing on reference method and choice of controls. Only the studies with control groups consisting of samples with known etiology other than *Salmonella* Typhi and blood culture negative samples were included in analysis. Studies which used laboratory confirmed *Salmonella* Paratyphi and/

or malaria were also not included to evaluate the effects of using *Salmonella* Paratyphi and/or malaria cases as control in the sensitivity and specificity of TUBEX® TF. Estimates of the sensitivity and specificity of TUBEX® TF were presented in forest plots using Review Manager 5.3 while a summary receiver operating characteristics (SROC) curve as well as summary test accuracy measures were obtained using the user written program "metandi" in Stata IC ver. 14.

RESULTS

A total of five studies were included. Across the extracted studies, the sensitivity of TUBEX® TF ranged from 75 to 95% while its specificity ranged from 80 to 94%. Metaanalysis showed an average sensitivity of 82% (95% CI: 72 – 89%) and an average specificity of 85% (95% CI: 80 – 89%). This pooled sensitivity and specificity were found to be higher than the pooled estimates which included studies using paratyphoid cases as controls.

CONCLUSIONS

The analysis illustrates that choice of controls in the clinical performance evaluation is very critical to estimate the true sensitivity and specificity of serological tests such as TUBEX® TF for the diagnosis of typhoid infection.

19. CONTROLLING THE MBARE TYPHOID OUTBREAK, HARARE (2016-2017)

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BACKGROUND

Typhoid fever is a systemic bacterial infection caused by *Salmonella* enteric serotypes *S.* typhi and *S.* paratyphoid typhi and it remains a significant health challenge in developing countries like Zimbabwe. The City of Harare has had periodic outbreaks of typhoid since 2010, mainly affecting the western suburbs. In October 2016, a typhoid outbreak started in the southern suburb of Harare in Mbare.

METHODS

An epidemiological outbreak investigation was instituted and line lists were analysed to describe the outbreak and to determine the source and potential areas for spread. Spot maps were created to plot cases and boreholes. An environmental assessment including lab testing was done to describe the water and sanitation issues in Mbare. Laboratory investigations were done on stool and blood samples to confirm cases and assess antibiotic sensitivity.

RESULTS

As of 1 February, 2017, there have been 207 suspected cases plus 28 confirmed cases and 2 deaths (Case Fatality Rate= 0.9%). Cases in Mbare have been reported since 21 October, 2016. Environmental assessment found broken and blocked sewer lines and a limited supply of piped water with residents relying heavily on borehole water for consumption. Borehole analysis showed that 20 out of the 42 boreholes in Mbare were contaminated with faecal coliforms or *Salmonella* species. The attack rate was higher in males and children <15 years.

CONCLUSIONS

This was a common source outbreak due to the breakdown of water and sewage systems and the reduced supply of municipal water. Contamination of borehole water at such a level showed that in the cities reliance should be on piped water system and all efforts should be made to improve the water supply and repair sewer lines to prevent the occurrence of further outbreaks.

20. DEVELOPMENT OF REAL TIME POLYMERASE CHAIN REACTION FOR THE DETECTION OF *SALMONELLA* IN STOOL SPECIMENS

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BACKGROUND

Salmonellae are among the leading cause of bacteraemia and death in sub-Saharan African children. The burden of *Salmonella* in Africa and the link between *Salmonella* exposure within the gastrointestinal tract and blood stream is poorly understood in part due to lack of reliable diagnostic test for detection of *Salmonella.* Stool culture, which is the gold standard for *Salmonella* detection, is less sensitive and time consuming. In this study, we aimed at validating Quantitative Real Time-Polymerase Chain Reaction (RT-PCR) test for the detection of *Salmonella* in stool specimens from a cohort of *Salmonella* asymptomatic children.

METHODS

RT-PCR tests using primers from Tetrathionate (TTR) respiration gene and *Salmonella* Invasion gene A (InvA). TTR and InvA RT-PCR assays were tested for inclusivity using different *Salmonella* strains and exclusivity was tested using different gram positive and negative non *Salmonella* bacteria. PCR efficiency and limits of detection were determined using *Salmonella* Typhimurium D23580 reference strain. The primers were also validated against stool culture for *Salmonella. Salmonella* exposure events in 409 stool samples collected from a cohort of healthy children aged 6-18 months was also determined and sensitivity and specificity rates of the assays were calculated.

RESULTS

Both TTR and InvA RT-PCR demonstrated 100% inclusivity and between 87% and 94% exclusivity rates. Both assays had superior limits of detection of up to 1 CFU/ml when sub cultured in selenite F broth with 98% PCR efficiency. Sensitivity and specificity of TTR was 73.91%, 91.3% and 96.89%, 95.08% and for InvA it was 78.26%, 82.61% and 92.49%, 90.41% for neat and selenite sub cultured stool samples respectively.

CONCLUSION

TTR and InvA RT-PCR assays demonstrated superior performance than stool culture. Selenite sub culturing of the samples improves performance and reduces cross reactivity. The two primers can be used together as a diagnostic tool for surveillance studies.

21. ASSESSMENT OF THE ANTIBODY-IN-LYMPHOCYTE SUPERNATANT ASSAY FOR ENTERIC FEVER DIAGNOSIS IN TWO HUMAN CHALLENGE STUDIES AND PROSPECTIVE EVALUATION IN AN ENDEMIC AREA OF NEPAL

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BACKGROUND

Antibody-in-lymphocyte supernatant (ALS) assay, which detects ex vivo antibody production by newly formed B cells, could offer improved sensitivity and specificity over blood culture for enteric fever diagnosis. Here, we characterise ALS assay in two human challenge studies in Oxford and evaluate assay performance in febrile adult patients in Kathmandu, Nepal.

METHODS

Heparinised blood samples were taken from participants during challenge with *Salmonella* Typhi or *S.* Paratyphi A; and from patients in Kathmandu on presentation and 1, 12 and 26 weeks. Peripheral blood mononuclear cells were separated, washed, and cultured *ex vivo. In vitro* IgA antibody production specific for membrane preparation (MP), lipopolysaccharide or flagellin antigens was measured by ELISA of ALS. Diagnostic performance of anti-MP IgA responses at presentation (primary outcome) were compared with blood culture (reference standard) by discordant pairs and area under the curve (AUC) receiver-operator characteristic (ROC) curve analyses.

FINDINGS

In 23 participants challenged with typhoid, anti-MP responses were 91% (95%CI 72–99) sensitive for typhoid diagnosis (fever and/or bacteraemia). In 40 participants challenged with paratyphoid, anti-MP responses were 95% (74–100) sensitive and 57% (34–78) specific for paratyphoid diagnosis, with an AUC ROC of 85% (74–97). In both studies, higher ALS responses were associated with longer duration of bacteraemia ($p<0.05$). In 173 patients in Nepal, anti-MP responses were 86% (70–95) sensitive and 51% (43–60) specific for blood culture confirmed typhoid/paratyphoid diagnoses, with an AUC ROC of 79% (70–88). High ALS responders were more symptomatic ($p=0.024$), and had lower white cell counts than low responders ($p=0.001$).

CONCLUSIONS

The ALS assay is sensitive in identifying bacteraemic enteric fever patients, however better reference standards are needed to ascertain accurate test specificity. The ALS assay could be used to improve enteric fever burden assessments and the accuracy of vaccine efficacy studies.

22. LABORATORY SURVEILLANCE OF PAEDIATRIC ENTERIC FEVER IN NEPAL REVEALS RE-EMERGENCE OF *SALMONELLA ENTERICA* SEROVAR TYPHI STRAINS SUSCEPTIBLE TO CHLORAMPHENICOL AND COTRIMOXAZOLE

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BACKGROUND

Enteric fever accounts for the majority of invasive bacterial disease among children in Nepal. Multi-drug resistant *S.* Typhi refers to isolates which are resistant to first line antibiotics, namely chloramphenicol, ampicillin and cotrimoxazole, that were a major public health problem a decade ago.

Methods: Isolates were obtained from children attending the Patan Academy of Health Sciences (PAHS) hospital between 2008 and 2016. 188 *S.* Typhi isolates were subject to antibiotic sensitivity testing via Kirby-Bauer disk diffusion tests. The EUCAST guidelines were used to gauge chloramphenicol, co-amoxiclav, trimethoprim-sulfamethoxazole, ceftriaxone, nalidixic acid and ciprofloxacin susceptibility of the isolates. Molecular analysis of isolates obtained from 2008 to 2015 was undertaken to identify genes and SNPs associated with drug resistance.

RESULTS

Of the 188 isolates tested, 142 (>75%) were resistant to nalidixic acid. Ninety (48%) isolates were resistant to ciprofloxacin. Only 6 (3%) and 3 (1.5%) isolates demonstrated resistance to cephalosporins and co-amoxiclav respectively of which most were from 2016. 92% of isolates were sensitive to both first line drugs chloramphenicol and cotrimoxazole, while a further 3% were sensitive to at least one. Single Nucleotide Polymorphisms (SNPs) in *gyr*A, conferring resistance to fluoroquinolones, were seen in 107 (76%) isolates and MDR genes were identified in 7 (5%) isolates. These MDR genes, which are usually seen within the incHI1 plasmid, were seen in the bacterial genome in the 7 isolates.

CONCLUSIONS

Fluroquinolones have little role to play in the treatment of enteric fever in Nepal today. The re-emergence of strains which are sensitive to chloramphenicol and cotrimoxazole suggests that *S.* Typhi adapts reversibly to antibiotic pressure. This finding could be exploited to plan sustainable treatment programmes in endemic areas.

23. DOES THIS FEBRILE PATIENT HAVE A TYPHOID FEVER?

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BACKGROUND

Typhoid fever remains a problem of concern in Africa. The gold standard for diagnosis of typhoid fever is blood culture (BC), which is often not available in many developing countries. It would be helpful to have alternative diagnostic approaches. The clinical examination may aid in this process. The objective of this study was to systematically review the accuracy of clinical signs, WHO case definition and Widal test for the diagnosis of typhoid fever in patient with fever.

METHODS

The data source was MEDLINE (last five years 2009-2014) searches of English-language articles that compared of clinical signs with a reference gold standard for diagnosis of typhoid fever. From this, the likelihood ratios (LRs) were calculated for the individual findings described, along with the 95% confidence intervals (CIs). Of the 59 studies identified by the search strategy, 2 studies were used for accuracy analysis.

RESULTS

S. Typhi was isolated from 162 (3.7%) of 4373 blood cultures processed, collected among patients with fever from two studies. Having chills (likelihood ratio [LR], 2.18; 95% confidence interval [CI], 1.483.23), abdominal pain (LR, 2.17; 95% CI, 1.26-3.71), bloody stools (LR, 3.56; 95% CI, 1.04-12.11) and the existence of convulsions (LR, 4.36; 95% CI, 0.58-33.1) slightly increase the likelihood of typhoid fever. The presence of respiratory syndrome such as cough (LR,

0.91; 95% CI, 0.63-1.31), or having breathing difficulties (LR, 0.6; 95% CI, 0.08-4.19), with wheeze (LR, 0.51; 95% CI, 0.13-1.99) or crepitations (LR, 0.44; 95% CI, 0.06-3.07) makes the diagnosis of typhoid fever slightly less likely.

CONCLUSIONS

In resource-limited settings, diagnostic algorithm should include typhoid fever in febrile patients: chills, abdominal pain, bloody stools and convulsions.

24. SANITATION AND HYGIENE PRACTICES AMONG TYPHOID FEVER CASES IN NENO, MALAWI

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BACKGROUND

Typhoid fever, a fecal oral disease caused by *Salmonella* Typhi, is common in areas where hygiene and sanitation is very poor. We investigated the hygiene and sanitation practices among Typhoid cases in Neno, Malawi, from July to October 2016.The district, which has about 150,000 people, has an ongoing Typhoid epidemic currently in its 13th week.

METHODS

During community contact tracing of Typhoid fever cases, we administered a structured questionnaire to the head of the household to assess hygiene and sanitation practices. The data was entered in Microsoft excel 2013 and analyzed using statalC version 14.

RESULTS

We followed 63 cases living in 54 households with a diagnosis based on fever for at least 3 days and a positive Typhoid serological rapid test. Each household had median 5 people (range 2-13). Although all households have a pit latrine, about 72% share the pit latrine with other households. Water is obtained both from borehole (n=49, 92%) and the nearby river (n=39, 74%) and both water sources are within 30 minutes walking distance (n=51, 98%). Apart from chlorine, households do not use any other methods of treating water. During the visits, 41% of households had no chlorine available for use and among those getting water direct from river (n=39), 54% had no chlorine. 64% (n=34) reported using water and soap for handwashing, followed by water only (n=18,34%) and water and ash(n=1,2%). 72% (n=39) of the households had no soap available for handwashing during the visit.

CONCLUSIONS

Our ability to contain the epidemic depends on addressing the poor hygiene and sanitation within the villages. Based on these findings, we started 1) community, household, and school-based education on hygiene and sanitation 2) routine weekly distribution of chlorine 3) intensified contact tracing 4) diversified methods of treating water in the households.

25. ASYMPTOMATIC CARRIAGE OF *SALMONELLA* SPP. AMONG FOOD HANDLERS AT A TERTIARY-CARE HOSPITAL

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BACKGROUND

Carriage of typhoidal salmonellae is a well-known risk factor for food-borne enteric fever transmission. The burden of *Salmonella* carriage among professional food handlers in highly endemic countries such as Pakistan is unknown, but has been observed to be high among street vendors. Chronic carriage among food handlers operating in catering establishments, including in medical institutes and hospitals, can result in large nosocomial and community outbreaks, as catering services are trusted to be free of pathogens by the populace. We report carriage rates in a cohort of professional food handlers employed by food services at a medical institute in Karachi, Pakistan.

METHODS

We examined employee records of all food handlers hired by the food services, at the Aga Khan University Hospitals, from 2006-2015. There were 152 unique records. The food services pre-employment and annual screening is linked to the Employee Health Unit of the institute and all employees found to be infected or carriers are treated by a physician. A hygiene education program is also mandatory for food service employees. Data was abstracted in MS Excel for employees followed up over the study years. The cohort is described.

RESULTS

Our sample consisted of 145 men and 9 women. In 2006, 78 employees were inducted for pre-employment screening. Thereafter, on an average, 8±6 employees were inducted each year. Approximately, 112±20 follow-up stool cultures were performed each year. Over the 10-year period, 12 cases with *Salmonella* positive stool cultures were identified. All *Salmonella* cases were identified on follow-up annual cultures and none on pre-employment screening. Furthermore, all positive species were non-typhoidal. These included the following: three cases of *Salmonella* Group B, one case of *Salmonella* Group C1, four *Salmonella* Group C2, one *Salmonella typhimurium*, and three cases of non-serotypeable *Salmonella enterica*. Additionally, 59 and 20 instances of positive cultures for *Campylobacter* spp. and *Shigella* spp. respectively were identified. Of these, only 9 and 1 cases respectively of *Campylobacter* and *Shigella* were identified on pre-employment screening, implying asymptomatic shedding whereas all other cases were detected on investigation of gastroenteritis or annual follow-up.

CONCLUSIONS

The carriage rate of *Salmonella* spp. among professional food handlers in our cohort is low. Since typhoidal salmonellae were not observed, their carriage in the larger population of professional food handlers is likely to be very low. Routine pre-employment screening and hygiene education of all food handlers, as in our model cohort, can identify asymptomatic shedding of gastroenteritis pathogens which can be a potential trigger to improve hygiene practices among professional food handlers.

26. PREVALENCE OF MALARIA AND TYPHOID CO-INFECTION IN NORTH INDIA

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BACKGROUND

Both typhoid and malaria are diseases of epidemiological importance globally. Co-infection of malaria and typhoid poses a serious problem leading to misdiagnosis and mismanagement

resulting in either under-treatment or over-treatment. Hence it is important to correctly determine the prevalence of typhoid and malaria co-infection.

METHODS

The objective of this study was to estimate the burden of malaria and typhoid co-infections in our settings. The study was done from July 2014 to July 2016. A total of 3,010 samples were analysed in the microbiology laboratory for the diagnosis of typhoid fever and malaria co-infection. Peripheral blood smear examination, rapid diagnostic test (RDT), blood culture and Widal test were done for the diagnosis of malaria and typhoid infections respectively.

RESULTS

Out of 60 blood culture positive samples, 48 (1.6%) were positive for malaria by both peripheral smear examination and RDT. Amongst malaria positive cases, 12 were positive for *Plasmodium falciparum*, 36 for *Plasmodium vivex* and one had mixed infection. Seroprevalence of typhoid infection by Widal was found to be 10% (300/3010). Gold standard tests for both the infections revealed that true co-infection was present only in 1.6% (48/3010) cases, while co-infection rate using Widal test and RDT was found to be 3.4% (105/3010). 100 Widal positive and RDT negative samples were randomly selected and subjected to PCR. 15 such cases were found to be positive by PCR.

CONCLUSION

The prevalence of malaria typhoid co-infection was low as compared to other studies. Molecular tests like PCR should be explored to find out asymptomatic malaria co-infection in patients with enteric fever. Further studies are imperative to determine the true rate of co infection and factors leading to development of co-infection.

27. INVESTIGATING THE MUCOSAL ANTIBODY RESPONSE IN TYPHOID AND PARATYPHOID FEVER

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BACKGROUND

Design of diagnostic tools and efficacious vaccines against enteric fever is hampered by our limited understanding of localisation of the pathogen in the body and of the balance of mucosal and systemic responses preceding and following clinical manifestation of infection. We hypothesised that clinical symptoms of enteric fever may be linked to the level of intestinal mucosal response specific to *Salmonella* antigens and investigated this in a controlled human infection model (CHIM).

METHODS

Using an established enteric fever CHIM in a non-endemic setting, we compared serum and copro-antibody responses from healthy volunteers within two groups: immunologically naïve volunteers with no prior exposure to *Salmonella* Typhi or *Salmonella* Paratyphi; and volunteers previously-exposed to *Salmonella* Typhi or *Salmonella* Paratyphi in earlier challenge studies. Antigen-specific (O9:LPS or O2:LPS) IgA and total IgA ELISA assays were undertaken.

RESULTS

High levels of total IgA were observed in serum and remained unchanged from baseline, up to 28 days after challenge. Consistent with published data on infection of naïve volunteers in such a setting, levels of IgA antibody against the O antigen increased in the serum after challenge mainly in participants with clinical symptoms of disease, peaking at day 14. At the time of submission, the specific responses to the O antigen in the stool samples, in contrast, could not be correlated with clinical outcome. Nevertheless, stool anti-O antigen IgA levels in 8/14 participants increased by 2-fold or greater at day 14. A transient drop in antigen-specific IgA was observed in some participants at day 7 after challenge.

CONCLUSIONS

These are the first data on non-specific and antigen-specific IgA from stool samples during acute enteric infection. A coproantibody response specific to the pathogen was observed but no correlation could be found with clinical outcome.

28. EXPLORING NATURAL KILLER (NK) CELL RESPONSES IN TYPHOID VACCINATION USING A RE-STIMULATION ASSAY

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BACKGROUND

While it is well-known that antibodies and antigen-specific T cells play important roles in vaccinemediated protection against typhoid fever, we have yet to understand the protective mechanisms. In a recent vaccine trial we uncovered significant differences in the transcriptional response to two live attenuated oral typhoid vaccines. Gene transcriptional modules linked to NK cells were positively enriched in the response to Ty21a, which provided 35% [95% CI -5 to 60] protective efficacy against experimental challenge, and negative enrichment scores were observed in response to the less protective experimental vaccine M01ZH09 (protective efficacy 13% [95% CI -29 to 41]).

METHODS

In vitro stimulation of peripheral blood mononuclear cells (PBMCs) with live attenuated *S.* Typhi vaccine strains Ty21a and M01ZH09 followed by flow cytometry for NK cell activation was performed to validate differences in transcriptional profile observed in the vaccine trial. Re-exposure of PBMCs from vaccinated individuals to *S.* Typhi with flow cytometric detection of markers of NK cell activation and functional activity is being performed currently. These experiments investigate whether the capacity of NK cells to respond to re-exposure associates with responses to experimental challenge four weeks after vaccination.

RESULTS

Our data show an increased capacity to activate NK cells in a mixture of PBMCs *in vitro* associated with the more protective vaccine strain Ty21a compared with the less protective vaccine strain M01ZH09. Ongoing experiments may associate the capacity to respond rapidly to re-exposure to *S.* Typhi with clinical outcome parameters such as time to diagnosis.

CONCLUSIONS

Our transcriptional data from a recent vaccine study strongly suggests a role of NK cells in response to vaccination against typhoid fever. Validation of these data in *in vitro* experiments indicates an association of NK cell responses with the more protective vaccine, Ty21a, and may associate with clinical parameters measured following experimental challenge.

29. FROM RIVER TO RESIDENCE: INTER-SCALAR ENVIRONMENTAL DETERMINANTS OF TYPHOID IN CENTRAL DIVISION, FIJI

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BACKGROUND

Interactions between distal ecological conditions and proximal conditions of the lived environment and the microbiological and physicochemical characteristics of residential settings deserve greater attention for their potential to influence the risk of typhoid transmission.

METHODS

We calculated burden and spatiotemporal nature of enteric fever attributable to *Salmonella* Typhi in Central Division, Republic of Fiji, and defined level of disease incidence and recurrence at a sub-catchment scale. We used quantitative analysis to explore relationships between subcatchment environmental characteristics and incidence and recurrence of typhoid (January 2013 – July 2015). Using a case-control design at residential scale, we investigated bacterial contamination and chemical composition of water and soil as vehicles of exposure, complementing these data with observational analysis of residential living conditions and spatial analysis of household position at case and control locations.

RESULTS

There were 236 confirmed typhoid fever cases in 18 of 23 inhabited sub-catchments (370, 570 population) over the study period. Average incidence per sub-catchment was high at 205.9/100,000, with cases recurring each calendar year in 26% of sub- catchments. The most parsimonious models for incidence and recurrence included total high erosion risk area (p=0.034,0.05), % area highly erodible (p=0.028,0.09), connectivity between road and river networks (p=0.063,0.11) and riparian forest fragmentation (p=0.026,0.13) as predictor variables. At residential scale typhoid exposure risk was significantly associated with phosphate (OR 4.235, p=0.042) and *E. coli* concentrations (OR 2.248, p=0.029) in toilet drainage soil and external (OR 3.712, p<0.001), drinking water (OR 2.732, p =0.003) and sanitary (OR 1.973, p=0.031) factors with mechanistic connections to determinants at subcatchment scales.

CONCLUSIONS

This study suggests that anthropogenic alteration of land cover and hydrology at distal and proximal scales increases risk of exposure where sediment yields increase following runoff and combines with practices associated with faecal contamination of residential spaces facilitating increased transmission of typhoid fever.

30. ANTI-VI ISOTYPE AND SUBCLASS-SPECIFIC ASSAYS FOR SERUM AND PLASMA ANTIBODY QUANTIFICATION

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BACKGROUND

Typhoid Vi-vaccine trials incorporating measures of vaccine immunogenicity typically assess serum anti-Vi antibody titres. The aim of this study was to repurpose commercial Vi antibody immunoassay kit components to develop and optimise serum IgA, IgM, and IgG_{1-3}-specific anti-Vi antibody assays. A secondary aim was to validate the use of plasma samples (rather than serum) for anti-Vi antibody quantification with the unmodified commercial kit.

METHODS

One hundred and eleven participants enrolled in a typhoid vaccine trial were randomised to receive an active typhoid vaccine (Vi-polysaccharide/Vi-tetanus toxoid) or control, prior to oral *Salmonella* Typhi challenge one month later. Participants were actively observed for clinical or bacteriological confirmation of typhoid diagnosis. Anti-Vi IgG titre was quantified in all participants, and IgA, IgM, and IgG_{1-3} in 36 participants before vaccination, one month after vaccination, and one month after infection. Matched post-vaccination plasma and serum samples from 39 participants were also assayed using an unmodified commercial immunoassay kit (VaccZyme™ Human Anti-*Salmonella* Typhi Vi IgG Enzyme Immunoassay Kit, The Binding Site).

RESULTS

Preliminary results indicate that post-vaccination anti-Vi pan-IgG, IgA, IgM, and IgG_{1-3} titres significantly correlated with protection from *S.* Typhi infection. Vaccine-specific levels of protection will be calculated upon completion of the vaccine trial in December 2016. Post-vaccination plasma and serum anti-Vi IgG titres were significantly correlated, with corresponding mean plasma titres 12% lower than in serum.

CONCLUSION

This project successfully optimised the VaccZyme™ Kit for anti-Vi IgA, IgM, and IgG_{1-3} quantification within a clinical trial context, for use as a possible correlate of protection. Furthermore, a correlation between serum and plasma anti-Vi IgG titres was demonstrated, suggesting that the kit may be suitable for use with plasma samples. Our findings bear relevance for teams seeking to investigate the humoral immune response to typhoid vaccination and challenge, with further potential applications in serosurveillance.

31. EVALUATING T FOLLICULAR HELPER CELL RESPONSES TO TYPHOID VACCINES

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BACKGROUND

Vi-polysaccharide vaccines have been available for more than two decades and provide moderate protection against typhoid disease. Despite this, these vaccines are not widely used in endemic countries. As a T-independent antigen, Vi-polysaccharide is poorly

immunogenic in young children, has a short duration of protection and lacks booster responses with antigen re-exposure. Vi-conjugate vaccines overcome these limitations by inducing T-cell dependant responses, which are required to evoke immunological memory. We assessed subsets of circulating T follicular helper cells in humans, after immunisation with a Vi-polysaccharide or Vi-tetanus toxoid conjugate vaccine.

METHODS

Twenty-five healthy participants enrolled in a clinical vaccine trial measuring the efficacy of Vi-tetanus toxoid conjugate and Vi-polysaccharide vaccine versus a control conjugate vaccine were selected for in-depth immuno-profiling. Vaccination-associated T follicular helper (Tfh) cell response was evaluated with flow cytometry before vaccination, and 7, 10 and 28 days after vaccination. The generation of a memory B cell response was quantified by ELISpot analysis, and anti-Vi antibody responses measured by ELISA. Antibody functionality was assessed using a serum bactericidal assay (SBA).

RESULTS

There was a significant induction of PD1+CCR6-CXCR3-CXCR5+CD4+ T cells in participants who developed an anti-Vi antibody response following vaccination. This Th2-like TfH subset has been identified as a quiescent precursor to cells with capacity to provide B cell help. The expansion of this rare TfH population correlated positively with changes in anti-Vi antibody titre as well as the functionality of antibody response, as measured by SBA. PD1+CCR6-CXCR3-CXCR5+CD4+ T cell induction was also shown to positively correlate with changes in the frequency of circulating antigen-specific memory B cells after vaccination.

CONCLUSION

Detailed immuno-profiling has implicated PD1+CCR6-CXCR3-CXCR5+CD4+ T cells as key drivers of specific and functional immune responses to vaccination against *S.* Typhi. The identification of this TfH subset following glycoconjugate vaccination may represent an important correlate of long-lived immunity and potentially protection.

32. PLASMA CYTOKINE RESPONSES TO *SALMONELLA* TYPHI VACCINATION AND INFECTION IN A HUMAN CHALLENGE MODEL

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BACKGROUND

Cytokines are important mediators of immune cell activation, their measurement providing important insights into the dynamics of a host immune response. In multiple human typhoid vaccination/challenge models, we determined the plasma cytokine responses characteristic of vaccination and infection.

METHODS

Using multiplexed cytokine technology (8-20 analytes), we quantified plasma cytokine responses to vaccination with two live attenuated oral vaccines, parenteral Vi polysaccharide or Vi-conjugate vaccine, and subsequent experimental infection with *S.* Typhi. Samples were taken at multiple time points before and after vaccination, challenge (*S.* Typhi exposure), and confirmed typhoid infection, to assess cytokine responses to each of these events. Analysis of baseline cytokine levels with respect to the development of typhoid was performed to investigate their relationship with susceptibility to infection.

RESULTS

Statistically significant increases from baseline levels was identified in sCD40L, EGF, CX3CL1, and CXCL1 at 12 hours post-challenge, while IL17A, CXCL10, IL-8 and IL-6 were seen to decrease at this time point. These responses were independent of the subsequent development of typhoid infection, and returned to baseline levels at 24 hours after challenge. Pre-challenge levels of CX3CL1, IFNg, IL-6, IL-17A and VEGF were significantly higher in individuals who were subsequently diagnosed with typhoid infection. Analysis of cytokine responses following Vi polysaccharide and conjugate vaccinations is ongoing and may provide insights into mechanisms of protection.

CONCLUSIONS

The presence of a transient increase in plasma cytokines shortly after exposure to *S.* Typhi is a highly reproducible signature detected in our typhoid human challenge model. Although further validation is needed, these cytokines in blood may arise from inflammation at the gut mucosa. The increased level of baseline inflammatory markers in those who develop typhoid infection raises the possibility that the host's immune activation state on exposure may be an important factor in determining an individual's susceptibility to infection.

33. EPIDEMIOLOGY OF TYPHOID IN NENO, MALAWI

C Kachimanga[1], B Khongo[1], M Jamu[1], T Gates[1], J Meiring[2], MA Gordon[3], M Mwesawina[4], A Banda[4], B Kalombo[5], S Epiphi[5], L Nazimera[5]

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BACKGROUND

Neno district in Southern Malawi (150,000 population) is currently experiencing an epidemic of Typhoid fever (*Salmonella* Typhi). After confirmation of the epidemic by blood-culture, a case-definition based on fever for at least 3 days and a positive Typhoid antibody test was used. A sub-set of cases continue to be blood-culture confirmed. By October 2016, 13th week after index case, the district had treated 160 cases of Typhoid fever. We present demographic, clinical characteristics and outcomes of Typhoid fever cases in Neno.

METHODS

Following clinical case-definition and fluoroquinolone treatment, Typhoid fever cases had a home-visit shortly after diagnosis. During the visit, we conducted household/community case identification and referral, education on food handling, sanitation and hygiene, and distribution of chlorine. We also retrospectively collected data on demographic, clinical and household characteristics of the cases. The data was entered in Microsoft Excel, cleaned and analyzed using StataIC version14.

RESULTS

We tracked 63 Typhoid fever cases living in 54 households. The median age of the cases was 12 years (range: <1yr-66), with males slightly older than females (Median age for Males was 13 while females was 9); 68% (n=43) of all cases were less than 20 years old. Case-definition diagnosis was made median 10 days after onset of fever (range: 1-30 days). Apart from fever, other commonly-reported symptoms included headache (61%), abdominal pain (54%), diarrhea (47%), vomiting (30%), coughing

(16%) and constipation (5%). No patient reported neurological and/or intestinal perforation as complications. Among all cases of Typhoid fever, only 8 patients were admitted to hospital and no case fatalities were reported.

CONCLUSIONS

Typhoid fever cases presented with symptoms similar to other common diseases like malaria. Since the epidemic is ongoing, we are intensifying community and facility case finding and treatment and updated data will be presented.

34. SOCIAL AND ECONOMIC BURDEN OF TYPHOID FEVER: A QUALITATIVE STUDY FROM KATHMANDU AND SURROUNDING COMMUNITIES

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BACKGROUND

Typhoid fever is a significant contributor to infectious disease mortality and morbidity in South Asia. With increasing antimicrobial resistance, commonly used treatments are less effective and risks increase for complications and hospitalizations. During an episode of typhoid fever, households experience multiple social and economic costs that are often undocumented. The primary objectives of this study were to: 1) contextualize the experiences of households affected by typhoid fever from pre-diagnosis through treatment and on-going engagement in preventive practices; 2) provide perspectives from health care providers and outreach workers regarding the challenges related to diagnosis, treatment, and prevention of typhoid fever; and, 3) identify avenues for interventions to improve access to care and disease prevention.

METHODS

Qualitative interviews were conducted in August 2015 with 8 physicians and 22 households with typhoid fever cases confirmed by blood culture. Three focus group discussions were conducted with Public Health Centre providers and Female Community Health Volunteers. Data were also collected on household monetary and time costs associated with disease episodes. Research sites included Kathmandu Valley and surrounding rural areas.

RESULTS

Data reveal delays accessing healthcare, financial and time cost burdens on households, and the need to increase health literacy regarding typhoid fever prevention. Data illustrate the impact of limited laboratory diagnostic tools on health care providers' abilities to distinguish typhoid fever from other febrile conditions and treatment challenges associated with antimicrobial resistance.

CONCLUSIONS

Typhoid fever burden remains high in Nepal. These contextual data provide important information regarding the significant social, economic, and physical costs associated with typhoid fever. Further research on these social and economic burdens in Nepal and other endemic settings is needed to supplement on-going surveillance, cost-of-illness studies, and vaccine demonstration projects to ensure that household and community experiences are an integral part of future policies, and treatment and prevention programs.

35. PRESCRIBING TREND AND COST OF TREATMENT OF ENTERIC FEVER IN NEPAL

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BACKGROUND

Enteric fever is a major public-health problem in Nepal despite efforts to control the disease. Information on prescribing practice and treatment cost are crucial for disease control programs.

METHODS

Medical prescriptions of enteric fever cases were reviewed to analyze the prescribing trends for diagnosis and treatment at different levels of health care facilities located across the country.

RESULTS

A total of 115 enteric fever cases were reviewed of which 100 were outpatient and 15 were inpatient cases. Among outpatients, 33% were presented at Primary, 36% at District and 31% at Zonal /Tertiary level health care facilities. Highest incidence was among patients of age group 21-30 years, while no significant gender difference was found. Among inpatient cases, the average duration of hospitalization was 4.2 days. Widal test was commonly prescribed (58%) for diagnosis while blood culture/sensivity was prescribed only in 33% cases (at hospital level only). Cefixime was the most commonly prescribed antibiotic (64%) followed by azithromycin (19%) in out-patients while ceftriaxone was commonly prescribed (in 80%) among inpatients. Combination therapy with two or more antimicrobials was prescribed in 23% cases. Antipyretics, anti-inflammatory, vitamins, proton pump inhibitors were also commonly prescribed. The average treatment cost increased by three fold among inpatients compared to outpatients. Medicines, diagnostics and other hospital-care cost constitute 57%, 26% and 17% of treatment cost respectively.

CONCLUSIONS

Widal test continues to be carried out commonly for diagnosis of enteric fever. Treatment was not based on culture sensitivity test, raising the risk for not receiving appropriate diagnoses and treatment. Use of ciprofloxacin has declined. Cephalosporins prescribed empirically at all levels of healthcare facilities warrants continuous monitoring of resistance. There is a need to strengthen diagnostics for the generation of reliable burden data and rationalize treatment.

36. INCREASING MULTIDRUG AND FLUOROQUINOLONE RESISTANCE AMONG *SALMONELLA* TYPHI FROM SPORADIC OUTBREAKS IN KENYA

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BACKGROUND

Typhoid fever (TF) caused by *Salmonella* Typhi remains a major public health problem in Kenya. A systematic surveillance in in two slum areas in Nairobi, revealed a crude incidence of TF of 247 cases per 100,000 person-years of observation (pyo), with highest rates in children 5–9 years old (596 per 100,000 pyo). Currently over a third of *S.* Typhi isolates are multidrug-resistant (MDR), and show reduced susceptibility to fluoroquinolones; the drugs of choice for treatment of MDR cases. The situation is worrying especially for resource-limited settings where the few remaining effective antimicrobials are either unavailable or too expensive to be afforded by the general public. The main objective of this study was to

evaluate the trends in AMR among *S.* Typhi isolated from patients attending hospitals in Nairobi in the last 5 years.

METHODS

We assessed the susceptibility to commonly available antimicrobials of 225 *S.* Typhi isolates from 5 years of study (2009-2014) from sporadic outbreaks in clinics around Nairobi. We used the disk and MIC method to determine antimicrobial resistance patterns and determined genetic basis of resistance by PCR.

RESULTS

S. Typhi outbreaks were due to a single haplotype H58, which is the main cause of epidemics in SE Asia. Over last 5 years only 17.9% were fully sensitive. The majority (60.5%) were multiply resistant to commonly available drugs - ampicillin, chloramphenicol, tetracycline (MICs > 256µg/ml) and co-trimoxazole (MIC > 32µg/ml). Nalidixic resistance was observed in 10% in 2009 to 18% in 2014 of isolates while resistance to ciprofloxacin susceptibility increased from 5% to 10% in 2014.

CONCLUSION

The rate of increase in MDR over the last 5 years is worrying as more *S.* Typhi become less susceptible to fluoroquinolones. Improved hygiene and sanitation and use of WHO-recommended vaccines should be considered for effective management of MDR TF.

37. INVASIVE SALMONELLOSIS IN HIV-UNINFECTED PATIENTS IN SOUTH AFRICA 2003-2013

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BACKGROUND

HIV-associated invasive nontyphoidal *Salmonella* (iNTS) infection has responded to antiretroviral programmes in South Africa. HIV-uninfected patients can acquire infection in association with predisposing immunosuppressive conditions. This study aimed to define risk factors for mortality in HIV-uninfected patients, to improve patient management.

METHODS

Salmonella isolates received from diagnostic laboratories around South Africa were serotyped in CED and antimicrobial susceptibility testing done. Data including basic demographic information, HIV status, outcome and other risk factors was collected at selected sites.

RESULTS

Between 2003 and 2013, we identified 8617 iNTS cases; HIV status was known for 3285 (38.1%): 615 (18.7%) were HIV-uninfected. Incidence rates per 100,000 population increased from 2003 (22 cases [0.06/100,000]) to 2013 (98 cases [0.21/100,000]) (incidence rate ratio [IRR] 1.11, 95% confidence interval (CI)=1.09-1.14, P<0.001). Males numbered 318/615 (51.7%). Ages were available for 613/615 (99.7%): <5 years: 375 (61.2%); 5-14 years: 29 (4.7%); 15-24 years: 27 (4.4%); 25-54 years: 135 (22.0%); ≥55 years: 47 (7.7%). Risk factors were identified in 308 (50.1%) patients: including malignancy (32/308; 10.4%) and protein energy malnutrition (children) (64/376; 17.0%). Two (0.6%) patients had malaria. Outcome was known for 602 (97.9%) patients: 96 (15.6%) died. On univariate analysis, mortality was associated with age ≥55 years (Odds Ratio [OR]=6.6; 95 % CI=3.4-12.8; P<0.001), severity of illness (OR=4.8; 95% CI=1.8-12.3; P=0.001), nosocomial infection (OR=1.7; 95% CI=1.0-3.2.8; p=0.05) and comorbidity (OR=2.6; 95% CI=1.6-4.2; P<0.001). *Salmonella* serotype and multidrug resistance were not contributory. On multivariate analysis, mortality was associated with age ≥55 years (adjusted OR [AOR]=5.5; 95% CI=2.5-12.4-12.9; p<0.001) severity of illness (AOR=4.7; 95% CI=1.7-12.8; p=0.003) and comorbidity (AOR=2.3; 95% CI=1.3-4.1; p=0.006).

CONCLUSIONS

Mortality due to iNTS in HIV-uninfected patients in South Africa is primarily associated with older age and disease severity. Reasons for increasing incidence rates remain undefined but may be associated with increasing poverty and food security issues.

38. *SALMONELLA ENTERICA* SEROTYPE TYPHI IN SOUTH AFRICA: DEFINING CASES, CLUSTERS AND OUTBREAKS

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BACKGROUND

Salmonella enterica serotype Typhi (*Salmonella* Typhi) is endemic in South Africa. Incidence rates are ~0.1 per 100,000. Nonetheless, typhoid fever outbreaks are reported, complicated by imported cases from ongoing outbreaks on the country's borders. This study was undertaken to establish whether molecular methods could differentiate between local and imported cases, to support the epidemiological investigation.

METHODS

In January 2016, a renewed programme of case follow-up and contact tracing was introduced. Active laboratory-based surveillance complemented these efforts through phenotypic and genotypic analysis (Pulsed-Field Gel Electrophoresis [PFGE] and Multiple-Locus Variable-Number Tandem Repeats Analysis [MLVA] and WGS) of *Salmonella* Typhi isolates from cases and contacts.

RESULTS

By mid-November 2016, 90 typhoid fever cases had been reported in South Africa. Cases appeared predominantly associated with the 2012 Zimbabwean clone. Two typhoid fever clusters were identified in Gauteng and Western Cape (WC) provinces respectively. One Gauteng cluster was related to a domestic worker returning from Zimbabwe, the second to endemic infection: the index case had travelled locally. Both clusters were highly related on PFGE and MLVA. The first WC typhoid fever cluster included both cases and carriers in an extended family. PFGE patterns and MLVA profiles were identical. The second WC cluster showed a different *Salmonella* Typhi PFGE pattern and MLVA profile compared with the first and was considered unrelated. MLVA profiles of these isolates showed single locus variations, but were interpreted as related to one other. One WC cluster and both Gauteng clusters were related to Zimbabwean outbreak cluster. WGS results confirmed these relationships.

CONCLUSIONS

MLVA and PFGE could not differentiate between endemic typhoid fever, secondary to the Zimbabwean outbreak, or imported cases. Further WGS analysis is planned to compare these clusters with other *Salmonella* Typhi isolates identified in 2016 and locally acquired versus imported isolates from previous years.

39. A GENOTYPING SCHEME FOR *SALMONELLA ENTERICA* SEROVAR TYPHI, THE CAUSE OF TYPHOID FEVER

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BACKGROUND

Typhoid caused by *Salmonella enterica subsp*. enterica serovar Typhi (*S.* Typhi) is a global health problem. *S.* Typhi exhibits minimal genetic variation, which makes discrimination of isolates in epidemiological studies challenging. Public health laboratories have utilised methods such as pulsed-field gel electrophoresis, which provide limited discrimination and phylogenetic information. *S.* Typhi classification has been based on genotyping of 88 single nucleotide polymorphisms (SNPs) allowing subdivision of the population into 85 haplotypes. Subsequently, whole genome sequencing (WGS) has been used to identify more SNPs within the *S.* Typhi genome providing greater resolution to the scheme.

METHODS

We utilized data from WGS of 1,831 *S.* Typhi isolates sourced from over 60 countries to generate a robust genotyping scheme that provides high-resolution phylogenetic information. We explored the utility of the genotyping framework to predict the geographical source of 99 travel-associated *S.* Typhi in the United Kingdom.

RESULTS

We identified a set of 68 SNPs that can be used genotype *S.* Typhi into the four primary clusters, 16 clades and 49 subclades. For each of these groups, we identified one SNP to be used for genotyping. For the travel-associated isolates, prediction of geographical origin based on the closest strain of known location in the global framework would have yielded the correct region of origin in all cases, and the correct country of origin in 71% of cases (95% confidence interval of 66%-76%).

CONCLUSION

Our extended genotyping scheme gives greater discriminatory power and improved phylogenetic information than the existing scheme. Analysis of novel *S.* Typhi isolates to the global population framework is predictive of geographic origin at the regional level and has potential to predict origins to the country of origin level. This approach forms a robust framework for tracking typhoid in the field and will enable enhanced surveillance of this important disease.

40. A FALSE REPORTED TYPHOID OUTBREAK DUE TO INADEQUACIES IN TYPHOID SURVEILLANCE

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BACKGROUND

The Health Management Information System reported 1549 cases of typhoid fever in 2015 and 1743 in 2016 in Nakaseke District. The Uganda Ministry of Health has provided surveillance case definitions on typhoid fever to districts; however, adherence is unknown. We conducted an investigation to determine whether an outbreak had occurred, and evaluated the adherence to the surveillance guidelines.

METHODS

We compared the number of typhoid cases reported during January – April 2016 in three health facilities in Nakaseke District and the same time period in 2016. We extracted patient medical records to assess adherence to surveillance guidelines, especially in regard to standard surveillance case definitions, and to identify any cases of perforations. We also examined freshly admitted typhoid in-patients and reviewed laboratory and data collection procedures. We collected blood specimens from 5 freshly diagnosed typhoid patients for culture confirmation.

RESULTS

Nakaseke District reported 560 typhoid cases during January to June 2016, compared to 291 reported cases during the same time-period in 2015. Of the admitted patients reviewed, 28% (5/18) met the surveillance case definition. Of the 1025 records reviewed in 2016, 81% (829/1025) of diagnoses were clinical only, and 19% (192/1025) had a positive Widal test as the supporting laboratory evidence. All 5 samples from the freshly diagnosed patients cultured negative for typhoid at the reference laboratory. No cases of perforations were identified in area hospitals during the time periods under review.

CONCLUSIONS

No evidence supported that a typhoid outbreak had occurred in the district. The increase in the reported typhoid cases was likely due to inadequate use of standard surveillance case definitions and use of unreliable laboratory diagnostic tests. We recommend enforcing the use of surveillance case definitions for typhoid reporting, and developing laboratory capacity for typhoid diagnosis.

41. INFLUENCE OF CLIMATIC FACTORS ON TYPHOID FEVER: A SYSTEMATIC REVIEW

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BACKGROUND

Climate change is predicted to influence seasonal climate patterns and the severity of extreme weather events, which could have a substantial effect on typhoid and paratyphoid transmission. We conducted a systematic review to determine the association of seasonal climatic variables and typhoid fever.

METHODS

We searched EMBASE, MEDLINE, Global Health and Web of Science for epidemiological studies of any design published before May 16, 2016, screened titles and abstracts, and extracted data in duplicate. Eligible studies evaluated the association between typhoid fever and precipitation, temperature or major climatic events. We examined these associations by geographic region, study setting and design, and by the socioeconomic status of the study population.

RESULTS

The search yielded 12,934 studies after de-duplication, of which 30 were included in our final analysis. The majority of studies were conducted in Asia (60%) and Africa (20%) and in low-income, urban settings. Most of the studies (70%) did not use quantitative analytical methods and only described the association of interest. Twenty-eight of the studies assessed the pattern of typhoid fever in the context of wet and dry seasons, which were defined by seasonal precipitation, flooding, or drought. In Asia, 75% of the studies found a positive association between typhoid fever and wet monsoon conditions, while in Africa, 66% of studies reported a positive association between typhoid fever and seasonal drought.

CONCLUSION

Our analysis suggests that there are distinct geographic trends in the association between typhoid fever and seasonal climate variables, but few studies have tried to quantify these relationships. This review highlights the importance of climatic factors on typhoid fever transmission. A better qualitative and quantitative understanding of the relationship between climatic factors and typhoid seasonality can aid the prevention typhoid fever and mitigate the effects of climate change.

42. TYPHOID FEVER TRENDS IN NEPAL: ANALYSIS FROM OM HOSPITAL RESEARCH CENTER AND ANTIMICROBIAL RESISTANCE SURVEILLANCE IN NEPAL

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BACKGROUND

Typhoid fever remains as a major public-health challenge in Nepal. Monitoring of typhoidal Salmonellae was included in National Antimicrobial Resistance (AMR) Surveillance following an outbreak due to multi-drug-resistant strains in Bharatpur, in 2002.

METHODS

Salmonella enterica Typhi and Paratyphi reported through AMR Surveillance and Om Hospital and Research Center (OHRC), Kathmandu were analyzed to investigate temporal and geographical distribution, patients' gender and age, the changes in serotypes and antimicrobial resistance.

RESULTS

A total of 3453 *Salmonella enterica* isolates from Nationwide AMR surveillance at four different time intervals and 584 isolates reported from OHRC during 2009 to 2014 were analyzed. Yearly breakdown showed 512, 1269, 1035 and 637 isolates from AMR surveillance in the years 2004, 2009, 2012 and 2014 respectively while 63, 207, 30, 69, and 215 isolates were reported from OHRC from 2009 to 2013 respectively. AMR surveillance showed increase in proportion of *S.* Paratyphi A from 29% to 50% from 2004 to 2012, which dropped to 34% in 2014. At OHRC, *S.* Paratyphi A remained the major serotype (60%) from 2009-2014. Majority of the isolates were from male (60%) and highest incidence (26%) in children aged 0-14 years was observed from AMR survey in 2004. In 2009 and subsequent years it shifted to the age group 15-29 years (28%). Typhoid cases were recorded all round the year with peaks during May to August. Resistance to classical agents (Ampicillin-Chloramphenicol-Cotrimoxazole) dropped from 4% in 2004 to 0.6% in 2014, whereas that of Nalidixic acid (NA) increased from 8% to 94% from 2004-2014. *In-vitro* resistance to Ciprofloxacin emerged in 2009 (10%) which increased to 80% in 2014.

CONCLUSIONS

*S.*Typhi and *S.* Paratyphi A are equally implicated in enteric fever in Nepal. Classical agents showed good in-vitro activity against typhoidal salmonellae. Decreasing susceptibility to NA and Ciprofloxacin raises concern on typhoid treatment practice in the country.

43. TYPHOID AND INTS INCIDENCES IN PRE-SCHOOL CHILDREN IN AFRICA: RESULTS FROM THE TYPHOID SURVEILLANCE IN AFRICA PROGRAM (TSAP)

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BACKGROUND AND METHODS

Invasive bacterial infections (IBI) are an important cause of febrile disease in children and adults in sub-Saharan Africa (sSA). From 2011 to 2013 the authors conducted the Typhoid Fever Surveillance in Africa

(TSAP) program in Ghana, Burkina Faso, Senegal, Guinea-Bissau, Sudan, Ethiopia, Kenya, Tanzania, Madagascar and South Africa. Standardized surveillance for bacterial pathogens was put in place and 13,431 blood cultures were performed. 568 non-contaminant bacteria were isolated among which 135 were *Salmonella* Typhi and 94 were non-typhoidal *Salmonella* (iNTS) serovars.

In October 2017, the World Health Organization (WHO) Scientific Advisory Group of Experts (SAGE) will make recommendations for new typhoid conjugate vaccines to be included into the Gavi portfolio. Towards this end, apt vaccination strategies, particularly target age groups need to be defined. Here we present data on the disease burden of *S.* Typhi and iNTS disease for children <5 years of age.

RESULTS

For *S.* Typhi, 37/135 isolates were identified in children <5 years of age, the majority in Ghana (15), Kenya (13), Burkina Faso (7) and Guinea-Bissau and Tanzania each 1. No isolates were yielded in Madagascar, Sudan, South Africa and Ethiopia in that age-group. For iNTS disease, 71/94 isolates were found in children less than 5 years of age, Ghana (52), Burkina Faso (9), Guinea-Bissau (6), Kenya (2), Tanzania and Madagascar each one; no iNTS in that age-group was identified in Sudan, South Africa or Ethiopia. During the conference, we will present further stratification and incidences for these age-strata.

CONCLUSION

The TSAP data have implications for future vaccination programs. *S.* Typhi does not constitute a major cause of IBI under the age of 24 months in our study sites; yet, novel conjugate vaccines should be given prior to that age to ensure that *S.* Typhi can be prevented in higher risk groups from 24 months and beyond. iNTS disease, in contrary, is prevalent in infants and young children and an early deployment of iNTS vaccines to children less than one year of age would be required to ensure that the majority of cases can be prevented.

44. NO ASSOCIATION BETWEEN *SALMONELLA* INTESTINAL CARRIAGE AND SCHISTOSOMA MANSONI INFECTION IN HEALTHY INDIVIDUALS, DEMOCRATIC REPUBLIC OF THE CONGO

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BACKGROUND

In Sub-Saharan Africa, *Schistosoma* infection is mentioned as a risk factor for *Salmonella* carriage. We assessed the co-presence of intestinal *Salmonella* and *Schistosoma* in a rural site in the Democratic Republic of the Congo (DRC, Kifua II village, Kongo Central Province), endemic for *Schistosoma* infection and invasive salmonellosis.

METHODS

From November 2015 to March 2016 (during the rainy season), healthy inhabitants aged ≥1 year were asked to give two consecutive stool samples after informed consent. Samples were assessed for *Salmonella* (culture with Selenite broth and *Salmonella-Shigella* agar) and *Schistosoma* eggs (microscopy, Kato Katz).

RESULTS

Overall, 2.007 stool samples were collected from 1.108 participants (representing 88,6% of the population n = 1,250); median age (interquartile range (IQR)) was 15 (7-35) years. Half of participants (n = 567; 51,2%) were *Schistosoma mansoni* positive. *Schistosoma* egg load was light in 51% (n = 291), moderate in 31% (n = 173) and heavy in 18% (n = 103) of *Schistosoma*-infected participants. A total of 40 (3,6%) participants were found carriers of non-typhoidal *Salmonella*; none of the samples grew *Salmonella* Typhi. Mean age ± standard deviation of *Salmonella* carriers was 25 ± 19 years and did not differ from the non-*Salmonella* infected participants (22 ± 19 years, p = 00,32); male-to-female rates were 1:1,5 and 1:1,1 respectively (p = 0,37). *Salmonella* was isolated in similar proportions among *Schistosoma*-infected and non-infected participants (4.4% (25/567) and 2,8% (15/541) respectively, p = 0,14). Egg loads among *Salmonella-Schistosoma* co-infected participants were mostly light (n = 12; 48%) and heavy (n = 9; 36%). Follow-up of 17 *Salmonella* carriers revealed a single participant with repeat culture for *Salmonella*, 4 weeks after the initial sampling.

CONCLUSIONS

The present study, conducted in a rural area in DRC showed (i) *Salmonella* intestinal carriage rates of 3,6% which were (ii) not associated with *Schistosoma mansoni* intestinal infection.

45. INVESTIGATION OF AN OUTBREAK OF TYPHOID FEVER IN THREE SCHOOLS IN MALOSA DISTRICT, SOUTHERN MALAWI, USING ENVIRONMENTAL SAMPLING AND NOVEL SEROLOGY

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BACKGROUND

Starting in June 2016, a rapid increase in incidence of typhoid fever centred around three residential schools, including a nursing college, was noted in Malosa region, southern Malawi. We report a description of the outbreak together with the public health response, which included environmental sampling and serological survey.

METHODS

A suspected case of typhoid fever was defined as unexplained onset of fever, plus at least one of headache, abdominal pain, diarrhoea, or vomiting, with a negative malaria rapid-diagnostic test. Blood cultures were taken from a sample of patients fitting the case definition. Environmental samples of the gravity-fed water source supplying the institutions, together with tap-supplies and stool from food-handlers were taken. Samples were analysed for the presence of *Salmonella* spp. using standard culture. AntiVi antibody testing will be performed, along with a combination of other novel antigens at three and six months post outbreak. Participants with high titres will have microbiological screening of stool to investigate the relationship with bacterial stool shedding.

RESULTS

245 cases were recorded during the outbreak in a population estimated at 1,200, suggesting an attack rate of 19.5%. There was one recorded death. *Salmonella* Typhi was confirmed in blood cultures of five cases. Environmental sampling did not identify *S.* Typhi but non-typhoidal *Salmonella* was grown from the chlorinated water supply. Data from serological sampling will be available in February.

CONCLUSIONS

This outbreak of typhoid fever, with a high attack rate in a well-circumscribed cohort, has enabled investigation into the potential source of infection as well as novel serological sampling to determine rates of exposure and chronic carriage. We highlight the need for rapid case identification, treatment, source control and enhanced diagnostics in this setting.

46. THE STRATEGIC TYPHOID ALLIANCE ACROSS AFRICA AND ASIA; A STUDY OF BURDEN, TRANSMISSION, ANTI-MICROBIAL RESISTANCE AND IMPROVED DIAGNOSTICS IN ENTERIC FEVER ACROSS AFRICA AND ASIA

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BACKGROUND

With an estimated 21 million infections globally each year, typhoid fever is a significant public health problem. Recently published mathematical models have highlighted limitations in our current understanding of typhoid biology that hinder the design of effective control strategies. These data gaps include a lack of accurate age stratified incidence for disease or sub-clinical infection across different endemic settings; little understanding of the natural immunity that follows infection and the rate at which this immunity wanes; and uncertainty around the relative importance of shedding during acute disease and chronic typhoid carriage in transmission.

METHODS

Three urban sites with known high rates of typhoid disease but with differing endemic/epidemic transmission status were selected: Blantyre (Malawi), Kathmandu (Nepal) and Dhaka (Bangladesh). A census of 100,000 people has been enumerated from which a two-year period of passive surveillance for acute cases of typhoid fever is being performed. Within these populations, ~8500 age stratified individuals will be enrolled into serological surveys to assess the rate of sub-clinical infection/exposure and enable the identification of chronic carriers. Household level studies for serological and microbiological evidence of transmission will be performed around acute and chronic cases. Healthcare utilization and water, sanitation and hygiene surveys will be performed in 735 households providing data on the percentage of population seeking healthcare at our study sites. Census and survey data is collected electronically using ODK, and data are uploaded onto MySQL databases. Host and bacterial genetics; transcriptomic; metabolomic; microbiome; and diagnostic sub-studies are also underway. ISRCTN 12131979.

RESULTS

Census enumeration is complete. Passive and serological surveillance are ongoing, along with clinical samples for a package of novel diagnostics. Data from healthcare utilization and household transmission studies are currently being captured. A detailed quality assurance programme with appropriate quality controls has been put in place.

CONCLUSION

The STRATAA study will provide key data on age stratified incidence, transmission dynamics, sub-clinical infection, host and bacterial genetics and new diagnostics that will inform the development of typhoid control strategies through the implementation of vaccine programmes.

47. SALMONELLA OUTBREAK INVESTIGATION IN BISHA REGION KSA

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BACKGROUND

Enteric (typhoid and paratyphoid) fever is less a common cause of morbidity and mortality among the indigenous population of kingdom of Saudi Arabia (KSA). Cases tend to occur more commonly in foreign laborers, who recently arrived from their home countries, and some of these cases have shown resistance to conventional enteric fever therapy. We observe 16 cases of *Salmonella* in King Abdullah Hospital Bisha out of 26 reported. We undertook this case investigation to assess the magnitude of the problem in Bisha region of southern Saudi Arabia. King Abdullah Hospital (KAH) is the main recipient of 7 hospitals and 800 primary health care centers.

METHOD

All cases of food poisoning were investigated in KAH Bisha. The study periods extended for 6 months. Cases investigated for culture (blood, stool, urine or bone marrow), or a rise in widal agglutination titer of more than two-fold. The case records of these patients were analyzed regarding history, physical examination, investigations, treatment and outcome.

RESULTS

All women with all age groups seen, 64% age 40 to 55, 22% from ages 15 to 39, 15% from ages 9 to 14 years seen. Significant different clinical presentation with different incubation period were seen despite of same source of infection. The disease was of acute illness but no mortality was found. Thrombocytopenia was found in 20% of cases. Leucopenia was found in 10%, while anemia found in 10% of cases, 40% shows electrolyte imbalance. Liver function test was normal in 80% of cases.

48. THE ECONOMIC BURDEN OF TYPHOID FEVER IN AFRICA: A MULTI-COUNTRY STUDY

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BACKGROUND

The economic burden of typhoid fever (TF) on the endemic population and health care settings of Africa is poorly recognized. The data on economic burden is essential for conducting economic evaluation needed for decision making on typhoid interventions such as new conjugate vaccine introduction. Here we describe the study design, methodology and updates of cost of illness (COI) studies to understand economic burden of typhoid fever in four African countries as part of the Severe Typhoid Fever in Africa (SETA) project.

METHODS

The COI study primarily aims to estimate direct costs to individuals and health care system as well loss of productivity due to illness. The COI is measured among blood culture confirmed and clinically diagnosed but blood culture negative typhoid fever cases. The background health care utilization costs are measured among healthy neighborhood controls enrolled under SETA. The COI is also estimated for blood culture confirmed invasive non-typhoidal *Salmonella* (iNTS) and for *S.* Paratyphi. The COI measurement includes face-to-face participant serial surveys to measure out-of-pocket expenditures and productivity loss due to illness over time until recovery, and detailed estimation of service delivery costs at selected health facilities. The survey is administered as soon as diagnosis is confirmed (3-7 days), a week later (12-14 days), a month after (28-30 days) and after three months (90 days) from day of study enrolment if illness persists.

RESULTS

Six months after commencement of the study, the preliminary results will be presented to provide early overview of the COI findings in four African countries. This will include deliberation of COI estimation model, and descriptive data on out of pocket expenditures and productivity loss.

CONCLUSIONS

The results from this study will provide new insights on economic burden of enteric fever in Africa, help in economic evaluation and decisions on typhoid vaccine introduction.

49. THE QUALITY OF LIFE AND LONG-TERM SOCIO-ECONOMIC IMPACT OF TYPHOID FEVER COMPLICATIONS IN AFRICA: A MULTI-COUNTRY STUDY

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BACKGROUND

The long-term impact of typhoid fever complications on quality of life (QoL) and socio-economic aspects have never been studied. Based on what is known about typhoid fever epidemiology, clinical outcomes and incidence of complications, the illness is expected to affect individuals and family for long duration. As a part of the Severe Typhoid Fever in Africa (SETA) project, we present study design, methodology and updates on QoL and long-term socio-economic impact measurement of typhoid fever complications in four African countries. This study will help in understanding broader socio-economic and intangible impact of typhoid fever complications on affected families and on society.

METHODS

This study aims to measure implications of illness on QoL of individuals; social, emotional and financial burden on affected families over one year period after blood culture confirmation of typhoid fever compared to matched healthy neighborhood controls. Both cases and controls are interviewed face-to-face, serially 7-8 times over one year period using three predeveloped, validated and structured questionnaires. The QoL will be tracked starting from the day of SETA enrollment (0 day), immediately after blood culture results are available for cases (3-7 days), two weeks after enrollment (12-14 days), at around one month (28 days) and every three months thereafter (90, 180, 270, 360 days). Two other questionnaires, one for measuring financial burden and another for measuring caretaker burden will be administered along with the QoL questionnaire seven times starting from the second interview.

RESULTS

The overview, updates and initial results will be presented six months after the study commencement in four African countries. This will include descriptive data on study participants and deliberation of analytical methods.

CONCLUSIONS

The QoL and socio-economic burden of typhoid fever and complications may help to appreciate better the social needs and equity aspects of typhoid fever control from policy perspectives.

50. MONITORING AND EVALUATION OF A MULTI-COUNTRY SURVEILLANCE SYSTEM: SEVERE TYPHOID IN AFRICA PROGRAMME (SETA)

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BACKGROUND

The Severe Typhoid in Africa Programme (SETA) is a standardized, multicountry, surveillance network with the purpose of estimating the burden and severity of invasive salmonellosis. Monitoring and evaluation (M&E) of the surveillance network/system is important for data quality and comparability across sites; however, there is limited published evidence on the best approaches and strategies to implement adequate M&E for communicable disease, multi-country, standardized surveillance studies, such as SETA. We present the process to develop the M&E plan for SETA and the lessons learnt during the pilot testing of the plan.

METHODS

Different steps were undertaken to develop the SETA M&E plan. First, the key elements and data flow through the surveillance system were ascertained and described. Second, the core activities and minimum standards required for the project to meet its main deliverables were identified and put on a list. Third, using the two pieces of information mentioned above, a compilation of monthly

monitoring data, indicators, targets associated with indicators and thresholds for actions were developed. Fourth, systematic field monitoring assessment visits were scheduled, and tools to report information on a monthly basis and during the monitoring visits were drafted. Lastly, pilot testing of the M&E strategies and documents took place at two of the six SETA countries. During the field visits, the M&E plan was presented and discussed with the principal investigator and his/her team. Concerns and challenges that could be faced by the local team to implement some of the required study procedures were expressed and addressed at the start of the visits. The core activities and minimum standards listed were observed and documented.

RESULTS

Two main lessons were learnt. First, each site organized the logistics to implement the study standard procedures differently. This resulted in a variety of approaches that needed to be registered and documented. Second, not all study procedures scheduled to be assessed could be observed. This was due to absence of patients at the recruitment healthcare facilities at the moment of the visit, and follow-up visits scheduled outside of the time period of the visit.

CONCLUSION

The logistics and organization to implement the study standard procedures may vary across SETA sites. An M&E plan than can leverage the unique strategies or approaches of each site to implement the surveillance system will help to ensure data quality, comparability, and good performance across sites.

51. SPATIAL EPIDEMIOLOGY OF TYPHOID FEVER IN MEKNES CITY, MOROCCO

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BACKGROUND

With an annual incidence above the national average, typhoid fever is a major public health problem in Meknes City (Morocco). The factors influencing the spatial and temporal distribution across the city are poorly understood.

METHODS

This study aimed to analyze the epidemiological and spatial pattern of typhoid fever in Meknes City over the period 2008-2013. Case occurrences data were collected from 30 health centers, geocoded to infra-communal level, and used in epidemiological and space-time analysis together with demographic, socio-economic, and environmental variables.

RESULTS

The epidemiologic profile has brought out the influence of age (children between the age of 5-14 years are the most affected) and time (number of cases increases during summer period) on the distribution of typhoid fever; but sex has no significant influence on it. The spatial patterns showed the aggregation of areas with high risk of typhoid fever infection in the northwest of the city and characterized by the proximity to fields irrigated by wastewater. With a spatio-temporal approach, the said pattern occurs during the summer season. This finding was supported by the negative correlation between the incidence of disease and proximity to irrigated areas. No statistical association was found with illiteracy rate and basic amenities variables.

CONCLUSIONS

A better understanding of the distribution of typhoid fever in Meknes City, and the study of its relation to potential environmental risk factors is an important step towards an efficient system for monitoring and preventing this type of food and waterborne diseases.

52. INVASIVE SALMONELLOSIS AMONG CHILDREN UNDER FOUR YEARS AT QUEEN ELIZABETH CENTRAL HOSPITAL IN BLANTYRE, MALAWI

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BACKGROUND

Reports of invasive nontyphoidal Salmonella and typhoid fever in Malawi have largely being derived from blood-culture confirmed cases seeking health care at Queen Elizabeth Central Hospital (QECH) in Blantyre. However blood culture has low sensitivity and likely underestimates reported case numbers. In this study we have used both blood culture and PCR to estimate the level of underreporting, which potentially impacts decision-making processes.

METHODS

Blood culture and PCR were performed on blood collected from 646 children with nonspecific febrile illness between August 2014 and July 2016, aged 0-4 years, median 1.3. DNA was extracted from blood after a pre-enrichment step in tryptone soy broth and ox-bile. Pan-Salmonella, S.Typhi (STY) and S. Typhimurium (STM) specific primers were used in the PCR.

RESULTS

Blood culture and PCR simultaneously identified 10 STM (1.5%) and 10 STY (1.5%) cases. Two cases (0.3%) with growth of S. Enteritidis and S. Typhimurium respectively were detected on PCR with the pan-Salmonella primer only. PCR was negative in three cases (0.5%) with growth of S. Typhi, and in five cases (0.8%) with growth of S. Typhimurium. There was no Salmonella growth on culture in six STM PCR confirmed cases, in four STY PCR confirmed cases and in two PCR confirmed cases where only the pan-Salmonella primer was positive.

CONCLUSIONS

A combination of both methods increased the percentage of reported cases from 4.8% to 6.7% in this cohort of young children. As expected there is underreporting of salmonellosis at Queen Elizabeth Central Hospital in Blantyre.

53. SEROTYPES AND ANTIMICROBIAL SUSCEPTIBILITY PATTERNS OF *SALMONELLA* SPECIES CAUSING ENTERIC FEVER IN NORTHERN SRI LANKA

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BACKGROUND

Enteric fever is a common food- and water-borne disease in Sri Lanka. The highest number of cases is reported in Northern Province, mostly based on clinical diagnosis. Microbiological information is significantly lacking from this region due to a 26-year ethnic war which ended in 2009. *Salmonella* Paratyphi A is the main serotype identified in studies outside northern Sri Lanka. While *S.* Paratyphi A was predominant (86%) in adults, *Salmonella* Typhi was predominant (85.7%) in children. Ciprofloxacin resistance was 100% in *S.* Paratyphi A and 50% in *S.* Typhi. Reduced ceftriaxone susceptibility was reported. This study aimed to determine *Salmonella* species serotypes and antimicrobial susceptibilities related to enteric fever in northern Sri Lanka.

METHODS

A two-and-a-half year prospective descriptive study was done at the Microbiology Department, Teaching Hospital Jaffna, Sri Lanka, analyzing blood culture isolates of *Salmonella* species from adult and paediatric patients with enteric fever. Blood culture processing, organism identification and antimicrobial susceptibility testing were performed according to standard laboratory methods.

RESULTS

Blood cultures were positive in 13.5% (40/295) samples and all revealed *Salmonella* Typhi. Majority (25/40) were in the 13-60 year age group. 14/40 were in children. Ciprofloxacin resistance was 100% [complete (33/40) or intermediate (7/40)]. Nalidixic acid resistance was 85%. Ampicillin, chloramphenicol, trimethoprim-sulfamethoxazole showed 67.5%, 82.5%, 82.5% sensitivity respectively; 20% of isolates were multidrug-resistant. Ceftriaxone sensitivity was 100%.

CONCLUSIONS

Enteric fever in all age groups in northern Sri Lanka is caused by *Salmonella* Typhi which is 100% ciprofloxacin resistant. The serotype and ciprofloxacin susceptibility pattern differs significantly from other regions of the country. Post-war environment and living conditions in northern Sri Lanka has made the population vulnerable to salmonellosis. Broadening the target group typhoid vaccination already in place and optimizing standards of living conditions need to be implemented as preventive measures due to high occurrence of this morbid disease.

54. AN ENVIRONMENTAL SURVEY OF DRINKING WATER IN KAMPALA, UGANDA, DURING A TYPHOID FEVER OUTBREAK

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BACKGROUND

In 2015, a typhoid fever outbreak began in downtown Kampala and spread into adjacent districts. Ground water was suspected, but unconfirmed, as the source of the outbreak. In response, an environmental survey of improved and unimproved drinking water sources was conducted in areas in the city with high case numbers.

METHODS

A total of 122 samples were collected from 12 different water types and tested for *E. coli*, free chlorine, and conductivity. An additional 37 samples from seven water types and 16 paired large volume (20 L) samples were also collected and tested for the presence of *S.* Typhi.

RESULTS

E. coli was detected in 60% of kaveras (i.e., drinking water sold in plastic bags) and in 80% of refilled water bottles; free chlorine was not detected in either water type. Elevated conductivity readings suggest that kaveras and refilled water bottles likely contained ground water, as opposed to treated water supplied by the Kampala water utility and licensed vendors. Most jerry cans (68%) contained *E. coli* and most free chlorine residuals were well below the WHO recommendation. All unprotected springs and wells and more than 60% of protected springs contained *E. coli.* Water samples collected from the water utility were found to have acceptable free chlorine levels and no detectable *E. coli.* While *S.* Typhi was not detected in water samples collected for this investigation, *Salmonella* spp. were detected in four unprotected springs, one protected spring, and one refilled water bottle.

CONCLUSIONS

These data, in conjunction with *E. coli* data, provide clear evidence that unprotected and protected springs and unlicensed vended water represented a risk for typhoid transmission. Despite the high incidence of typhoid fever globally, relatively few outbreak investigations incorporate drinking water testing. Results from prompt drinking water quality investigations might help identify contaminated sources, which could lead to rapid interventions.

55. THE SUSCEPTIBILITY PATTERN OF *SALMONELLA* SPECIES TO COMMONLY USED ANTIBIOTICS IN THE BAMENDA DISTRICT HEALTH AREA, CAMEROON

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BACKGROUND

The susceptibility of *Salmonella* bacteria to commonly used antibiotics is threatened by the emergence of resistance strains. The organism has rapidly gained resistance to antibiotics like ampicillin, ceftriaxone, and cotrimoxazole, and also to previously efficacious drugs like ciprofloxacin. The objective of this study was to provide information about the level of resistance that is presented by *Salmonella* isolates to commonly prescribed antibiotics to incite continuous monitoring of antibiotic sensitivity patterns; to provide suitable guidelines for treatment and thereby reducing mortality due to therapeutic failure.

METHODS

A cross-sectional study was carried out from September to November 2014 at the Regional Hospital Bamenda, Cameroon. The study population was patients of all age groups presenting with symptoms of Salmonellosis. The Salmonellae were isolated from stool by culturing in *Salmonella-Shigella* Agar and Kliger Iron Agar, the later in which the isolates produced specific biochemical characteristics which were conclusive. Antibiotic susceptibility

was done by the disc diffusion method using Mueller-Hinton Agar following both CLSI and EUCAST manual instructions.

RESULTS

A total of 253 samples were collected and 22 cases were positive for *Salmonella* species with a prevalence of 8.70%. The susceptibility of the isolated Salmonellae to seven antibiotics with ciprofloxacin having an overall sensitivity of 52.38%, ofloxacin, 47.62%, ceftriaxone, 47.62%, and gentamicin, 38.10%. Chloramphenicol had sensitivity percentage of 28.57%, while co-trimoxazole and amoxicillin had a high resistance level of 100.00% (0% sensitivity).

CONCLUSIONS

The fluoroquinolones were found to be the best drugs for the treatment of typhoid; but there was also a noticeable emergence of Amoxicillin-, Cotrimoxazole-, Chloramphenicol-resistant Salmonella accentuating the growing concern about the presence and the spread of multidrug resistant Salmonellosis; underscoring the need for the rational application of antibiotics and other necessary interventions that will help to control the menace of antibiotic resistance.

56. NON-TYPHOIDAL *SALMONELLA* MIXED INFECTIONS AMONG CHILDREN WITH BACTERAEMIA ADMITTED TO THE MANHIÇA DISTRICT HOSPITAL

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BACKGROUND

Non-typhoidal *Salmonella*, particularly *Salmonella* Typhimurium and *Salmonella* Enteritidis have emerged as an important cause of infantile or HIV-infected adult bacteraemia in sub-Saharan Africa. Mixed *Salmonella* infections with different serovars in the same patient have rarely been reported previously. Here we present 11 cases of bacteraemia in children with simultaneous detection of two strains assigned to different serovars of *Salmonella* in a single episode.

METHODS

Twenty-five *Salmonella*-positive blood samples recovered from children admitted to the Manhica District Hospital were investigated. The obtained isolates were shipped to Universidad de Oviedo (Spain) for characterization with regard to serovar, antimicrobial resistance profile (phenotype/responsible genes), plasmid content, phage type, PFGE and MLST.

RESULTS

Of the 25 *Salmonella* strains, 21 were *S.* Enteritidis and 15 *S.* Typhimurium. PCR revealed mixed infections by both serovars in 11 patients. *S.* Enteritidis isolates showed six PFGE profiles, most belonged to ST1479, and all except two were multidrug resistant (ampicillin, chloramphenicol, streptomycin, sulfonamides, tetracycline and trimethoprim), due to the presence of pUO-SeVR1-like plasmids. *S.* Typhimurium showed eight PFGE patterns and belonged to sequence type ST313. 12 *S.* Typhimurium were also MDR (ampicillin, chloramphenicol, streptomycin, sulfonamides and trimethoprim), associated with the existence of pSLT-BT-like or pSLT-A130-like plasmids. Most *S.* Enteritidis and *S.* Typhimurium isolates were PNR, indicating that previously unrecognized phage types are circulating in Mozambique.

CONCLUSIONS

We report the occurrence of mixed infections by *S.* Typhimurium ST313 and *S.* Enteritidis ST1479 in Mozambican children. Derivatives of the *Salmonella* virulence plasmids pSEV (pUO-SeVR1-like) and pSLT (pSLT-BT-like and pSLT-A130-like) are responsible for the MDR phenotype shown by most isolates.

57. ANTIMICROBIAL SUSCEPTIBILITY AND RESISTANCE PATTERNS OF *SALMONELLA* TYPHI DURING THE 2015 TYPHOID OUTBREAK IN KAMPALA, UGANDA

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INTRODUCTION

Antimicrobial resistance (AMR) in *Salmonella enterica* serovar Typhi is a growing, global problem. In 2015, Kampala experienced a typhoid outbreak. Antimicrobial susceptibility and resistance testing was performed on confirmed isolates.

METHODS

From February to June 2015, at the MRC/UVRI laboratories, blood cultures for 320 cases were sub-cultured and suspect colonies were identified using biochemical tests and *Salmonella* antisera. Susceptibility testing was performed following the British Society for Antimicrobial Chemotherapy, 2015 guidelines. Ciprofloxacin, ceftriaxone, co-trimoxazole, chloramphenicol, ampicillin nalidixic acid and perfloxacin were tested. Quality control testing was done at CDC in Atlanta. Testing for antimicrobial resistance genes was done using a DNA-based microarray (Alere Technologies GmbH, Germany) and sequencing done at the Sanger Institute in UK.

RESULTS

44 *Salmonella* Typhi strains were isolated. Susceptibility to ceftriaxone, co-trimoxazole, ampicillin and chloramphenicol were 100%, 77.3%, 77.3%, and 72.7% respectively. All strains showed reduced susceptibility to ciprofloxacin and 22.7% were multidrug resistant (MDR). All MDR isolates were positive for class 1 integrons, carried IncHI and IncQ plasmids plus genes that confer resistance to aminoglycosides, chloramphenicol, beta-lactams and co-trimoxazole. All sequenced isolates (n=29) were positive for MDR efflux pumps (mdtk and sdiA).

CONCLUSIONS

These results indicate the presence of *Salmonella enterica* serovar Typhi strains in Uganda with reduced susceptibility to ciprofloxacin, one of the frontline treatments of typhoid. Integron positive MDR Salmonella is of key importance and there is need to evaluate their contribution to AMR not only in *S.*Typhi but also in other priority bacteria in the country and beyond. The development and implementation of strategies to contain the spread of AMR infections are urgently needed, not least the creation of national AMR surveillance systems linked to global systems.

58. LOSS OF PROTECTIVE HUMORAL AND CELLULAR IMMUNITY TO INVASIVE NONTYPHOIDAL *SALMONELLA* DURING *PLASMODIUM FALCIPARUM* MALARIA INFECTION IN MALAWIAN CHILDREN

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BACKGROUND

In malaria endemic settings, invasive nontyphoidal *Salmonella* (iNTS) infections are commonly associated with *Plasmodium falciparum* (*P.* falciparum) malaria infections, but the immunologic basis for this linkage is poorly understood. We hypothesized that *P.* falciparum malaria infection compromises humoral and cellular immunity to NTS which consequently increases susceptibility to iNTS infection.

METHODS

We prospectively recruited Malawian children aged between 6 to 60 months at Zingwangwa Community Health Centre, which were placed in the following groups; febrile with uncomplicated malaria (n=59), febrile malaria-negative (n=50), non-febrile malaria-negative (n=47). Only malaria-infected children were followed up for examination at days 14 and 30 in convalescence. Participants were clinically examined and sampled 3ml venous blood for analyses to investigate STm-specific serum or whole blood bactericidal activities, and neutrophil respiratory burst activity.

RESULTS

We found that serum bactericidal activity (SBA) to STm was significantly reduced in acute malaria-infected children (Median -0.201og10, IQR [-1.85, 0.32]) and at day 14 in convalescence (Median -0.49, IQR [-2, 0.49]) compared to febrile malaria-negative children (Median -1.85log10, IQR [-2.85,-1.24]). Both acute malaria-infected (Median 8.8% IQR [3.7, 20]) and febrile malaria-negative children (Median 9.4% IQR [4.4, 19.5]) had reduced STm-specific neutrophil respiratory burst activity compared to non-febrile malaria-negative children (Median 40.5% IQR [33, 65.8]).

CONCLUSIONS

P. falciparum malaria infection abrogates protective humoral immunity to STm in children through a mechanism that is not fully understood. Reduction in both humoral and cellular immunity to STm during malaria episodes underscores the malaria-related risk of iNTS in children from malaria endemic settings.

59. POTENTIAL THREATS FROM ANTIBIOTIC RESISTANT STRAINS OF NON-TYPHOIDAL *SALMONELLA* FROM CHICKEN FARMS IN UGANDA

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BACKGROUND

Non-typhoidal *Salmonella* (NTS) is a global food-borne pathogen that has been associated with many recent food-borne disease outbreaks, illnesses and an important public health challenge. It's mainly contaminated poultry meat, eggs, dairy products and sometimes vegetables which are the main sources of NTS. It is estimated that in Africa NTS actually cause more mortality than typhoid fever. In addition, there is a global threat of increasing development of resistance of NTS against commonly used antibiotics. This is especially important for critically important antibiotics used for treating humans. A better understanding of NTS with a focus on primary production units will enhance effective control strategies. The aim of this study was to determine antibiotic resistance in NTS isolates from chicken farms.

METHODS

A cross-sectional study was carried out between August 2015 and June 2016 in a randomly selected laying chicken farms in the districts of Masaka, Wakiso and Lira. Faecal samples were collected from poultry houses cultured, and NTS isolated and identified. Disk diffusion method was used to test for phenotypic resistance against 13 antibiotics.

RESULTS

Out of the 78 isolates, 45 (57.7%) were resistant to at least one of the 13 antibiotics. Resistance was significantly associated with district (p=0.034) with more resistant isolates from Wakiso. Multidrug resistance was seen in 12 isolates. The highest resistance was seen in ciprofloxacin, 51.3% of the isolates. This was followed by sulfamethoxazole (28.2%), trimethoprim (7.7%), trimethoprim/sulfamethazole (7.7%).

CONCLUSIONS

High level of resistance to commonly used human drugs in Uganda is observed. This is a potential public health disaster as resistance genes can be transferred to other pathogens. Efforts should be put in place to combat antibiotic resistance in zoonotic pathogens from primary production points.

60. TYPHOID PERFORATION ASSOCIATED WITH EXTENDED SPECTRUM β-LACTAMASE PRODUCING BACTERIA

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BACKGROUND

Intestinal perforation is one of the leading fatal causes of death among individuals mostly in developing countries. Although many reports have associated perforations with typhoid infections, reports on the role of other bacterial pathogens, especially resistant bacteria strains, in causing ileal perforations are limited. As part of an ongoing Severe Typhoid Surveillance for Africa (SETA) study in Ghana, we compiled data on ileal perforation cases and the bacteria associated with their occurrence.

METHODS

The ongoing SETA study is a nested cross-sectional and longitudinal study, which is designed to determine the burden of typhoid infections in Ghana. The study, which started in the month

of May, 2016, is being conducted at the Komfo Anokye Teaching Hospital and the Agogo Presbytarian Hospital.

RESULTS

A total of 547 subjects have been recruited into the study over the past seven months. The prevalence of typhoid (*Salmonella* Typhi) is 2.39% (95%CI = 1.33% - 4.15% and that of invasive Non-*Salmonella* Typhoid (iNTS) is 1.28% (95%CI = 0.56%-2.74%). Of all the subjects recruited, 1.65% (95%CI = 0.81% - 3.22%) experienced ileal perforation. All cases occurred in children less than 13 years and *Salmonella* organisms were not identified in blood cultures of any of the perforated cases except one with blood culture confirmed extended spectrum β-lactamase-producing *Escherichia coli.* Molecular analysis showed that the isolated bacteria had blaCTX-M and blaTEM -associated resistance genes. The patient responded well on meropenem and was discharged upon full recovery.

CONCLUSION

ESBL producing bacteria could be associated with common perforations often regarded as typhoid perforation in children. Physicians should be mindful of this and administer evidence-based therapy when encountered with similar situation.

61. PEDIATRIC ENTERIC FEVER CAUSED BY *SALMONELLA ENTERICA* AMONG PEDIATRIC PATIENTS: AN INSIGHT OF ANTIMICROBIAL SUSCEPTIBILITIES FROM NEPAL

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BACKGROUND

Enteric fever is a serious illness of young children in developing countries of the tropics and subtropics with substantial mortality and morbidity. However, treatment became more difficult for such patients due to lack of standardized treatment protocols and increasing resistance to commonly used antimicrobial agents. In this study, we investigated the common serotypes of *Salmonella enterica* involved in pediatric enteric fever cases and analyzed their antimicrobial susceptibilities towards common antimicrobials.

METHODS

A cross-sectional study was carried out among the pediatric patients of Manmohan Memorial Teaching Hospital, Kathmandu over a period of six months. A total of 960 blood samples collected from the febrile children suspected of suffering from enteric fever were cultured using standard microbiological techniques. Antibiotic susceptibility testing of the *Salmonella enterica* isolates against common therapeutic antimicrobials was performed by Kirby Bauer disk diffusion technique following Clinical and Laboratory Standards Institute guidelines. Minimum inhibitory concentration of ciprofloxacin and nalidixic acid was determined by agar dilution method.

RESULTS

About 5.1% of febrile children were suffered from *Salmonella enterica* associated enteric fever. Out of total 49 *Salmonella enterica* isolated, 27(55.2%) were *Salmonella* Paratyphi A and 22 (44.8%) were *Salmonella* Typhi. In antimicrobial susceptibility, all of them were susceptible to chloramphenicol and co-trimoxazole and about 85.8% of the isolates were susceptible to ampicillin. However, 42(85.8%) isolates were resistant to nalidixic acid and 14.28% of the isolates were susceptible to ciprofloxacin. Fortunately, none of the isolates were multidrug resistant.

CONCLUSIONS

Salmonella Paratyphi A is the most common agent responsible for pediatric enteric fever cases. However, decreased susceptibility of fluoroquinolones and increase in NARS strains states the inappropriateness of common empirical therapy. Promising susceptibilities towards conventional first line agents including ampicillin, cotrimoxazole and chloramphenicol is considered to be renaissance of these drugs to treat the enteric fever cases in pediatric patients.

62. SEQUENCING OF 10,000 *SALMONELLA* GENOMES: A WORLDWIDE EFFORT TO UNDERSTAND THE EPIDEMIOLOGY, TRANSMISSION AND VIRULENCE OF INVASIVE NON-TYPHOIDAL SALMONELLOSIS

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BACKGROUND

Non-typhoidal *Salmonella* (NTS) are typically associated with enterocolitis, often related to the industrialisation of food production. In sub-Saharan Africa (sSA) however, there have been numerous reports of NTS being associated with invasive disease (iNTS disease), causing an estimated 680,000 deaths each year worldwide, the majority of which occur in sSA (Ao et al., 2015). In addition to the high prevalence of immunosuppressive illness which predisposes to iNTS disease in sSA, new clades of *S.* Typhimurium and *S.* Enteritidis have been identified. These clades are characterised by genomic degradation, different prophage repertoires and novel multidrug resistant plasmids.

METHODS

In order to understand how these clades are contributing to the burden and severity of this disease, it is crucial to expand the molecular surveillance of Salmonellae from Africa and other parts of the world, including isolates associated with invasive disease, gastroenteritis and both animals and the environment. The "10,000 *Salmonella* genomes" project will generate information relevant to the epidemiology, drug resistance and virulence factors of Salmonellae using a whole-genome sequencing approach.

RESULTS

During the first months of the project, we have initiated collaborations with researchers from several African and Latin-American countries, assembling a diverse collection of clinical and environmental *Salmonella* isolates with associated metadata. It is hoped that this enormous dataset will contribute to our understanding of the evolution of iNTS-associated *Salmonella* as well as the zoonotic or environmental reservoir of human disease. Detailed analysis of the accessory genomes of these strains will be performed at the Earlham Institute (Norwich, UK) to identify genes associated with drug resistance and virulence. We are using a collaborative open-access philosophy to maximise the value of the worldwide *Salmonella*-research community and we welcome new collaborators. The resulting genome sequence data will contribute to public health control strategies in developing countries.

63. EPIDEMIOLOGY AND RISK FACTORS FOR TYPHOID FEVER IN CENTRAL DIVISION, FIJI, 2014-2016

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BACKGROUND

Typhoid fever is endemic in Fiji, with the highest reported annual number of cases of any country in the South Pacific, yet risk factors for disease have not been studied. The aim of this case-control study was to identify risk factors to inform targeted disease control programs.

METHODS

We sought patients with blood culture-confirmed typhoid fever from February 2014 through August 2016 and two age-interval, gender, ethnicity, and residential area matched controls per case. Matched uni-variable and multi-variable analysis were used to evaluate associations between exposures and risk of typhoid fever.

RESULTS

We enrolled 160 patients with typhoid fever and 319 controls. Of cases, the median (range) age was 27 (2-78) years, 82 (51%) were female, and 77 (48%) resided in a rural area. On multivariable analysis, having constant water availability (odds ratio [OR] =0.4; 95% confidence interval [CI] 0.2-0.9, population attributable fraction [PAF] = 16%), washing produce before eating (OR=0.4; 95%, CI 0.2-0.8, PAF = 19%), and using soap for hand washing (OR=0.5; 95%, CI 0.3-0.9, PAF = 28%) were found to be protective factors. Drinking surface water in the last 2 weeks (OR=5.6; 95%, CI 1.5-20.9, PAF = 8%), attending a mass gathering (OR=2.0; 95%, CI 1.1-3.7, PAF = 22%), and having an unimproved pit latrine (OR=166.3; 95%, CI 7.6-3659.1, PAF = 8%) were risk factors for typhoid fever.

CONCLUSIONS

Unimproved sanitation facilities appear to be a major source of *Salmonella* Typhi in Fiji. Our findings suggest transmission by drinking contaminated surface water and consumption of unwashed produce. Mass gatherings are common and appear to increase risk. Improved sanitation facilities that protect surface water and produce from contamination by human faeces are likely to contribute to typhoid control in Fiji.

64. INVESTIGATING GUT CELLULAR IMMUNITY IN A CONTROLLED HUMAN INFECTION MODEL OF TYPHOID FEVER

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BACKGROUND

T lymphocytes are crucial to clear *Salmonella* infections, however it is unclear whether infection leads to the differentiation of gut resident pathogen specific memory T cells capable to confer long-term protection. Our study investigates gut mucosal and peripheral T cell responses in healthy adults recruited in a *Salmonella* controlled human infection model. We hypothesise that T cell responses at the site of infection — the gut mucosa — might provide a more robust cellular correlate of protection than peripheral blood responses only.

METHODS

Endoscopic duodenal biopsies and peripheral blood samples were collected from participants at baseline and 4-7 weeks after challenge with a single oral dose of live *S.* Typhi or Paratyphi A. Mononuclear cells were isolated in parallel from intestinal biopsies and blood. Three different *ex-vivo* infection models were undertaken to determine the frequency of *Salmonella* specific T cells. CD4+, CD8+, MAIT and gamma delta T cells were assessed by flow cytometry for their capability to produce cytokines (IFN-γ, TNF-α, IL-17 and IL-2) and up-regulate the activation/memory marker CD40L.

RESULTS

Upon *ex-vivo* infection the predominant cytokines produced by intestinal CD4+ cells are TNF-α and IL-17, conversely blood CD4+ cells produce more IFN-γ. Prior to challenge, the frequency of circulating antigen specific IFN-γ producing CD4+ cells appears to correlate with previous exposure to *Salmonella.* The number of antigen-specific cytokine-producing cells increased post-challenge, with a pronounced increase in the fraction of CD4+ cells upregulating CD40L in response to antigen stimulation. A larger frequency of antigen specific cells was observed in both mucosa and blood from individuals who developed enteric fever upon challenge than those who did not. Mucosa resident gamma delta and MAIT cells were less responsive to *in vitro* bacterial stimulation when compared to peripheral blood cells.

CONCLUSIONS

Our *ex-vivo* infection model has enabled us to characterise changes in the frequency of *Salmonella* activated T cells isolated from gut mucosa and peripheral blood before and after human controlled infection with *Salmonella* Typhi and Paratyphi A. Moreover, distinctive patterns of cytokine producing cells have been identified in both compartments. Ongoing analysis may offer insights into possible correlates of protection or associations with clinical presentation.

65. MOLECULAR EPIDEMIOLOGY OF QUINOLONE RESISTANT *SALMONELLA* TYPHI AND *SALMONELLA* PARATYPHI A FROM INDIA

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BACKGROUND

S. Typhi and *S.* Paratyphi A are human adapted serovars, and emergence of antibiotic resistance is directly related to antibiotic use in humans. It is thus important to study whether this resistance to fluoroquinolone is emerging during treatment in different hosts (mutations occurring in different bacterial strains) or clonal expansion of a successful strain by person-to-person spread (identical mutations associated with a single strain). Typing is an

important tool for surveillance and monitoring spread of resistance strains. In this study, we used Multi-locus variable number tandem repeats (MLVA-VNTR) typing method to study genetic diversity and epidemiology in the *S.* Typhi and *S.* Paratyphi A.

METHODS

A total of 664 isolates of *S.* Typhi and *S.* Paratyphi were isolated from 2006-2011. Isolates were identified by standard biochemical tests and serotyped using specific antisera. The antimicrobial susceptibility was performed by disk diffusion method according to the CLSI (2012). MIC (minimum inhibitory concentration) for nalidixic acid and ciprofloxacin were determined by E-Test (AB Biodisk, Solna, Sweden). Multidrug resistance (MDR) was defined as simultaneous resistance to ampicillin, chloramphenicol and co-trimoxazole. 104 isolates of *S.* Typhi (80 isolates) and *S.* Paratyphi A (24 isolates were studied. Isolates were selected on the basis of different MIC, fluoroquinolone resistance patterns, mutation in topoisomerase genes (*gyr*A,*gyr*B, *par*C and *par*E) and plasmid-mediated resistance gene (*qnr*A,B,S genes, *aac* (6')-*Ib*-cr and *qep*A). CT18 and Ty2 for *S.* Typhi and ATCC9150 for *S.* Paratyphi A were used as a reference isolates. Five VNTRs marker TR1, TR2, TR4699, Sal02 and Sal16 were used to establish the genetic diversity among fluoroquinolone resistant *S.* Typhi and *S.* Paratyphi A. MLVA typing was done by fluorescent PCR amplification of each VNTR locus separately. The fragment length analysis was done by capillary electrophoresis an automated ABI3130 Genetic analyzer (Applied Biosystems) and data analysed using GeneMapper (version 4.0) software (Applied Biosystems). The copy number was done by sequencing. A cluster dendrogram was constructed by the R-software (R version 2.15.2 (2012-10-26), to represent the genetic relationships of the MLVA profile on the basis of copy number. The diversity index (DI) was generated using two methods: Simpson's diversity and Hunter-Gaston diversity.

RESULT

Total 80 *S.* Typhi isolates differentiated into 73 MLVA profiles and 24 *S.* Paratyphi A isolates differentiated into 11 different MLVA profile with reference isolates. Our data showed that TR2, Sal02, TR4699 and Sal02 marker have more allelic distribution for *S.* Typhi and *S.* Paratyphi A, respectively. The discriminatory power was 0.999 for both *Salmonella.* Phylogenetic analysis showed that the MLVA profiles can be divided into five and four clusters for *S.* Typhi and *S.* Paratyphi A, respectively.

CONCLUSION

Epidemiological studies of pathogens are of great importance in controlling their dissemination. The cluster analysis findings supported heterogeneous clone dispersion for *S.* Typhi i.e. all resistance phenotypes were distributed simultaneously in the environment while *S.* Paratyphi A isolates were homogeneous clone with limited diversity, i.e., all phenotype are clonally spreading in the community. To our knowledge this is the first report of MLVA subtyping applied to *S.* Typhi and *S.* Paratyphi A from India. Rapid and high-level discriminatory power of MLVA may be useful for tracking and controlling the transmission of *S.* Typhi isolates during epidemiological investigations.

66. *SALMONELLA ENTERICA* SEROVAR PARATYPHI A INFECTIONS IN INDIA

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BACKGROUND

Typhoid and paratyphoid are clinically indistinguishable. Comparative data of incidence, clinical presentation, antibiograms and molecular characterization of *S.* Typhi and *S.* Paratyphi A is scarce but vital for understanding disease epidemiology and formulating therapeutic and vaccination policies.

METHODS

A retrospective hospital based study was undertaken between January 1999 and September 2011. Clinical, microbiological and epidemiological profile of *S.* Typhi and *S.* Paratyphi A were investigated.

RESULTS

The proportion of *S.* Typhi:*S.* Paratyphi A was 7.6: 1 (1999) and 2.5:1 (2004) and reverted back to 8.6:1 (2011). Paratyphoid fever was significantly more frequent in older age groups and was associated with milder disease with only 11.8% patients requiring hospitalization. The incidence of multidrug resistance in *S.* Typhi was declining, but 21% of them were still MDR. All isolates of *S.* Paratyphi A were resistant to nalidixic acid since 2003, as compared to 80% resistance in *S.* Typhi in 2005. High-level fluoroquinolone resistance was also seen first in *S.* Paratyphi A in 2003. Double mutation in *gyr*A and single mutation in *par*C were identified in ciprofloxacin resistant isolates of both serovars. Interestingly nalidixic acid resistant isolates of *S.* Paratyphi A and *S.* Typhi isolates carrying same single mutations at codon 83 in *gyr*A exhibited different ciprofloxacin MIC of 1.5 and 0.5 mg/ml respectively suggesting an additional mechanism of fluoroquinolone resistance in *Salmonella* serovar Paratyphi A. Studies with efflux pump inhibitor were suggestive of efflux mediated resistance which also contributed multiple antibiotic resistance in *S.* Paratyphi A. PFGE of the isolates of the two serovars suggested that molecular epidemiology of the two serovars is significantly different.

CONCLUSION

The disease epidemiology clinical presentation and mechanism of resistance differ in the two serotypes. In absence of licensed vaccine for *S.* Paratyphi A this could result in increase in Paratyphoid cases and failure of preventive strategies which are focused on Typhoid fever. Vaccination and therapeutic policies need reassessment.

67. EXPLORING GLOBAL TYPHOID CONTROL WITH THE CONSOLIDATED FRAMEWORK FOR IMPLEMENTATION RESEARCH

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BACKGROUND

Typhoid remains a major global cause of morbidity in low- and middle-income countries, significantly contributing to mortality in some age groups and settings. Over the last decades, typhoid rates have been successfully reduced with interventions such as improved/safe water sources, adequate sanitation, appropriate personal and food hygiene practices and vaccination. Past research has primarily focused on monitoring typhoid rates with little attention to how these interventions had been implemented. This research addresses this gap by examining implementation of typhoid control interventions in eight countries: Nigeria, South Africa, Pakistan, India, Bangladesh, Chile, Vietnam, and Thailand. The study uses the Consolidated Framework for Implementation

Research (CFIR) to identify which of 39 CFIR factors are most strongly associated with implementation success.

METHODS

In each of the eight countries, four to six public health experts with extensive experience in typhoid control will be interviewed about country specific interventions, initiative outcomes, as well as barriers and facilitators to implementation and monitoring. Participants will also fill out a questionnaire assessing the importance of the CFIR factors relative to the implementation of typhoid interventions.

CONCLUSION

Identifying contextual factors associated with implementation success has implications for advancing implementation knowledge and for improving implementation practice in global health. For instance, factors emerging as most important can be manipulated in implementation planning to improve success. Comparisons across settings (health, mental health) can highlight the factors that are most robust, and set us on a path toward more effective implementation and better outcomes.

68. TYPHOID COST OF ILLNESS: KNOWNS AND UNKNOWNS

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BACKGROUND

The cost of illness (COI) of a disease includes treatment costs borne by the healthcare system, insurance structure and individuals as well as productivity loss among affected people and their families. Estimation of COI is essential for economic evaluation of disease prevention and control activities that provides evidence for policy decisions. Here we describe knowns and unknowns about typhoid fever COI research based on literature review.

METHODS

A literature search was conducted on PubMed and Embase following PRISMA guidelines to identify publications reporting typhoid fever COI. Selected studies are presented descriptively and a list of knowledge and gaps are developed in the area of study design, sample size, location, time and overall methodology.

RESULTS

The review suggests that the current data on typhoid fever COI is scanty, primarily due to scarce and outdated studies. Only three studies from six countries, two conducted more than a decade ago and one with small sample size, presenting 442 episodes with 17 from Africa feed to the knowledge pool of typhoid treatment costs and productivity loss. Besides COI, the long-term sequelae of typhoid fever, frequency of complications and mortality, and its socio-economic implications are other knowledge gaps.

CONCLUSIONS

Typhoid fever surveillance programs form an ideal platform for conducting COI and following up on long-term consequences. Such platforms can be used for follow up of laboratory confirmed typhoid fever cases and healthy community control to collect the costs and socio-economic burden at family level for a long duration. These studies in Africa and Asia will help in improving economic burden estimates necessary for cost-effectiveness analysis to aid informed decisions on typhoid prevention and control.

69. OBTAINING OF VI POLYSACCHARIDE CONJUGATE BATCHES USING TETANUS AND DIPHTHERIA TOXOIDS AT PILOT SCALE

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BACKGROUND

A Vi polysaccharide conjugate demonstrated high effectiveness in 2-5 year old children. It was safe, elicited protective levels of IgG anti-Vi in infants and was compatible with routine vaccines at this age. Based on this success, several vaccine candidates are been developed. Finlay Institute of Vaccines adapted the general conjugation method to a procedure to obtain Vi polysaccharide conjugates using tetanus and diphtheria toxoids as carrier proteins in compliance with WHO guidelines. This procedure was brought to pilot scale. In this work is reported the results of lots produced by the established technology.

METHODS

In these processes were used the tetanus (TT) and diphtheria (DT) toxoid batches TET-2014 and DIF2011 respectively, and Vi polysaccharide batches DF-PCST-301, 302 and 303, produced in GMP conditions. Modification of proteins started in 2-3 g and conjugation in 0.5-1 g of polysaccharide. Physicochemical characteristics of the conjugates were evaluated and preliminary stability studies were performed.

RESULTS

Recoveries were above 70%. The protein had very low aggregation, K_D remained unchanged and the average active groups introduced were between 6 and 8 per molecule for tetanus and 3 for diphtheria. The crude reactions were transparent solutions that easily filtrated by 0.2 µm. Polysaccharide recoveries were above 85%. The purified conjugates had consistent K_D and polysaccharide/protein ratios about 0.4-0.5 and 0.5-0.6 for Vi-TT and Vi-DT, respectively. The ^{1}H-NMR analysis showed that polysaccharide identity was maintained and the *O*-acetylation percentages were over 90%. Conjugates were immunogenic in BALB/c mice after one and two dose. Key conjugate features were maintained for 18 months.

CONCLUSIONS

Three Vi-TT and Vi-DT conjugates batches at pilot scale were obtained in compliance with WHO guidelines.

70. INVESTIGATING HUMORAL IMMUNITY TO PARATYPHOID FEVER IN A HUMAN CHALLENGE MODEL OF INFECTION

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BACKGROUND

Salmonella Paratyphi A (*S.* Paratyphi) is responsible for an increasing proportion of enteric fever cases, particularly in Asia. Live-attenuated and lipopolysaccharide O:2-antigen conjugate vaccines are in development, but immunological correlates of protection are not known. We aimed to study humoral-immunity to *S.* Paratyphi infection using a challenge/re-challenge model of infection.

METHODS

We recruited healthy volunteers into two groups: (1)Naïve volunteers with no prior exposure to *Salmonella* Paratyphi, and (2) volunteers previously exposed to *S.* Paratyphi in earlier challenge

studies. Participants were challenged/re-challenged with oral *S.* Paratyphi at a dose of 1-5x10^3 CFU. We measured antibodies to *S.* Paratyphi O:2 antigen at two time points, baseline and day 28 post-challenge, using an in-house ELISA in a subset of volunteers (Naïve=9; re-challenge=11).

RESULTS

An interim analysis has revealed a markedly lower attack rate following *S.* Paratyphi re-challenge compared with naïve controls, corresponding to an estimated 74% protection. We were unable to demonstrate a significant difference in baseline anti-O:2 IgG between naïve and re-challenge participants: naïve 160.4 EU (95% CI 38.9-202); re-challenge 441.4 EU (99.6-783.3). Diagnosed participants showed a higher fold-rise in antibody levels across the two time points than those who were undiagnosed: naïve 21.6 fold (95% CI 8.8-34.4) vs 1.0 (95% CI 0.9-1.1); re-challenge participants 6.8 fold (95% CI –1.1-14.7) vs 1.4 (0.7-2.0). Further ELISA/ASC data will be presented on a larger cohort currently undergoing challenge, including isotype-specific responses and baseline O:2 specific B*M* cell responses.

CONCLUSIONS

Understanding the role of O:2 antibodies in protection against paratyphoid fever is highly relevant to the development of a lipopolysaccharide O:2-antigen conjugate vaccine. In this study, neither baseline anti-O:2 concentration, nor fold-rise post-challenge, corresponded to protection against paratyphoid infection. Further functional antibody assays would be useful to clarify the role of anti-O:2 antibody in protection against paratyphoid fever.

71. EPIDEMIOLOGICAL STUDIES OF TYPHOID FEVER IN PREGNANT WOMEN IN A COMMUNITY IN CENTRAL NIGERIA

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BACKGROUND

Typhoid fever remains a major global health problem. *Salmonella* Typhi may be a cause of significant morbidity and mortality in both the mother and foetus in developing countries, where sanitation facilities, personal and food hygiene are inadequate. Thus, the present work was a retrospective and cross-sectional study of *Salmonella* infection among pregnant women in Shabu community of central Nigeria.

METHODS

Serological (Widal test) and bacteriological analyses were conducted among randomly sampled pregnant women in Shabu community of central Nigeria, and the results obtained were compared. Previous data on *Salmonella* infection among pregnant women were also collected and analysed.

RESULTS

The results obtained showed that 44 (88%) of the subjects were seropositive for typhoid fever, whereas 33 (66%) were positive based on bacteriological technique. Subjects between age groups; <19 and 30-40 years old had the highest prevalence of 100%. There was no statistically significant difference (P>0.05) between the prevalence of typhoid fever among the various age groups of the pregnant women examined. Retrospective survey also showed a high prevalence of 63%, with subjects belonging to the age group: 20-30 years old with the highest rate of infection (92%).

CONCLUSIONS

Pregnancy makes the host more vulnerable to typhoid fever by affecting the physiology of pivotal organs, as such early and prompts diagnosis so as to avoid the further materno-foetal complications is of great importance.

72. CAN TREATMENT OF ENTERIC FEVER STILL RELY ON FLUOROQUINOLONES?

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BACKGROUND

In Nepal, enteric fever still remains a persistent health problem for which fluoroquinolones are prescribed. Self-medication practices, over-the-counter sale of antibiotics and the ill practice of prescribing antibiotics without referring to antimicrobial susceptibility report has contributed to increased resistance. This study compares the changing antibiogram of *Salmonella enterica* serovar Typhi and *S.* Paratyphi A focusing on fluoroquinolones.

METHODS

The study was conducted at National Public Health Laboratory from January 2008 to December 2015 during which 5,146 blood cultures were processed. Presumptive *Salmonellae* were processed for antimicrobial susceptibility. Selected isolates (n=70) were subjected to MIC against Ciprofloxacin and Levofloxacin using Etest.

RESULTS

Of the 352 *Salmonella* isolates, 41% were *Salmonella enterica* serovar Typhi and 59% were *Salmonella enterica* serovar Paratyphi A. Change in prevalent species is noticeable. 39% of cases were from patients of 10-20 years age group with male predominance. Increase in Nalidixic acid resistant *Salmonella* (NARS) from 80% to 100% and rapid rise in ciprofloxacin resistance from 8.3% to 100% is alarming, however, MDR isolates have declined significantly. More than 92% of *S.* Typhi and 95% of *S.* Paratyphi A isolates were susceptible to chloramphenicol but 100% were susceptible to ceftriaxone. The range of MIC for ciprofloxacin and levofloxacin was found higher in *S.* Typhi (0.008-32 µg/ml and 0.25-16 µg/ml) as compared to *S.* Paratyphi A (0.38-2 µg/ml and 0.5-2 µg/ml). The MIC_{50} value for both drugs increased from 0.38 µg/ml in 2012 to 1µg/ml and 0.5 µg/ml respectively by 2015. A significant rise in MIC_{90} value for both fluoroquinolones (from 0.5 µg/ml in 2012 to 32 µg/ml and 16 µg/ml respectively in 2015) draws attention.

CONCLUSIONS

With increasing resistance to fluoroquinolones and the possibility of re-emergence of sensitivity to other drugs, treatment options need to be reconsidered.

73. DRIVERS OF TYPHOID FEVER TRANSMISSION IN KATHMANDU, NEPAL: A MATHEMATICAL MODELLING STUDY

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BACKGROUND

A substantial proportion of the typhoid fever burden occurs in South Asia. Kathmandu, Nepal experienced a marked increase in the number of diagnosed *Salmonella enterica* serovar Typhi cases between 2000 and 2003, which subsequently declined but to a higher endemic level than in 2000. This epidemic of *S.* Typhi coincided with the increased occurrence of multi-drug resistant typhoid and, in particular, the emergence of the *S.* Typhi H58 haplotype, but might also have been fuelled by the highly migratory population in Nepal.

METHODS

We used a mathematical modelling approach to investigate potential epidemic drivers and fit our mathematical model to weekly data on *S.* Typhi cases between April 1997 to June 2011 and to the age distribution of *S.* Typhi cases. We explored whether the epidemic of typhoid fever in Nepal was driven by (1) heightened levels of migration, (2) the emergence of multi-drug resistant typhoid or (3) a combination of both increased migration and rise in multi-drug resistant typhoid.

RESULTS

Models allowing for the migration of susceptible individuals, alone or in combination with the emergence of multi-drug resistance, provided a good fit to the data. The emergence of multi-drug resistant typhoid alone, either through an increase in disease duration or the transmission rate, could not fully explain the pattern of *S.* Typhi cases.

CONCLUSIONS

Our analysis suggests that the epidemics were caused by the migration of susceptible individuals to the capital and possibly aided by the emergence of multi-drug resistant typhoid. This underlines the importance of identifying and targeting migrant populations to prevent disease transmission and infection.

74. SEASONAL DYNAMICS OF TYPHOID AND PARATYPHOID FEVER

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BACKGROUND

Typhoid and paratyphoid fever are seasonal infectious diseases, but these seasonal dynamics are not fully understood. Therefore, we conducted a systematic review to characterise and quantify the seasonal variation of typhoid and paratyphoid fever studies worldwide.

METHODS

We reviewed the scientific literature (EMBASE, MEDLINE, Global Health and Web of Science) for studies, published before May 2016, which described the seasonal dynamics of typhoid or paratyphoid fever. We assessed the seasonal variation by plotting the average monthly proportion of cases by region, latitude, spatial scale and temporality. We also determined the mean timing of the peak and the seasonal variability and, finally, compared the seasonal dynamics and metrics for typhoid and paratyphoid fever.

RESULTS

We obtained 68 articles, which contained 104 datasets. The majority of datasets were historical studies (<1990) from Europe (62%), while 19 (18%) and 14 (13%) were mostly recent studies from Asia and Africa, respectively. Typhoid fever was more likely to be seasonal further from the equator, with a pronounced peak in August between 70-36° N (mostly European countries) and a peak period from May-October between 35-11°N (mostly Asian countries). These dynamics were not influenced by spatial scale or temporality. There was a clear trend in the mean timing of the peak, which shifted from August to January when ordered by latitude, from north to south. However, there was no pattern in the seasonal variability of typhoid fever by geographic region, latitude, spatial scale or temporality. Finally, the seasonal dynamics of typhoid and paratyphoid fever were not congruent in recent studies.

CONCLUSIONS

Our analysis found distinct seasonal patterns for typhoid fever, which were not compatible with those of paratyphoid fever. However, there was no clear trend in the seasonal variability. A better understanding of the seasonal dynamics and underlying drivers could aid preventative and control efforts.

75. STUDIES ON ANTIMICROBIAL RESISTANCE AND MOLECULAR SUBTYPING OF *SALMONELLA* TYPHI ISOLATES FROM KOLKATA DURING 2014-2015

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BACKGROUND

Typhoid fever is an acute, invasive and potentially fatal systemic infection caused by *Salmonella enterica* subspecies *enterica* serotype Typhi (*S.* Typhi). Antimicrobial therapy is the main mode of treatment but drug resistance to antimicrobials has become a problem in developing countries like India. Molecular subtyping is essential for discriminating *Salmonella enterica* serovar Typhi (*S.* Typhi) isolates leading to improved molecular epidemiological analysis for prevention and control of typhoid fever. Pulsed field gel electrophoresis (PFGE) is considered the gold standard for *Salmonella* molecular typing, while sequence-based multiple-locus variable-number tandem-repeat (VNTR) analysis (MLVA) provides high-level discrimination.

METHODS

A total of 176 *S.* Typhi isolates were collected from clinically suspected enteric fever patients attending various hospitals in Kolkata, India, from January 2014 to December 2015 and were tested for antimicrobial resistance following standard protocol. To assess genetic diversity, 50 representative strains of different resistance profile were analyzed by PFGE and MLVA.

RESULTS

A majority of the isolates were resistant to nalidixic acid (97.7%) followed by ciprofloxacin (29.5%). Only 3.4% MDR (resistance to ampicillin, chloramphenicol, cotrimoxazole) isolates and 1.1% of tetracycline and cotrimoxazole resistant isolates were found during this period. A single non conjugative plasmid of 180 kb was found in 83.3% (5/6) of MDR *S.* Typhi and one 50kb plasmid was found in tetracycline and cotrimoxazole resistant *S.* Typhi. Various AMR markers (*bla*TEM-1, *cat*A, *sul*1, *sul*2, *dfr*A15, *str*A-*str*B) and class 1 integron with *dfr*A7 gene were detected in MDR *S.* Typhi isolates by PCR and sequencing. PFGE subtyping divided the isolates into three clusters including 16 pulsotypes whereas MLVA subtyping divided the isolates into four clusters including 48 MLVA types.

CONCLUSIONS

The results of the present study suggests MLVA provides high level discrimination among clonal MDR, NALR and NALR-CIPR *S.* Typhi

isolates in PFGE. The study reiterated the importance of continuous monitoring of AMR and molecular subtypes of *Salmonella* isolates from endemic regions for better understanding of the disease epidemiology.

76. CHANGING PATTERN OF RESISTANCE TO ANTIMICROBIALS IN PATIENTS OF ENTERIC FEVER IN INDIA IN THREE DECADES: A SYSTEMATIC REVIEW

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BACKGROUND

The incidence of typhoid fever in India is rising with pooled estimate of 377 per 100,000 person-years in Delhi and Kolkata, affecting children aged 2-4 years most. Drug resistant typhoid fever has been a major challenge since 1980s. This paper aims to review and synthesize evidence regarding the pattern and trend of antibiotic resistance of *Salmonella* typhi in last three decades in India.

METHODS

A systematic search was conducted in Pubmed to include 51 peer-reviewed studies in English language, spanning 36 years till December, 2016. The methodological quality of the studies were assessed using method by Schehner et al, 2013. Three meta-analyses were conducted to determine pooled proportion of resistance of enteric Salmonella for each antibiotic in three time periods "1980-1990", "1991-2000", "Post 2000". A meta-analysis was done to determine 5-year period wise pooled proportion of MDR strains and the trend was developed.

RESULTS

A changing pattern of susceptibility from ciprofloxacin and third generation cephalosporins to chloramphenicol, cotrimoxazole, azithromycin is observed between 1980 and 2016. Resistance is highest for nalidixic acid with >90% resistance in last 3 years. 2 studies reported greater proportion of resistance in children compared to adults. Proportion of MDR strains increased from 1980s to 1990s and then again decreased. The pattern of MDR has changed in recent years from ACCoT to plasmid mediated quinolone and 3rd generation cephalosporin resistance. Use of newer antibiotics coincides with decline in MDR for a set of older antibiotics.

CONCLUSIONS

Our study provides evidence to inform the stewardship of antimicrobial use as well as ongoing discussion on vaccine introduction under India's national technical advisory group. While the proposal to increase access to antimicrobials through front-line workers needs to be reformulated by these findings, targeted introduction of conjugate vaccine may also be opted to overcome the challenge of multidrug resistance.

77. REVIVAL OF CONVENTIONAL FIRST LINE DRUGS IN *SALMONELLA ENTERICA* CLINICAL ISOLATES: ASSESSMENT OF MICS FOR THERAPEUTIC ANTIMICROBIALS IN ENTERIC FEVER CASES FROM NEPAL

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BACKGROUND

Enteric fever caused by *Salmonella enterica* is a life-threatening systemic illness of gastrointestinal tract especially in tropical countries. Antimicrobial therapy is generally indicated but resistance towards commonly used antibiotics has limited their therapeutic usefulness. Therefore, we aimed to determine the antimicrobial susceptibility pattern by minimum inhibitory concentration method of common therapeutic regimens against *Salmonella enterica* from enteric fever clinical cases.

METHODS

Patients suspected with enteric fever whose blood samples were submitted to microbiology laboratory of Manmohan Memorial Community Hospital, Kathmandu from March 2016 to July 2016 were studied. The *Salmonella enterica* clinical strains isolated from blood samples were subjected to antimicrobial susceptibility testing against common therapeutic antimicrobials by Kirby-Bauer disk diffusion method. The minimum inhibitory concentration of ciprofloxacin, Azithromycin, Chloramphenicol and Cefixime was determined by Agar dilution method based on latest CLSI protocol.

RESULTS

A total of 44 isolates of *Salmonella enterica* were recovered from blood samples of enteric fever cases. Out of them, 37 (84.09%) were *Salmonella* Typhi and 7 (15.9%) were *Salmonella* Paratyphi A. On Kirby Bauer disk diffusion antimicrobial susceptibility testing, entire isolates were susceptible to Ampicillin, Cotrimoxazole, Cefixime, Ceftriaxone, Azithromycin, Tetracycline and chloramphenicol. Thirty two (72.73%) of *Salmonella* strains were Nalidixic acid resistant and non-susceptible to Ciprofloxacin, Levofloxacin and Ofloxacin. On MIC determination, two *Salmonella* strains were ciprofloxacin resistant with MIC 1µg/ml and one was intermediate with MIC 0.5µg/ml. The MIC of Azithromycin was 0.125µg/ml whereas that for Chloramphenicol and Cefixime was (4.00-8.00) µg/ml and (0.0075-0.06) µg/ml respectively.

CONCLUSIONS

Despite global surge of antimicrobial resistance among *Salmonella enterica* clinical isolates, the level of drug resistance in our study was not so high. However, higher level of NARST strains limits therapeutic use of flouroquinolones and necessitates the routine monitoring of such resistance determinants in order to effective and rational management of enteric fever cases.

78. EVALUATION OF DIRECT SUSCEPTIBILITY TESTING BY DISK DIFFUSION OF *SALMONELLA* TYPHI AND *SALMONELLA* PARATYPHI FROM BLOOD CULTURE

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BACKGROUND

Direct susceptibility testing (DST) of organisms from blood culture saves time to appropriate antibiotic administration, and optimal management of infectious syndromes. The American Society for Microbiology recommends that DST methods from blood culture be validated against standard disk diffusion method with >90% categorical agreement (CA), and <10% errors. No DST methods have been previously reported or validated for *Salmonella* spp. In this study we have evaluated direct susceptibility testing of typhoidal *Salmonella* spp. from blood cultures.

METHODS

The study was performed at the Aga Khan University clinical microbiology laboratory in Karachi, Pakistan from June to September 2016. All blood culture bottles that flagged positive in BACTEC 9240 with gram negative rods on gram stain were subjected to identification

and DST by inoculating two-three drops of positive blood culture broth on Mueller Hinton agar and homogenized by swabbing. Disks were inoculated within 15 minutes; zone diameters interpreted after 18 hours. Next day identification of *Salmonella* spp. by antigen detection and susceptibility testing were performed using standardized inoculum (0.5 McFarland) on 24-hour colonies and zone diameters interpreted on day 3 according to breakpoints provided by Clinical Laboratory Standards Institute. CA, very major (VME – resistant strain appearing sensitive), major (ME – sensitive strain appearing resistant), and minor errors (MnE – resistant or sensitive isolates as intermediate or vice versa) were calculated in MS Excel.

RESULTS

100 isolates of *S.* Typhi (n=80) and *S.* Paratyphoid A (n=20) were included. There was 100% CA between standard and DST methods for ampicillin, chloramphenicol, cotrimoxazole, ceftriaxone and cefixime, and 95% CA for ciprofloxacin with 5% MnEs. No VMEs or MEs were observed.

CONCLUSIONS

DST performance for *Salmonella* Typhi and Paratyphi A from blood cultures is comparable to susceptibility testing from standardized inoculum and should be used routinely in high volume laboratories in typhoid endemic regions. However, laboratories should validate DST processes locally for quality assurance.

79. LABORATORY DETECTION OF TYPHOIDAL SALMONELLAE IN URINE CULTURES IN A TYPHOID ENDEMIC SETTING

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BACKGROUND

Despite several advances in clinical microbiology diagnostics, improved detection of typhoidal salmonellae in cultures (blood, urine, or stool) remains a challenge. Urine cultures may show growth of *Salmonella enterica* serovars Typhi or Paratyphi A in the second week of illness, albeit with low sensitivities. In addition to being highly specific, culture diagnosis has the advantages of informing molecular epidemiology and antibiotic susceptibilities. However, many urine culture systems are not designed to detect salmonellae and this may lead to a missed opportunity in diagnosing enteric fever as the cause of an undiagnosed febrile illness, especially in children where urine cultures are performed as part of fever evaluation. We present retrospective urine culture positivity rates for *Salmonella* Typhi and Paratyphi A from an endemic region.

METHODS

Retrospective laboratory records of urine cultures performed from 1996 to 2015 were retrieved from archives of the Intergrated Laboratory Management Systems at the Aga Khan University clinical microbiology laboratory. The laboratory has used the cysteine-lactose-electrolyte-deficient (CLED) medium for urine cultures throughout the study years, followed by biochemical identification with the API 20E system (BioMereiux) for isolate identification. Data was exported to MS Excel. Results with *Salmonella* species were identified after removal of duplicates and frequencies were calculated.

RESULTS

We identified 138 reports (0.03% of all positive urine cultures; with 50,000 positive urine cultures reported annually) of *Salmonella* species in urine cultures during 20 years of study period from 1996-2015. Of these 38.4% (n=53) were *Salmonella* Typhi and 23.2% (n=32) were *Salmonella* Paratyphi A, while 38.4% (n=53) were non-typhoidal salmonellae. Around 56% (n=97) of the cases were male, and male to female ratio was 1.29. Disc diffusion testing showed 63% (n=87), 30% (n=41), 84% (n=116), 17% (n=23), 64% (n=88) and 61% (n=83) of the isolates were sensitive to ampicillin, chloramphenicol, cefixime, ciprofloxacin, ceftrixaone and cotrimoxazole, respectively.

CONCLUSION

Laboratory personnel should be alert to the possibility of both typhoidal and non-typhoidal *Salmonella* species in urine cultures in typhoid endemic countries. Further identification of isolates having a similar biochemical profile to *Salmonella* species should be performed, especially if screening agars (eg. chromagars) are used that do not identify salmonellae.

80. SURVEILLANCE OF THREE LARGE COHORTS FOR TYPHOID FEVER: THE STRATEGIC TYPHOID ALLIANCE ACROSS AFRICA AND ASIA

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BACKGROUND

Typhoid fever, predominant in South and South East Asia, causes 26.9 million cases and 269,000 deaths, while Non-typhoid *Salmonellosis*, prevalent in sub-Saharan Africa, causes 93.8 million cases and 155,000 deaths globally each year. Estimates of disease incidence and severity are not current. There are also knowledge gaps on carriage and transmission mechanisms, asymptomatic infections and infection-derived immunity. We aim to address these questions with surveillance of large population cohorts in three countries.

METHODS

The Strategic Typhoid Alliance across Africa and Asia (STRATAA) study has enrolled cohorts of individuals and their households from three urban settings in Dhaka, Bangladesh; Blantyre, Malawi; and Lalitpur, Nepal. Key demographic information on household members was obtained via an enumerator-administered tablet-based questionnaire. Individuals in the cohort with acute febrile illnesses suspected to be enteric fever are being assessed by passive surveillance.

RESULTS

A total of 26,119, 23,567 and 24,502 households with 110,731, 97,510 and 102,963 individuals were enrolled in Dhaka, Blantyre and Lalitpur respectively. Consent was denied by 20.8%, 5.1% and 6.1% of respective households. The average household size was 4.2(SD=1.8), 4.4(SD=2.1) and 4.2(SD=2.2) members in the respective sites. 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. In 8 weeks of passive surveillance in Dhaka, 14/112(12.5%) blood culture positive fevers were detected. Similarly in 4 weeks in Blantyre, 4/54 (7.4%) fevers were positive; while 18/107 (16.8%) fevers were blood culture positive in Lalitpur in 18 weeks.

CONCLUSIONS

We have successfully enrolled large cohorts in 3 countries totaling 311,204 individuals. Ongoing research will establish burden and transmission of typhoid from surveillance in healthcare facilities with community case-investigation and using serosurveys to estimate

incident infection. Early data have already highlighted a considerable burden of disease and the need for preventive strategies.

81. ENTERIC WITH TWIST — A CASE OF ENTERIC FEVER WITH MULTIPLE COMPLICATIONS

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BACKGROUND

Enteric fever is a systemic infection caused by Salmonella enterica. It has a wide spectrum of clinical presentation. The rare manifestations include gastrointestinal bleeding, intestinal perforation, pancreatitis, endocarditis, orchitis, myocarditis, parotitis, pneumonia, arthritis, and osteomyelitis. A rare presentation of enteric fever with multi organ failure in a 10 year old girl is reported here.

CASE REPORT

A 10 year old girl with high grade fever, vomiting, loose stools of 4 days, positive widal and S. typhi positive blood culture was diagnosed as enteric fever, managed with ciprofloxacin, was ventilated, dialysed and on inotropic support for 2 days due to ARDS and ARF before transferring to our hospital for further management. She was not vaccinated against typhoid. She was continued on ventilator and inotropic support, was started on IV Ceftriaxone. Prolonged dialysis was required due to severe metabolic acidosis, low urine output, high S.creatinine (3.7). CPK level was 6039. Peripheral smear was suggestive of microangiopathic haemolytic anemia with thrombocytopenia. The serum LDH level was high (3947). Initial echocardiography showed myocarditis. Patient developed one episode of seizures. MRI brain showed PRES changes with old infarct in posterior fossa and left frontal lobe. She developed left sided consolidation with pleural effusion, ICD was inserted. The pleural fluid revealed WBC 1150,N3,L97,RBC 1000, with no growth in culture. In view of abdominal distension, CT abdomen was done, showed bulky pancreas. S-amylase was 147IU/microl. After a month stay in PICU she was maintaining saturation in room air. Her serial echo was normalized, urine output improved. Physiotherapy was given and she was discharged only on antiepileptic drugs.

DISCUSSION

Enteric fever with multiorgan failure is being reported in adults rarely seen in children. She presented with toxic myocarditis, hemolytic uremic syndrome, rhabdomyolysis, pneumonia and pancreatitis. Hypovolemia, metabolic acidosis, acute kidney injury and disseminated intravascular coagulation were due to rhabdomyolysis.

CONCLUSIONS

This is a rare case where multiple complications are seen in a single patient. Early diagnosis and interventions, high level of critical care were key factors for favourable outcome in this patient. A high level of suspicion required for all probable complications. Proper and timely vaccination would have averted these complications.

82. STUDY OF AZITHROMYCIN SENSITIVITY PATTERN OF *SALMONELLA ENTERICA* IN PEDIATRIC POPULATION

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BACKGROUND

Enteric fever is a major public health problem in tropical countries including India. It is complicated by a high level of drug resistance which some isolates display to drugs routinely used in treatment. Azithromycin may be a treatment option for such isolates. There have been reports of increasing resistance to azithromycin in India when compared to developed countries. The objectives of the study were to analyze azithromycin susceptibility in culture positive enteric fever and to evaluate the relationship between ciprofloxacin and azithromycin sensitivity and resistance patterns.

METHODS

It is a retrospective study of case records of 363 children in the age group of 0-18 years diagnosed with culture proven enteric fever, at Manipal hospital, Bangalore, India, between June 2012 and June 2016. Inclusion criteria – Presence of clinical signs and symptoms compatible with enteric fever and isolation of *S.* Typhi or *S.* Paratyphi from blood. Blood culture was done by BacT/Alert 3D system and serotypes were identified by biochemical tests or Vitek method. Susceptibility to antimicrobial drugs was tested by the disc diffusion according to Kirby Bauer method. Azithromycin and ciprofloxacin discs with a concentration of 15µg / ml and 5 µg / ml respectively were used to determine minimum inhibitory concentration (MIC) for disc diffusion testing by E- test. They were interpreted based on CLSI guidelines 2016. Exclusion criteria – Enteric fever diagnosis based only on clinical and serologic grounds.

RESULTS

There were 280 *S. enterica* serovar Typhi (77.13%) and 83 serovar Paratyphi A strains (22.86%) among the 363 enteric fever children. All the 363 salmonella isolates were susceptible to azithromycin and third generation cephalosporins. Azithromycin MICs were 0.064-12 µg/mL among the 363 isolates and no increase in resistance has been seen during the study period. There has not been any increased MIC for azithromycin in ciprofloxacin resistant isolates.

CONCLUSIONS

S. Typhi continues to remain susceptible to azithromycin and third generation cephalosporins. There has been no trend of increasing resistance to azithromycin over the years. Azithromycin can be safely used in the isolates resistant to ciprofloxacin as there is no significant correlation between their resistance. Azithromycin should be used judiciously considering the risk of developing drug resistance.

83. EVALUATION OF *IN VITRO* SYNERGY TESTING OF SOUTH AFRICAN INVASIVE *SALMONELLA* TYPHI ISOLATES USING THE LIOFILCHEM® MTS APPLICATION SYSTEM

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BACKGROUND

The recommended treatment in South Africa for invasive *Salmonella enterica* subspecies Typhi (*Salmonella* Typhi) infections is ciprofloxacin, or alternatively azithromycin or ceftriaxone. Combination therapy with an aminoglycoside and a cephalosporin was used before the introduction of the fluoroquinolones. The objective of this study was to explore a novel method to evaluate combination therapy *in vitro* to aid therapeutic options for typhoid fever. Synergy testing of current antibiotics for usage against typhoid fever was evaluated by *in vitro* testing of two antibiotics, by determining the cross gradient with minimum inhibitory concentration (MIC) strips.

METHODS

Synergy testing of twenty-five clinical invasive *Salmonella* Typhi strains was undertaken using Liofilchem® MIC strips. Antibiotic combinations included ciprofloxacin against ampicillin, amikacin, azithromycin, chloramphenicol, ceftriaxone and streptomycin. Isolates were sub-cultured onto Mueller Hinton agar and the MIC strips placed according to the manufacturer's instructions. MIC values were initially determined against single antimicrobials listed above. Ciprofloxacin strips were aligned at 90 degrees to the antibiotics listed at the point of the respective MIC for each isolate against each antimicrobial. A fractional inhibitory concentration index (FIC) calculation was used to interpret synergistic, additive, indifference and antagonistic interactions.

RESULTS

Of the 25 isolates, six FIC values were obtained for each isolate (150 in total). Synergy was seen in 24% (36/150) of combinations, additive inhibitions in 30.6% (46/150), indifference in 34.7% (52/150) and antagonism 10.6% (16/150). Ciprofloxacin and amikacin and ciprofloxacin and streptomycin were the most active combinations.

CONCLUSIONS

The MTS method proved to be useful in obtaining rapid results and was easy to use. Combination therapy may be an alternative for treatment of *Salmonella* Typhi infections resistant to one or more of the recommended antimicrobials in South Africa.

84. PRECLINICAL EVALUATION OF A *SALMONELLA* TYPHI POLYSACCHARIDE VI-DIPHTHERIA TOXOID (VI-DT) CONJUGATE VACCINE CANDIDATE AGAINST TYPHOID FEVER

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BACKGROUND

Typhoid fever continues to be a major public health problem according with estimates of World Health Organization. Conjugation of polysaccharides to an immunogenic protein revert the Timo independent pattern of polysaccharides to a T-dependent pattern and induce immune response in infants. The aim of this work was to obtain and evaluate a conjugate candidate vaccine against this disease.

METHODS

Vi polysaccharide of *Salmonella* Typhi was conjugated to diphtheria toxoid (Vi-DT) via a carbodiimide-mediated reaction. Analytic assays were done to formulations at 10µg/ml and 20µg/ml. Immunogenicity and protective capacity of conjugates were evaluated in BALB/c or C57BL/6 mice.

RESULTS

All lots of conjugate formulations showed similar characteristics. Vi-DT conjugates were immunogenic in BALB/c mice and the immune response was dose dependent. The addition of at least a 50% of unconjugated Vi to Vi-DT, did not affect the conjugate's immunogenicity. Memory B cell and memory T cell responses after booster dose with a plain polysaccharide vaccine were induced. Conjugates were also protective after challenge with a *Salmonella* Typhi strain F9 and mucin as virulence inductor in C57BL/6 mice

CONCLUSIONS

These results demonstrated that Vi-DT conjugates are immunogenic and protective in animal models, encouraging us to continue the development of a conjugate vaccine against typhoid.

85. SELECTION OF POLYSACCHARIDE LENGTH, CONJUGATION PROCEDURE AND CARRIER PROTEIN FOR VI POLYSACCHARIDE CONJUGATE OBTAINING

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BACKGROUND

There is an estimate of 11.9 million cases of typhoid fever, with 190,000 deaths every year. The development of conjugate vaccines provides an opportunity to better combat this serious disease. This work evaluated the influence of some parameters in physicochemical and immunological characteristics of Vi polysaccharide conjugates and characterized the immune response of a selected conjugate.

METHODS

The parameters evaluated were: polysaccharide length (native or fragmented), linker (no linker, hydrazine or ADH) and carrier protein (DT or TT). The conjugates were analyzed by colorimetric methods, SEC-HPLC and H^1-NMR. The immune response was evaluated in BALB/c mice.

RESULTS

All conjugates were suitable physicochemical characteristics, with higher KD for conjugate obtained from fragmented polysaccharide and for conjugate without linker. All conjugates were more immunogenic than the unconjugated polysaccharide. The avidity of IgG antibodies generated by the fragmented polysaccharide conjugate was greater than the rest of the conjugates immunized. For native Vi ADH conjugated to DT was observed a mixed Th1/Th2 response pattern of isotypes and cytokines. It was shown that the conjugate induces a memory response and that the presence of free polysaccharide in the same amount as the conjugate does not affect the IgG response.

CONCLUSIONS

In summary, the study determined the parameters which influence physicochemical and immunological characteristics and demonstrated a thymus-dependent response against the conjugate.

86. A NGS APPROACH TO CHARACTERIZE DRUG RESISTANCE OF *SALMONELLA ENTERICA* SEROVAR TYPHI

Arif M Tanmoy[1,2,3], Emilie Westeel[3], Alain Rajoharison[3], Luiz G Almeida[4], Maksuda Islam[2], Ana TR Vasconcelos[4], Florence Komurian-Pradel[3], Samir K Saha[2] and Hubert P Endtz[1,3]

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BACKGROUND

Enteric fever is a systemic illness, predominantly caused by *Salmonella enterica* serovar Typhi. Globally, it affects an estimated 17-22 million people/year, with about 200,000 deaths, especially in the developing countries including Bangladesh. Timely treatment with appropriate antibiotics is crucial. However, the emergence of antimicrobial resistance (AMR), specifically to ampicillin(AMP), chloramphenicol(CHL), cotrimoxazole(SXT) and ciprofloxacin(CIP) has reached an alarming level and become major public health threat. AMR is encoded on multiple chromosomal and extra-chromosomal genes that can be identified by the Next Generation Sequencing (NGS). So, our study aimed to detect the molecular pathways responsible for AMR & predict the phenotypic-susceptibility from Whole Genome Sequence (WGS).

METHODS

During 1999–2013, >3000 *Salmonella* Typhi were isolated from blood of enteric fever patients at Dhaka Shishu (children) Hospital, Bangladesh. 551 strains were selected (337 hospitalized & 214 attending outpatient facility) for the study. Strains were confirmed by biochemical and specific-antisera tests. Antimicrobial susceptibility was measured by disk-diffusion (CLSI-2016). WGS was done with Illumina-Hiseq and is being analyzed using de-novo assembly (Newbler), own-scripts to attain closed genome, comparative-genomics (Mauve) and annotation (SABIA).

RESULTS

39%(215/551) of selected strains was multidrug resistant (MDR, resistant to AMP-CHL-SXT), from 38%(6/16) in 1999, to 26%(12/47) in 2013. In contrast, 87%(481/551) of selected S. Typhi strains was CIP-non-susceptible, ranging from 50%(8/16) in 1999, to 89%(42/47) in 2013. Preliminary mapping results showed presence of plasmid pHCM1 (contains AMR-genes) and pHCM2 in 9%(50/551) and 41%(228/551) of selected strains respectively. A *Salmonella* Genomic Island (SGI11, contains AMP/CHL/SXT-resistance genes) was found in 98%(211/215) of MDR strains. In contrast, only 22%(47/215) MDR strains had pHCM1.

CONCLUSION

Successful analysis of the WGS data, combined with the clinical and laboratory metadata will help us to identify the molecular pathways for AMR. This could also serve as the preliminary step to design a real-time characterization tool for enteric pathogens based on genomic information on AMR.

87. ENTERIC FEVER AND HOUSEHOLD WATER SUPPLY: DETECTION OF *SALMONELLA ENTERICA* SEROVAR TYPHI AND PARATYPHI IN THE SUPPLY WATER OF URBAN DHAKA, BANGLADESH

Arif M. Tanmoy[1], Jason R. Andrews[2], Mohammad S.I. Sajib[1], Maksuda Islam[1], Stephen Baker[3], Stephen P. Luby[2], Samir K. Saha[1,4]

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BACKGROUND

Although *Salmonella enterica* serovars Typhi and Paratyphi are known to be transmitted through the fecal-oral pathway, the proportion of transmission that occurs through direct interpersonal or intra-household transmission versus transmission through an environmental reservoir is uncertain. Understanding transmission pathways can help focus prevention efforts. We attempted to replicate recent work in Kathmandu, Nepal, which found high concentration of *S.* Typhi and Paratyphi in public drinking water sources.

METHODS

Blood-culture positive *S.* Typhi/Paratyphi cases at Dhaka Shishu Hospital and Shishu Syastho Foundation Hospital, Dhaka, were enrolled. A field worker collected one liter of water from the source of household drinking water and kept at 4°C until processed. Each water sample was filtered (0.45µm), followed by DNA-extraction (Epicentre metagenomic water-DNA Kit) and qPCR for detection of *S.* Typhi (target gene STY0201) and *S.* Paratyphi (target gene SSPA2308). A standard curve was prepared using different concentrations of positive-control to calculate DNA copy numbers.

RESULTS

We recruited 59 patients with culture-confirmed enteric fever (48 *S.* Typhi; 11 *S.* Paratyphi), visited their homes, and collected water for qPCR. Among these water samples, 36 (61%) were positive for *S.* Typhi, 14 (24%) for *S.* Paratyphi and 11 (19%) for both. Twenty-seven (46%) Typhi cases had a cycle-threshold (Ct) <35, in contrast to only 2 (3%) for Paratyphi. Median DNA copy number/liter of water was 934 (IQR: 361-1952) for *S.* Typhi and 266 (IQR: 183-963) for *S.* Paratyphi.

CONCLUSIONS

This preliminary finding on presence of *S.* Typhi and Paratyphi in water supply of urban Dhaka, where prevalence of enteric fever is high, strengthens the claim that supplied water disseminates these organisms. The replication of the results from Kathmandu suggests that this approach can be useful in identifying the high burden communities that could benefit from interventions to prevent enteric fever.

88. A RANDOMIZED, OBSERVER-BLINDED, PHASE I STUDY TO ASSESS THE SAFETY AND IMMUNOGENICITY OF VI-DT CONJUGATE VACCINE COMPARED TO VI-POLYSACCHARIDE (TYPHIM VI®, SANOFI PASTEUR) TYPHOID VACCINE IN HEALTHY FILIPINO ADULTS AND CHILDREN

Samuel Teshome[1], Mario Rosario Capeding[2], Yang Hee Kim[1], Jiwook Park[1], Ju Yeon Park[1], Deok Ryun Kim[1], Yun Chon[1], Sue Kyoung Jo[1], JaeSeung Yang[1], Sushant Sahastrabuddhe[1], Jean-Louis Excler[1]

[1]International Vaccine Institute, Seoul, South Korea; [2]Research Institute of Tropical Medicine, Manila, the Philippines

BACKGROUND

Vaccination with Vi- polysaccharide vaccine has been shown to protect individuals from typhoid fever but their use is hampered by several limitations: T-cell independent immune response mechanism with no development of immune memory; less effective and immunogenic in children <2 years of age; no boosting effect following vaccination and shorter duration of protection requiring revaccination every 3 years. With the initial know-how from US NIH, IVI developed a new typhoid conjugate vaccine (Vi-DT), Vi- polysaccharide conjugated to diphtheria toxoid (DT). The technology was transferred to SK Chemicals, Republic of Korea, in August 2013.

METHODS

This is a Phase I randomized, observer-blinded study to assess the safety and immunogenicity of Vi-DT conjugate vaccine compared to Vi-Polysaccharide vaccine. Healthy male and female participants aged 2-45 years were enrolled stratified into 18-45, 6-17, and 2-5 years age de-escalation study. The study was conducted at the Research Institute for Tropical Medicine (RITM), Manila, The Philippines. A total of 144 participants were randomized between Test (Vi-DT) and Comparator (VI Polysaccharide) vaccines administered at 0 and 4 weeks. Since the comparator vaccine is administered as a single dose, the second dose administered was a flu vaccine to keep the blinding. The Primary objective is to evaluate the safety of 25 µg of Vi-DT typhoid conjugate vaccine, while the secondary objectives are to assess the immunogenicity of 25 µg of Vi-DT typhoid conjugate vaccine and to compare the safety and immunogenicity of Vi-DT with Vi- Polysaccharide typhoid vaccine.

RESULTS

48 participants in each age cohort for a total of 144 participants were randomized and enrolled to Vi-DT vs Typhim-Vi + Vaxigrip

(comparator) group. Blinded safety data was generated for each cohort and submitted for review and approval to safety monitoring committee and institutional review boards. Approval by the safety monitoring committee and institutional review boards was required for age de-escalation enrollment. No severe adverse event was reported. The vaccines were safe and generally well tolerated with mild to moderate solicited adverse events. The immunogenicity results will be presented.

CONCLUSIONS

The Vi-DT vaccine deserves further evaluation in humans in particular in younger children less than 2 years of age. This typhoid vaccine will be an important addition to existing typhoid fever control and prevention methods.

89. ELECTRONIC DATA CAPTURE FOR LARGE SCALE TYPHOID SURVEILLANCE, HOUSEHOLD CONTACT TRACING, AND HEALTH UTILIZATION SURVEY: STRATEGIC TYPHOID ALLIANCE ACROSS AFRICA AND ASIA

Deus Thindwa[1*], Yama G Farooq[2*], Mila Shakya[3], Nirod Saha[4], Susan Tonks[2], Yaw Anokwa[5], Carl Hartung[5], Andrew Pollard[2], Robert S. Heyderman[1,6] on behalf of STRATAA Study Consortium

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BACKGROUND

Paper based systems for data collection and management are labour intensive and can result in slow, poor quality data collection, and increased data cleaning time. In contrast, electronic data capture systems have potential to automate validation to pre-emptively correct data errors in real time. In STRATAA, we have used Open Data Kit (ODK) and Structured Query Language (SQL) routines to generate timely, high volume and quality data.

METHODS

STRATAA is a comprehensive programme assessing the population dynamics and epidemiology of typhoid fever in Malawi, Bangladesh and Nepal to inform design of vaccine and public health interventions. Census and survey data collection forms were developed through a structured iterative process and then implemented using ODK, with customizations by Nafundi, on Android-based tablets. Data are uploaded onto MySQL databases, where SQL routines are run nightly to enforce data cleaning on critical variables beyond ODK's validation routines. Daily anonymized data are backed up from 3 sites centrally. Database reports and descriptive analyses are generated weekly. To assess efficiency and quality of data capture, volume, accuracy and time of census data collection were quantified.

RESULTS

We recorded demographics of 311,204 individuals from 74,475 households in three countries within average of 14.7 weeks range (13-16) using 20, 25, and 37 enumerators from Malawi, Bangladesh and Nepal respectively. Overall, 28.4 errors per 10,000 data points were found; 3.4, 7.6, 17.4 errors per 10,000 data points for Malawi, Bangladesh, Nepal respectively. These values meet acceptable quality threshold of 50 errors per 10,000 data points established by the Society for Clinical Data Management.

CONCLUSIONS

This robust, easy to use system allowed for high volume data to be collected over short time periods. Errors were low and varied moderately by country. Access to data is in real time, facilitating quality checking and decision making.

90. INVESTIGATING THE CONTRIBUTION OF FOOD ANIMALS TO HUMAN NON-TYPHOIDAL *SALMONELLA* DISEASE IN EAST AFRICA

Kate M. Thomas[1], Ruth N. Zadoks[2], Gary C. Barker[3], Jackie Benschop[4], Joram Buza[5], Sarah Cleaveland[2], Margaret Davis[6], Nigel P. French[4], Rudovick R. Kazwala[7], Blandina T. Mmbaga[8], Niwael Mtui[9], Gerard Prinsen[10], Jo Sharp[11], Emmanuel Swai[9], John A. Crump[1]

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BACKGROUND

Invasive non-typhoidal *Salmonella* (NTS) is estimated to cause 680,000 deaths annually, mostly in Africa. NTS is an important cause of diarrhoea and bacteraemia in Tanzania. We are investigating the potential contribution of the ruminant and poultry meat pathway to human NTS disease in northern Tanzania.

METHODS

Using an interdisiplinary team consisting of social, biological and quantitative scientists, we are applying supply and value chain analysis, microbiological, epidemiological and mathematical modelling methods to integrate the information supply in a One Health approach to assess the contribution of food animals to NTS disease. Data and sample collection was performed in the Kilimanjaro and Arusha Regions in Tanzania. Faeces, carcass swabs, and meat from cattle and goats were obtained at slaughter and from butchers. Cloacal swabs were obtained from live chickens on farms. Environmental samples were taken from the slaughter and butcher sites. Modified FDA-BAM methods were used for NTS isolation. The genetic relatedness of Tanzanian NTS isolates from animals and East African NTS isolates from human stool and bloodstream will be compared using ribosomal Multilocus Sequence Typing and core genome sequence typing.

RESULTS

To date, our analysis has supply chains of varying lengths and complexity, including formal and informal slaughter locations and eateries. NTS have been recovered from 4 (2.2%) of 185 chicken cloacal swab samples, 2 (1.2%) of 166 cattle faecal samples, 6 (3.6%) of 165 goat faecal samples, 26 (11.8%) of 220 beef samples, 7 (4.9%) of 143 goat meat samples, 0 (0.0%) of 116 cattle carcass swabs, 1 (0.8%) of 129 goat carcass swabs and 14 (12.2%) of 115 of environmental samples.

CONCLUSIONS

We have isolated NTS from cattle, goat, and chicken samples. Further isolate characterisation and modelling will indicate if and how livestock contributes to human NTS disease.

91. VARIATIONS OF INVASIVE *SALMONELLA* INFECTIONS BY POPULATION SIZE IN ASANTE AKIM NORTH MUNICIPAL, GHANA

Ligia M. Cruz Espinoza[1], Chelsea Nichols[1], Yaw Adu-Sarkodie[2,3], Hassan M. Al-Emran[4,5], Stephen Baker[6], John D. Clemens[7], Denise Myriam Dekker[4,5], Daniel Eibach[4,5],Ralf Krumkamp[4,5], Kennedy Boahen[2], Justin Im[1], Anna Jaeger[4], Vera von Kalckreuth[1], Gi Deok Pak[1], Ursula Panzner[1], Se Eun Park[1], Jin Kyung Park[1], Nimako Sarpong[2], Heidi Schütt-Gerowitt[1,3], Trevor Toy[1], Thomas F. Wierzba[1], Florian Marks[1,a], and Jürgen May[4,5,a]

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BACKGROUND

The Typhoid Fever Surveillance in Africa Program (TSAP) estimated adjusted incidence rates (IRs) for *Salmonella enterica* serovar Typhi and invasive nontyphoidal *S. enterica* serovars (iNTS) of >100 cases per 100 000 person-years of observation (PYO) for children aged <15 years in Asante Akim North Municipal (AAN), Ghana, between March 2010 and May 2012. We analyzed how much these rates differed between rural and urban settings.

METHODS

Children recruited at the Agogo Presbyterian Hospital and meeting TSAP inclusion criteria were included in the analysis. Towns with >32 000 inhabitants were considered urban; towns with populations <5200 were considered rural. Adjusted IRs for *Salmonella* bloodstream infections were estimated for both settings. Setting-specific age-standardized incidence rates for children aged <15 years were derived and used to calculate age-standardized rate ratios (SRRs) to evaluate differences between settings.

RESULTS

Eighty-eight percent (2651/3000) of recruited patients met inclusion criteria and were analyzed. IRs of *Salmonella* bloodstream infections in children <15 years old were >100 per 100 000 PYO in both settings. Among rural children, the *Salmonella* Typhi and iNTS rates were 2 times (SRR, 2.2; 95% confidence interval [CI], 1.3–3.5) and almost 3 times (SRR, 2.8; 95% CI, 1.9–4.3) higher, respectively, than rates in urban children.

CONCLUSIONS

IRs of *Salmonella* bloodstream infections in children <15 years old in AAN, Ghana, differed by setting, with 2 to nearly 3 times higher rates in the less populated setting. Variations in the distribution of the disease should be considered to implement future studies and intervention strategies.

92. A SYSTEMATIC REVIEW OF THE INCIDENCE, RISK FACTORS AND CASE FATALITY RATES OF INVASIVE NONTYPHOIDAL *SALMONELLA* (INTS) DISEASE IN AFRICA (1966 TO 2014)

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BACKGROUND

Data on the burden of iNTS disease in Africa are sparse and generally have not been aggregated, making it difficult to describe the epidemiology that is needed to inform the development and implementation of effective prevention and control policies. The study aims to document the geographical spread of iNTS disease reported over time in Africa, and describes its reported incidence, risk factors and CFR.

METHODS

This study systematically reviewed the literature on the occurrence, incidence and case fatality rate (CFR) of invasive nontyphoidal *Salmonella* (iNTS) disease in Africa from 1966 to 2014. This study involved a comprehensive search of PubMed and Embase databases using a comprehensive search string.

RESULTS

We found that Nontyphoidal *Salmonella* (NTS) have been reported as a cause of bacteraemia in 33 out of 54 African countries, spanning the five geographical regions of Africa, and especially in sub-Saharan Africa since 1966. Our review indicates that NTS have been responsible for up to 39% of community acquired blood stream infections in sub-Saharan Africa with an average CFR of 19%. *Salmonella* Typhimurium and Enteritidis are the major serovars implicated and together have been responsible for 91% of the cases of iNTS disease (where serotype was determined), reported in Africa. The study confirms that iNTS disease is more prevalent amongst Human Immunodeficiency Virus (HIV)-infected individuals, infants, and young children with malaria, anaemia and malnutrition.

CONCLUSIONS

In conclusion, iNTS disease is a substantial cause of community acquired bacteraemia in Africa. Given the high morbidity and mortality of iNTS disease in Africa, it is important to develop effective prevention and control strategies including vaccination.

93. CELL-MEDIATED IMMUNE RESPONSES ELICITED IN VOLUNTEERS IMMUNIZED WITH THE NOVEL LIVE ORAL *SALMONELLA ENTERICA* SEROVAR PARATYPHI A VACCINE STRAIN CVD1902

Rezwanul Wahid, Karen L. Kotloff, Myron M. Levine, Marcelo B. Sztein

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BACKGROUND

A candidate live oral attenuated *S.* Paratyphi A (PA) vaccine strain (CVD1902) harboring mutations in *guaBA* and *clpX* gene was developed to combat paratyphoid A fever. In this study, we evaluated whether immunization with CVD1902 elicits PA-specific T-cell mediated immune (CMI) and B memory responses in humans.

METHODS

Peripheral blood mononuclear cells (PBMC) were obtained before and 28 days after immunization from two cohorts of volunteers who participated in a Phase-1 clinical trial. Each cohort consisted of 6 vaccinees (Cohorts 4 and 5 receiving a single oral dose with 10e9 and 10e10 CFU of CVD1902. respectively) and 2 Placebo controls (Saline only). Cytokines in culture supernatants (IFN-γ, RANTES, TNF-α, IL-10, and IL-23P40) were measured following *in vitro* stimulation with PA particles or PA flagella. We also evaluated the induction of B memory (B_M) cells against PA-LPS, using a standard B_M protocol, in 11 vaccinees and 4 placebo controls (cohorts 4 and 5).

RESULTS

Significant post-vaccination increases (> 2 fold from pre-vaccination levels) for at least one of the cytokines evaluated was observed in 5 of 6 (83%) vaccinees, while 4 (67%) of them showed increases in two or more cytokines. None of the 2 placebo controls (0%) showed cytokine responses. Post-vaccination increases in PA-LPS-specific IgG and IgA BM (>15 spot forming cells/10e6 expanded PBMC above pre-vaccination levels) were observed in 7 of 11 (64%) and 6 of 11 (55%) vaccinees, respectively, but not in placebo controls (0 of 4).

CONCLUSIONS

Previous extensive studies with live oral typhoid vaccine (Ty21a) and volunteers challenged with wild-type *S.* Typhi suggested that CMI responses may play a critical role in protection against typhoid fever. The data showing similar T and B cell-mediated PA specific-CMI responses elicited by CVD1902 in humans suggests that this might be an effective vaccine against paratyphoid A fever.

94. A CROSS-SECTIONAL SEROEPIDEMIOLOGICAL SURVEY FOR TYPHOID FEVER IN FIJI

Conall Watson

London School of Hygiene & Tropical Medicine

BACKGROUND

Fiji, an upper-middle income state in the Pacific Ocean, has been experiencing an upturn in confirmed case notifications of typhoid fever. Important questions about typhoid in Fiji remain unanswered.

METHODS

To characterize the epidemiology of typhoid infection and immunity in Fiji, we conducted a cross-sectional sero-epidemiological survey measuring IgG against the Vi antigen of *Salmonella* enterica, serovar Typhi by ELISA to estimate the effect of age, ethnicity and other variables on seroprevalence. Epidemiologically relevant cut-off titres were established using a mixed model analysis of data from recovering culture-confirmed typhoid cases.

RESULTS

A total of 1787 participants were enrolled and successfully assayed, of which 1,531 from areas that had not been previously vaccinated (seropositivity 32.3% (95%CI 28.2 to 36.3%)) and 256 were from areas that had been previously vaccinated (seropositivity 71.5% (95%CI 62.1 to 80.9%)). There were no significant differences in seropositivity prevalences by ethnicity, which is in contrast to disease surveillance data in which the indigenous iTaukei Fijian population are disproportionately affected. Using multivariable logistic regression, seropositivity was associated with increased age (odds ratio 1.3 (95% CI 1.2 to 1.4) per 10 years) the presence of a pit latrine (OR 1.6, 95%CI 1.1 to 2.3) as opposed to a septic tank or piped sewer and residence in settlements rather than residential housing or villages (OR 1.6, 95% CI 1.0 to 2.7).

CONCLUSIONS

Increasing seropositivity with age is suggestive of low-level endemic transmission in Fiji. Improved sanitation where pit latrines are used and addressing potential transmission routes in settlements may reduce exposure to *S.* Typhi. Widespread subclinical infection suggests there may be a role for typhoid vaccination in Fiji, in addition to public health management of cases and outbreaks. Serosurveys using anti-Vi ELISA can be utilised to inform typhoid control.

95. ESTIMATING CASE FATALITY RATE OF BLOOD CULTURE CONFIRMED TYPHOID FEVER IN DHAKA, BANGLADESH

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BACKGROUND

Case fatality rate estimates for typhoid fever are central to estimating disease burden, but are scarce. Estimates range from 0-15%, with active population based surveillance reporting lower rates presumably due to early detection and hospital based surveillance with higher estimates given their sicker patients. We measured the case fatality rate among patients who had blood culture confirmed typhoid in Dhaka Bangladesh.

METHODS

Between January and December 2010, we prospectively followed patients with blood cultures positive for *Salmonella* Typhi, identified from six private laboratories utilized by both hospitals and outpatient private practitioners throughout Dhaka, Bangladesh. We collected antibiotic resistance information from the laboratories. Study personnel interviewed patients via telephone 30 days after blood culture collection to obtain information on antibiotic use and complications.

RESULTS

1,336 patients were enrolled; 59% were male, 41% were female, with an average age of 15. 98% experienced fever, 25% required hospitalization and 4 patients died from *S.* typhi (0.3%, 95% CI 0.28-0.32%). The four patients who died were all female and had an average age of 45 years old (range 40-65). 14% of isolates were resistant to chloramphenicol, ampicillin and co-trimoxazole; 38% were resistant to azithromycin. 47% started antibiotics prior to blood cultures, with another 17% starting antibiotics after cultures but before results were reported. Culture results caused 55% to switch antibiotics.

CONCLUSIONS

This study found a 0.3% case fatality rate for blood culture confirmed typhoid fever among a mixed population of sicker, hospitalized patients and healthier outpatients in urban Bangladesh. This assessment did not capture the experience of people too poor to secure a blood culture, but offers a low cost strategy to generate an empirical estimate and explore case fatality in other contexts. Future studies should track antimicrobial resistance and its impact on patient outcomes.

CONFERENCE INFORMATION

CONFERENCE REGISTRATION

The registration desk is located in the downstairs lobby of the conference center.

REGISTRATION OPERATING HOURS

Tuesday, 4 April 2017 **7:30-16:30**
Wednesday, 5 April 2017 **8:00-16:30**
Thursday, 6 April 2017 **8:00-16:30**

NAME BADGES

Each attendee 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 and social functions.

POSTER PRESENTATIONS

Poster presenters can set up their presentations between 7:30 and 8:30 Tuesday, 4 April 2017. If you need assistance setting up your poster, please report to the Secretariat Office next to the Plenary Hall. All posters need to be removed from boards by 18:30 on Thursday, 6 April 2017.

Posters will be on display for the entire conference. All poster presenters should stand by their posters during the following times to answer questions from attendees one-on-one:

Tuesday, 4 April **15:00-15:30**
Wednesday, 5 April **15:00-15:30**
Thursday, 6 April **10:45-11:15**

MOBILE PHONES

As a courtesy to fellow delegates and speakers, please ensure your mobile phones are switched off during Conference sessions.

REFRESHMENTS

Lunch will be served daily in Katonga Hall and coffee breaks will be served in the Victoria Gallery Lobby. Both are located up the stairs outside the plenary hall.

SPECIAL DIETARY REQUIREMENTS

Thank you for notifying the Conference Organizers of any special dietary requirements. Please be advised that this information has been supplied to the Conference venue and all food will be appropriately labeled. All meat is Halal.

WIRELESS ACCESS

Attendees have access to free wireless internet during the Conference; this is most suitable for web browsing, twitter and email access.

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PLACES OF INTEREST

Explore nearby attractions, including the Entebbe Botanical Gardens (35 km), Ngamba Island Chimpanzee sanctuary (36 km), Sezibwa Falls (40 km) and Mabira Forest (56 km).

CREDIT CARDS

American Express, Diners, MasterCard and Visa are accepted but not widely used. Some large hotels, restaurants, travel agencies and shops in urban areas accept credit cards.

BANK FACILITIES

Generally Mon-Fri 8:30-14:00, Sat 9:00-12:00. Forex bureaux are open until 1700 and able to do electronic transfers to and from overseas.

CURRENCY

The local currency is the Uganda Shilling (UGX). Notes are in denominations of UGX50,000, 20,000, 10,000, 5,000, 2,000 and 1,000. Coins are in denominations of UGX500, 200, 100, 50, 10, 5, 2 and 1. However, UGX1,000 notes are soon to be replaced by coins. Try not to accept very old or damaged notes where possible, as some places may refuse to take them.

The US dollar, euro and pound sterling are all recognized currencies in Uganda, and both euros and dollars are now widely accepted for cash payments. Other international currencies may also be accepted in some places in the major cities, although visitors may struggle with other currencies in smaller towns.

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