Accelerating Impact Through Mindful Management of Innovation

Jerome H. Kim, MD

13th Typhoid & Other Invasive Salmonelloses

6 December 2023

International Vaccine Institute

IVI supports vaccine development across the vaccine value chain

Vaccine Development Services*

Discover		Develop		Deliver		Epi. Surveillance	
Pre-Clinical Study & Support	Material production, test & release for toxicology studies	Assay Validation & Clinical Samples Evaluation	Critical assay development & optimization	Health Economic Study	Field-based data collection incl. costing & willingness to pay	Epidemiology/ Observational Study Support	Protocol dev. incl. definition of endpoint, bio investigation, & database
	Protocol dev.		Method validation according to ICH guidelines		Global/country analyses incl. invest., budget impact, cost-effectiveness, demand & disease burden		Prevalence & incidence est. of infection/disease severity
	CMO/CRO identification		Clinical sample evaluation in GCLP lab				Data for decision on vaccine introduction
Process & Analytical Dev.	Scalable & optimized processes for candidate Ag	Tech Transfer Support	Candidates & process transfer to CMOs & stability plan dev.				Site preparedness for Ph.3 trial & effectiveness study
	Analytical methods for qual. testing	Mfg. Support	Process scale-up & ensuring of commercial-scale mfg. & vaccine candidate supply			AMR Monitoring	AMR assessment & public database creation
	In vivo animal studies	Clinical Dev. & Regulatory Support	IPDP & CDP development	Policy & Advocacy Research		Vaccine Impact & Effectiveness Study	Mass vaccination campaign
			Clinical trial implementation & management in HIC & LMIC	Modeling	Vaccine impact & disease risk mapping etc.		Vaccine intro through health authorities
			Regulatory affairs consultation				Real-life vaccine performance assessment

Diseases

• iNTS	• Paratyphoid A	• Invasive Non-typhoidal Salmonella (iNTS)	• Dengue fever	• Typhoid
• Group A strep	• Zika	• MERS-CoV	• Cholera	• Cholera
• SFTSV	• Hantavirus Pulmonary Syndrome (HPS)	• Chikungunya	• Typhoid	• COVID-19
• Shigella		• Schistosomiasis	• AMR	• RSV
• Hepatitis A, B		• Typhoid	• GAS	• GAS
• Tuberculosis	• Lassa fever	• COVID-19	• iNTS	• Shigella
• HAdV-55	• MERS	• Cholera	• RSV	• AMR
• COVID-19		• Micro-needle array (MAP) Hep-B	• Schistosomiasis	

Cross-Functional Activities

IVI develops and supports:

- Translational Hubs
- Innovation Vaccine Research Centers
- Training and Capacity building
- Project Management

Managing Innovation to Impact

Impact
- **Lives saved**
- **↓ DALYs**
- **Healthier families**
  - **↓ poverty**
  - **↑ cognitive and physical development**
  - **↑ education**
- **↑ Economic growth**

NATIONAL VACCINATION PROGRAMS

DELIVERY

SUPPLY
VACCINE
DEMAND

New global health vaccines

NEED: A safe, effective typhoid conjugate vaccine

Developing Country Vaccine Manufacturer

Drug-resistant *S.* Typhi in Pakistan

WHO/SAGE
Gavi/UNICEF
ADVOCACY
NITAGs

Manufacturing
Clinical Development
NRA approval
WHO PQ

DEVELOPMENT AGENCIES
- KOICA, SIDA, DFID, USAID

FOUNDATIONS / TRUSTS
DONORS

- **Burden data**
- **Cost Effectiveness**
- **Investment Cases**
- **Full Public Value of Vaccines Analyses**
- **Support for NRA / NITAGs**

- **Clinical Development and Regulatory**
- **Biostatistics**
- **Data Management**
- **Support for PQ**

Technology Transfer & Mfr Support

DEVELOPMENT & DELIVERY

PUB HEALTH, ACCESS & VACCINE EPI

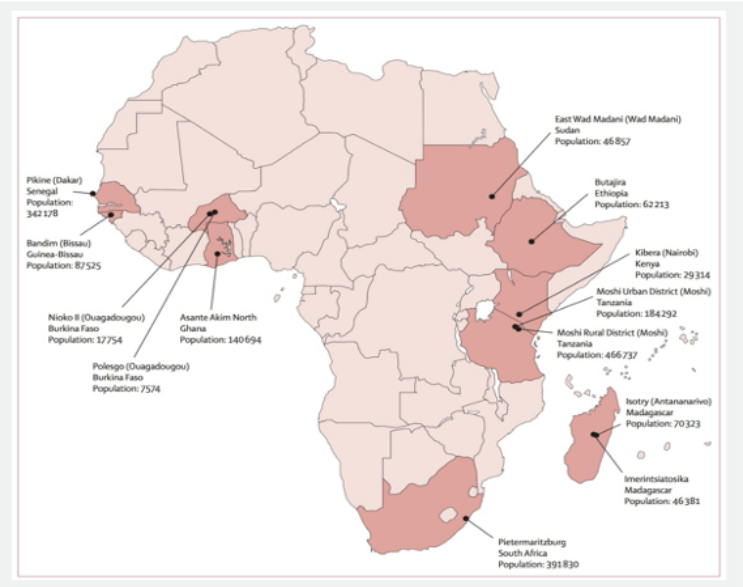
LABORATORY

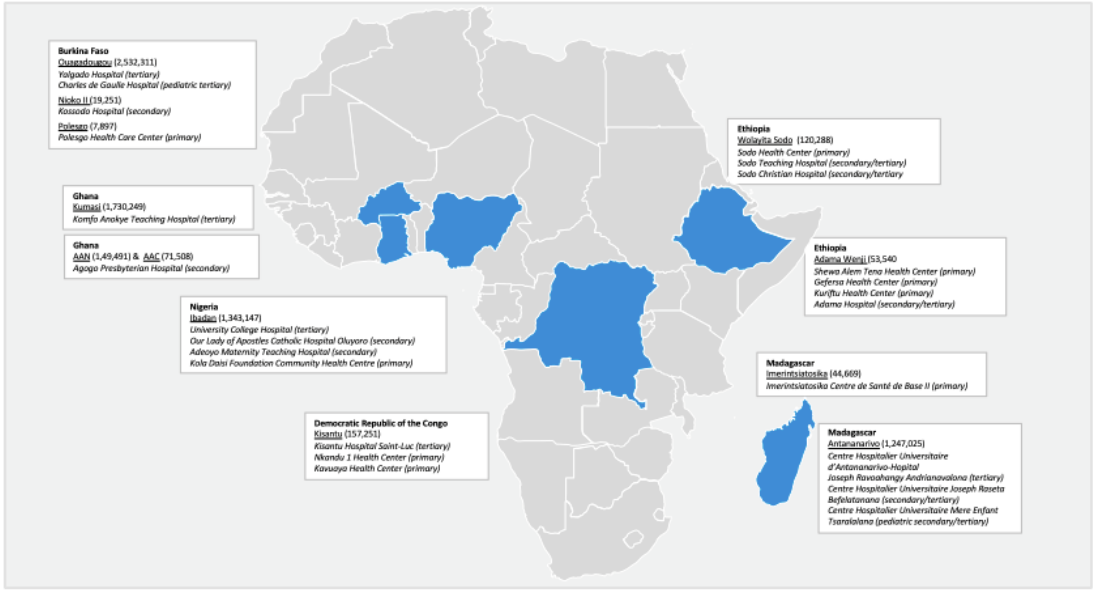
New vaccines

Understanding the burden of disease from *Salmonella* Typhi

DISEASE BURDEN

- 5 years of typhoid fever surveillance in 10 countries (Lancet GH, 2018)
- 5 years of severe typhoid surveillance in 6 countries (under review, pre-print available)





TSAP
Typhoid Fever Surveillance in Africa Program

SETA
Severe Typhoid Surveillance in Africa Program

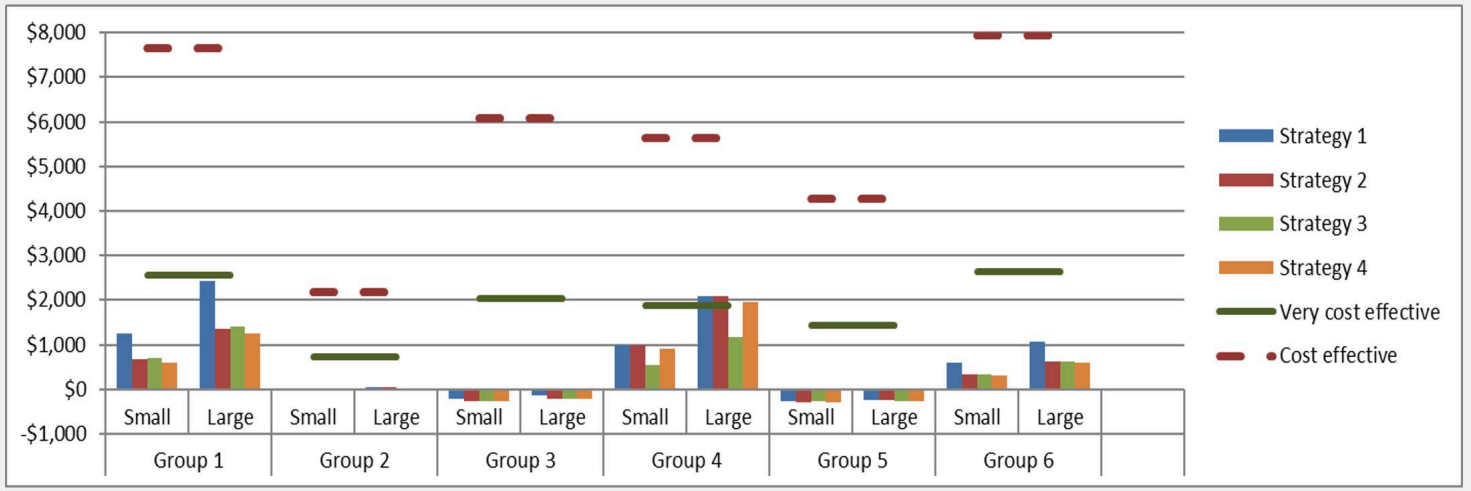
2010 - 2014

2015 - 2019

2007 ViVA
- Global Risk Factor Mapping

Dr. Florian Marks

TCV Cost Effectiveness Analysis



- Small target scenario – base population in either urban slums or rural areas without improved water
- Large target scenario – base population includes the whole population of a nation

Group 1	Group 2	Group 3	Group 4	Group 5	Group 6
North Africa	East Africa	South-East Asia	East Asia	Central Asia	Latin America
West Asia	Middle Africa			South Asia	
	South Africa				
:	West Africa	:	:	:	:

:

Vaccination strategy	Description
1	Infant routine & booster dose
2	Infant routine & booster dose & 1-14 catch-up
3	Infant routine
4	Infant routine & 1-14 catch-up

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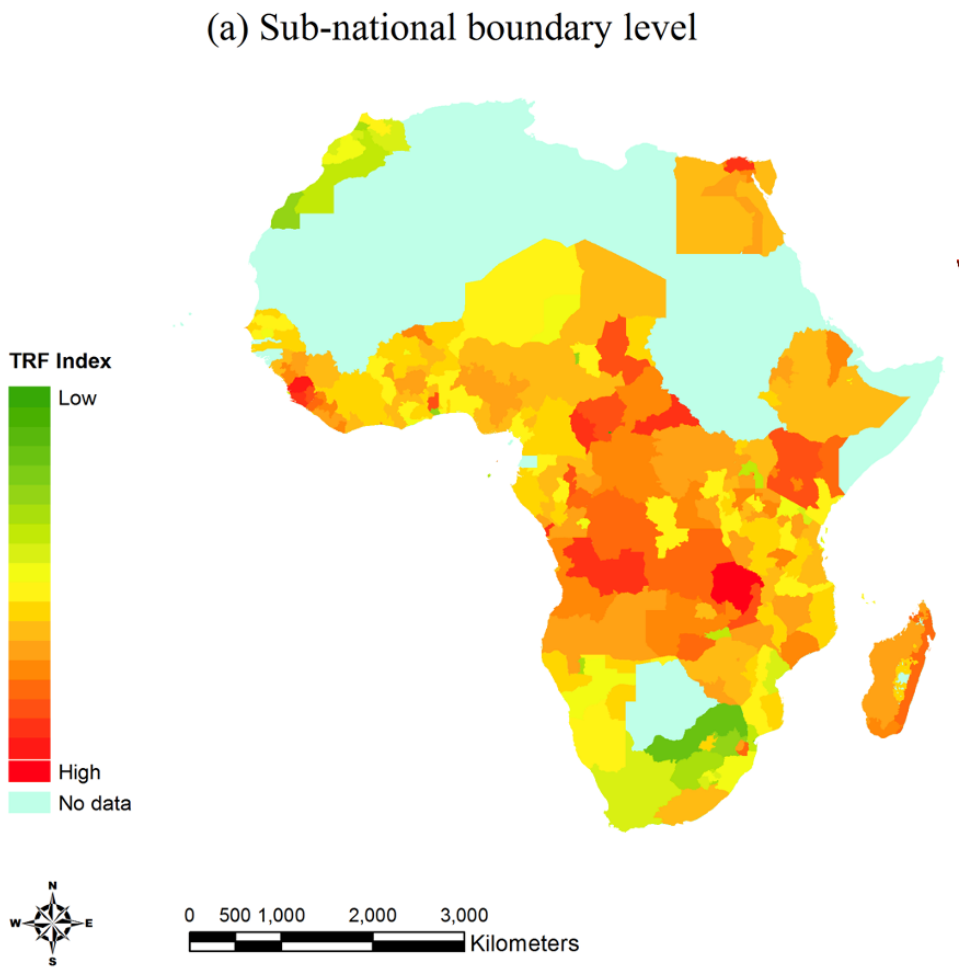
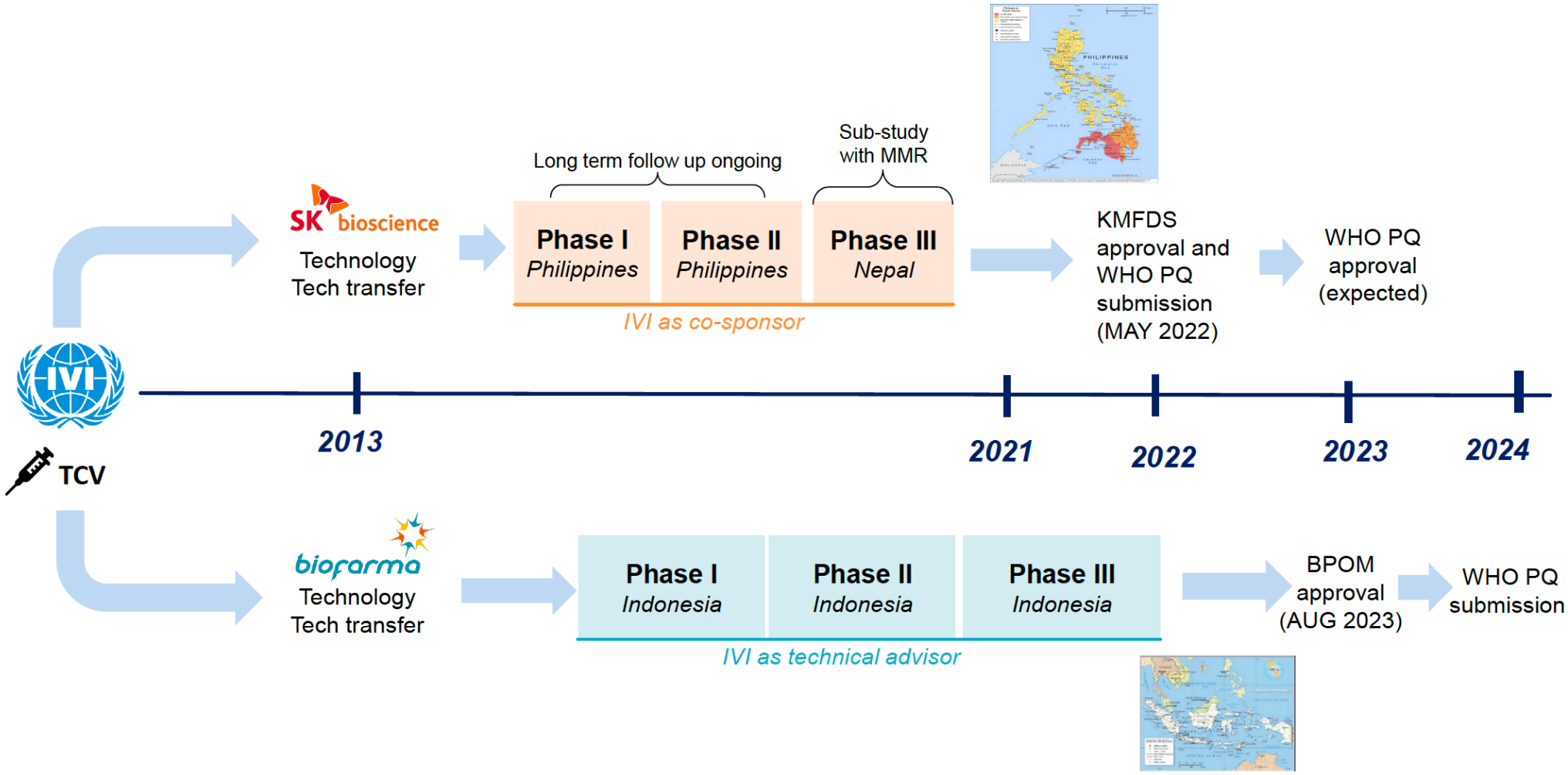


Lee, Mogasale, et al, unpublished

Lee, Mogasale, et al, 2016

Technology Transfer and Clinical Development of Vi-DT

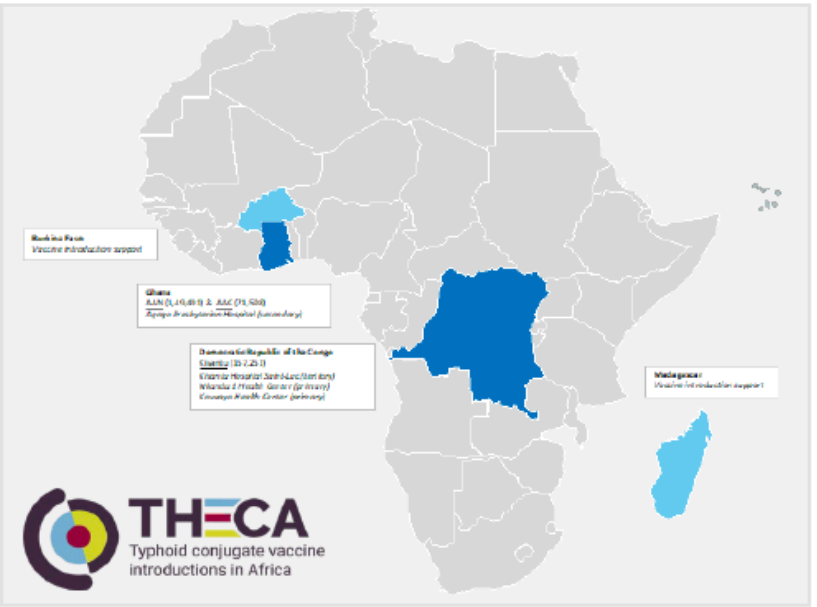


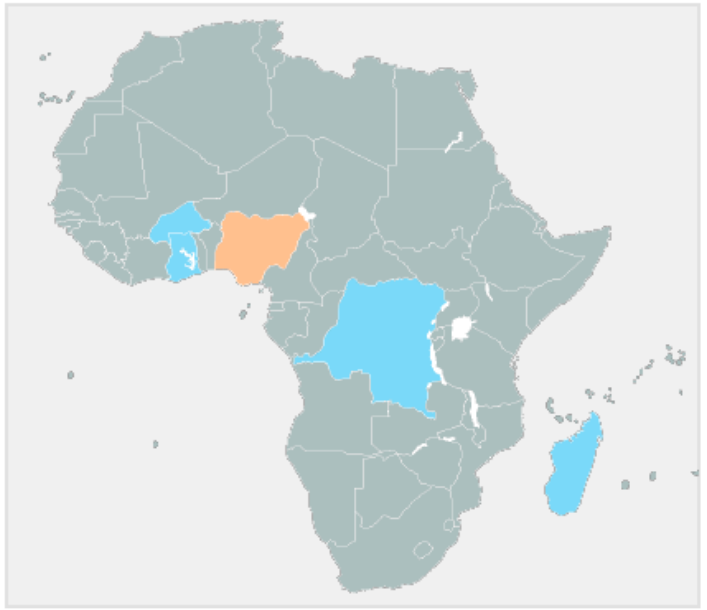
Dr. Sushant Sahastrabuddhe

TCV introduction and effectiveness evaluation

SUPPORT TCV INTRODUCTION

- Large Phase IV cluster randomized trial in Ghana.
- Mass vaccination → VE evaluation in DRC, Madagascar and Fiji island.
- Vaccine cost effectiveness analysis.





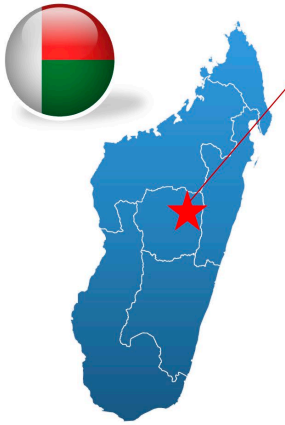
THECA
Typhoid conjugate vaccine effectiveness in Africa

2019 - 2025

SETA+/STIA
Severe Typhoid Surveillance in Africa Program

2020 – 2022 -> 2025

Typhoid Vaccination in Madagascar (TyMA)



Add-on: Vaccines and AMR

TyMA project

Surveillance
- Sustained high typhoid disease burden in Imerintsiatosika (10 years of data)
- Enhanced surveillance in Arivonimamo district

Vaccination
- Vaccinate **children** aged 1-<16 years of age with Vi-CRM$_{197}$

Study design
- Case control study to determine effectiveness

Upcoming plans
- Vaccination ongoing; anticipated until January 2024

Mozambique Typhoid Fever Surveillance Program (MOTIF)

Scope
- Typhoid fever surveillance capacity setup in Pemba and Nampula study sites
- Support potential Gavi application for national introduction

Current status
- Surveillance started in Nampula (Aug 2022; Pemba started in Mar 2023)
- Nine typhoid cases identified to date
- Dondo Q4/2023 (serosurvey and blood culture)

Screened	Enrolled	Enrolled subjects where blood for culture was collected*	Blood culture positive results
3,405	2,142	2,058	1. Any bacteremia including *Salmonella* Species n=342 2. Salmonella *Typhi* **n=17** 3. iNTS disease **n=19**

Study sites: Pemba, Nampula

Dr. Florian Marks

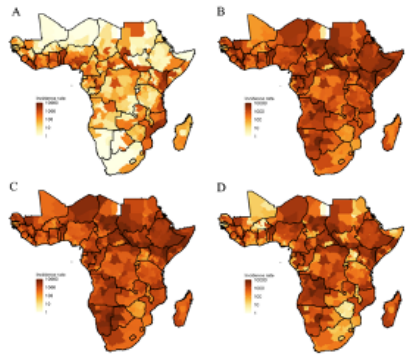
Impacts: a decade of work on Salmonelloses in Africa

Data/Samples use

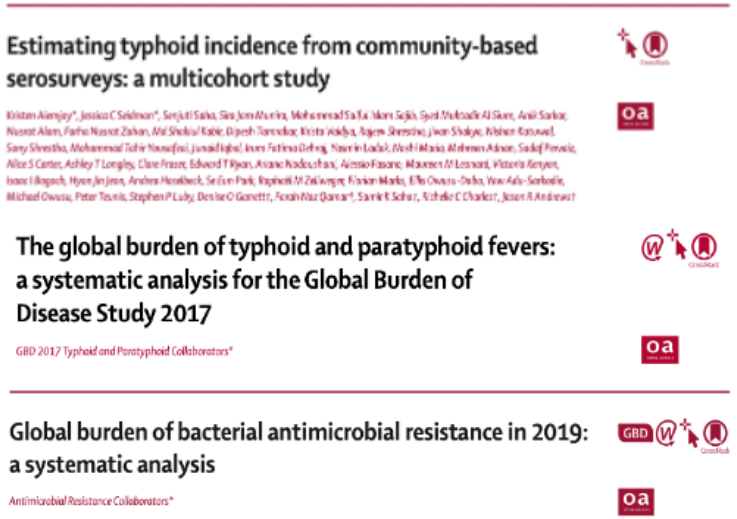
A decade of work for TCV vaccine introduction, other vaccine prioritization work, and use for other groups

- Sustained typhoid fever AND iNTS burden identified in African countries
- TCVs used now through studies in Ghana, DR Congo, Madagascar, Burkina Faso and introduced in **Liberia, Malawi, Zimbabwe** (2024)
- Other groups using data for advanced analysis (typhoid prediction, AMR, others)
- Other pathogens identified (iNTS -> stakeholder conference in 2024 in Kinshasa)

Stakeholder engagement to ensure data are used for impact



From: Jonghoon Kim, et al., submitted.
A: 0-1, B: 2-4, C: 5-14, D: >15 years of age



Capacity building

More than 1000 people employed, labs established, capacity-building. Use of sites for other diseases and by other groups

- Capacity built in African sites (>1,000 people funded through programs)
- Sites used by other partners; sites writing their own proposals
- Program platform for other work (HEV, GAS, HDSS site, climate change)

Opportunity: T*yphoid in Fiji – Vaccination and Elimination (TyFIVE) & TySICS*

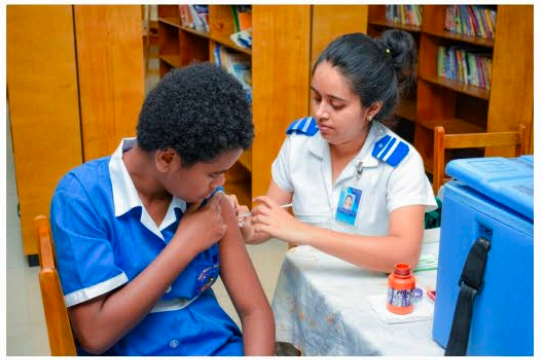
TyFIVE/TySICS

Typhoid in Fiji

- Important public health problem
- High burden in Northern Division
- Sero-prevalence (measure of past exposure) is higher than what the incidence would suggest, hinting at:
  - Substantial under-reported burden
  - Presence of asymptomatic transmission

Updates

- Vaccination complete (October 2023); coverage ca. 50%
- Case-control study ongoing



Dr. Florian Marks, Dr. Rafi Zellweger

New burden studies: *S.* Typhi & invasive non-typhoidal *Salmonella*

Diseases:

- *S.* Typhi present
- iNTS significant burden
- Highest pathogen found:
  - *S.* Infantis (!)
  - S. Typhimurium
  - S. Enteritidis

Serovar	PCR typing n (%)	WGS typing n (%)
Infantis	17 (38.6)	17 (38.6)
Typhimurium	12 (27.3)	12 (27.3)
Enteritidis	10 (22.8)	5 (11.4)
Dublin	0 (0.0)	5 (11.4)
Typhi	2 (4.5)	2 (4.5)
Paratyphi B	1 (2.3)	1 (2.3)
Choleraesuis	0 (0.0)	1 (2.3)
Kentucky	0 (0.0)	1 (2.3)
ND	2 (4.5)	0 (0.0)
Total	44 (100.0)	44 (100.0)

Tab. *Salmonella* isolates (stool) in 8 Hospitals

> PLoS One. 2017 Dec 21;12(12):e0189946. doi: 10.1371/journal.pone.0189946. eCollection 2017.

Characterization of Salmonella enterica isolates causing bacteremia in Lima, Peru, using multiple typing methods

Claudia Silva [1], Laura Betancor [2], Coralith García [3], Lizeth Astocondor [3], Noemí Hinostroza [3], Julieta Blaio [3], Javier Rivera [4], Lucía Perezgasga [3], Victoria Pérez Escanda [3], Lucía Yim [3], Jan Jacobs [5], Francisco García-Del Portillo [6], Salmotyph CYTED Network, José A Chabalgoity [2], José L Puente [1]

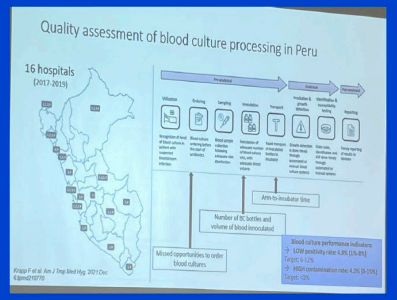
Multicenter Study > Am J Trop Med Hyg. 2021 Dec 6;106(2):432-440. doi: 10.4269/ajtmh.21-0770.

Underutilization and Quality Gaps in Blood Culture Processing in Public Hospitals of Peru

Fiorella Krapp [1], Claudia Rondon [1], Catherine Amaro [2], Evelyn Barco-Ysipén [3], María Valera-Krumdieck [4], Rubén Vásquez [4], Alexander Briones [3], Martín Casapía [3], Antonio Burgos [4], Favio Sarmiento López [4], Marina Villcapoma [3], Roberto Díaz Sipión [4], Miguel Villegas-Chiroque [4], Kelly Castillo [3], Jimena Pino-Dueñas [3], Edwin Cuaresma Cuadros [3], Hugo Alcalca-Salvador [3], René Campana [3], Teresa Peralta Córdova [4], Elizeti Sierra Chavez [4], Carla Aguado Ventura [4], Marjan Peeters [3], Jan Jacobs [3], Coralith García [3]

Plan:

- RA/MOU in progress
- Two-tiered approach
  - Y1: Multi-site assessment of burden using assay from Stanford/Harvard
  - Y2: Focusing on 1-2 sites to setup BC-based surveillance



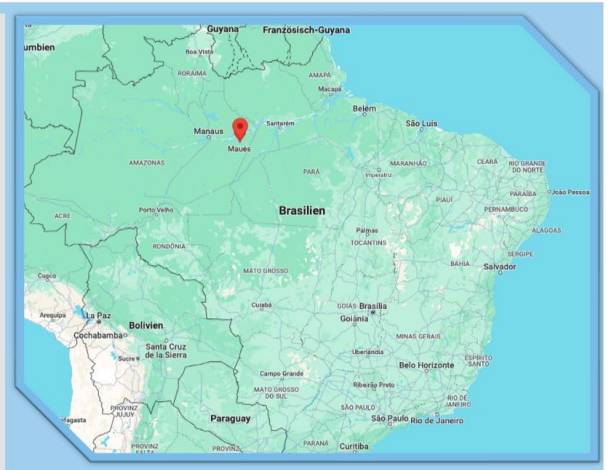
Objectives

Primary

- Estimate the seroprevalence/seroincidence of *S.* Typhi/Paratyphi among the indigenous population in Maués, Brazil

Secondary

- Compare the seroprevalence of *S.* Typhi and *S.* Paratyphi among the indigenous and non-indigenous population in Maués, Brazil
- Identify risk factors associated with seropositivity against *S.* Typhi/Paratyphi in both indigenous and non-indigenous population in Maués, Brazil.



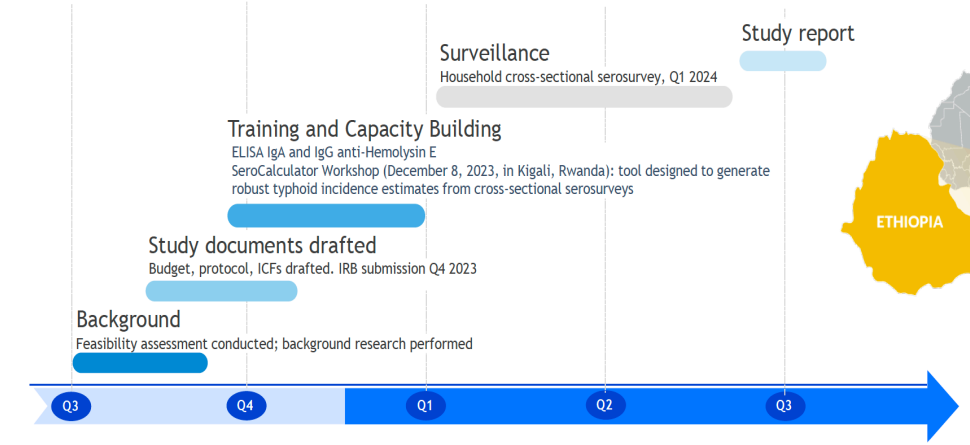
Site: Brazil: Maués

TSAP and SETA projects: Lower incidence rate of blood-culture *S.* Typhi fever cases compared to other African countries

Collaboration: IVI, Armauer Hansen Research Institute (AHRI) , Center for Innovative Drug Development and Therapeutic Trials for Africa (CDT-Africa)

- Estimate the seroprevalence, seroincidence and risk factors associated with seropositivity against S. Typhi and S. Paratyphi at selected districts in Ethiopia - **ELISA IgA and IgG anti-Hemolysin E**
- Identify clustering of *S.* Typhi and *S.* Paratyphi occurrence of cases – Household based

Timelines

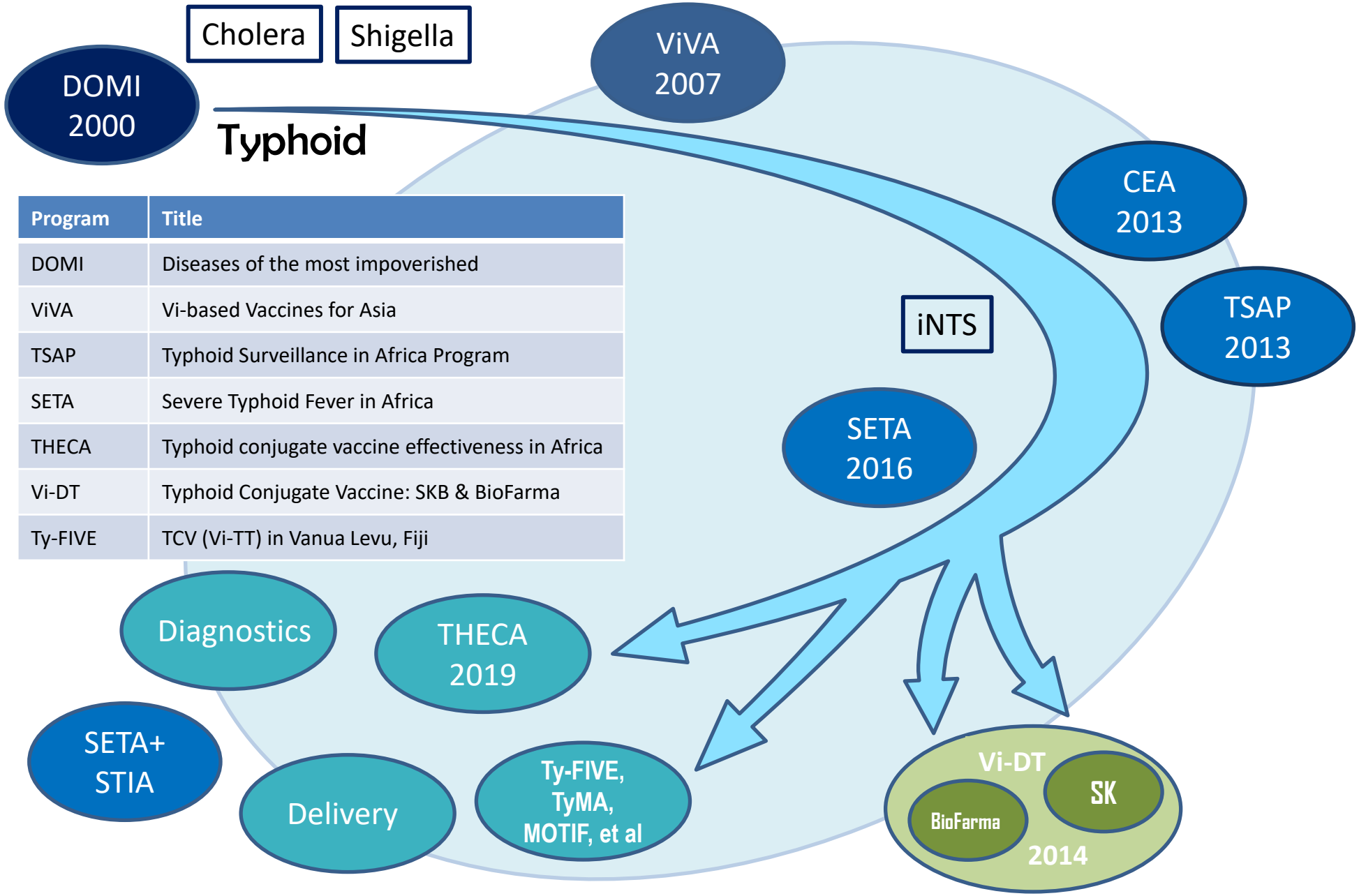


Latin America – Peru and Brazil

Africa - Ethiopia

Dr. Florian Marks, Dr. Birkneh Tadesse

IVI Typhoid Programs 2000 - 2023



Program	Title
DOMI	Diseases of the most impoverished
ViVA	Vi-based Vaccines for Asia
TSAP	Typhoid Surveillance in Africa Program
SETA	Severe Typhoid Fever in Africa
THECA	Typhoid conjugate vaccine effectiveness in Africa
Vi-DT	Typhoid Conjugate Vaccine: SKB & BioFarma
Ty-FIVE	TCV (Vi-TT) in Vanua Levu, Fiji

Need – Innovation – Impact (and thank you to our collaborators since 2000)

- Burden studies – DOMI, ViVA, TSAP, SETA (SETA+, STIA) include epidemiology, risk factors, early investment case, work with SAGE/Gavi
- Vi-DT TCV vaccine development – technology transfers (Shantha, SK Bioscience, BioFarma, Incepta)
  - SKB approved by MFDS, WHO PQ submitted (SKB)
  - BioFarma approved by BPOM, WHO PQ submission anticipated
- Effectiveness
  - THECA (TyVEGHA, TyVECO, TyMA)
  - Cost effectiveness
  - Support for Gavi applications
- Implementation / Uptake
- New innovation
  - Trivalent TCV-iNTS?
  - TCV MAP?

International Vaccine Institute

VACCINES FOR A HEALTHIER FUTURE

Thank You