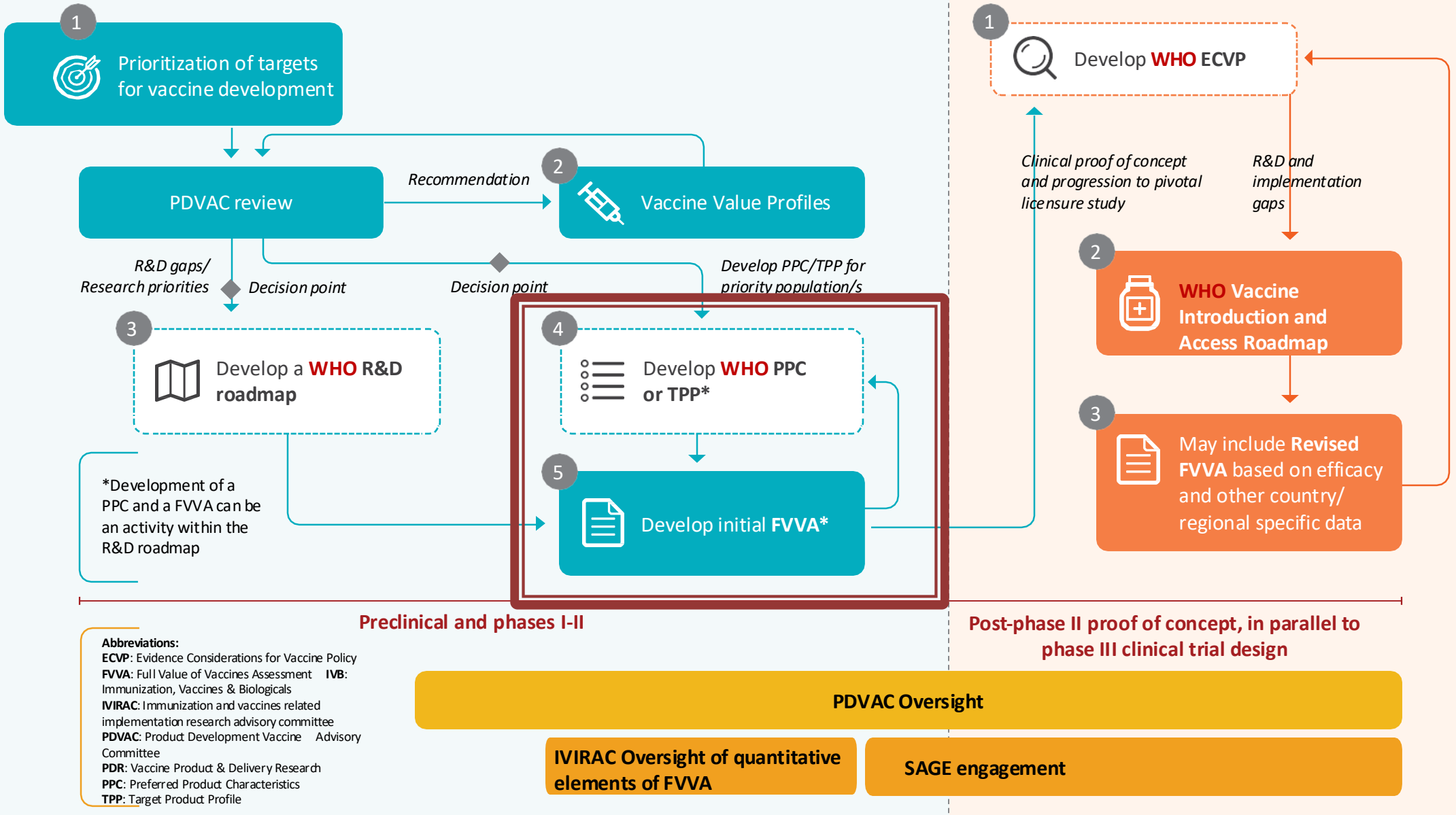
iNTS-FVVA project

Annelies Wilder-Smith, Rob Kaminski

Vaccine Development Immunization,
Vaccines and Biologicals Department

World Health Organization

Overview of WHO guidance to facilitate vaccine development to regulatory approval, policy and use



Abbreviations:
ECVP: Evidence Considerations for Vaccine Policy
FVVA: Full Value of Vaccines Assessment **IVB**: Immunization, Vaccines & Biologicals
IVIRAC: Immunization and vaccines related implementation research advisory committee
PDVAC: Product Development Vaccine Advisory Committee
PDR: Vaccine Product & Delivery Research
PPC: Preferred Product Characteristics
TPP: Target Product Profile

Slide credit: Birgitte Giersing, WHO/PDR

Overview of iNTS FVVA

Funded by the Wellcome Trust (to April 2025)

Principal Investigator: Dr Jerome Kim (IVI)

Objective: Develop an FVVA to understand the value of investment in an iNTS vaccine from a multi-stakeholder perspective

Scope redefined to **focus on trivalent iNTS +TCV vaccines**

FVVA partners

IVI-WHO joint project
Shift Health
LSHTM
Swiss TPH

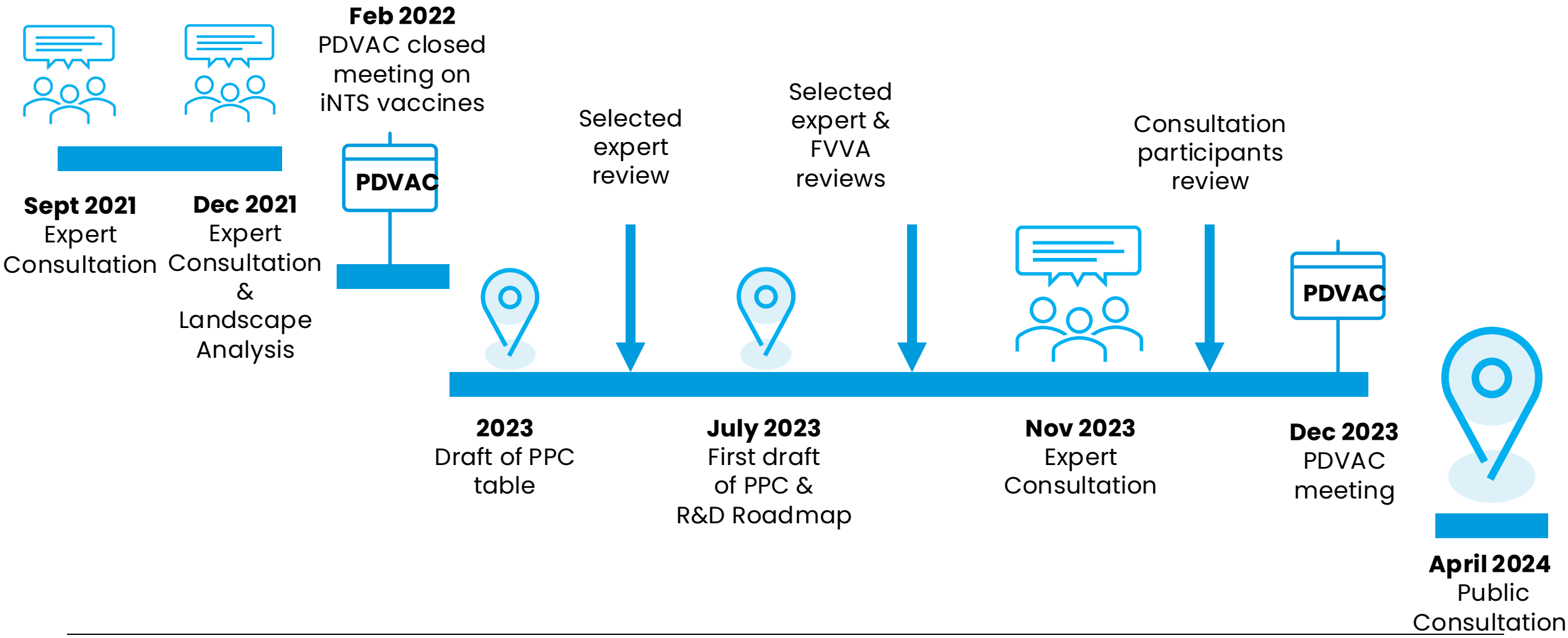
Research Steering Group

Pierre Balard
Martin Friede
Jerome Kim
Calman MacLennan
Jean-Louis Excler (IVI Project Lead)
Annelies Wilder-Smith (WHO Project Lead)

Overview of iNTS FVVA workstreams

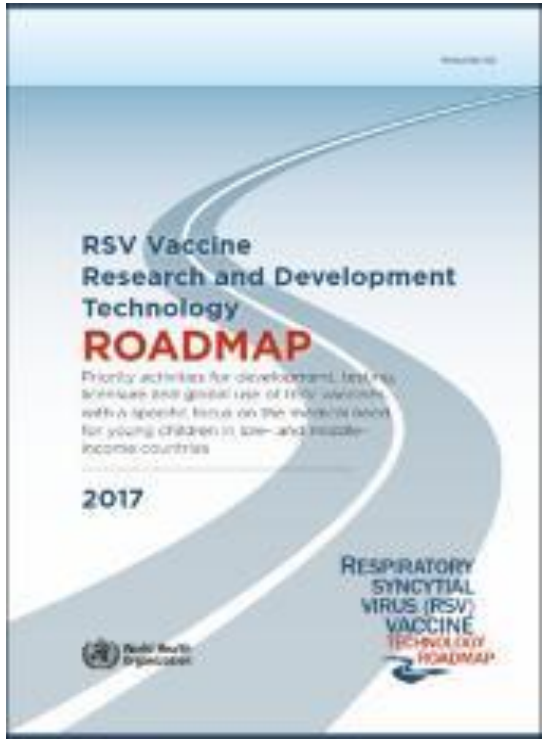
- **Aims 1-3 (WHO lead)**
  - Aim 1 - **Landscape analysis** of iNTS disease (epidemiology, diagnostics, knowledge gaps to accelerate development, licensure and use)
  - Aim 2 – **LMIC Stakeholder consultation** on vaccine use and demand
  - Aim 3 – **R&D Roadmap and Preferred Product Characteristics**
- **Aims 4 and 5 (IVI lead)**
  - Aim 4 – Determine the **Clinical Development Plan and Regulatory Pathway** to bring iNTS vaccines to licensure and WHO prequalification
  - Aim 5 - Develop **rationale for the development of an iNTS vaccine** through a Full Value of Vaccines Assessment
    - Business case (Shift Health)
    - Investment case - CEA for typhoid (Swiss TPH)
    - Investment case – Economic Evaluation of iNTS vaccines (IVI)
    - Broader societal benefit analysis (LSHTM)

Overview of timeline of development of PPC & R&D Roadmap



iNTS FVVA Aim 3 – WHO Preferred Product Characteristics and R&D Roadmaps

Preferred Product Characteristics (PPCs): define preferential attributes for vaccines to be used in LMICs



Roadmaps highlight priority activities for vaccine researchers, funders and product developers, with the goal to accelerate the pathway to availability and access in LMICs.

Agenda and Objectives

Global Non-typhoidal Salmonella Disease Burden

iNTS vaccine overview

iNTS Combo Meeting Objectives; iNTS CDP; iNTS Regulatory Science Objectives; Questions for Regulatory Science Meeting

Global burden of nontyphoidal *Salmonella* disease

John A. Crump, MB ChB, MD, DTM&H
Professor of Medicine, Pathology, and Global Health
University of Otago

WHO PDVAC
11 December 2024

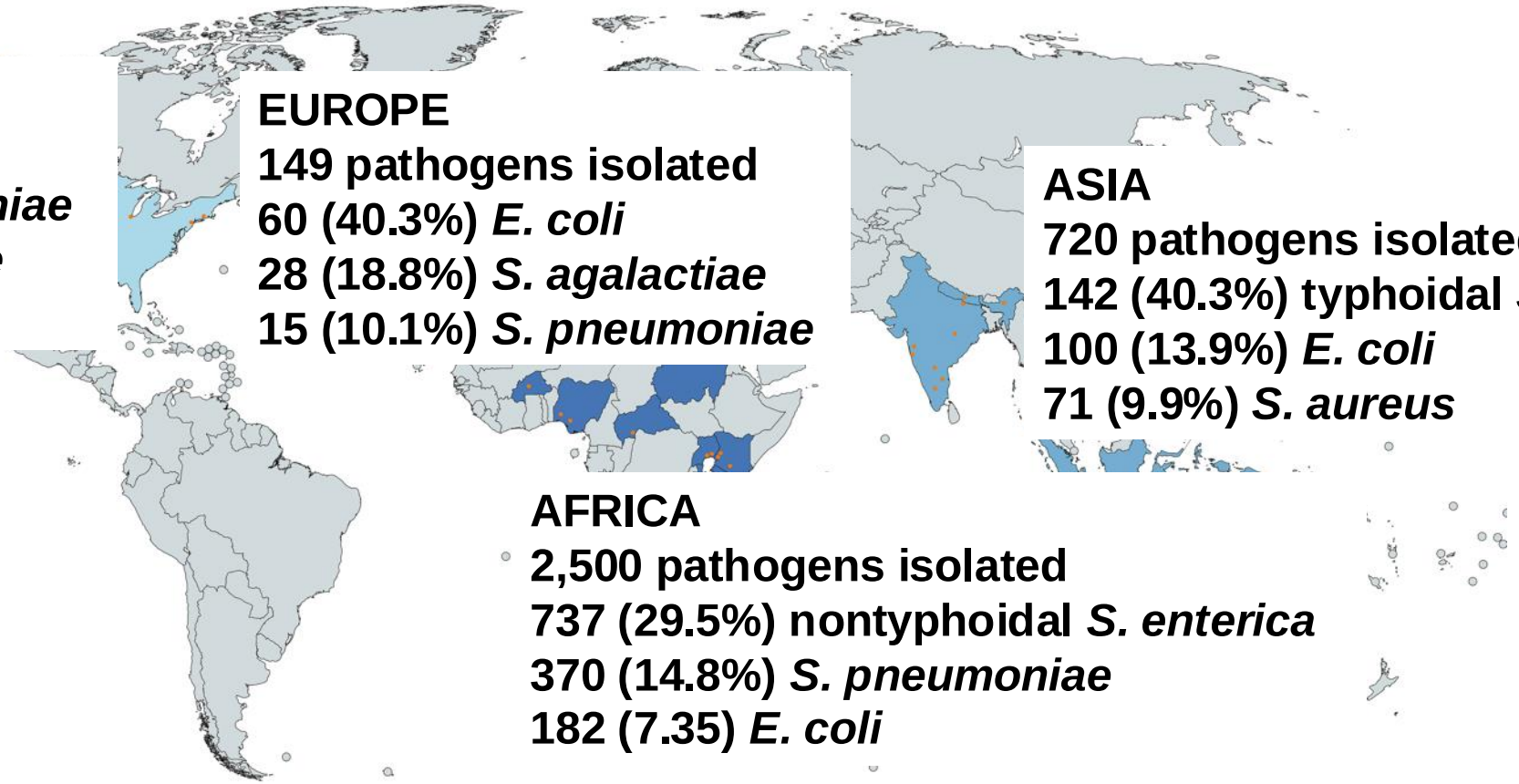
University of Otago
ŌTĀKOU WHAKAIHU WAKA

Overview

- **Nontyphoidal *Salmonella* invasive disease: iNTS**
- **Nontyphoidal *Salmonella* diarrhea disease: dNTS**

- **Prevalence of NTS bacteremia**
- **Antimicrobial resistance**
- **Prevalence of NTS serogroups and serovars**
- **Prevalence of NTS diarrhea**
- **Global burden of disease**

Prevalence of community-onset bloodstream infections among febrile inpatients: a systematic review and meta-analysis, 2019



AMERICAS
361 pathogens isolated
260 (72.0%) *S. pneumoniae*
47 (13.0%) *H. influenzae*
15 (4.2%) *E. coli*

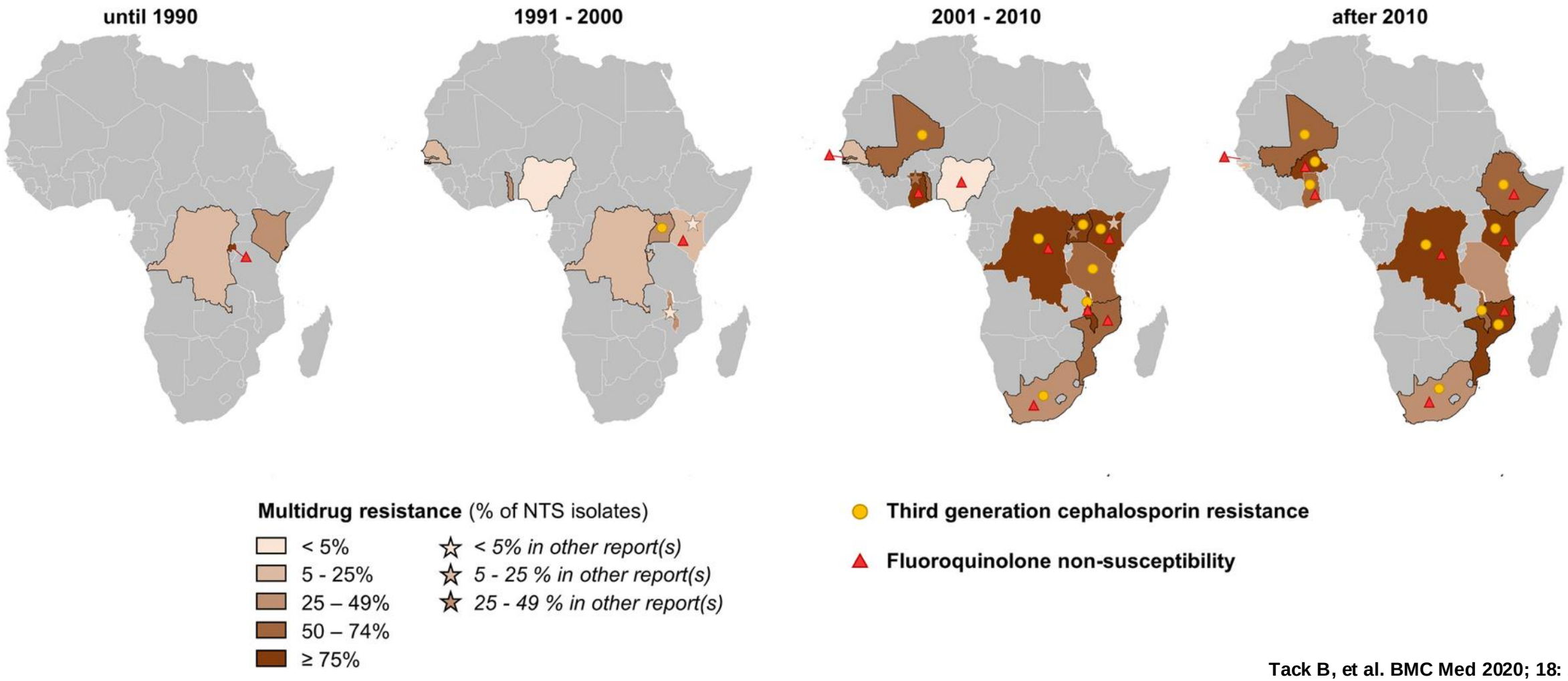
EUROPE
149 pathogens isolated
60 (40.3%) *E. coli*
28 (18.8%) *S. agalactiae*
15 (10.1%) *S. pneumoniae*

ASIA
720 pathogens isolated
142 (40.3%) typhoidal *S. enterica*
100 (13.9%) *E. coli*
71 (9.9%) *S. aureus*

AFRICA
2,500 pathogens isolated
737 (29.5%) nontyphoidal *S. enterica*
370 (14.8%) *S. pneumoniae*
182 (7.35) *E. coli*

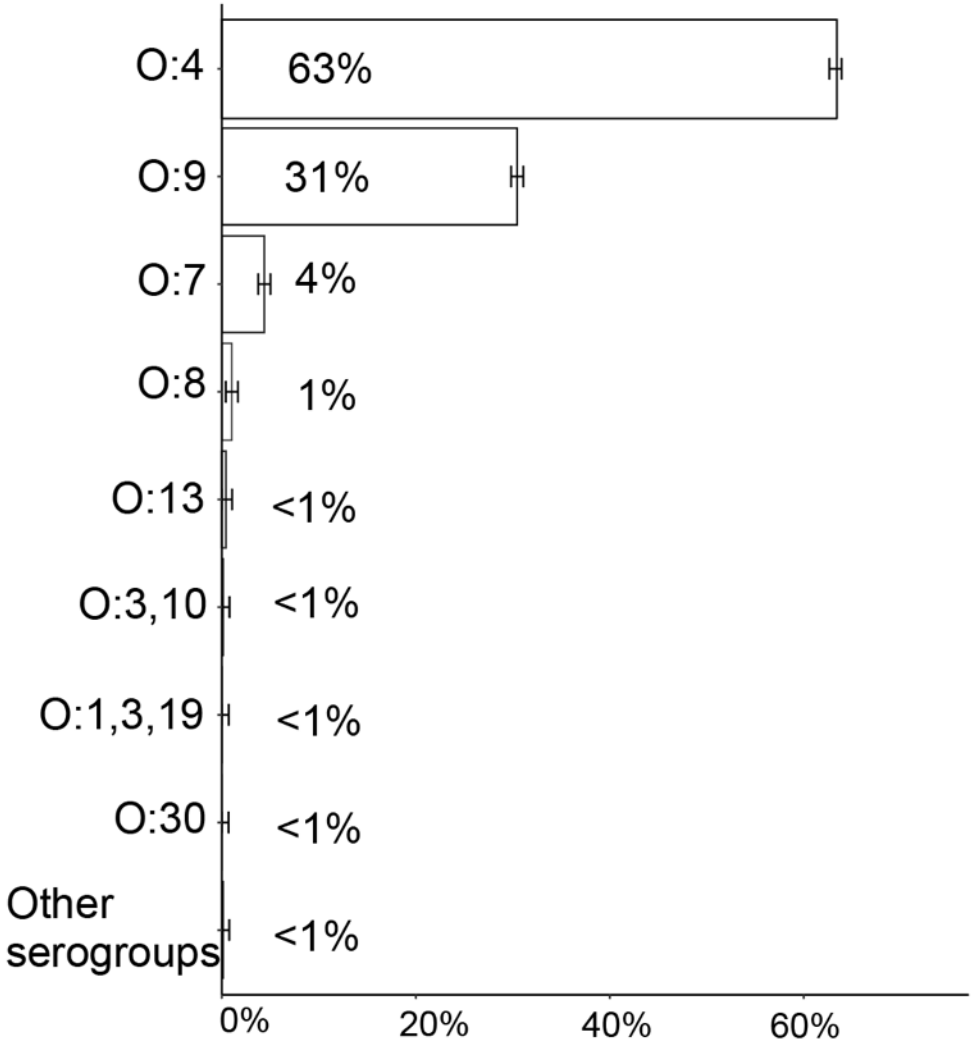
Marchello CS, et al. Antimicrob Agents Chemother 2019 64: e01974-19

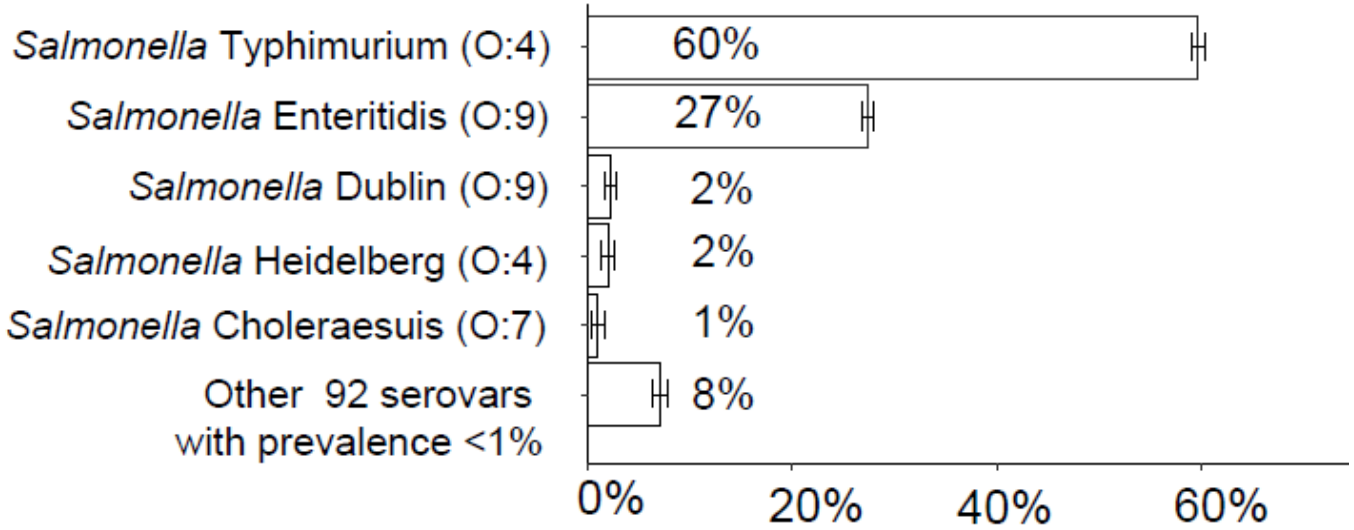
Invasive non-typhoidal *Salmonella* infections in sub-Saharan Africa: a systematic review on antimicrobial resistance



Tack B, et al. BMC Med 2020; 18: 212

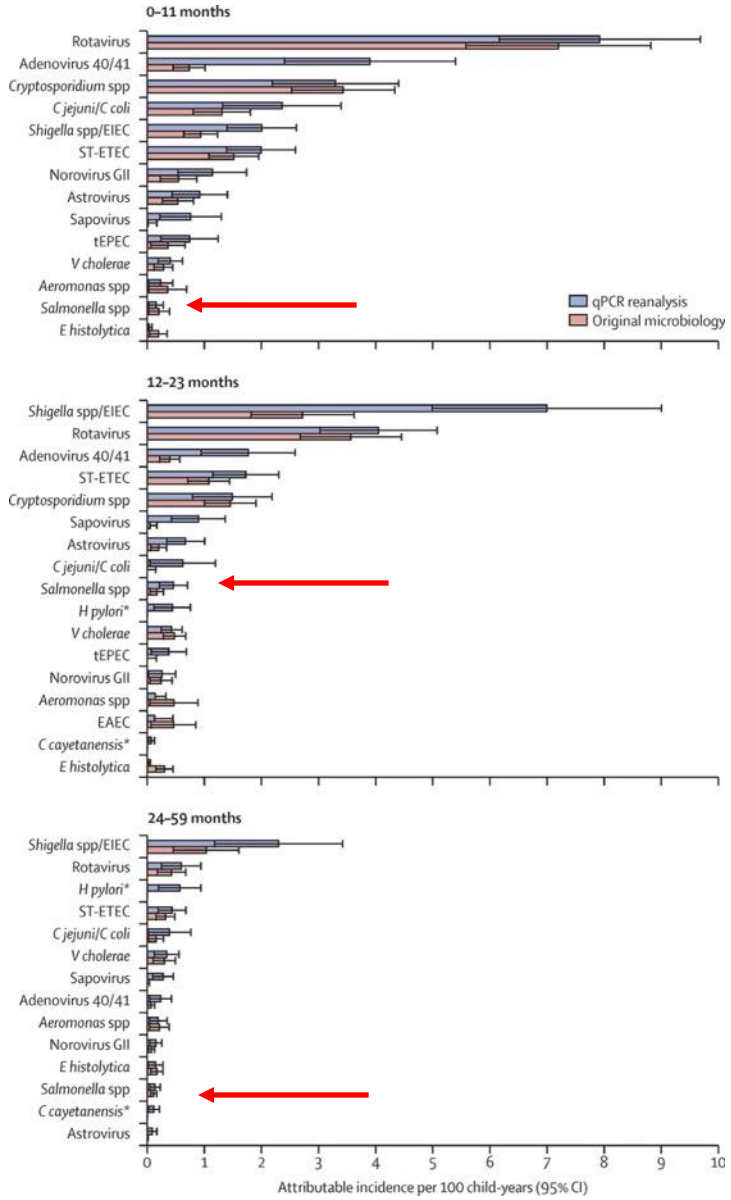
Crude prevalence of NTS serogroups and serovars among 24,253 isolates from normally sterile sites, global, 1941 - 2019





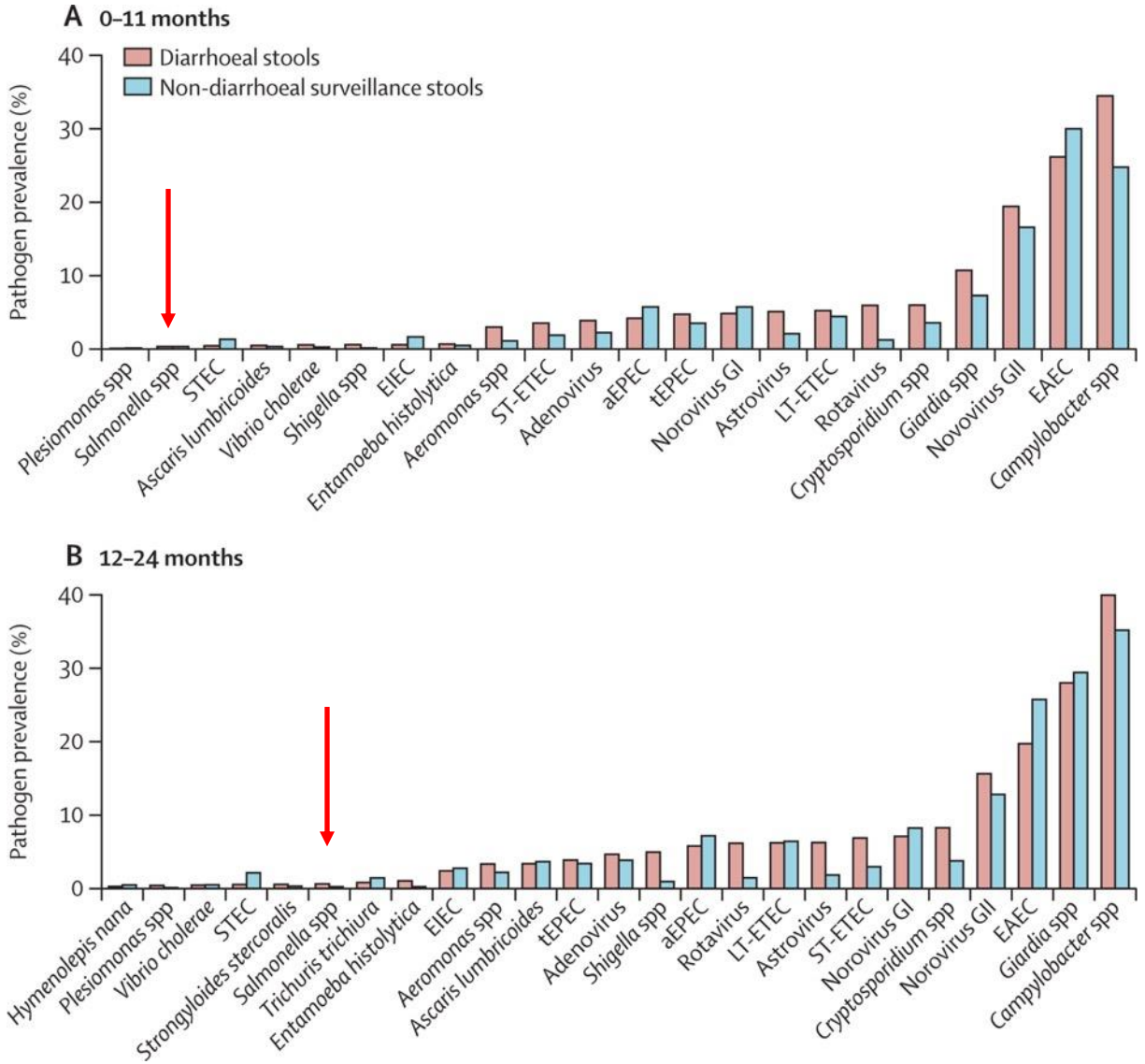
Hagedoorn NN, et al. Epidemiol Infect 2023; 152: e4

Pathogens detected in diarrheal and non-diarrheal stools, by age stratum, GEMS, Africa and Asia, 2009-14



Platts-Mills JA, et al. Lancet Global Health 2015; 3: e564-75

Pathogens detected in diarrheal and non-diarrheal stools, by age stratum, MAL-ED, Africa, Asia, and South America, 2009-14



Platts-Mills JA, et al. Lancet Global Health 2015; 3: e564-75

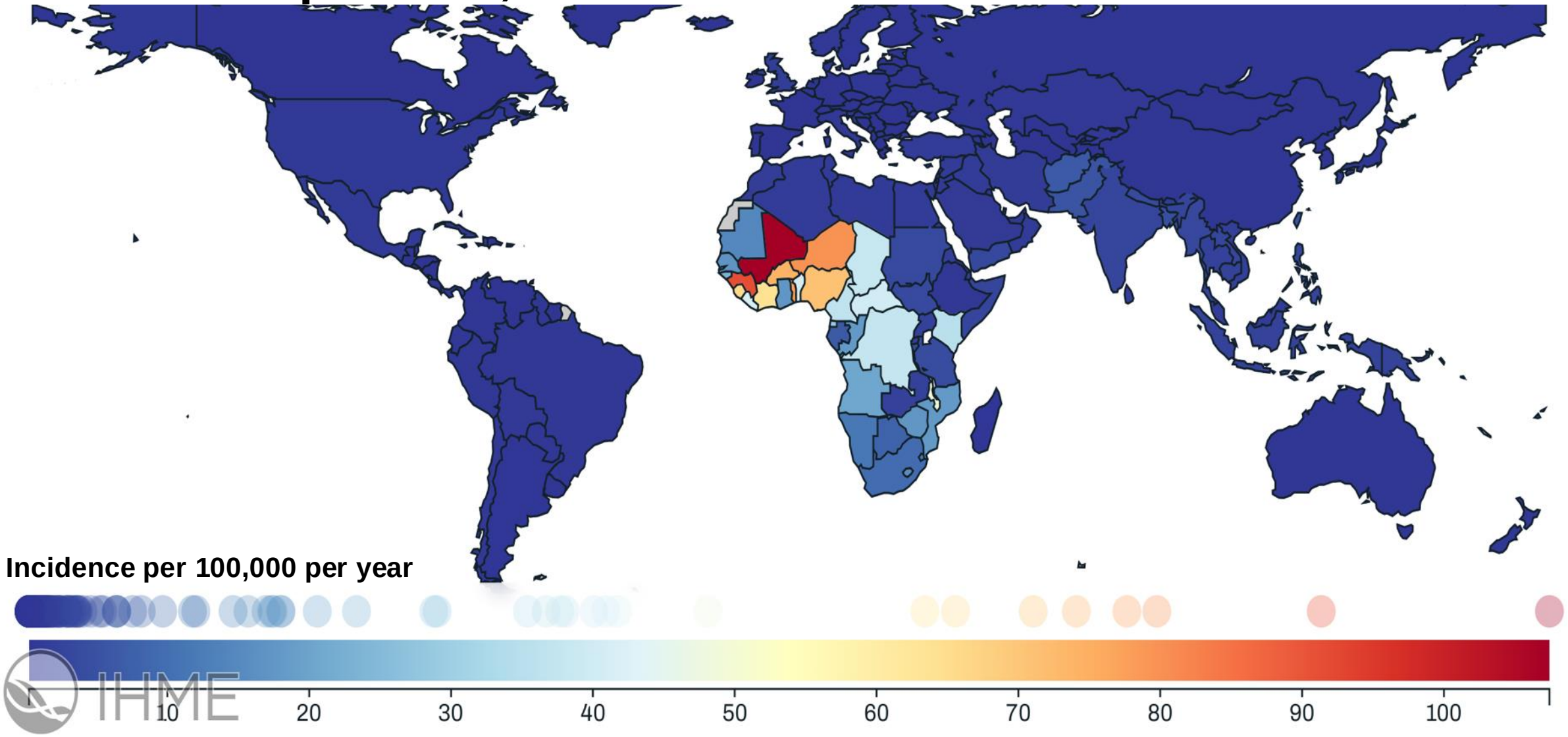
Typhoid, paratyphoid, invasive, and diarrheal nontyphoidal *Salmonella* burden, Global Burden of Disease 2021

Disease	Illnesses	Deaths	DALYs
Typhoid fever	7,154,555	93,333	7,087,733
Paratyphoid fever	2,166,063	14,127	1,011,842
Invasive nontyphoidal *Salmonella*	509,976	62,018	4,740,235
Diarrheal nontyphoidal *Salmonella*	Not reported	23,437	1,492,819

Typhoid and paratyphoid fever CFR <1%
iNTS disease CFR ~15%

https://vizhub.healthdata.org/gbd-results/

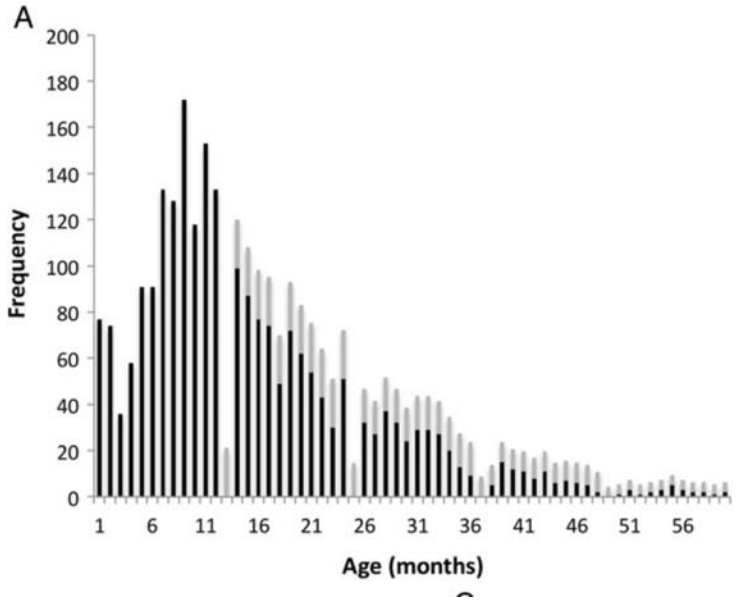
Nontyphoidal *Salmonella* invasive disease incidence per 100,000 persons, Global Burden of Disease 2021



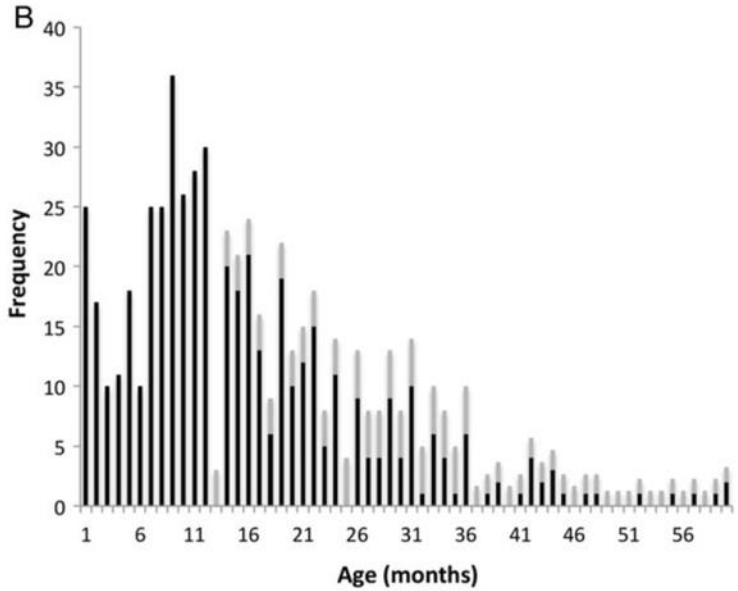
http://vizhub.healthdata.org/gbd-compare/

Age distribution by month of *Salmonella* Typhimurium, *Salmonella* Enteritidis, and *Salmonella* Typhi bacteremia and meningitis, children <5 years of age, Queen Elizabeth Central Hospital, Blantyre, Malawi, 1998-2014

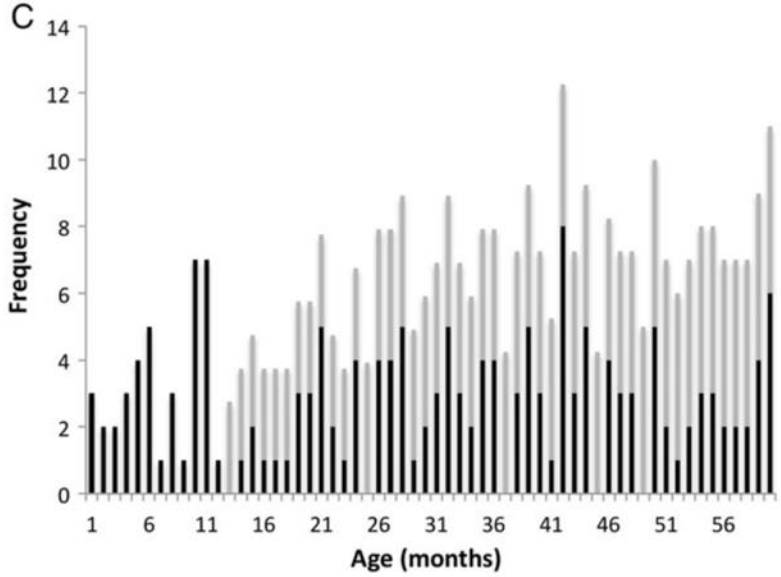
***Salmonella* Typhimurium**



***Salmonella* Enteritidis**

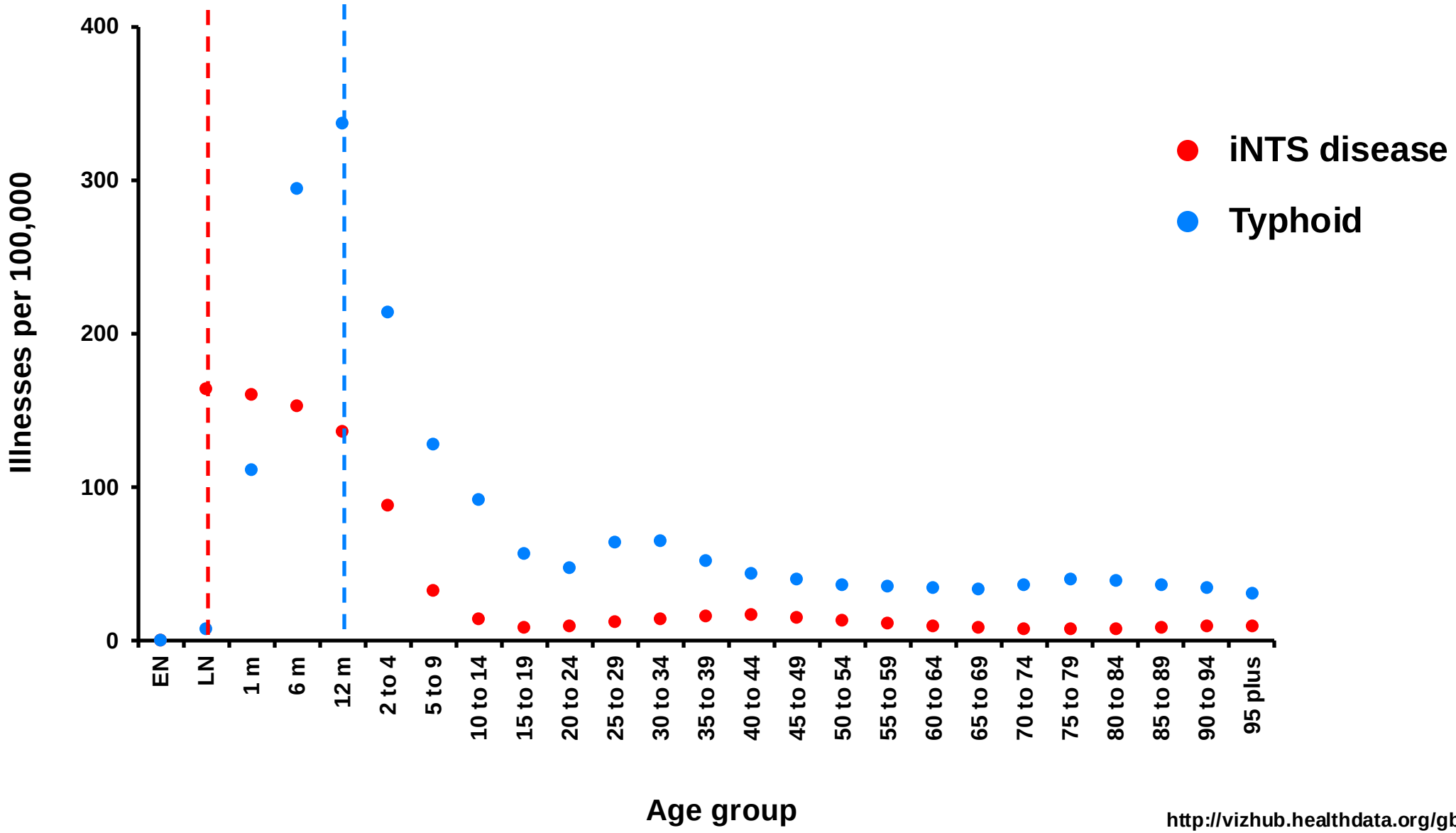


***Salmonella* Typhi**



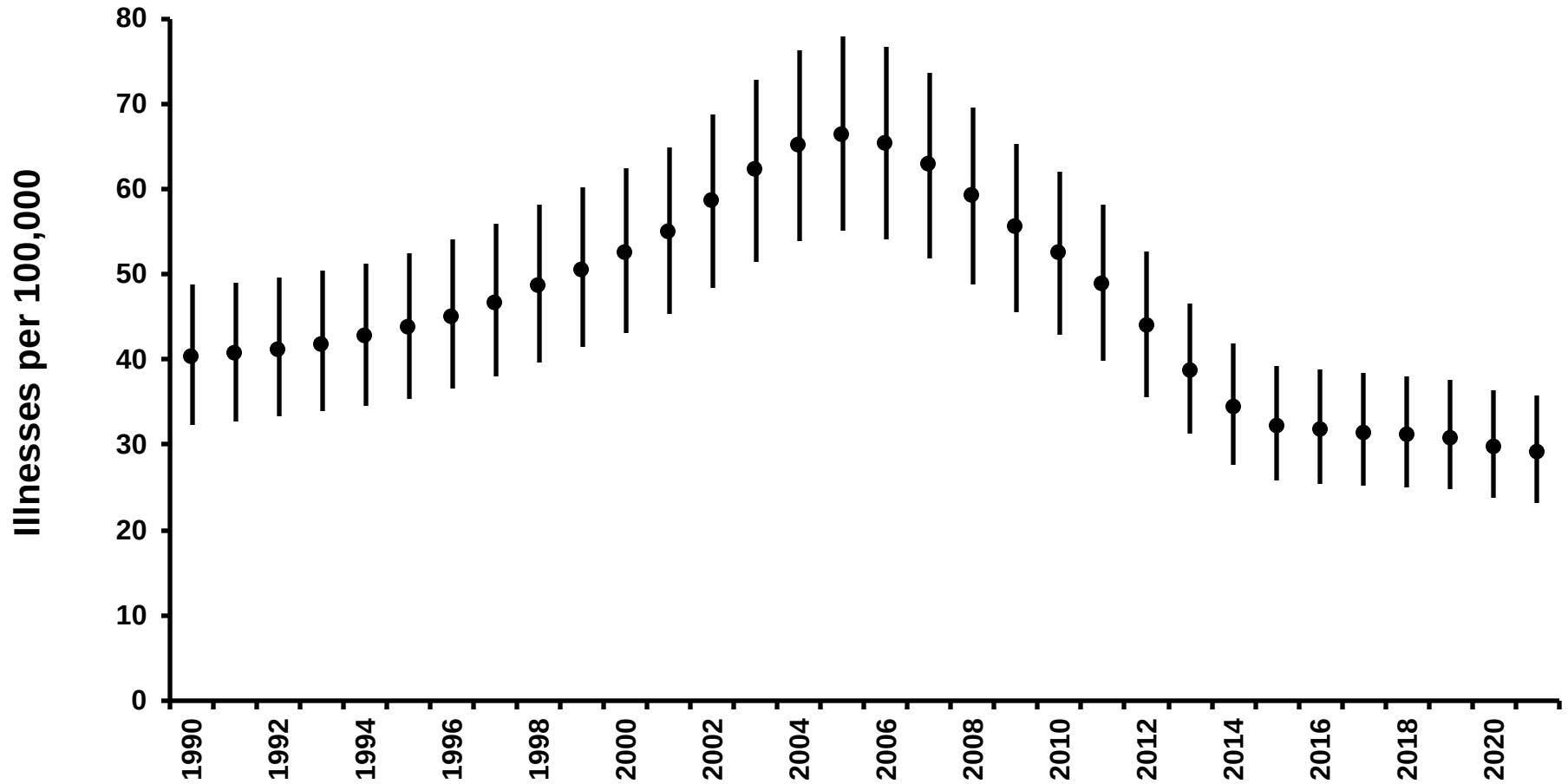
Feasey NA, et al. Clin Infect Dis 2015; 61 (suppl 4): S363-S371

Non-typhoidal *Salmonella* invasive disease incidence per 100,000 persons by age group, Africa, Global Burden of Disease, 2021



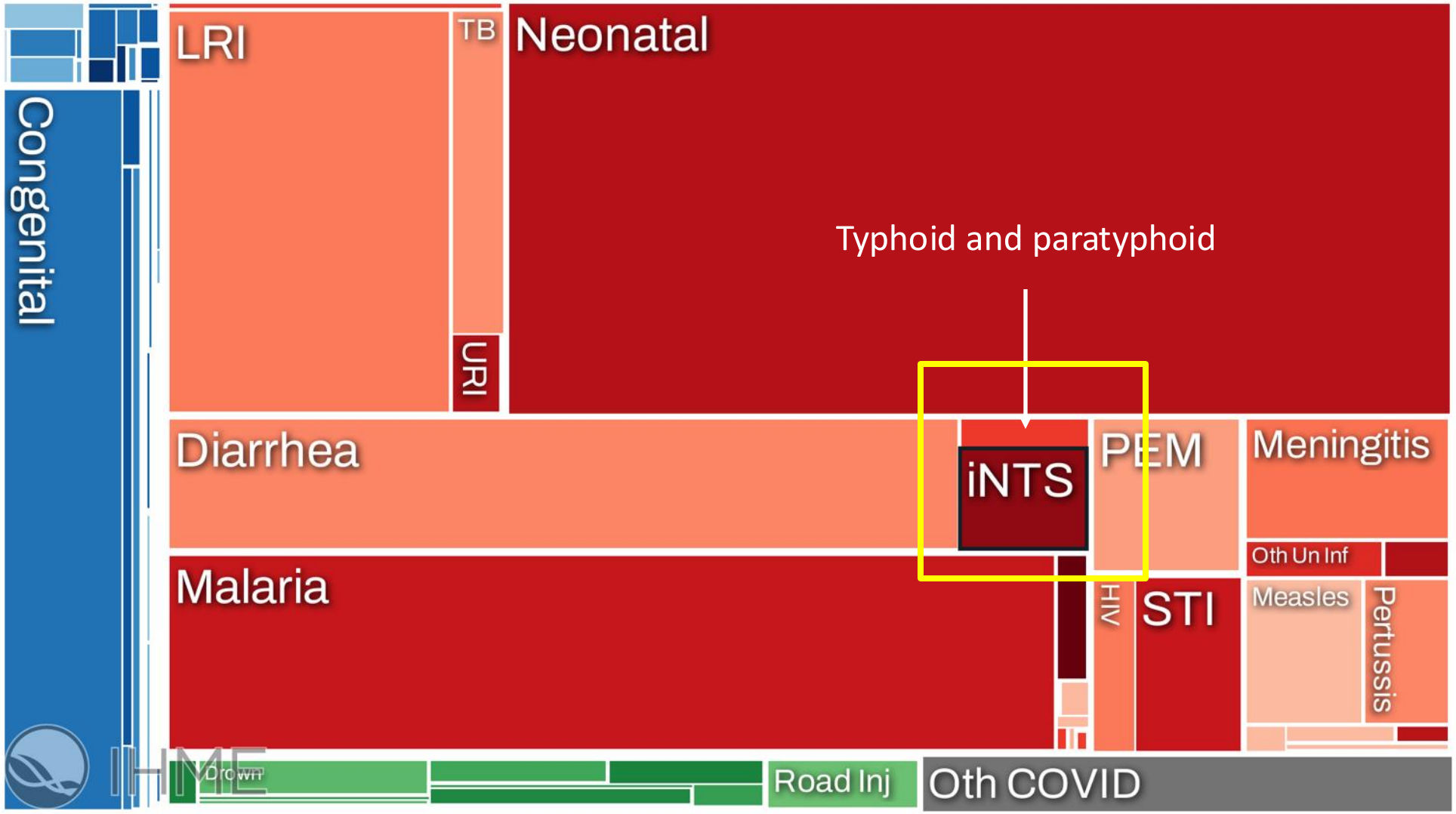
http://vizhub.healthdata.org/gbd-compare/

Non-typhoidal *Salmonella* invasive disease incidence per 100,000 persons per year, Africa, 1990-2021



http://vizhub.healthdata.org/gbd-compare/

Deaths by cause, <5 years of age, Africa, 2021



http://vizhub.healthdata.org/gbd-compare/

Conclusions

- **Non-typhoidal *Salmonella***
  - **Leading cause of community onset bloodstream infection and uncommon cause of child diarrhea in African countries**
  - **Antimicrobial resistance is a major problem**
  - **Serogroups O:4 and O:9**
  - **Serovars Typhimurium and Enteritidis**

- **Illnesses, deaths, and DALYS**
  - **iNTS incidence << typhoid or paratyphoid fever**
  - **iNTS deaths and DALYs → typhoid fever**
  - **iNTS deaths and DALYs >> paratyphoid fever or dNTS**
  - **Africa iNTS deaths under 5 year olds >> typhoid and paratyphoid combined**

- **iNTS incidence has levelled off in Africa for past decade**
  - **Limits of management of host risk factors**

Acknowledgements

- **Shruti Murthy, Nienke N. Hagedoorn, Christian S. Marchello, and Megan Birkhold**
- **Vacc-iNTS Consortium Collaborators**
- **European Commission Horizon 2020 research and innovation programme (grant number 815439)**

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AND GLOBAL HEALTH

Vacc
iNTS

iNTS Vaccine Pipeline

Calman A. MacLennan
WHO PDVAC, Geneva
December 11, 2024

Disclosure

- On December 2, 2024, I became an employee of Pfizer
- Pfizer is not developing a vaccine against *Salmonella* (as far as I am aware)

Global Burden of Disease 2019

	Deaths						DALYs					
Pathogen	All Ages	Lower CI	Upper CI	<5	Lower CI	Upper CI	All Ages	Lower CI	Upper CI	<5	Lower CI	Upper CI
Salmonella*	274,059			111,023			20,075,278			9,689,494		
Rotavirus	235,331	110,221	415,457	151,514	70,588	266,416	17,071,346	8,567,481	29,151,299	13,568,166	6,391,731	23,612,454
Shigella	148,202	61,975	284,541	93,831	35,860	185,931	10,602,910	4,538,791	20,242,702	8,402,887	3,274,243	16,542,456
Adenovirus	107,065	63,519	172,993	83,492	43,914	143,867	8,321,445	4,701,161	14,131,064	7,415,744	3,914,145	12,770,032
Cryptosporidium	133,423	26,424	360,303	77,523	15,962	190,426	8,170,908	1,797,798	20,226,898	6,862,766	1,463,118	16,773,435
Typhoid fever	110,029	52,810	191,206	18,934	7,228	38,033	8,053,346	3,864,905	13,925,252	1,635,423	625,745	3,279,949
Campylobacter	139,080	47,005	304,635	58,911	24,006	116,236	7,307,840	3,204,436	14,174,900	5,324,624	2,230,951	10,387,448
Cholera	117,241	71,090	177,806	55,701	28,044	93,931	7,134,552	4,032,717	11,139,174	4,837,150	2,438,859	8,153,152
Norovirus	135,798	25,103	303,735	43,481	11,754	99,172	6,879,357	2,085,136	14,198,132	3,962,128	1,192,131	8,842,284
Invasive Non-typhoidal Salmonella (iNTS)	79,046	43,013	124,207	49,869	27,161	80,009	6,114,292	3,323,425	9,705,739	4,318,828	2,355,108	6,931,248
Non-typhoidal Salmonella Diarrhea	61,647	4,376	190,566	39,493	4,376	107,810	4,269,216	475,319	12,056,915	3,500,124	426,309	9,395,645
Entamoeba	33,409	10,529	82,410	19,049	4,952	50,300	2,539,799	850,865	6,186,972	1,706,349	448,942	4,485,968
Aeromonas	28,019	12,945	50,322	19,651	7,871	39,046	2,073,448	932,430	3,883,407	1,744,504	709,751	3,449,201
Enterotoxigenic E coli	39,802	18,039	76,964	12,399	4,983	26,372	1,695,355	828,589	3,252,268	1,133,338	466,320	2,389,033
Enteropathogenic E coli	20,613	10,118	37,221	15,844	7,447	29,987	1,679,423	858,148	3,045,518	1,412,061	667,888	2,658,679
Paratyphoid fever	23,337	9,801	45,680	2,727	844	6,588	1,638,424	682,263	3,206,062	235,120	72,825	567,486
Clostridium difficile	32,134	28,131	36,549	2,102	1,306	3,218	870,814	722,988	1,052,360	182,179	113,038	278,999

*typhoid fever, iNTS, NTS diarrhea & paratyphoid fever

(Data from Global Burden of Disease 2019, Institute for Health Metrics and Evaluation)

All iNTS Vaccines are combination vaccines

Salmonella enterica, serovars:

- serovar Typhimurium
- serovar Enteritidis
- serovar Typhi
- serovar Paratyphi A

Remember dNTS disease!

(Hasso-Agopsowicz M EBioMedicine 2024 Nov 4:105424.)

Preclinical | Phase 1 | Phase 2 | Phase 3 | Licensed | WHO PQ

The *Salmonella* vaccine pipeline

Vi-CRM$_{197}$
Eubiologics

Vi-DT
Bio Farma

PedaTyph
BioMed

Vi-rEPA
LIBP

TypBar TCV
BBIL

TYPHIBEV
BioE

SKYTyphoid
SK Bioscience

Zyvac Tcv-PFS
Zydus

CVD 1902
BBIL / UMD

O:2-TT
LIBP / NIH

Vi- + O:2-MAPS
BCH / Affinivax

CVD 909 + CVD 1902
UMD / BBIL

SKYTyphoid + O:2-DT
IVI / SK

O:4- + O:9-MAPS
BCH

SKYTyphoid + O:4- + O:9-DT
IVI / SK

Zyvac Tcv-PFS + Vi DT
Zydus

Entervax ZH9PA + ZH9
Prokarium

TYPHIBEV + O:2-CRM
BioE / GVGH

Vi-TT + O:2-DT
SII

STm + SEn GMMA
GVGH

Typbar TCV + O:4- + O:9- flagellin
BBIL / UMD

TYPHIBEV + STm + SEn GMMA
GVGH / BioE

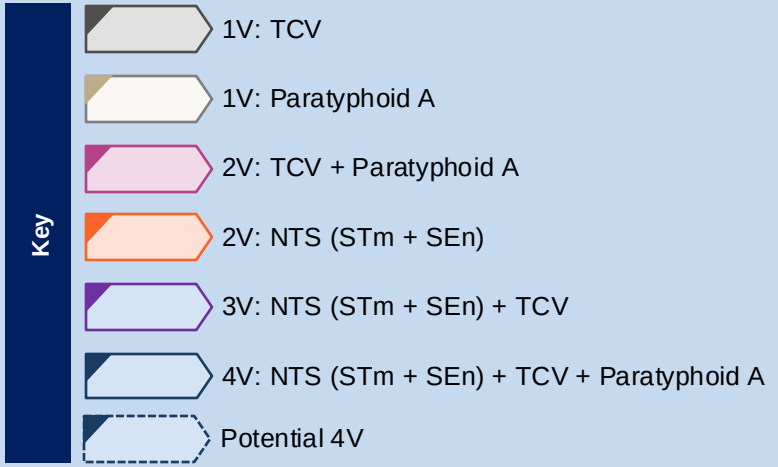
4V MAPS
BCH / Affinivax

4V
GVGH / BioE

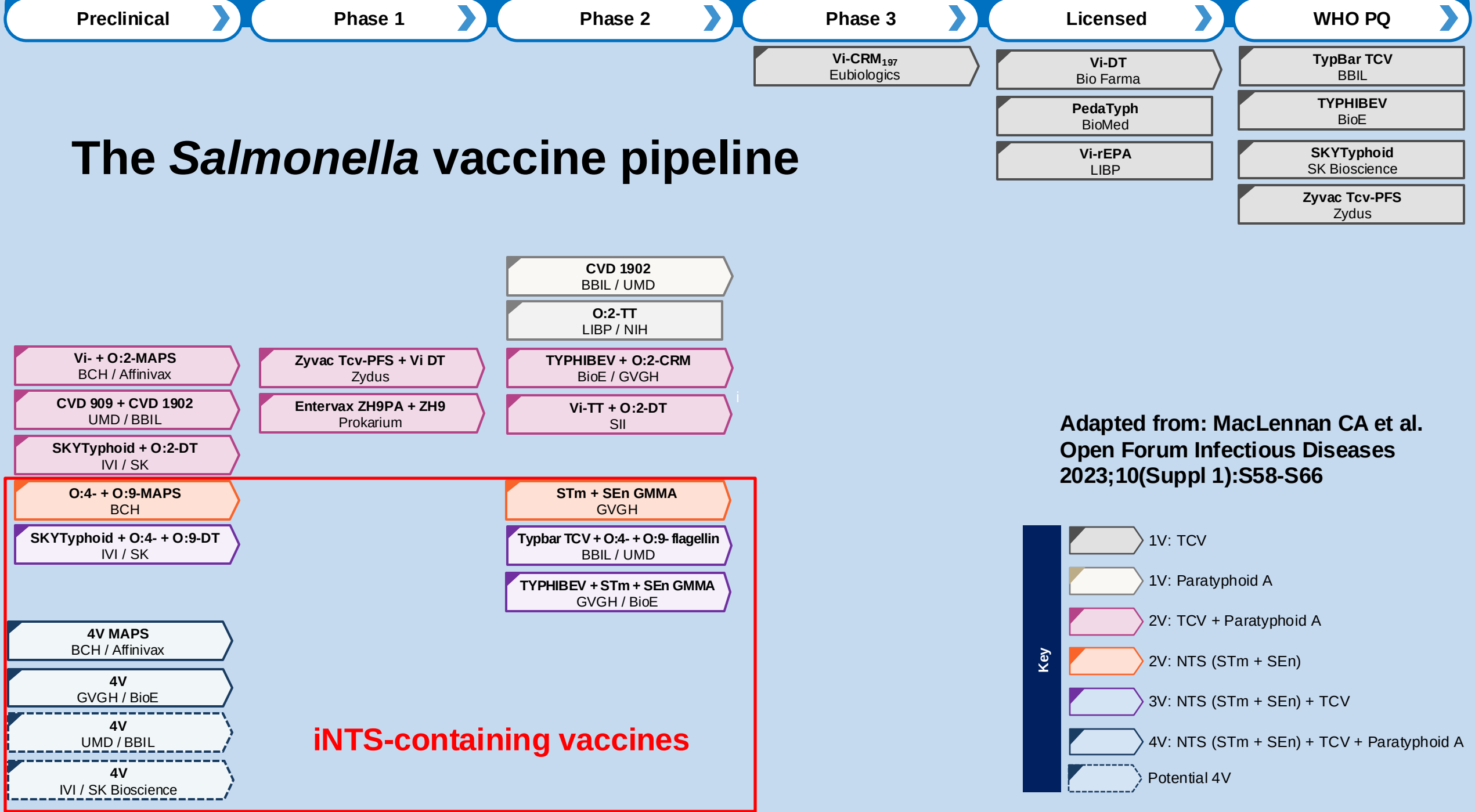
4V
UMD / BBIL

4V
IVI / SK Bioscience

Adapted from: MacLennan CA et al. Open Forum Infectious Diseases 2023;10(Suppl 1):S58-S66



The *Salmonella* vaccine pipeline



Immune mechanisms of protection

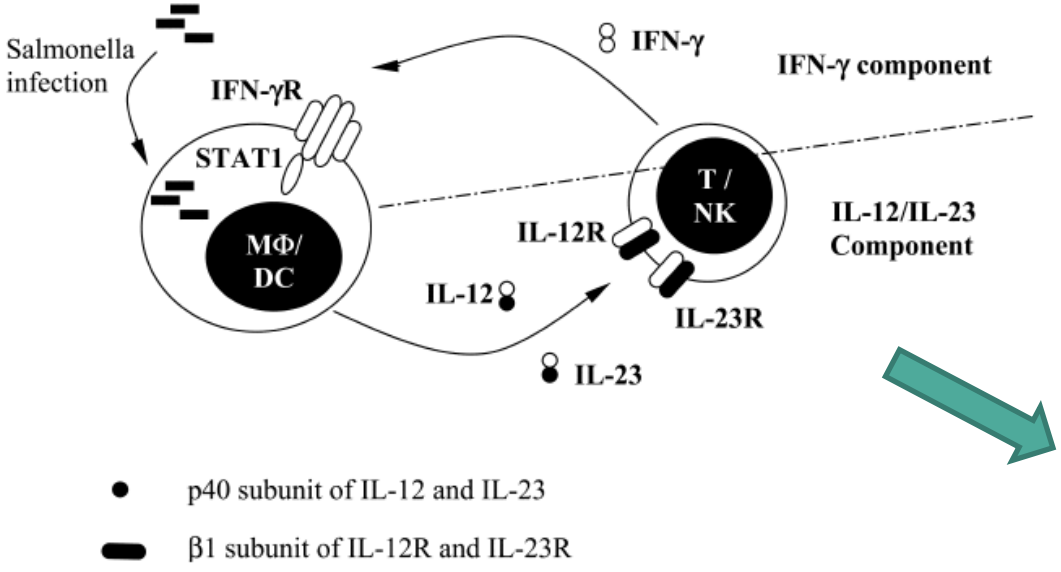
- All O-antigen-based
- UMD/BBIL – flagellin as carrier protein
- GVGH – OMV technology includes outer membrane proteins

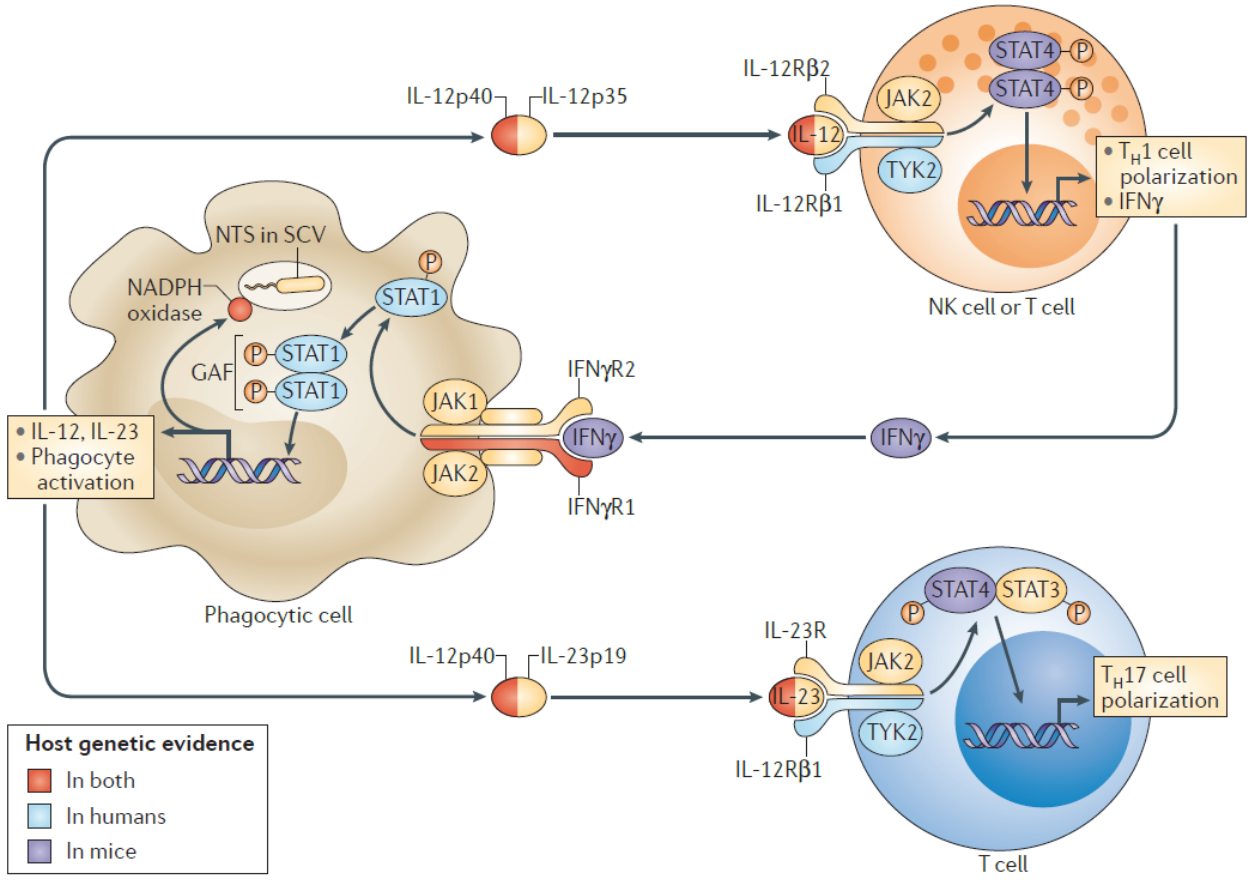
- Immunity:
- Antibody to O-antigen *(best characterised effector of protection)* – ALL.
- Pathogen-specific T-cells *(potential requirement for clearance from intracellular niche)* – UMD & GVGH & BCH

What are requirements for protection in different population groups?

- Immune naïve children – antibody may protect against fatal bacteremia (6 month to 3-year window)
- Is T cell immunity required for clearance in man?
- Will acquired immunity protect when comorbidities are present, particularly malaria & HIV?

IL-12-dependent IFNγ-mediated immunity and IL-23 signalling IN response to *Salmonella* infection



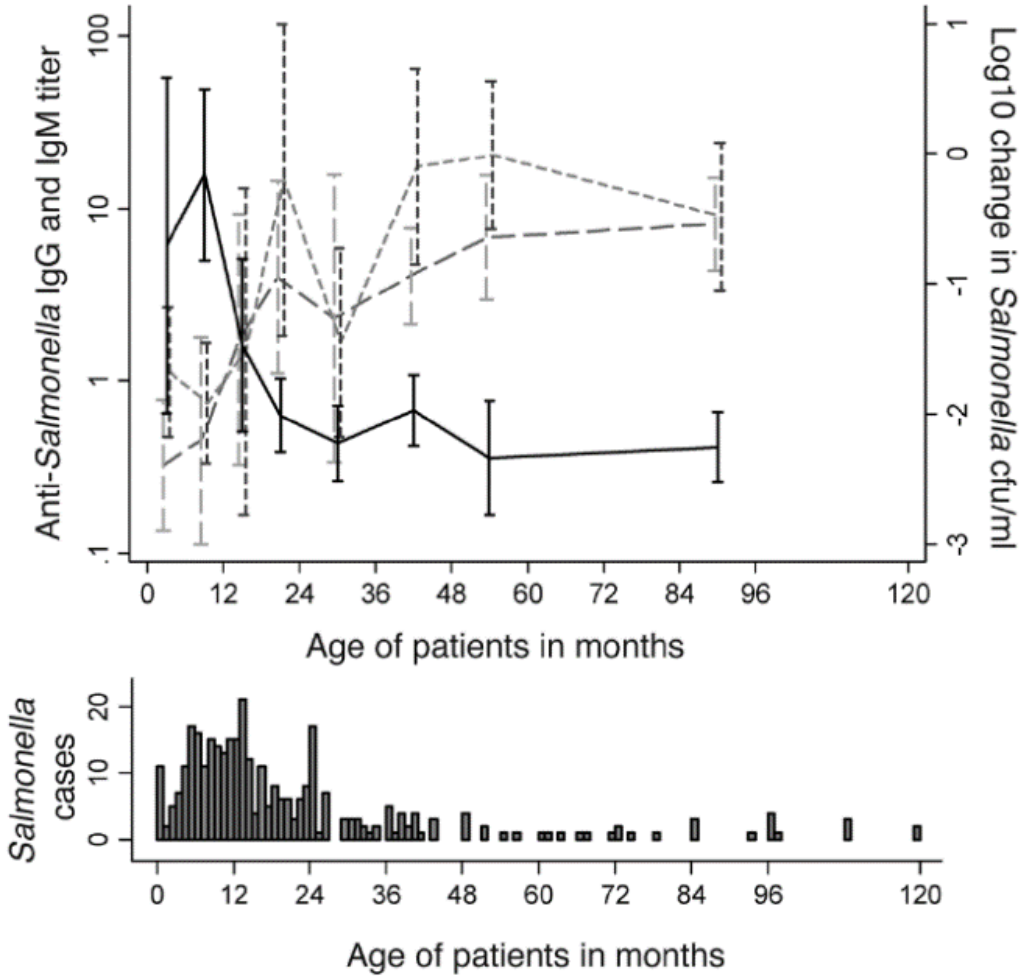


Genetic susceptibility to invasive *Salmonella* disease

James J. Gilchrist[1], Calman A. MacLennan[2,3] and Adrian V. S. Hill[1,2]

(Nat Rev Immunol 2015)

A role for antibodies in immunity to iNTS disease in African children



The neglected role of antibody in protection against bacteremia caused by nontyphoidal strains of *Salmonella* in African children

Calman A. MacLennan,[1,2,3,4] Esther N. Gondwe,[1,5] Chisomo L. Msefula,[1,4,5] Robert A. Kingsley,[6] Nicholas R. Thomson,[6] Sarah A. White,[1,7] Margaret Goodall,[2] Derek J. Pickard,[6] Stephen M. Graham,[1,5] Gordon Dougan,[6] C. Anthony Hart,[3] Malcolm E. Molyneux,[1,5] and Mark T. Drayson[2]

(J Clin Invest 2008)

Acquisition of bactericidal antibodies inversely corresponds to age at which African children are susceptible to iNTS disease

nature

RESEARCH HIGHLIGHTS

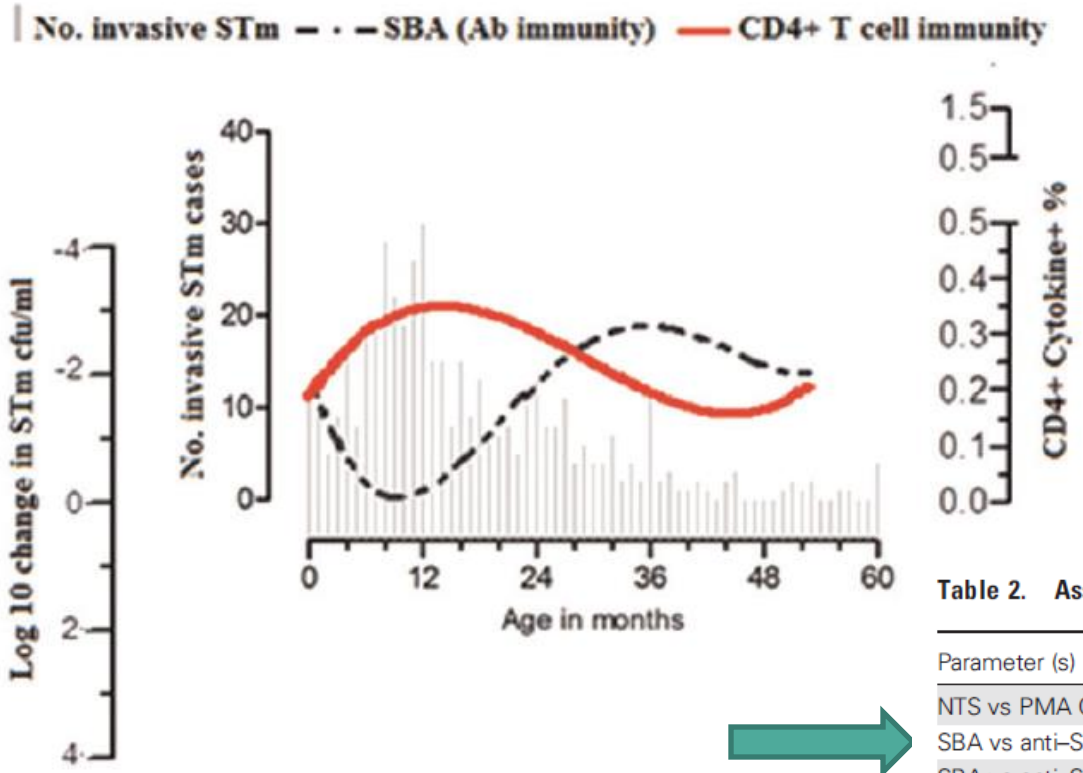
IMMUNOLOGY

Antibiotic antibodies

J. Clin. Invest. doi:10.1172/JCI33998 (2008)

The discovery of functional antibodies against strains of *Salmonella* that do not cause typhoid raises hopes that a vaccine can be developed. In Africa, such strains kill up to 24% of infected children in communities in which appropriate antibiotics and blood-culture facilities are available.

...and uncertainty about the role for T cells



Sequential Acquisition of T Cells and Antibodies to Nontyphoidal *Salmonella* in Malawian Children

Tonney S. Nyirenda,[1] James J. Gilchrist,[3] Nicholas A. Feasey,[1,4] Sarah J. Glennie,[1] Naor Bar-Zeev,[1] Melita A. Gordon,[5] Calman A. MacLennan,[6,7] Wilson L. Mandala,[2] and Robert S. Heyderman[1]

(J Infect Dis 2014)

Table 2. Association Between Immune Variables

Parameter (s)	XY Pairs	Spearman *r*	95% CI	*P* Value
NTS vs PMA CD4$^+$ cytokine$^+$	55	0.109	−.128 to .371	.426
SBA vs anti–STm-LPS IgG antibody titers	55	0.329	.552–.062	.01
SBA vs anti–STm-OMP IgG antibody titers	57	0.044	−.226 to .308	.741
SBA vs anti–STm-FliC IgG antibody titers	58	−0.001	−.266 to .264	.992
SBA vs anti–*E. coli*-LPS IgG antibody titers	50	0.031	−.257 to .314	.830
CD4$^+$ cytokine$^+$ vs anti–STm-OMP IgG antibody titers	65	0.137	−.117 to .375	.275
CD4$^+$ cytokine$^+$ vs anti–STm-FliC IgG antibody titers	67	0.174	−.075 to .404	.157
CD4$^+$ cytokine$^+$ vs anti–STm-OMP IgG antibody titers (early)[a]	39	0.405	.088–.647	.01
CD4$^+$ cytokine$^+$ vs anti–STm-FliC IgG antibody titers (early)[a]	38	0.394	.080–.637	.01
CD4$^+$ cytokine$^+$ vs anti–STm-LPS IgG antibody titers (early)[a]	36	−0.257	−.547 to .087	.129

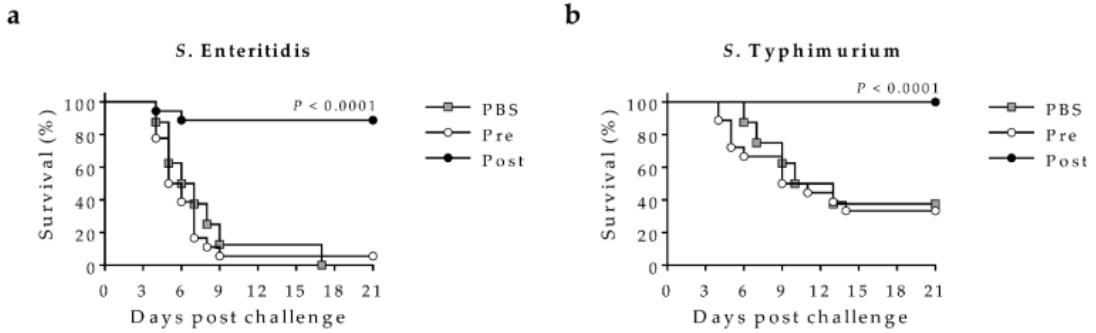
Sequential acquisition of T cells and antibodies to *Salmonella* Typhimurium in children

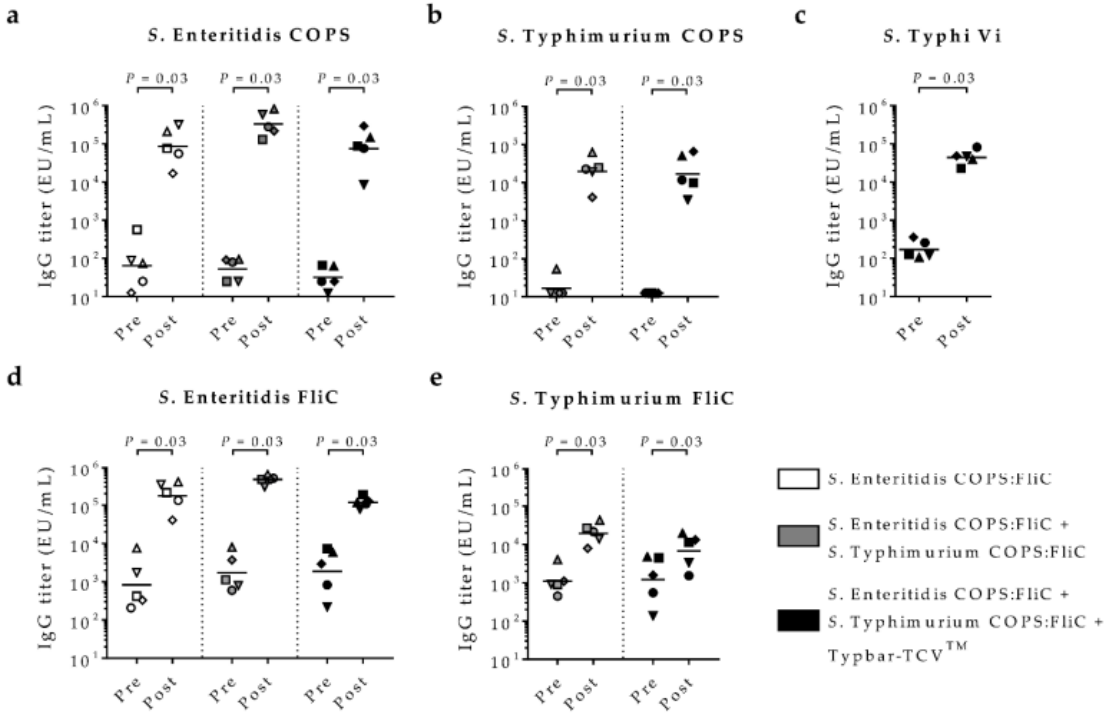
O:4-/O:9- flagellin + TypbarTCV, Bharat Biotech & University of Maryland

Immunogenicity and Induction of Functional Antibodies in Rabbits Immunized with a Trivalent Typhoid-Invasive Nontyphoidal *Salmonella* Glycoconjugate Formulation

Scott M. Baliban [1], Jessica C. Allen [1], Brittany Curtis [1], Mohammed N. Amin [1], Andrew Lees [2], R. Nageswara Rao [3], Gangadhara Naidu [3], Ramasamy Venkatesan [3], D. Yogeswara Rao [3], Vadrevu Krishna Mohan [3], Krishna M. Ella [3], Myron M. Levine [1] and Raphael Simon [1,*]

(Molecules 2018; 23: 1749)





O:4-/O:9- flagellin + TypbarTCV, Bharat Biotech & University of Maryland

Phase 1 Study

- ‘Salmonella Conjugates CVD 2000’
- ClinicalTrials.gov Identifier: NCT05525546
- randomized, placebo-controlled trial
- TSCV full-dose, TSCV half-dose,

TSCV dilutional half-dose, placebo

- Baltimore
- 80 participants
- August 2022 – August 2023
- Wellcome-funded

Phase 2 Study

- Trivalent Salmonella Conjugate Vaccine (TSCV)
- ClinicalTrials.gov Identifier: NCT05784701
- age-descending, randomized, placebo-controlled trial
- TSCV full-dose, TSCV half-dose, TypbarTCV, placebo
- 3 sites in Sub-Saharan Africa (Mali, Ghana, Malawi)
- 800 participants
- April 2023 – April 2025 (primary completion date)
- Wellcome-funded

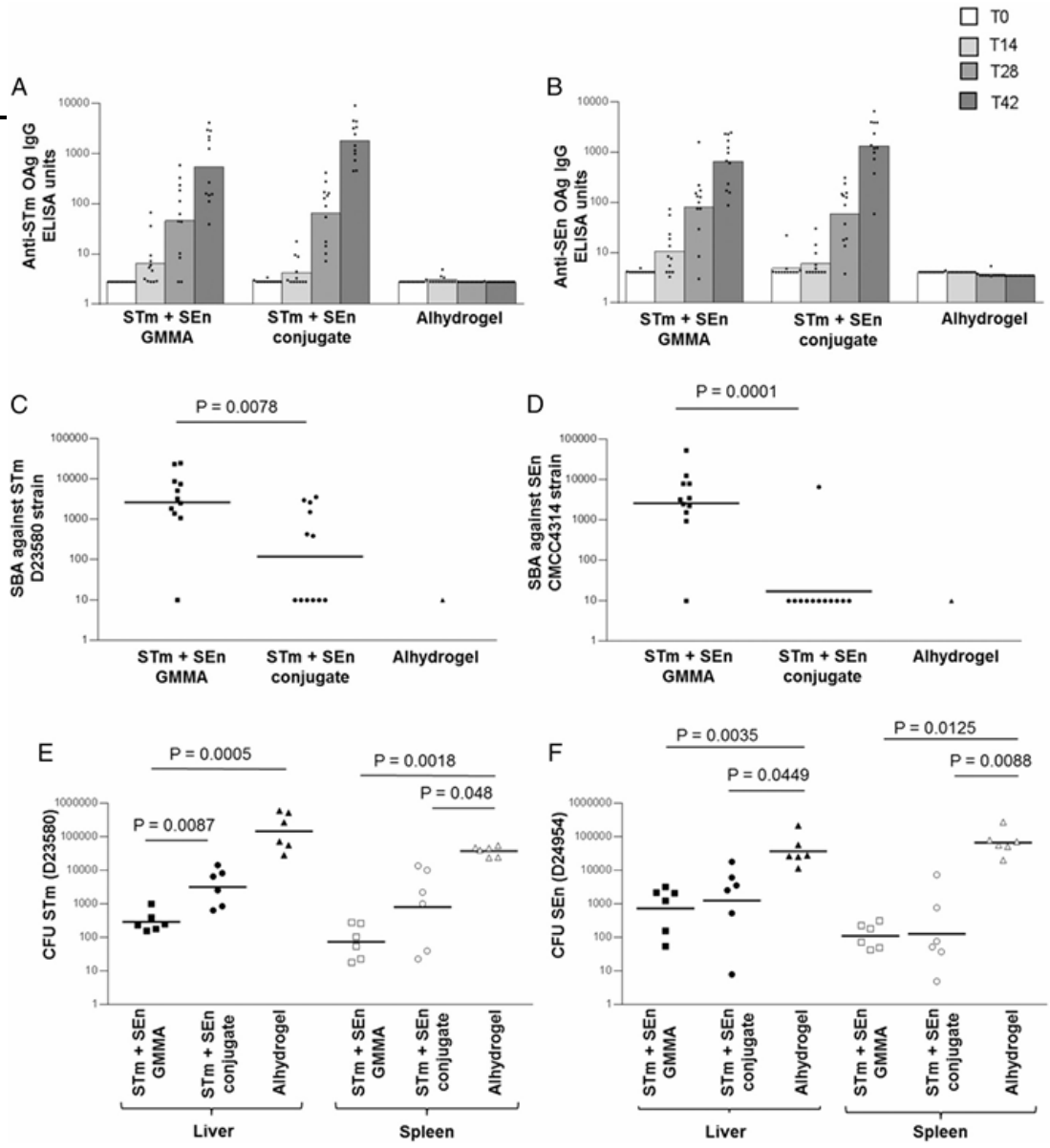
STm GMMA + SEn GMMA, GVGH

Comparative immunogenicity and efficacy of equivalent outer membrane vesicle and glycoconjugate vaccines against nontyphoidal *Salmonella*

Francesca Micoli[a,1], Simona Rondini[a], Renzo Alfini[a], Luisa Lanzilao[a], Francesca Necchi[a], Aurel Negrea[a], Omar Rossi[a], Cornelia Brandt[b], Simon Clare[b], Pietro Mastroeni[c], Rino Rappuoli[d,1], Allan Saul[a], and Calman A. MacLennan[e]

(PNAS 2018; 115: 10428-10433)

- Preclinical comparison of equivalent OMV/GMMA & glycoconjugate vaccines
- OMV/GMMA:
  - 'Vehicle' for O-antigen delivery
  - Also deliver pathogen-specific protein antigens to immune system – potential role in clearance of intracellular bacteria



STm GMMA + SEn GMMA +/- Typhibev, GVGH & Biological E

2V Vaccine: STm GMMA + SEn GMMA

- **GSK H04_01TP FTiH Ph1** adults - Horizon 2020 - UK
- **GSK H04_02TP Ph1b** adults - Horizon 2020 – Kenya
- **GSK H04_03TP Ph2** age de-escalation infants - EDCTP – Ghana

3V Vaccine: STm GMMA + SEn GMMA + Typhibev

- **GSK H08_01TP FTiH Ph1/2a** adults - CARB-X - Belgium and Malawi

O:4- + O:9-MAPS, Boston Children's Hospital

vaccines

MDPI

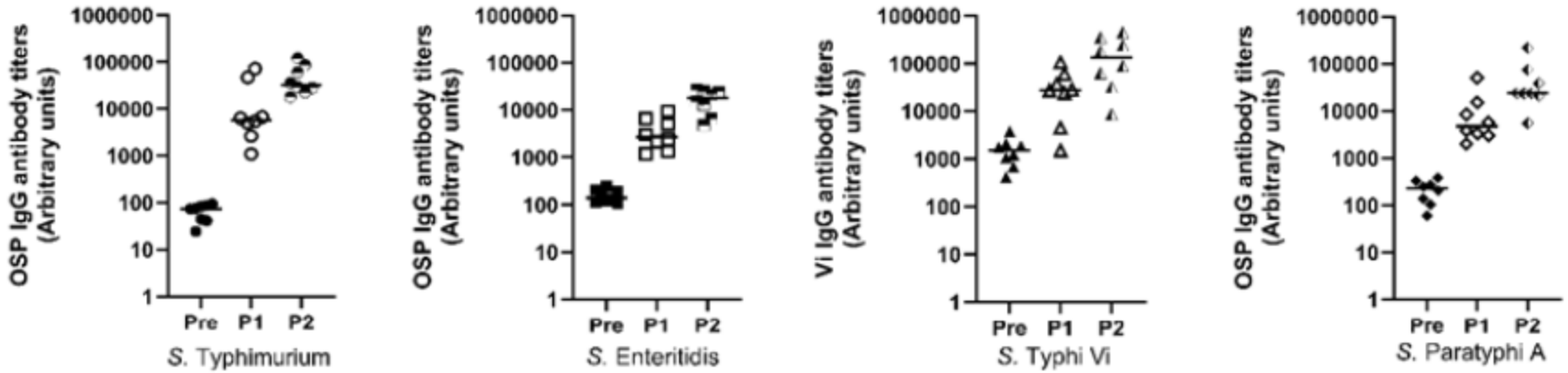
Article

Induction of Broad Immunity against Invasive Salmonella Disease by a Quadrivalent Combination Salmonella MAPS Vaccine Targeting Salmonella Enterica Serovars Typhimurium, Enteritidis, Typhi, and Paratyphi A

Emily M. Boerth [1], Joyce Gong [1], Becky Roffler [1], Claudette M. Thompson [1], Boni Song [1], Sasha F. Malley [1], Angelika Hirsch [1], Calman A. MacLennan [2], Fan Zhang [1], Richard Malley [1] and Ying-Jie Lu [1,*]

(Boerth EM Vaccine 2023; 11:1671-2644)

- Multiple Antigen-Presenting System (MAPS) technology
- Rhizavidin – biotin link
- SseB Salmonella T3SS protein as carrier
- Preclinical studies



O:4-DT + O:9-DT + SKYTyphoid, IVI & SK Bioscience

- IVI – SK Bioscience partnership
- 3x DT conjugates: O:4, O:9, Vi
- Vi-DT WHO prequalified TCV
- Preclinical studies & GLP/toxicology

Trivalent Vi–iNTS conjugate vaccine

An invasive infection of the bacteria Salmonella enterica and S. typhimurium, iNTS causes gastroenteritis, high fever, bloodstream infections, sepsis, and potentially even death. iNTS is linked with poverty, malnutrition, poor sanitation, and lack of safe drinking water. Sub-Saharan Africa and Eastern Europe have the highest incidence rates of iNTS, and infants, young adults, and immunocompromised individuals—including those infected with HIV and malaria—are particularly at risk of infection. The disease is often fatal if untreated and there are no licensed vaccines available.

(International Vaccine Institute. Vaccines for a safer future. 2020.)

Full Value of Vaccines Assessment for invasive Non-Typhoidal Salmonella Vaccines (iNTS FVVA)

Jean-Louis Excler

PDVAC, 11 Dec 2024

International Vaccine Institute

Agenda

IVI-WHO-WT consultation on iNTS combination vaccines, 12-13 Dec 2024, Geneva

IVI-WHO regulatory consultation on iNTS combos, 4-5 Feb 2025, Nairobi

IVI-WHO-WT consultation on iNTS combination vaccines, 12-13 Dec, Geneva

- Several iNTS vaccines are currently under development; however, the **pathway to marketing authorization has been a key challenge**

- There is also g**rowing urgency to develop combination vaccines** due to increasingly crowded EPI schedules

- This meeting aims to gather **expert input on critical considerations** for iNTS combination vaccines and further inform the FVVA.

- The meeting will also on the clinical development pathway by identifying critical questions for regulators, in preparation for a Regulatory Science meeting scheduled for Q1 2025.

IVI-WHO-WT consultation on iNTS combination vaccines, 12-13 Dec, Geneva

Objectives

- Receive updates on interim results from iNTS clinical studies and trials
- Explore and inform iNTS combination vaccine strategies
- Receive updates from an African stakeholder workshop on country-level perspective and priorities to guide the development of standalone and combination iNTS vaccine strategies.
- Identify key issues related to the clinical and regulatory pathways to accelerate development of iNTS-containing vaccine candidates.

Expected Outcomes

- Identify areas of alignment on potential iNTS combination vaccines, as well as further advancing regarding clinical and regulatory pathways and FVVA.
- A meeting report summarizing key discussions, deliberations, and recommendations for next steps to accelerate development of iNTS-containing vaccines for the vaccine developers.

IVI - WHO consultation on regulatory considerations to support licensure of iNTS vaccines for use in children in LMICs, 4-5 Feb 2025, Nairobi

- The WHO R&D technology roadmap for iNTS vaccines emphasises the **need to establish a regulatory pathway** to licensure in LMICs.
- Several iNTS vaccines are currently in development, however, **the pathway to marketing authorization for iNTS has been a critical question** for vaccine developers

- Emphasized at an IVI-WHO Consultation on *Salmonella* Combination Vaccines (December 4, 2023, Kigali, Rwanda), this meeting is a **follow-up of the IVI-WHO-WT Consultation** on Dec 12-13, 2024, Geneva.

- The meeting aims to **delineate regulatory requirements** to align the clinical development of iNTS containing vaccines and provide guidance to developers, manufacturers, and policy makers.

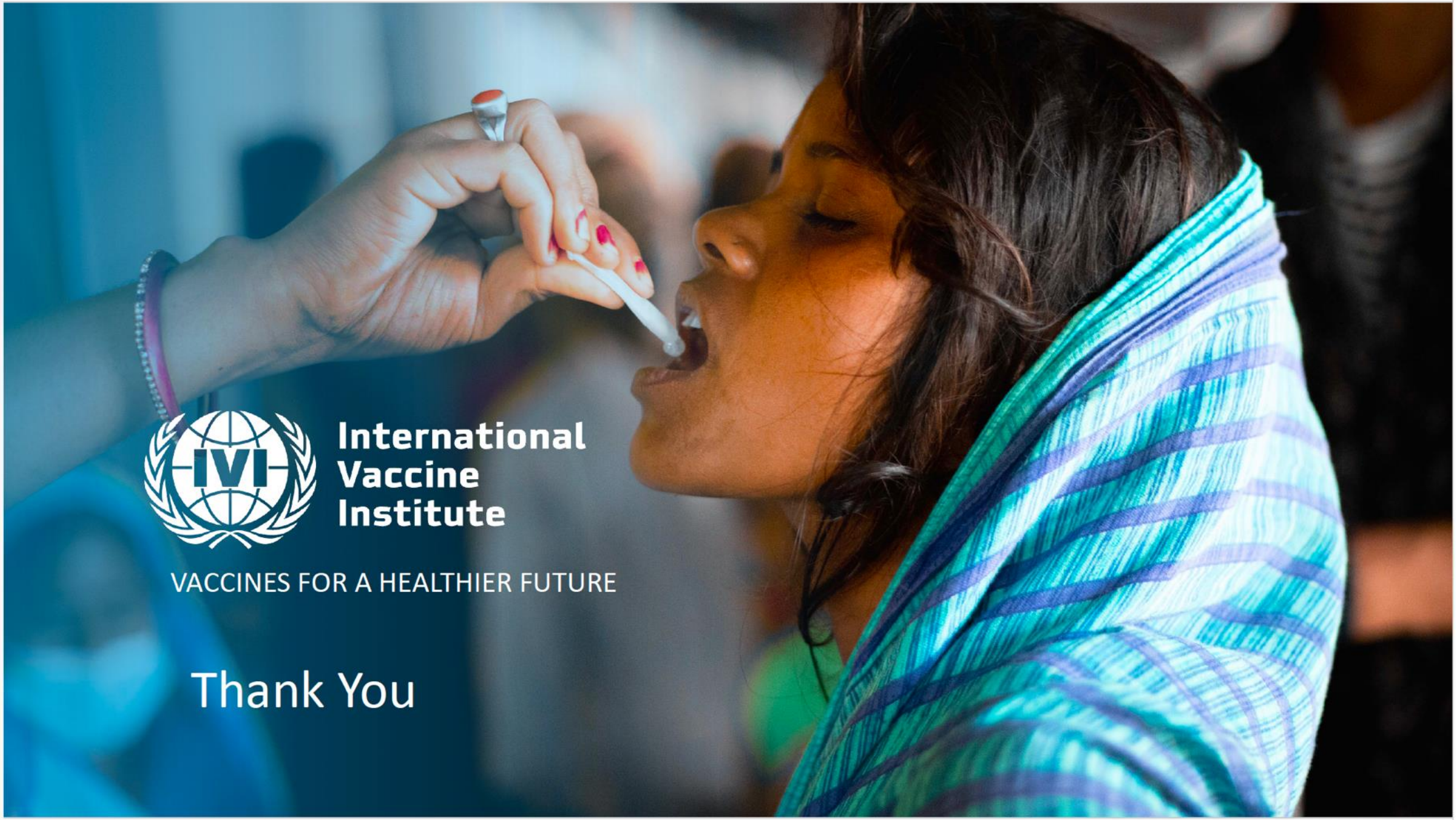
IVI - WHO consultation on regulatory considerations to support licensure of iNTS vaccines for use in children in LMICs, 4-5 Feb 2025, Nairobi

Objectives

- **Raise awareness** of iNTS burden and iNTS vaccine development status
- Review the **current clinical development plan considerations**, available **interim safety and immunogenicity data**, and preparations for future field efficacy studies and post-licensure effectiveness studies in high-burden countries
- **Identify key issues for clinical trial design** including primary clinical endpoints, clinical case definition, and microbiological case detection method(s)
- **Identify key issues on immunological endpoints and assays**, areas that require additional discussion and alignment for licensure as well as data needed to inform future efficacy study design and post-licensure effectiveness studies

Expected Outcomes

- Trigger a sustained engagement from regulators on iNTS vaccine development for LMICs, based on awareness of the burden of disease and public health need for a vaccine
- Gain understanding of expectations and requirements from LMIC regulators with their inputs and recommendations on iNTS clinical development and gaps to be filled by developers and manufacturers
- Produce a meeting report summarizing key discussions, deliberations, and recommendations to accelerate development of iNTS-containing vaccines in compliance with regulators' requirements


International
Vaccine
Institute
VACCINES FOR A HEALTHIER FUTURE
Thank You

Regulatory Questions

Q1: The WHO iNTS PPC indicates the target population is infants and young children 6 to 36 months of age though there is uncertainty particularly regarding the most appropriate lower age bound. One potential combination vaccine includes iNTS and TCV. TCV is not currently licensed in infants below 6 months. Could the regulatory community opine on whether non-inferiority for the TCV component (in the iNTS/TCV combination vaccine) should be determined in infants below 6 months given the vaccine is not licensed below 6 months?

Q2: If an iNTS vaccine was to be combined with a licensed product (for example TCV), could the regulatory community discuss whether the safety of the standalone iNTS vaccine would need to be established prior to demonstrating the safety, immunogenicity and efficacy of the combination iNTS + TCV vaccine in phase 1, phase 2a, and phase 3 studies, respectively.

Q3: A combination vaccine consisting of Typhi/Paratyphi/TCV/iNTS could potentially provide necessary coverage in Asia and Africa. However, each population would be immunized with a vaccine component not specific to their global region. Can the regulatory community provide insights into what benefit-risk analysis would be required to for market authorization/licensure?

PDVAC Questions

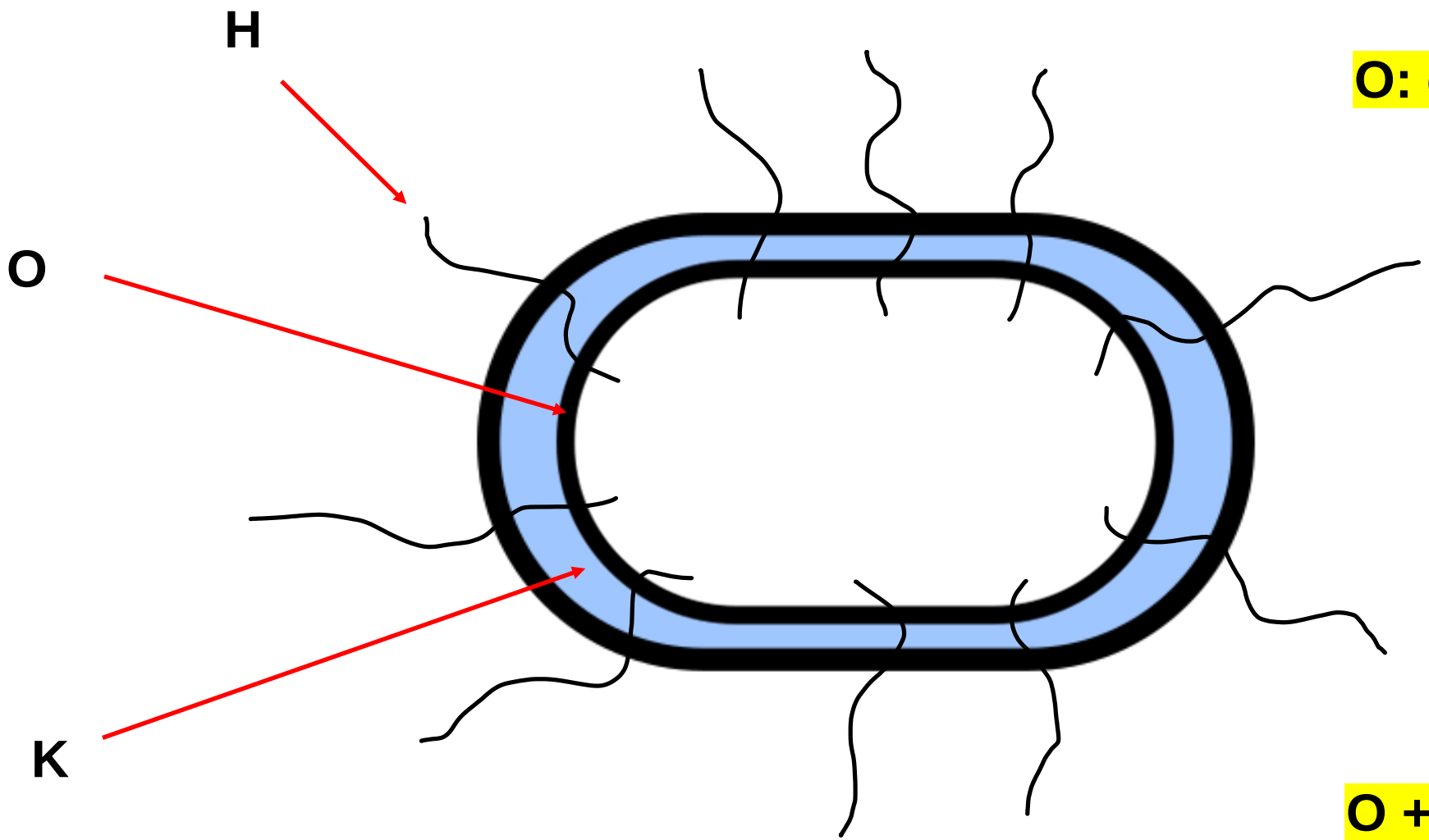
Does PDVAC agree with the scope of the questions for the Regulatory Science Meeting?

Does PDVAC agree on expanding the discussions on combination iNTS beyond other Salmonella vaccines?

BACKUP SLIDES

Child with nontyphoidal *Salmonella* invasive disease

Salmonella enterica: pathogen and typing



O: defines serogroup

O + H: defines serovar

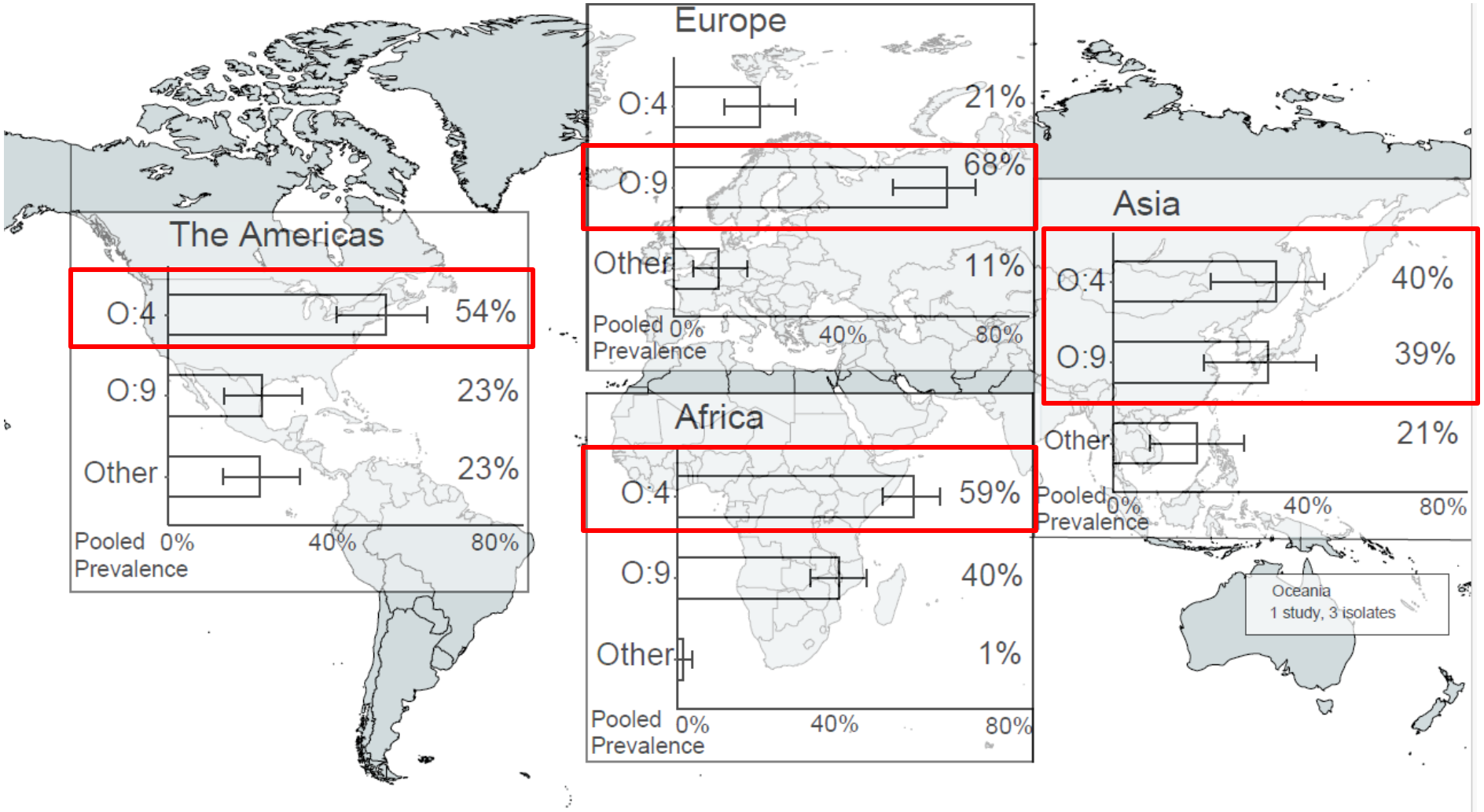
Pooled prevalence of NTS serogroups and serovars among isolates from normally sterile sites, global, 1941 - 2019

Serogroup	Pooled prevalence, %	(95% CI)
O:4	44.6	(36.2-48.2)
O:9	45.5	(37.0-49.1)
Others	9.9	(6.1-13.3)

Serovar	Pooled prevalence, %	(95% CI)
Typhimurium	40.2	(29.5-44.2)
Enteritidis	41.4	(30.5-45.3)
Others	18.4	(11.4-22.9)

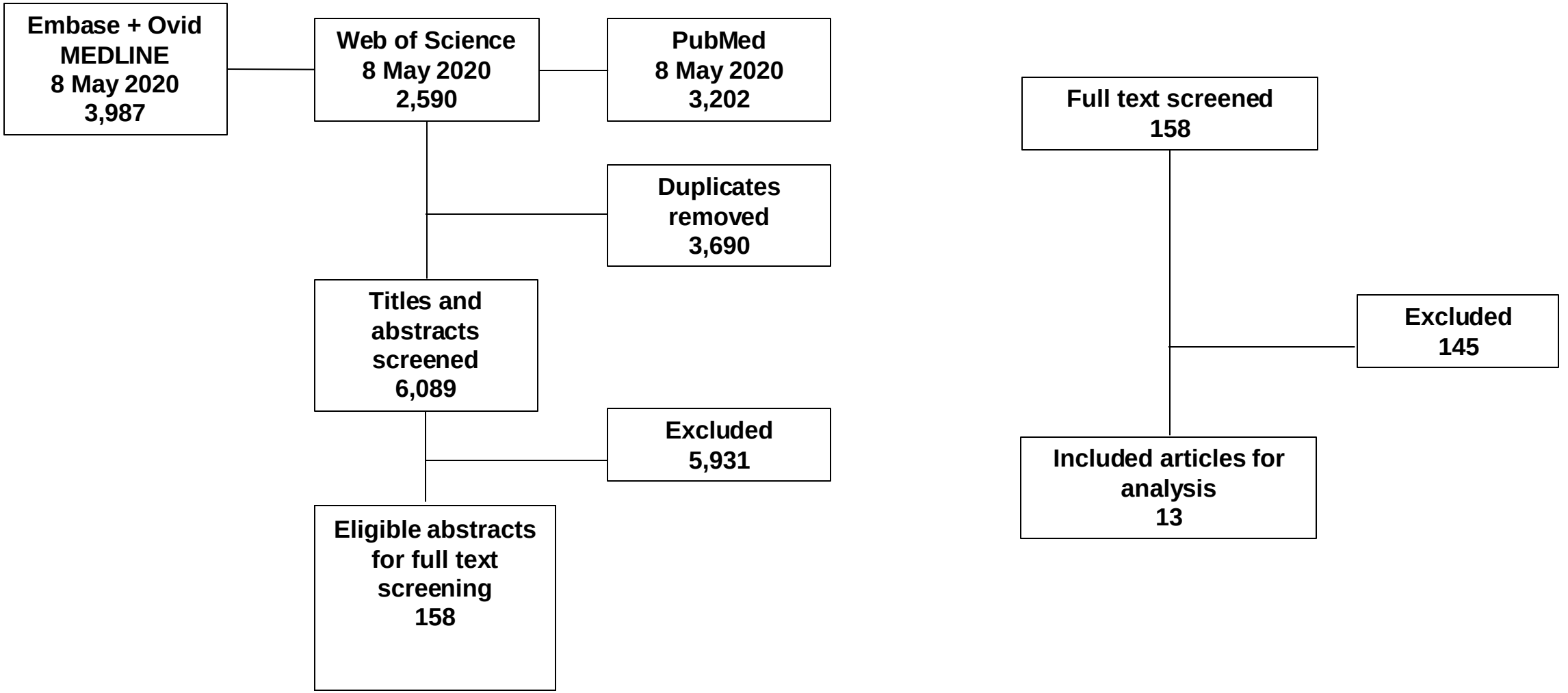
Hagedoorn NN, et al. Epidemiol Infect 2023; 152: e4

Pooled prevalence of NTS serogroups among isolates from normally sterile sites by UN region, 1941 - 2019



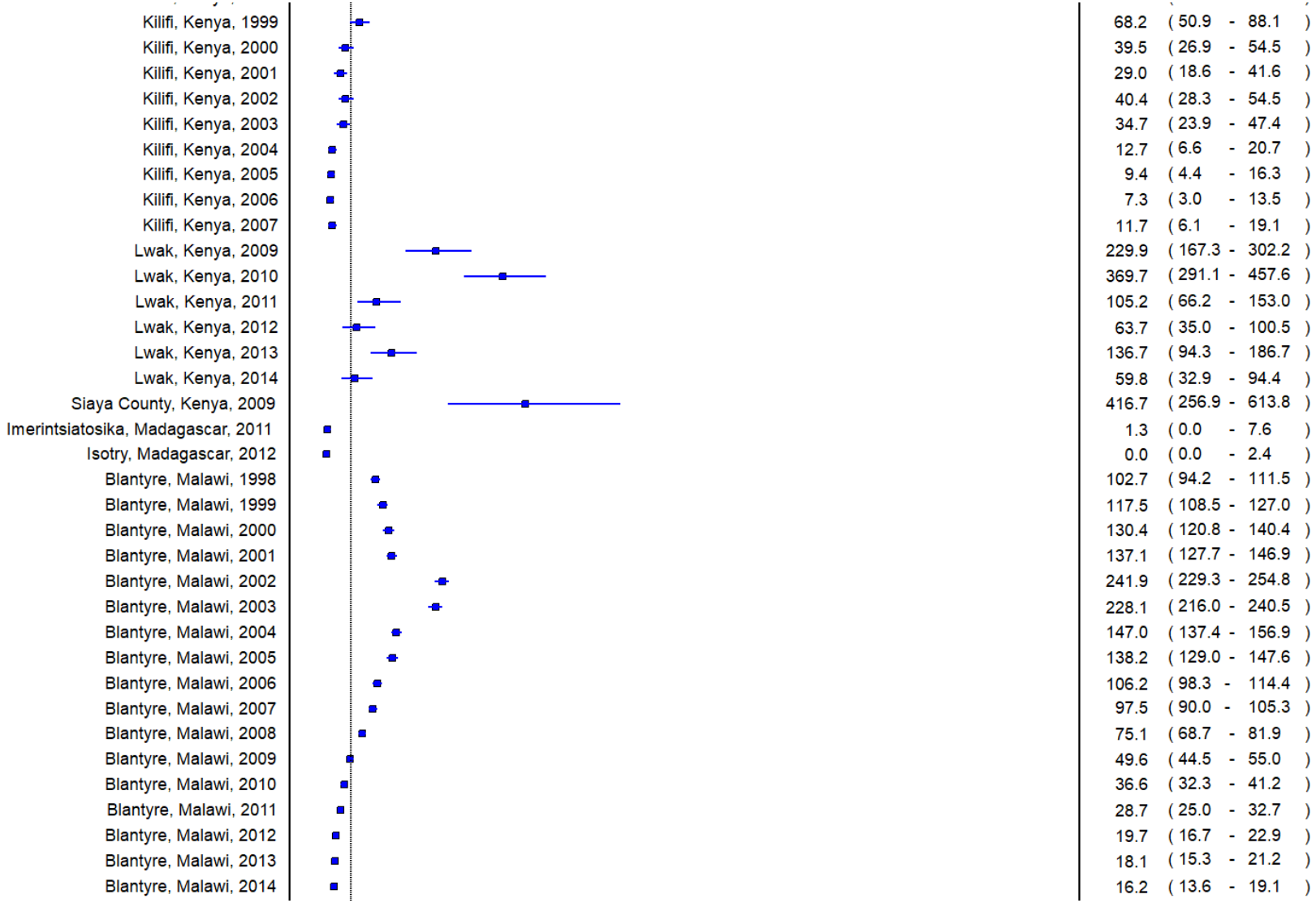
Hagedoorn NN, et al. Epidemiol Infect 2023; 152: e4

PRISMA diagram for incidence of non-typhoidal *Salmonella* invasive disease systematic review



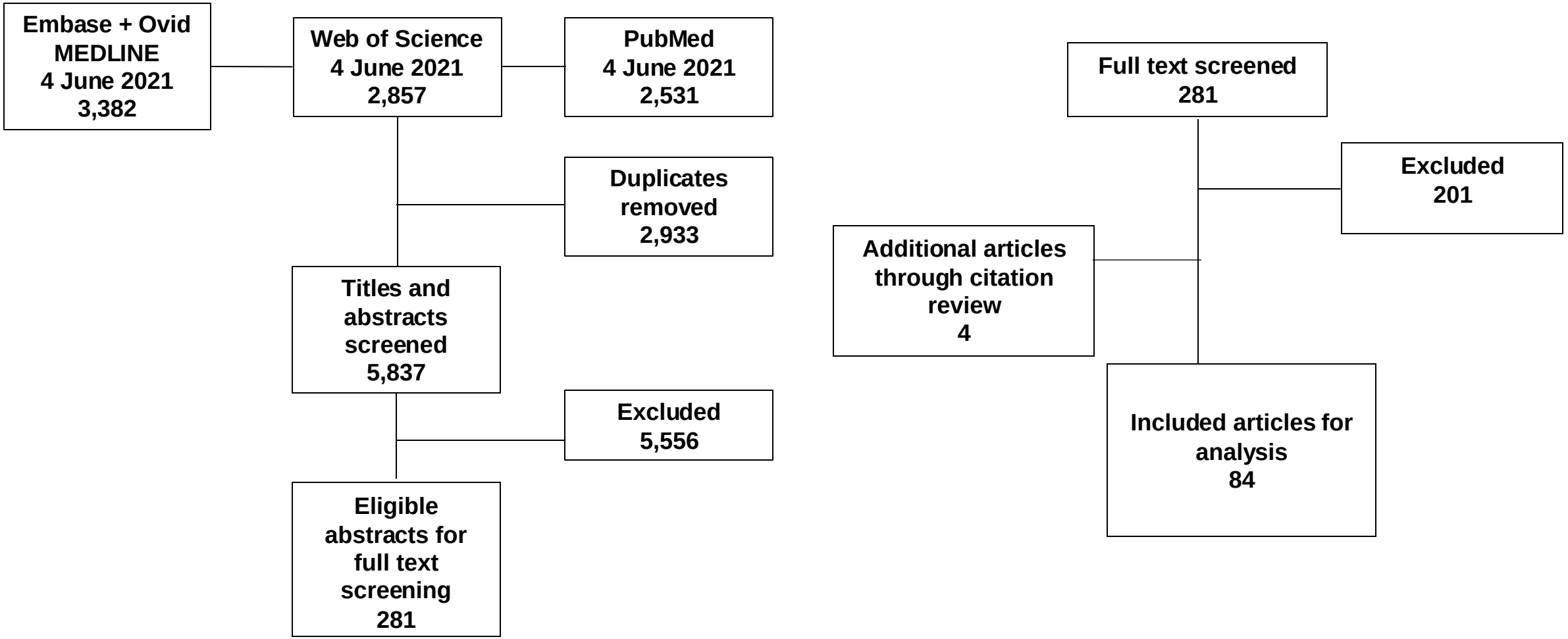
Marchello CS, et al. J Infect 2021; 83: 523-532

Forest plot of incidence estimates in Kenya and Malawi over consecutive years



Marchello CS, et al. J Infect 2021; 83: 523-532

PRISMA diagram for complications and deaths for non-typhoidal *Salmonella* invasive disease systematic review



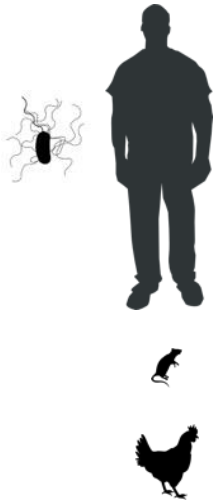
Marchello CS, et al. Lancet Infect Dis 2022; 22: 692-705

Chain of infection: reservoir, source, and mode of transmission

Molecular reservoir attribution

Molecular source attribution

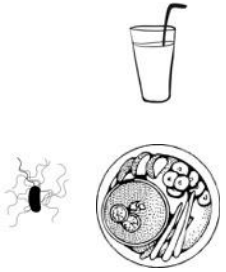
Reservoir



Portal of exit

Source

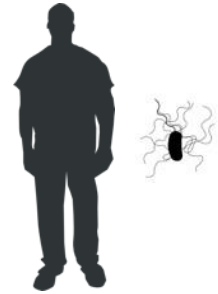
Mode of transmission



Other

Portal of entry

Susceptible host



Source-assigned case-control study

Host risk factors

- **Host risk factors**
  - **Extremes of age**
  - **Malnutrition, acute > other**
  - **Malaria, recent > current**
  - **HIV, adults > children**
  - **Anemia**
  - **Sickle cell disease**

- **Most studies are hospital-based**
  - **Systematic review (Helen Dale)**
  - **Berkson's-type collider bias: bias in assessment of relationship between an exposure and a disease due to the conduct of the study in a clinic, where attendance was affected by both exposure and disease**
  - **Few studies assess multiple host risk factors simultaneously**

Adjusted attributable fraction percent of nontyphoidal *Salmonella* stool culture positive with moderate-to-severe diarrhea, by age stratum and site, GEMS, Africa and Asia, 2007-11

Age group, months	Basse, Gambia	Bamako, Mali	Manhiça, Mozambique	Nyanza Province, Kenya*	Kolkata, India	Mizapur, Bangladesh	Karachi, Pakistan
0-11	-	-	-	-	-	4.2 (2.2, 6.2)	-
12-23	-	-	-	3.2 (0.5, 6.0)	-	-	-
24-59	-	-	-	3.7 (1.2, 6.1)	-	-	-

*Predominantly in *Salmonella* Typhimurium ST313 in cases and controls

Kotloff KL, et al. Lancet 2013; 382: 209-22

Adjusted attributable fraction percent of nontyphoidal *Salmonella invA* qPCR stool positive with moderate-to-severe diarrhea, by age stratum and site, GEMS, Africa and Asia, 2007-11

Age group, months	Basse, Gambia	Bamako, Mali	Manhiça, Mozambique	Nyanza Province, Kenya	Kolkata, India	Mizapur, Bangladesh	Karachi, Pakistan
0-11	0.7 (0, 3.0)	0.7 (0, 2.1)	1.3 (0, 2.7)	0.7 (0, 3.1)	0.1 (0, 0.8)	0.4 (0, 3.3)	0.2 (0, 0.9)
12-23	3.9 (1.0, 7.1)	2.5 (0.9, 4.8)	2.8 (0.1, 5.7)	2.3 (0.7, 4.3)	0.2 (0, 0.9)	1.2 (0.3, 3.2)	0.2 (0, 1.2)
24-59	3.4 (1.1, 6.9)	2.1 (0.7, 4.2)	0.5 (0, 2.2)	3.4 (1.6, 5.9)	0.6 (0, 1.6)	0.2 (0, 1.0)	1.9 (0.4, 4.0)

Liu J, et al. Lancet 2016; 388: 1291-301

Nontyphoidal *Salmonella* as a cause of diarrhea in Africa

- **Malnutrition and Enteric Disease Study (MAL-ED)**
  - **Prospective birth cohort study from birth to 24 months of age with twice weekly community surveillance for diarrhea and routine collection of non-diarrheal stools from eight sites in South America, Africa, and Asia**
  - **Stool culture-based analysis**

Platts-Mills JA, et al. Lancet Global Health 2015; 3: e564-75

Adjusted attributable fraction percent of nontyphoidal *Salmonella* stool culture positive with diarrhea, by age stratum and site, MAL-ED, Africa, Asia, and South America, 2009-14

Age group, months	Dhaka, Bangladesh	Vellore, India	Bhaktapur, Nepal	Naushero Feroze, Pakistan	Venda, South Africa	Haydom, Tanzania	Fortaleza, Brazil	Loreto, Peru
0-11	-	-	-	-	-	-	-	-
12-24	-	0.7 (0.7, 0.7)	0.5 (0.5, 0.5)	-	-	-	0.5 (0.5, 0.5)	0.3 (0, 0.5)

Platts-Mills JA, et al. Lancet Global Health 2015; 3: e564-75

Nontyphoidal *Salmonella* isolated from paired blood and stool samples of children with fever and bacteremia, Democratic Republic of the Congo

- **Bloodstream infection study among febrile infants and children at hospital of Saint-Luc in Kisantu, Kongo-Central province, Democratic Republic of the Congo, November 2013 to April 2017**

- **299 children with nontyphoidal *Salmonella* bacteremia had stool culture**
  - **105 (35.1%) had NTS detected in stool**
  - **74 (70.5%) Typhimurium ST313, 27 (25.7%) Enteritidis ST11**
  - **87 (29.1%) had blood and stool NTS pairs for comparison**
  - **82 (94.3%) pairs identical by MLVA, median SNP difference 1 by WGS**

- **1,598 non-febrile hospitalized controls**
  - **34 (2.1%) had NTS detected**

Phoba M-F, et al. PLoS Neglect Trop Dis 2020; 14: e0008377

Nontyphoidal *Salmonella* as a cause of diarrhea in Africa

- **WHO burden of disease estimates, 2010**
  - **9% of diarrheal illnesses and 11% of diarrheal deaths in the WHO African region attributed to NTS**

- **Global Enterics Multi-center Study (GEMS)**
  - **3-year, prospective, age-stratified, matched case-control study of moderate-to-severe diarrhea in children aged 0–59 months residing in censused populations at four sites in Africa and three in Asia**
  - **Stool culture-based analysis**
  - **Re-analysis by TaqMan Array Card targeting *Salmonella* invasion protein *invA gene***

Platts-Mills JA, et al. Lancet Global Health 2015; 3: e564-75

Incidence of non-typhoidal *Salmonella* invasive disease meta-analysis

- **Overall pooled incidence (95% CI): 44.8 (31.5–60.5) per 100,000 persons per year**
  - **Africa region: 51.0 (36.3–68.0)**
  - **Asia region: 1.0 (0.2–2.5)**

- **Five studies provided age stratified incidence**
  - **Unable to meta-analyze, however younger age groups between zero and five years consistently had higher iNTS incidence than older populations**

- **Variation in incidence in both place and time**

Marchello CS, et al. J Infect 2021; 83: 523-532

Complications of non-typhoidal *Salmonella* invasive disease meta-analysis

- **1,824 complication events were identified among 6,974 study participants**
- **Prevalence of some author-defined complications:**
  - **Septicemia: 171 (57.2%) of 299**
  - **Anemia*:* 580 (47.3%) of 1,225**
  - **Extraintestinal focal infections: 66 (9.2%) of 721**
  - **Pleuropulmonary infection: 17 (8.3%) of 240**
  - **Mycotic aneurysm: 124 (6.2%) of 1,991**
  - **Encephalitis: 3 (4.8%) of 62**
  - **Endocarditis: 6 (1.6%) of 366**

Marchello CS, et al. Lancet Infect Dis 2022; 22: 692-705

Deaths from non-typhoidal *Salmonella* invasive disease meta-analysis

- **Median (interquartile range) case fatality ratio (CFR) across all 97 estimates: 13.3% (5.5-22.7%)**

- **Overall pooled CFR (95% CI) estimate: 14.7% (12.2-17.3%)**

Marchello CS, et al. Lancet Infect Dis 2022; 22: 692-705

Extrapolation, modelling, and burden of disease

- **WHO Foodborne Diseases Epidemiology Reference Group (WHO FERG), 2010**
  - **Hierarchical random effects model without explanatory variables**
  - **Being updated by FERG 2, 2025**

- **Institute for Health Metrics and Evaluation (IHME), Global Burden of Disease 20**
  - **Non-linear mixed-effects model that uses a Bayesian cascading geographic hierarchy in which all data are pooled to estimate a global fit**
  - **DisMod**

https://www.who.int/groups/foodborne-disease-burden-epidemiology-reference-group-(ferg)
https://www.healthdata.org

Potential coverage of NTS invasive disease vaccine targets based on global systematic review of NTS serogroup and serovar crude prevalence

Vaccine target serovar (serogroup)	Serogroup: assuming cross-protection for serovars in the same serogroup	Serovar: without assuming cross-protection
Salmonella Typhimurium (O:4)	63%	60%
Salmonella Enteritidis (O:9)	31%	27%
Salmonella Typhimurium and *Salmonella* Enteritidis	94%	87%

Hagedoorn NN, et al. Epidemiol Infect 2023; 152: e4