Context: Background, objectives and key outcomes of WHO consultations (2021) on NTS and broadly protective Salmonella vaccines

Adwoa Bentsi-Enchill

WHO HQ (IVB/PDR)

PDVAC meeting on iNTS vaccines

07 Feb 2022

Background

- **Public health need for vaccines against NTS serovars not well characterized**
  - NTS recognized as an important cause of bacteremia (iNTS) in sub-Saharan Africa, especially in children and people living with HIV infection
  - diarrheal disease caused by (dNTS) usually considered a mild, self-limiting disease but burden not as well characterized (incl geographic and age patterns) vis-à-vis iNTS.

- **IVI and WHO funded to develop Full Value of Vaccines Assessment (FVVA) for iNTS vaccines**
  - To understand the value of investment in an iNTS vaccine from a multi-stakeholder perspective

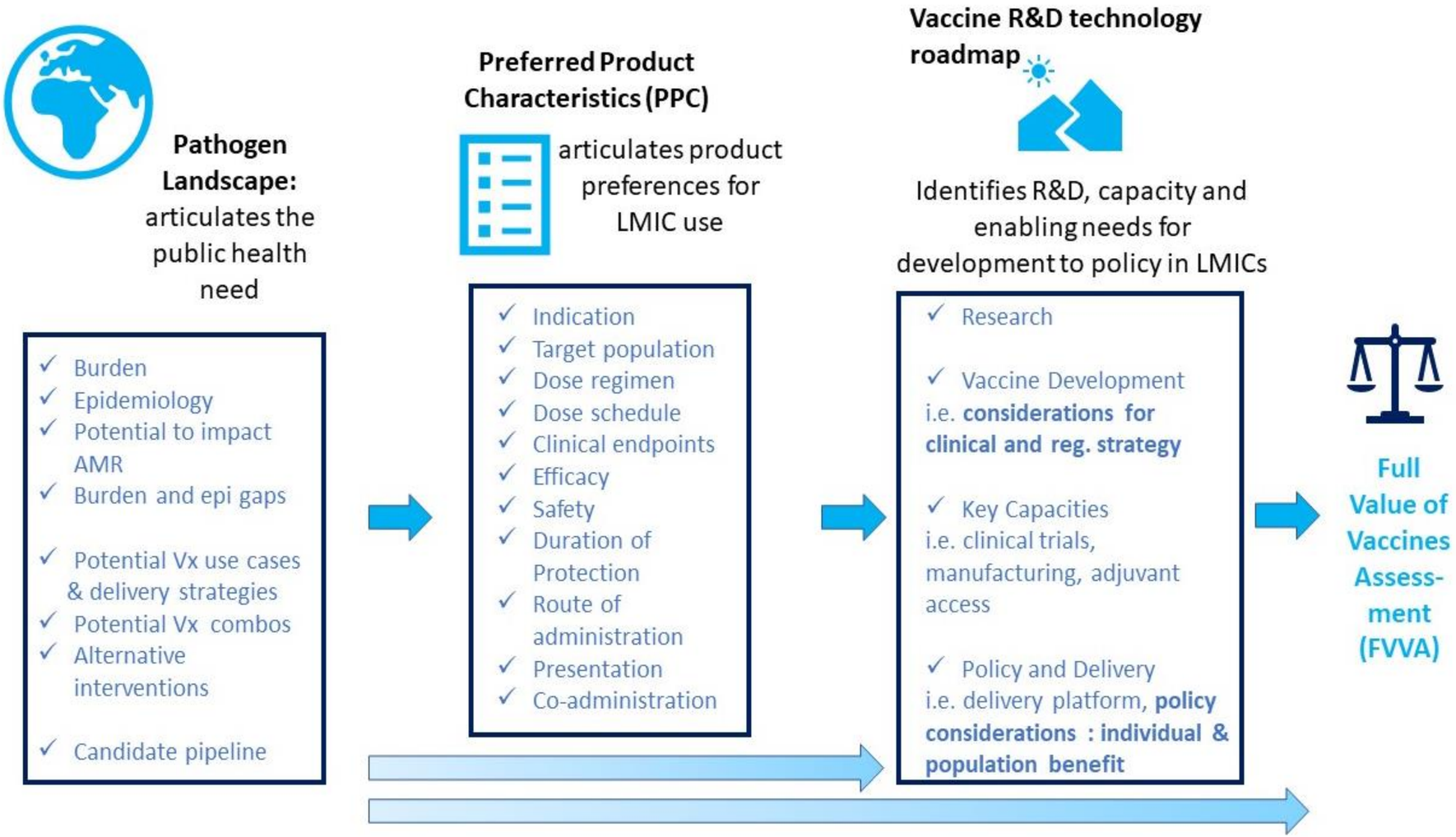
- **Multi-stakeholder interest in defining the targets for broadly protective Salmonella vaccine(s)** against multiple serovars of Salmonella (NTS, paratyphoid A, typhoid).
  - optimal public health impact and demand/preferences from end-users and decision makers in endemic countries?

Overview of iNTS FVVA

- Funded by the Wellcome Trust (3 year grant to April 2024)
- PI: Dr Jerome Kim (IVI) and Project Lead: Dr Jean Louis Excler (IVI)

- Aims 1- 3 (under WHO lead)
  - Aim 1 - **Landscape analysis** of iNTS including epidemiology, current point of care (POC) rapid diagnostic tests, and knowledge gaps to accelerate development, licensure and use where it is most needed.
  - Aim 2 – **LMIC Stakeholder consultation** for vaccine use and demand
  - Aim 3 – R**&D Roadmap and Preferred Product Characteristics**
- Aims 1- 3 (under 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 (IVI)
    - Broader societal benefit analysis (LSHTM)

WHO guidance to facilitate vaccine research and product development (supported by PDVAC*)



* Product Development for Vaccines Advisory Committee

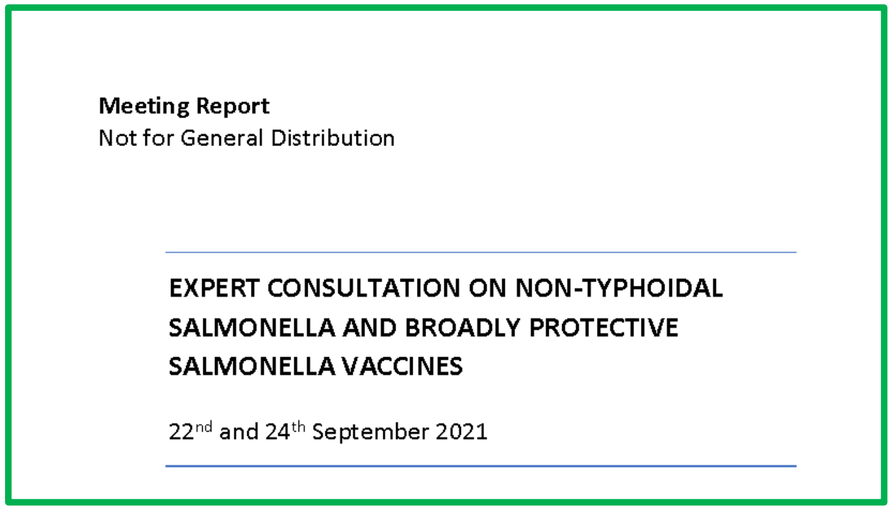
Overview of consultations to date

Scoping meeting

1. Expert consultation on scope of non-typhoidal Salmonella (NTS) and broadly protective Salmonella vaccines

Specific iNTS FVVA workstreams

2. Expert consultation on invasive non-typhoidal Salmonella (iNTS) landscape analysis
3. LMIC stakeholder consultation on iNTS vaccine use case and demand



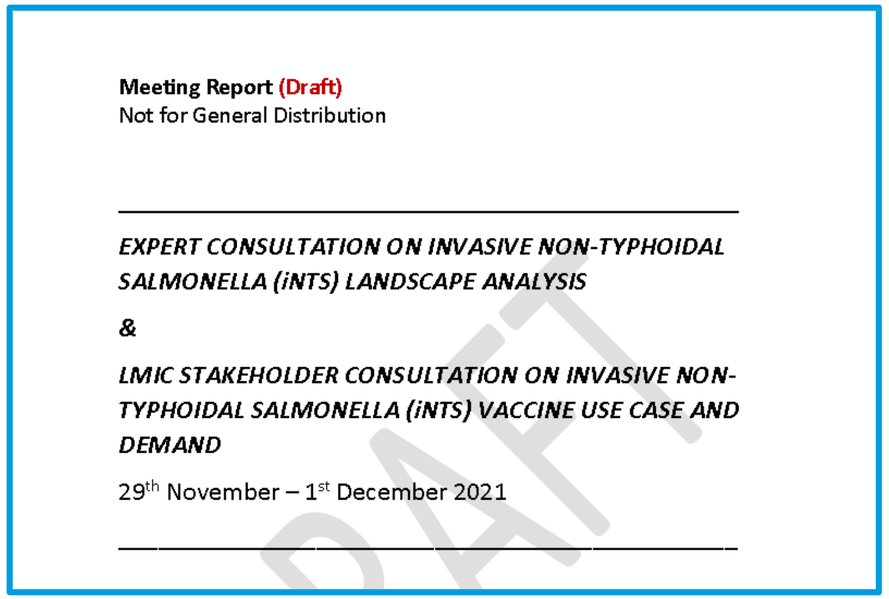
Meeting Report
Not for General Distribution

EXPERT CONSULTATION ON NON-TYPHOIDAL SALMONELLA AND BROADLY PROTECTIVE SALMONELLA VACCINES

22nd and 24th September 2021

Stakeholders represented (broadly):

- Salmonella experts (academicians/researchers, lab, AMR, modellers etc.)
- Other implementing partners (IVI/FVVA, Vacc-iNTS)
- Developers and manufacturers
- National decision makers (esp. in 3rd consultation)
- Funders
- PDVAC members



Meeting Report (Draft)
Not for General Distribution

EXPERT CONSULTATION ON INVASIVE NON-TYPHOIDAL SALMONELLA (iNTS) LANDSCAPE ANALYSIS

&

LMIC STAKEHOLDER CONSULTATION ON INVASIVE NON-TYPHOIDAL SALMONELLA (iNTS) VACCINE USE CASE AND DEMAND

29th November – 1st December 2021

Expert consultation on scope of non-typhoidal Salmonella (NTS) and broadly protective Salmonella vaccines

(22 and 24 Sept 2021)

Objectives

- Provide an update of the latest epidemiology and disease burden data for iNTS and NTS diarrheal disease (dNTS), as well as the estimates of potential vaccine preventable disease burden.
    - basis for defining the long-term objectives for NTS vaccine development
- Discuss the basis, targets and pathways for development of a broadly protective Salmonella vaccine (incl. combinations of typhoid, Paratyphoid A and NTS vaccine components).
- Consider the landscape of and different approaches to potential combination vaccine candidates, as well as an overview of progress and technical feasibility of candidates in the pipeline.

Key conclusions from Sept 2021 consultation (1)

- **Value proposition for including dNTS in an NTS vaccine should be considered when more data are available.**
  - Better understanding of the differences between etiology studies and IHME estimates
  - Relationship between asymptomatic carriage, diarrheal and invasive disease (determinants for each not well understood).
- **Inclusion of additional NTS serovars for a regional vaccine not warranted at this point**
  - can be complicated; may also lead to reluctance of regulators and users when evaluating the value of specific vaccine formulation(s).
- **Market shaping for combination vaccines will be essential**
  - incl. engagement with manufacturers/developers to share their value proposition of different vaccine combinations).

Key conclusions from Sept 2021 consultation (2)

- **Robust understanding of country and regional perspectives** with respect to priority vaccine combinations will be critical to informing the vaccine development strategy.

- Important to understand potential implications of future **NTS vaccines able to target AMR NTS strains**
  - an NTS vaccine that reduces prevalence of resistant strains + antibiotic use has potential to drive the overall vaccine value.

iNTS FVVA Workstream 1

Expert consultation on invasive non-typhoidal Salmonella (iNTS) landscape analysis

(29-30 Nov 2021)

Objective

- To review the current evidence on iNTS disease, understand the knowledge gaps that need to be addressed to accelerate vaccine development, licensure and use and define a way forward for addressing those gaps.

iNTS FVVA Workstream 2

LMIC stakeholder consultation on iNTS vaccine use case and demand

(01 Dec 2021)

Objective

- To collate LMIC stakeholder perspectives on potential iNTS vaccine use case and future demand.

Key outcomes of Nov/Dec 2021 consultations

- **Agenda for today's meeting** to report on key takeaways and remaining gaps and questions
- Basis for preparing for development of PPC and Roadmap (Next steps)
- Meeting report to be finalized
- Peer review publication planned

Current PDVAC meeting

Objectives are to:

- Summarize learnings from the recent WHO global stakeholder consultations on NTS and broadly protective Salmonella vaccines;
- Review status of the NTS and combination Salmonella vaccine development pipeline;
- Communicate areas of consensus and uncertainty in the strategy towards development of an NTS-containing vaccine;
- Report on the consultation with LMIC stakeholders on the perceived public health need for an NTS vaccine.

Expected Outcomes:

- To receive input from PDVAC on the potential NTS/Salmonella combination vaccine strategies, and priority areas of focus for the NTS vaccine FVVA;
- To create alignment with a broad set of stakeholders on the short-, medium- and long-term goals of NTS vaccine development as IVI/WHO embark on their FVVA development.

Thank you

Learnings and key takeaways related to nontyphoidal *Salmonella* epidemiology

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

Meeting on invasive nontyphoidal *Salmonella* invasive disease vaccines
Product Development for Vaccines Advisory Committee
World Health Organization
7 February 2022

UNIVERSITY of OTAGO
SAPERE AUDE
Te Whare Wānanga o Otāgo

Overview

- ***Salmonella enterica* basics**
- **Clinical disease**
- **Reservoir, source, and mode of transmission**
- **Prevalence studies**
- **Burden of disease**
- **Nontyphoidal *Salmonella* invasive disease in person, place, and time**
- **Serovars and serogroups associated with invasive disease**
- **Antimicrobial resistance**
- **Nontyphoidal *Salmonella* diarrheal disease and fecal shedding**
- **Epidemiology data gaps**

Salmonella enterica basics

- **Typhoidal *Salmonella***
  - ***Salmonella enterica* serovars Typhi, Paratyphi**
  - **Human host restricted**
  - **Febrile illness, bloodstream infection: typhoid and paratyphoid (enteric) fever**

- **Non-typhoidal *Salmonella***
  - **>2,500 serovars e.g., Typhimurium, Enteritidis**
  - **Non-human animals: generalist, host adapted, host restricted**

Non-typhoidal *Salmonella* infection in humans

- **Industrialized countries**
  - **Foodborne transmission**
  - **Common cause of self-limited diarrhea**
  - **Occasionally invasive disease: infants, elderly, immunocompromised**

- **Sub-Saharan Africa**
  - **Reservoirs, sources, and modes of transmission poorly understood**
  - **Uncommon cause of moderate to severe diarrhea**
  - **Leading community-onset bloodstream infection**

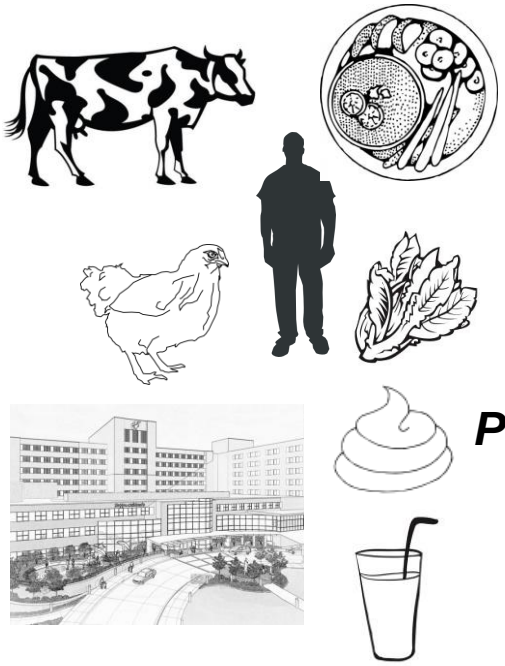
Clinical features

- **Febrile illness with sepsis**
  - **Difficult to distinguish from other causes of fever**
  - **Clinical overlap with malaria and pneumonia**
  - **Usually not associated with diarrhea**
  - **Frequently associated with serious complications, including meningitis in endemic areas**

- **Case fatality ratio**
  - **15%**

Marchello CS, et al. Lancet Infect Dis 2022; online ahead of print

Pathway to invasive NTS in sub-Saharan Africa



Environmental risk factors

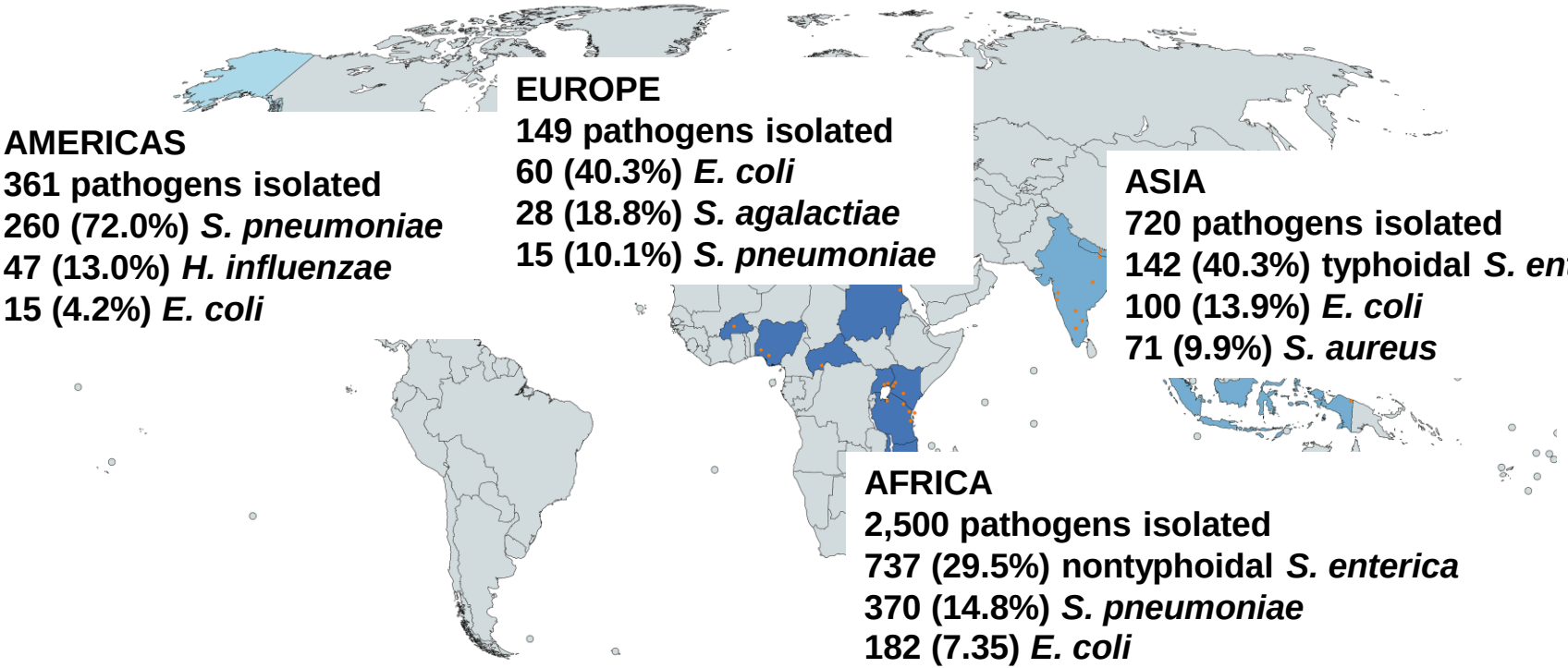
Poorly understood

Host risk factors

Well understood

Exposures **NTS infection/colonization** **Invasive NTS 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*

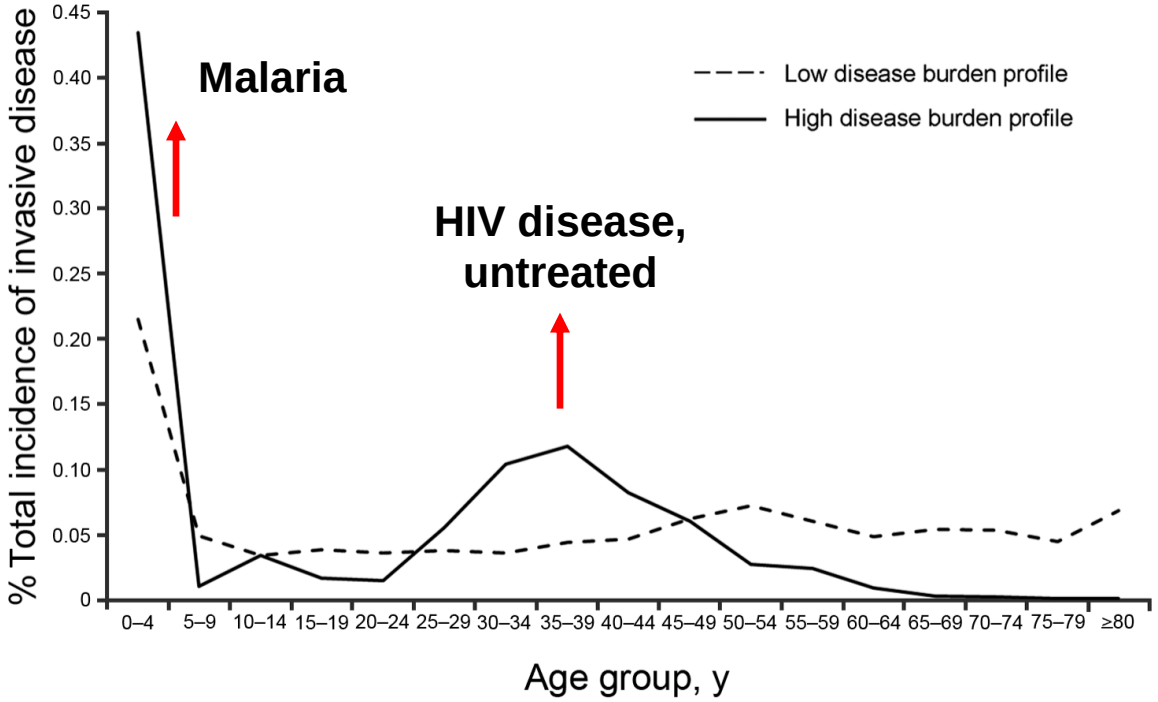
Marchello CS, et al. Antimicrob Agents Chemother 2019; 64: e01974-19

Published estimates of nontyphoidal *Salmonella* invasive disease

	Year			
Metrics	**2010**	**2010**	**2017**	**2019**
Origin	**US CDC, others**	**WHO FERG**	**IHME**	**IHME**
Coverage	**Global**	**Global HIV deaths excluded**	**Global HIV deaths excluded**	**Global HIV deaths excluded**
Illnesses, millions (95% UI)	**3.41 (2.08-6.51)**	**0.63 (0.39-0.94)**	**0.53 (0.41-0.71)**	**0.59 (0.49-0.72)**
DALYs, millions (95% UI)	**-**	**3.90 (2.40-5.79)**	**4.26 (2.38-7.38)**	**6.11 (3.32-9.71)**
Deaths (95% UI)	**681,000**	**63,000 (39,000-94,000)**	**59,100 (33,300-98,100)**	**79,046 (43,013-124,207)**

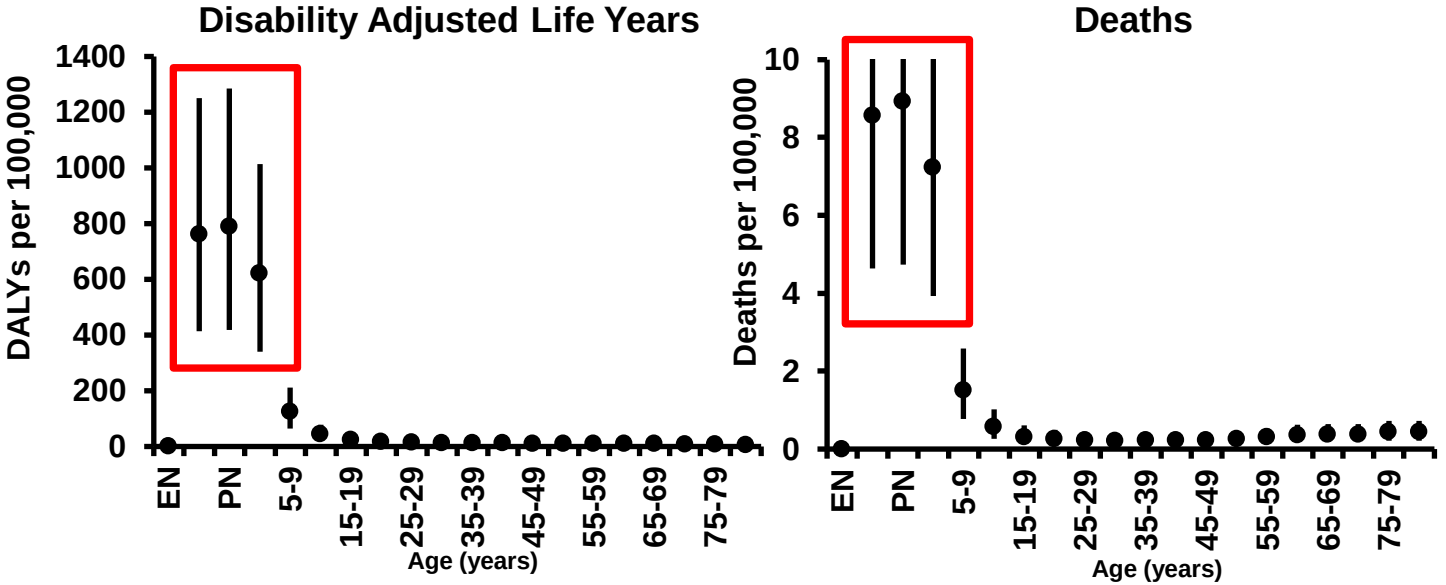
Ao TT, et al. Emerg Infect Dis 2015: 21: 941-9
Kirk MD, et al. PLoS Med 2015; 12: e1001921
GBD 2017 Non-Typhoidal Salmonella Invasive Disease Collaborators. Lancet Infect Dis 2019; 19: 1312-24
Global Health Data Exchange: http://ghdx.healthdata.org

Proportion of nontyphoidal *Salmonella* invasive disease, by age group, from low-incidence settings in the United States and high-incidence settings in Malawi and South Africa



Ao TT, et al. Emerg Infect Dis 2015; 21: 941-9

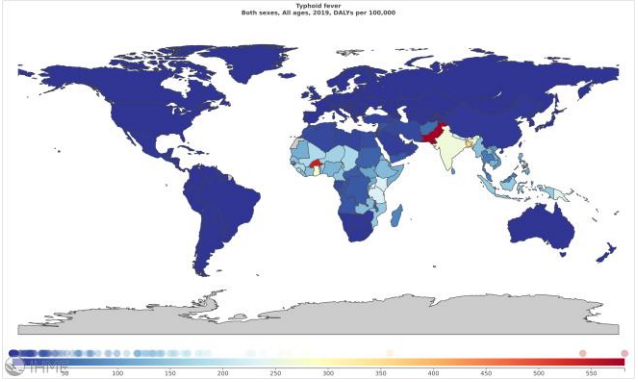
Nontyphoidal *Salmonella* invasive disease DALYs and deaths by age, worldwide, Global Burden of Disease 2019



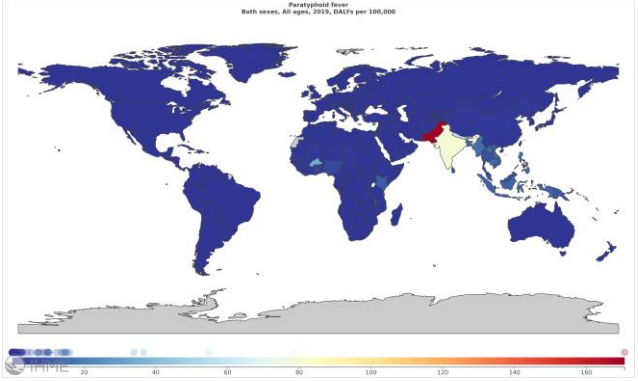
http://vizhub.healthdata.org/gbd-compare/

Disability adjusted life years per 100,000 persons for typhoid, paratyphoid, and nontyphoidal *Salmonella* invasive disease, 2019

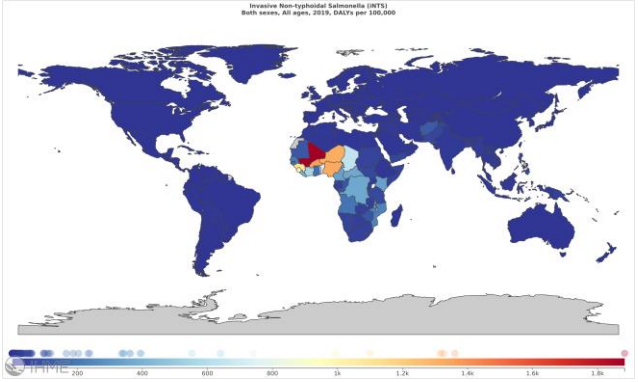
Typhoid fever



Paratyphoid fever



Nontyphoidal *Salmonella* invasive disease



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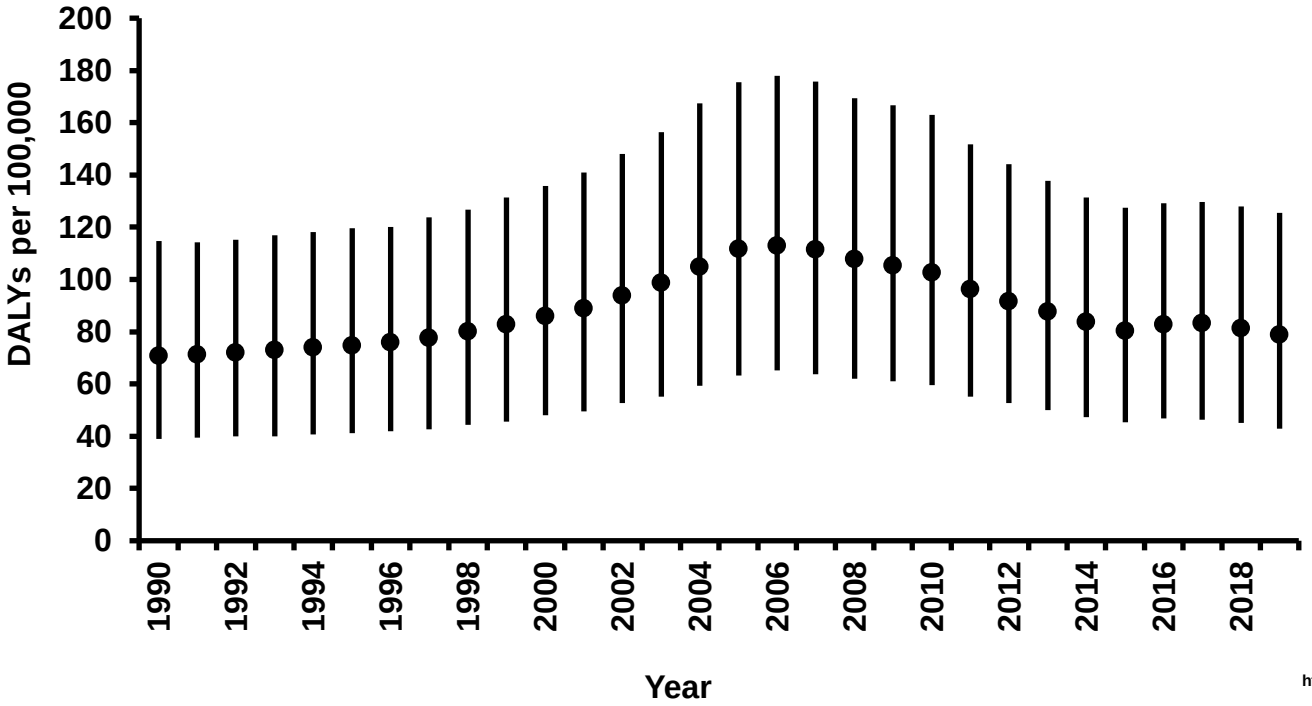
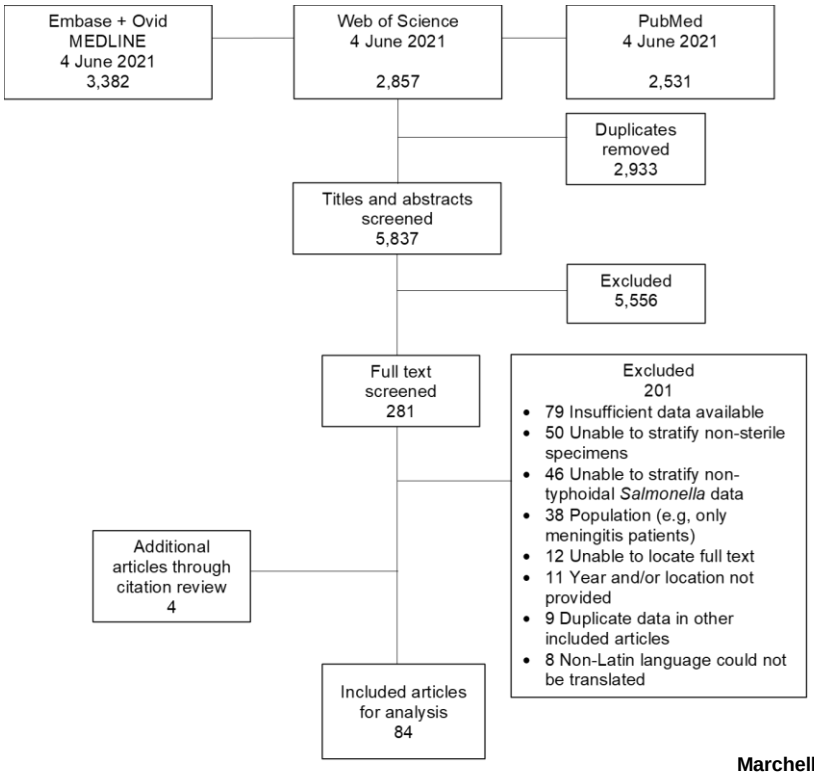
Nontyphoidal *Salmonella* invasive disease disability adjusted life years per 100,000 persons, IHME GBD 2019



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

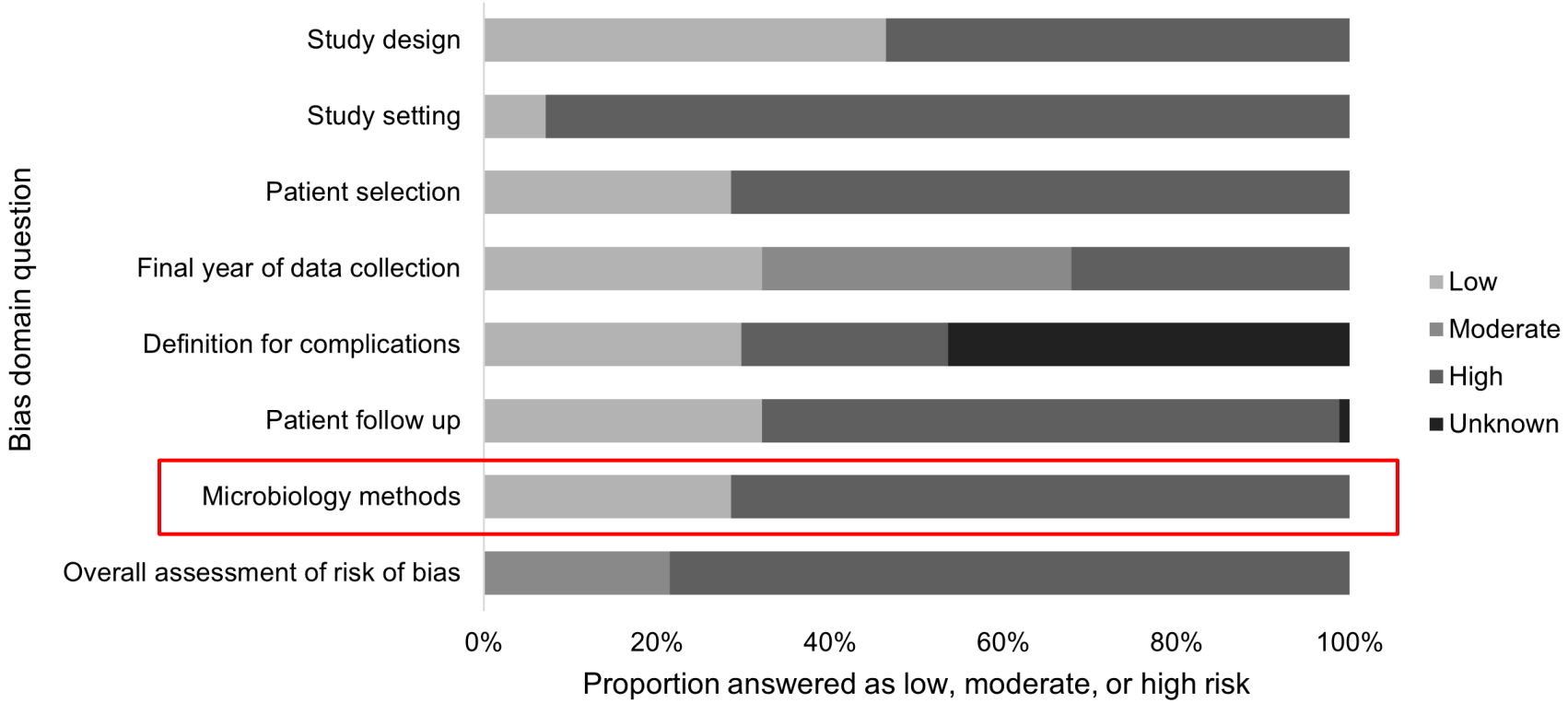
PRISMA flow diagram of search strategy and selection of studies for complications and mortality of non-typhoidal *Salmonella* invasive disease, global, 1971-2019*



Marchello CS, et al. Lancet Infect Dis 2022; online ahead of print

*Multiple exclusion reasons could be assigned to each study, resulting in the sum of individual exceeding the total

Quality assessment for risk of bias of included studies on complications and mortality of non-typhoidal *Salmonella* invasive disease, 1971-2019



Prevalence of leading non-typhoidal *Salmonella* serovars isolated from the bloodstream, global, 1971-2019 (n=12,977)

Serovar	n	Proportion of iNTS disease, %
Typhimurium	5,934	45.7
Enteritidis	4,112	31.7
Dublin	403	3.1
Virchow	186	1.4
Isangi	172	1.3
Choleraesuis	134	1.0
Heidelberg	90	0.7
Java	54	0.4
Oranienburg	47	0.4
Infantis	46	0.4
Newport	42	0.3
Stanley	38	0.3
Panama	36	0.3
Poona		0.3
Corvallis		0.2
Saintpaul	25	0.2
Schwarzengrund	22	0.2
Montevideo	21	0.2
Chester	19	0.1
Bovis-morbificans	17	0.1
Colindale	15	0.1
Krefeld	15	0.1
Brandenburg	15	0.1
Hadar	14	0.1
Agona	10	0.1
Copenhagen	5	<0.1
Berta	4	<0.1

1,372 (10.6%) not serotyped

Marchello CS, et al. Lancet Infect Dis 2022; online ahead of print

Prevalence of leading non-typhoidal *Salmonella* serogroups isolated from the bloodstream, global, 1971-2019

Serogroup	n	Proportion of iNTS disease, %
O4	6,207	47.8
O9	4,555	35.1
O7	621	4.7
O8	100	0.8
O13	36	0.3
O1,3,9	15	0.1

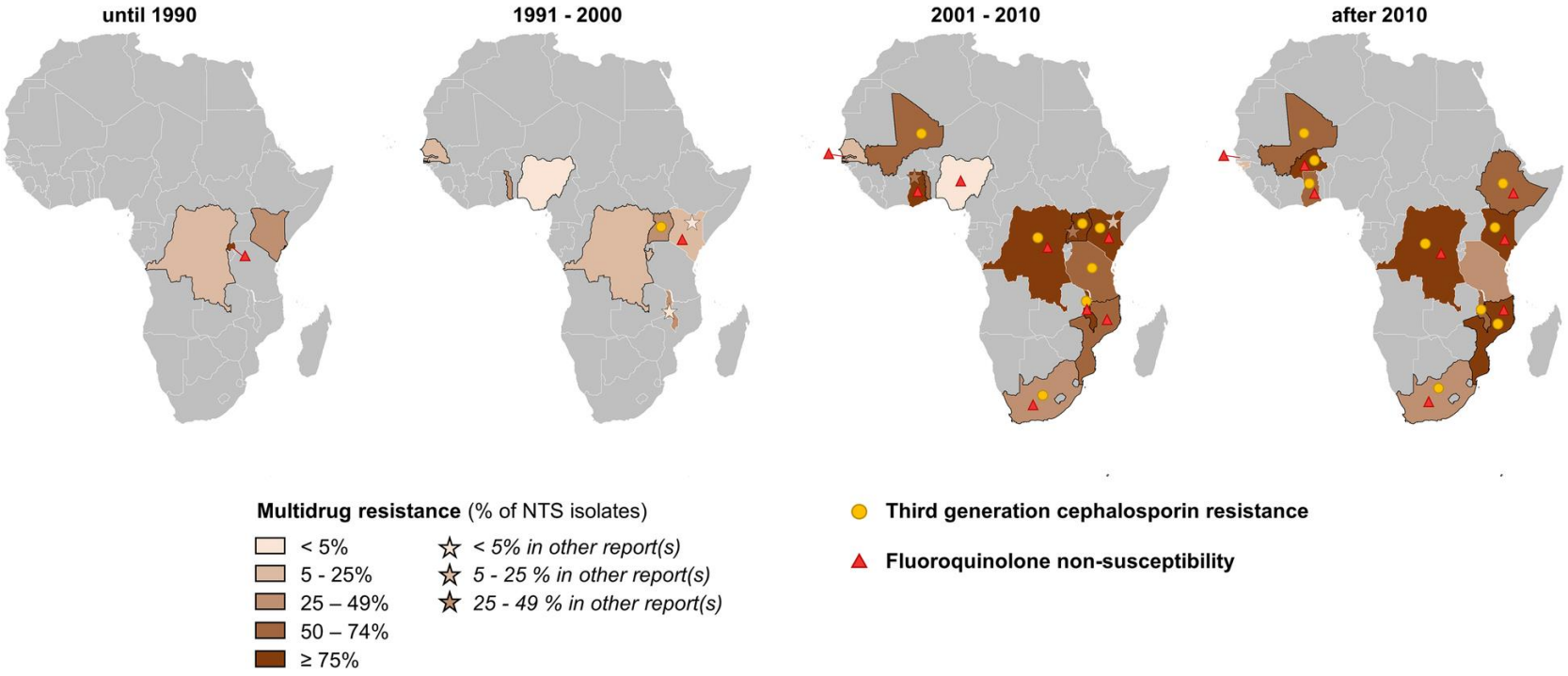
Marchello CS, et al. Lancet Infect Dis 2022; online ahead of print

Top five non-typhoidal *Salmonella* serovars with serogroup isolated from the bloodstream by UN region, 1971-2019

UN region, n isolates	Serovar	(serogroup)	N serovar	Proportion serovar by region, (%) *
Africa, n=8,917	Typhimurium	(O4)	5,111	(57.3)
	Enteritidis	(O9)	2,613	(29.3)
	Dublin	(O9)	250	(2.8)
	Isangi	(O7)	172	(1.9)
	Choleraesuis	(O7)	7	(<0.1)
Americas, n=166	Heidelberg	(O4)	55	(33.1)
	Enteritidis	(O9)	39	(23.5)
	Typhimurium	(O4)	12	(7.2)
	Oranienburg	(O7)	7	(4.2)
	Choleraesuis	(O7)	4	(2.4)
Asia, n=851	Enteritidis	(O9)	271	(31.8)
	Typhimurium	(O4)	259	(30.4)
	Choleraesuis	(O7)	123	(14.5)
	Virchow	(O7)	16	(1.9)
	Krefeld	(O1,3,9)	15	(1.8)
Europe, n=3,043	Enteritidis	(O9)	1,189	(39.1)
	Typhimurium	(O4)	552	(18.1)
	Virchow	(O7)	167	(5.5)
	Dublin	(O9)	153	(5.0)
	Java	(O4)	45	(1.5)

*Denominator includes untyped isolates

Emergence of multidrug resistance, third-generation cephalosporin resistance, and fluoroquinolone non-susceptibility among nontyphoidal *Salmonella* bloodstream isolates by decade, sub-Saharan Africa



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

Nontyphoidal *Salmonella* as a cause of diarrhea in Africa

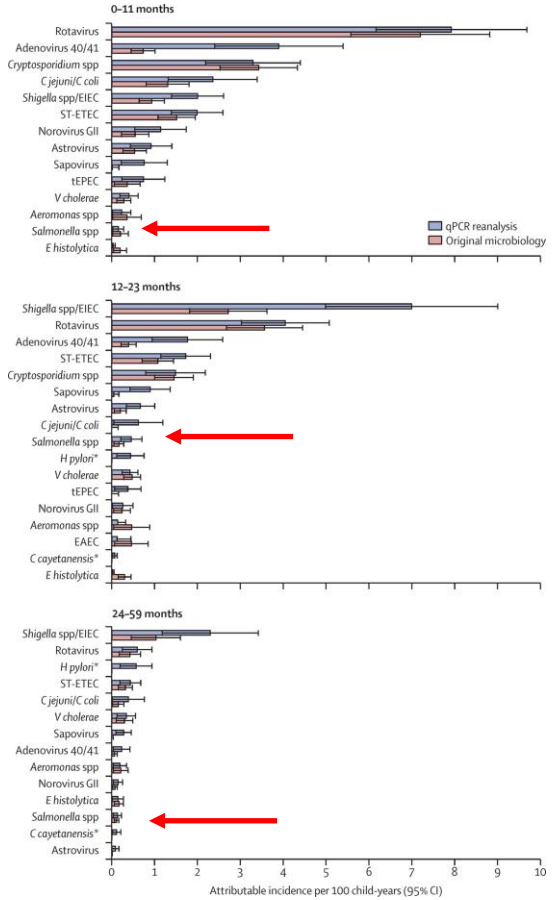
- **WHO burden of disease estimates, 2010**
  - **9% of diarrheal illnesses and 11% of diarrheal deaths in the WHO African region attributed to NTS**

- **Rigorous moderate-to-severe diarrhea etiology studies suggest that NTS is an uncommon cause in sub-Saharan African countries**

- **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***

Kirk MD, et al. PLoS Med 2015; 12: e1001921
Platts-Mills JA, et al. Lancet Global Health 2015; 3: e564-75

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



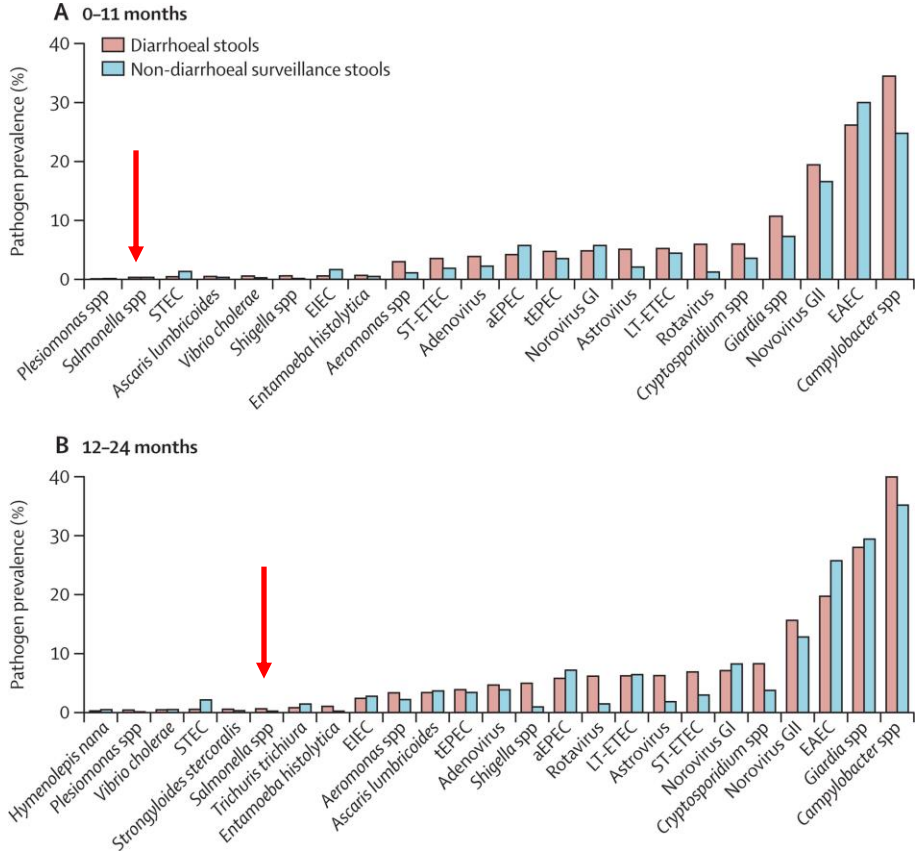
Platts-Mills JA, et al. Lancet Global Health 2015; 3: e564-75

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

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

Consensus on data regarding exclusion of nontyphoidal *Salmonella* diarrheal disease

- **Diarrheal disease is common in sub-Saharan African countries but nontyphoidal *Salmonella* is an uncommon cause of moderate-to-severe diarrhea**

- **More data are needed to support a value of vaccine case that includes nontyphoidal *Salmonella* diarrheal disease**

Overview of epidemiology data gaps

- **Disease incidence, complications, deaths**
  - **Narrow age bands in first year of life**

- **High quality serovar data, including on regional variation**

- **Improved understanding of human fecal shedding**
  - **Role of humans as reservoirs, fecally contaminated vehicles as sources**
  - **Role of shedding in immunity and disease**
  - **Implications for indirect protection by vaccines**

- **Attribution for host risk factors**

- **Environmental risk factors**

- **Nontyphoidal *Salmonella* diarrhea**
  - **Reconcile burden estimates with etiology studies**

Acknowledgements

Participants, too numerous to list

Observers

WHO Regional Offices

WHO Headquarters, including secretariat

World Health Organization
Vaccine Product & Delivery Research (PDR)
Immunization, Vaccines and Biologicals (IVB)

Summary of learnings from recent WHO-convened consultations on modelling estimates of iNTS vaccines potential impact

Gianluca Breghi – Fondazione Achille Sclavo

FROM: EXPERT CONSULTATION ON INVASIVE NON-TYPHOIDAL SALMONELLA (iNTS) LANDSCAPE ANALYSIS

29th November 2021

iNTS Disease modeling and vaccination impact estimates

Recent literature is making more and more evidences available, but:

- data underlying estimates are still limited
- iNTS disease is still suffering from a long neglection due to:
  - inadequate field diagnostic tests
  - misdiagnosis
  - frequent co-morbidities

Disease modeling may help:

- projecting epidemiological trends bridging by consensus existing data to areas where they are not yet available, replacing them later on with new data
- simulating vaccine strategy impacts in terms of morbidity and mortality

2 models were developed for sSA within the EU-H2020 Vacc-iNTS* project:

- Three-component model: Compartmental SIR-like transmission model, vaccination impact and dose forecast (*Fondazione Achille Sclavo*)
- Probability of Occurrence model (*IVI/Univ. Of Cambridge*)

* *Advancing a GMMA-based vaccine against invasive non-typhoidal salmonellosis through Phase I trial in Europe and sub-Saharan Africa.*

The project has received funding from the EU Horizon 2020 Research and Innovation programme under grant agreement n.815439

Compartmental SIR-like iNTS disease transmission model and vaccination impact for sSA

1. Projects infections/deaths modeling interactions of parameters obtained from peer-reviewed literature

- 20 Parameters included in the current model
- Applied to Population pyramid, by country http://population.un.org/wpp/
- Simulations: all SSA in aggregate, and each country separately
- Vaccination schedule: routine 6w. and 9 m. with EPI; 1 dose for catch-up

Current limitations:

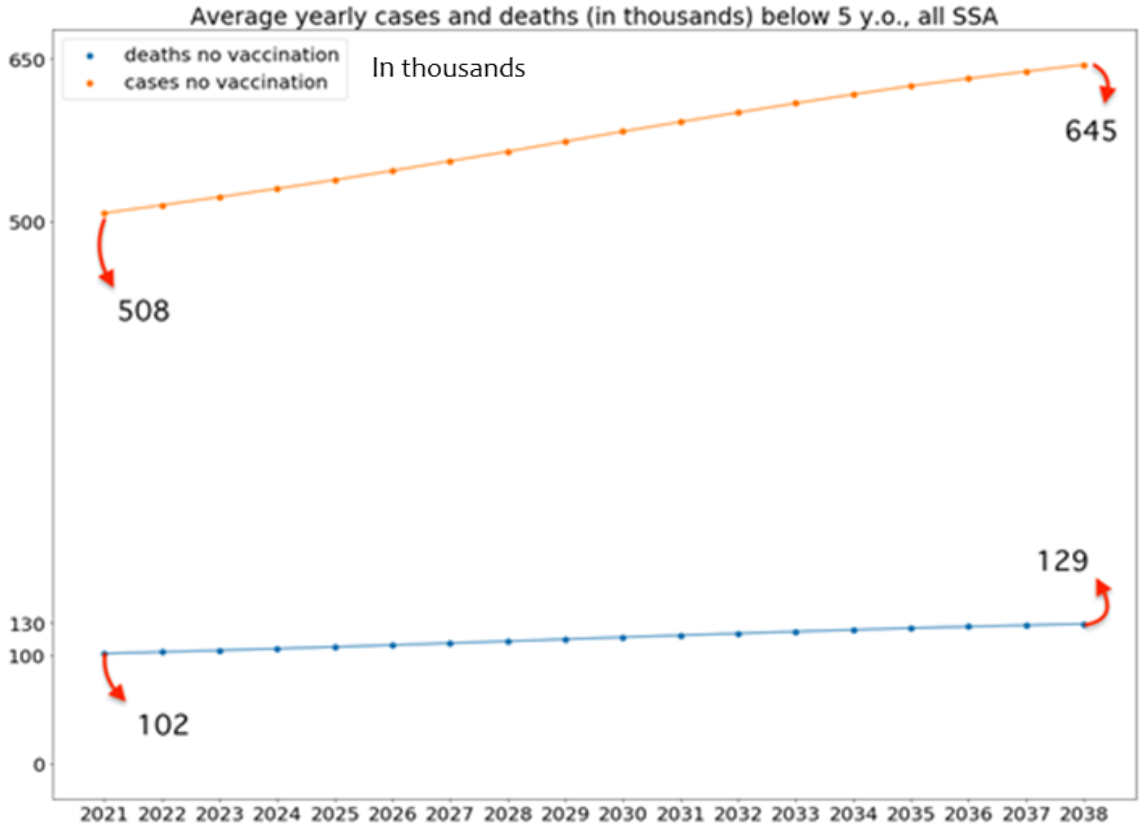
✓ **The model uses:**

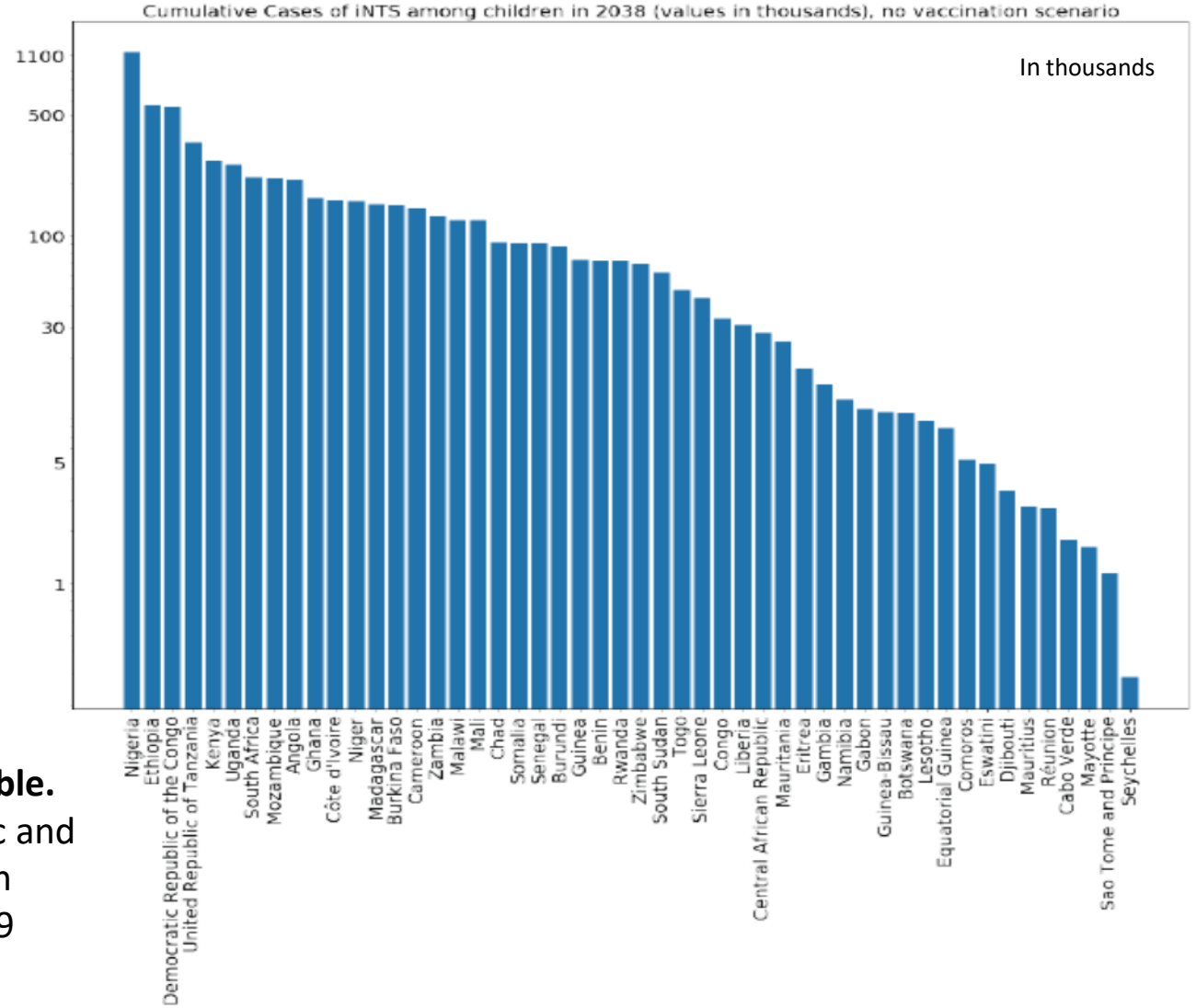
1. a first set of parameters to be updated in the future at the country level from literature or consensus
2. vaccine efficacy assumptions to be updated as soon as clinical study results

✓ **Further granular forecasts may be provided adding parameters like:** incidence and CFR by country, narrower age classes, rural/urban populations, rainy/dry areas, other conditions (malnutrition)

1. Projections: annual and cumulative infections and deaths 2028-2038

Number of infections and deaths are projected at constant infection rate and CFR, in population under 5 for sSA





First-cut estimates to be updated when new data will be available.

Sub-Saharan Africa: as defined in: U.N. Department of Economic and Social Affairs, Population Division (2019). Probabilistic Population Projections Rev. 1 based on the World Population Prospects 2019 Rev. 1 http://population.un.org/wpp/

2. Vaccination impact on infections and deaths in sSA

An immunization campaign including catch-up + routine vaccination is applied to the projected B.o.D.

Limitations and Assumptions:

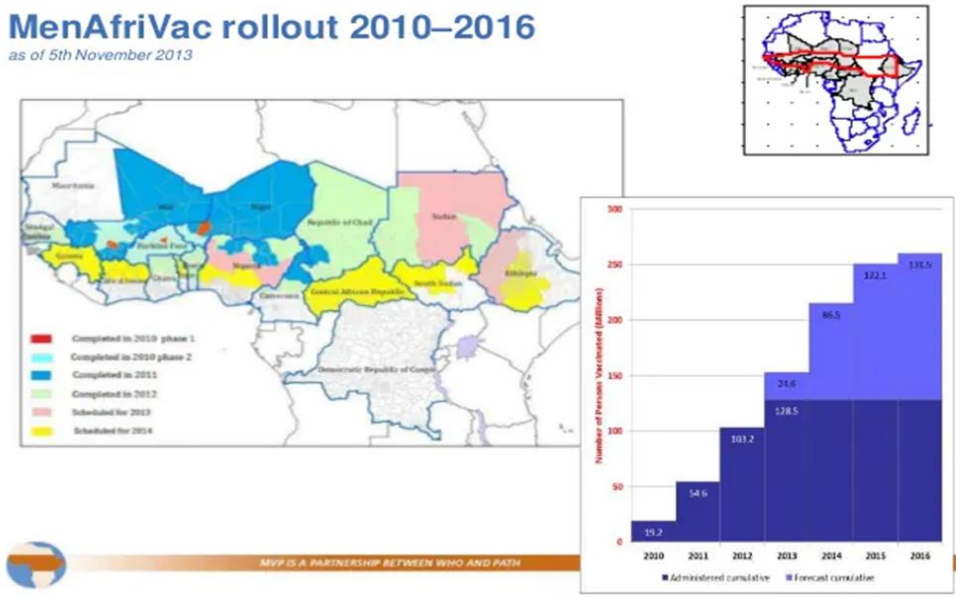
- Vaccine efficacy, dosing, coverage may be modified as needed
- Introduction in 2028 of a bi-valent iNTS vaccine: *S.* enteritidis + *S.* typhimurium
- Results reported for the period: 2028 – 2038

Catch-up vaccination done in 12 months in 2028

- Target populations: children 13 to 60 months
- Coverage: 90% with 1 dose
- Coverage in countries already>90% = 2019 WUENIC DTP1

Routine vaccination: starts 2029/30, data reported up to 2038

- Target populations: surviving newbors
- Coverage: 2019 WUENIC DTP1 constant over the period
- Routine: 2 doses at 6 w. and 9 m. with MCV

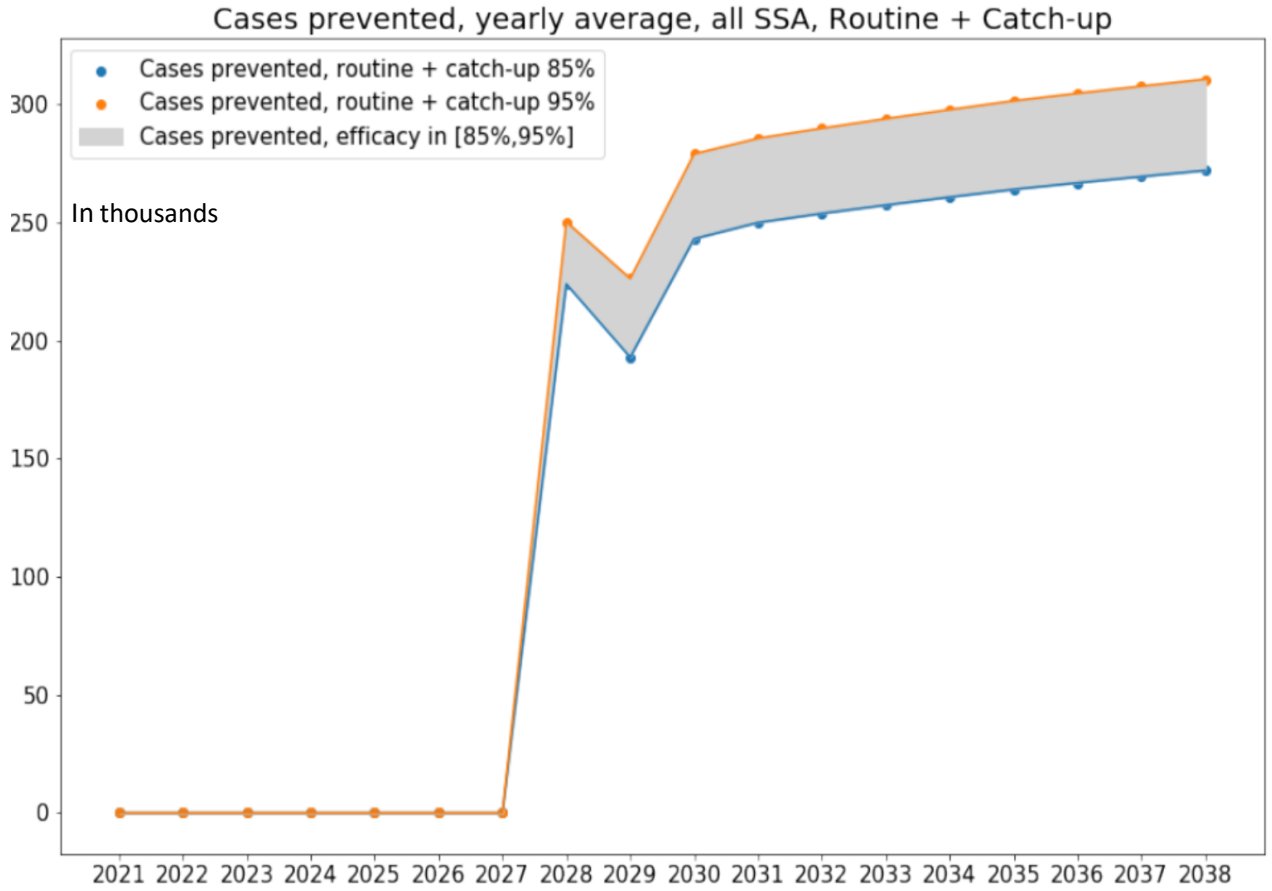


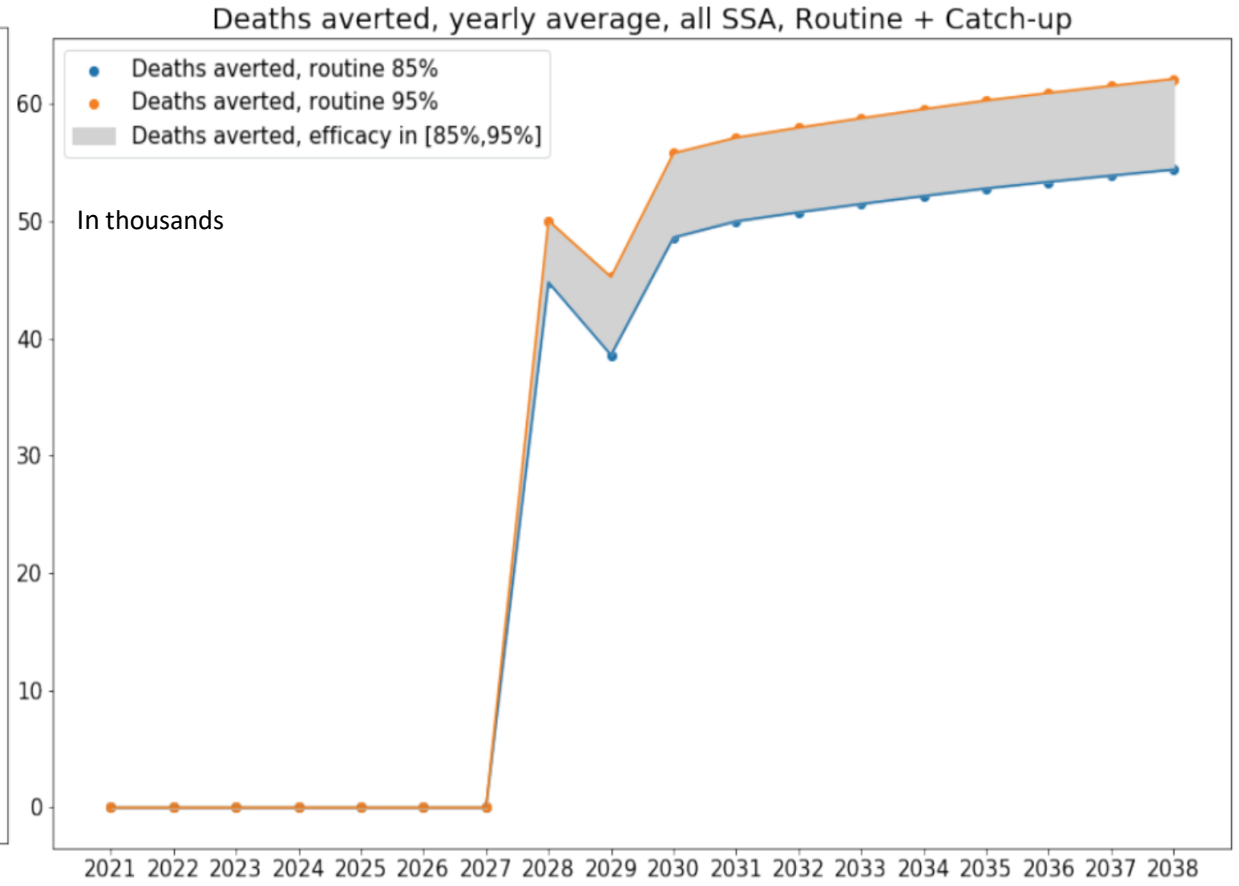
Assumptions: immunization protects from clinical symptoms, not from infection; no herd protection effect; 2 vaccine efficacies

Sources: Population: UN Population Division and WHO, last accessed August 2021; Coverage rates: WUENIC from WHO, last accessed September 2021

2. Cases prevented, deaths averted, yearly averages 2028–2038, 85% and 95% V.E.

Significant early impact in sSA of a catch-up campaign, stabilized by ensuing routine vaccination

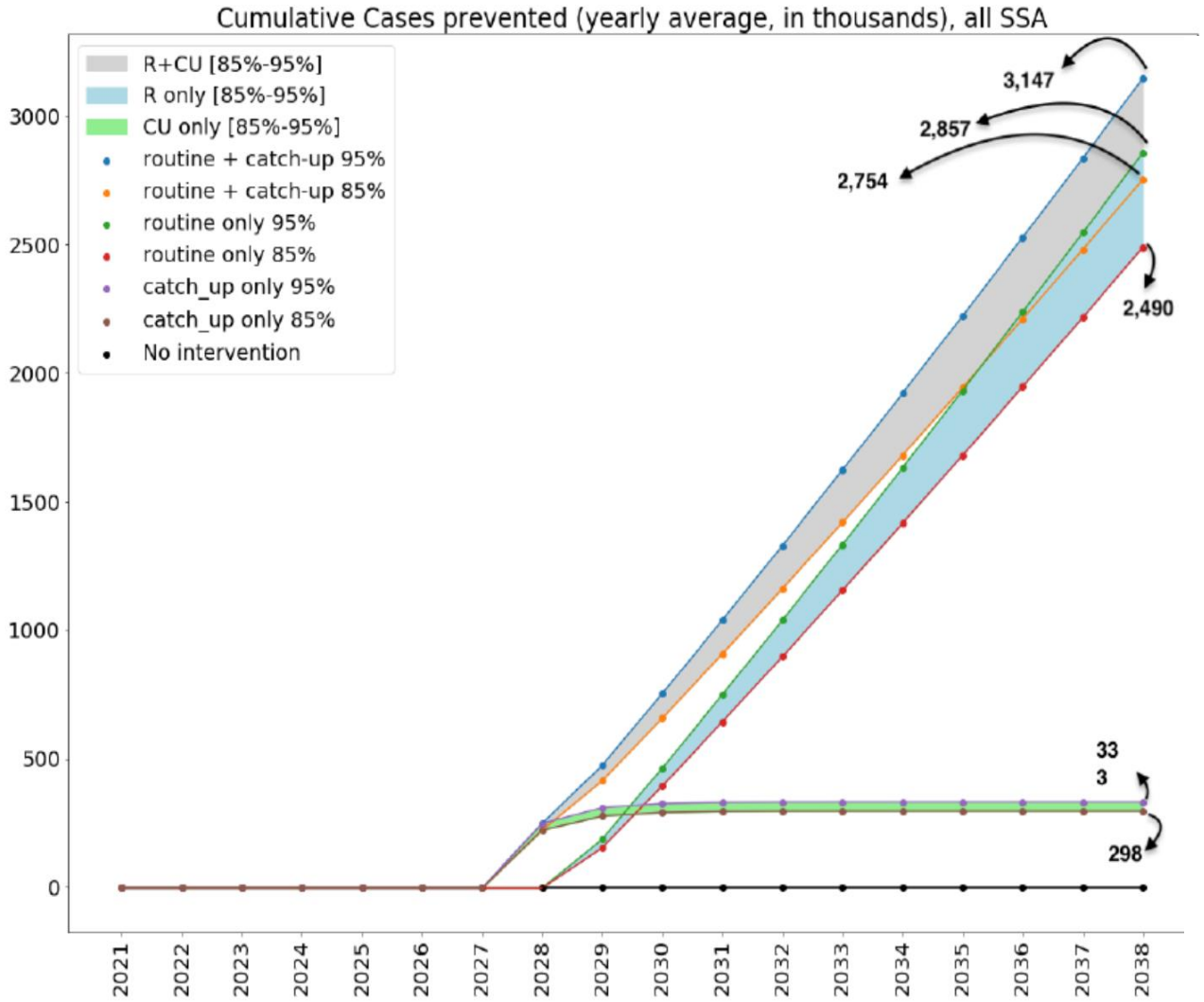


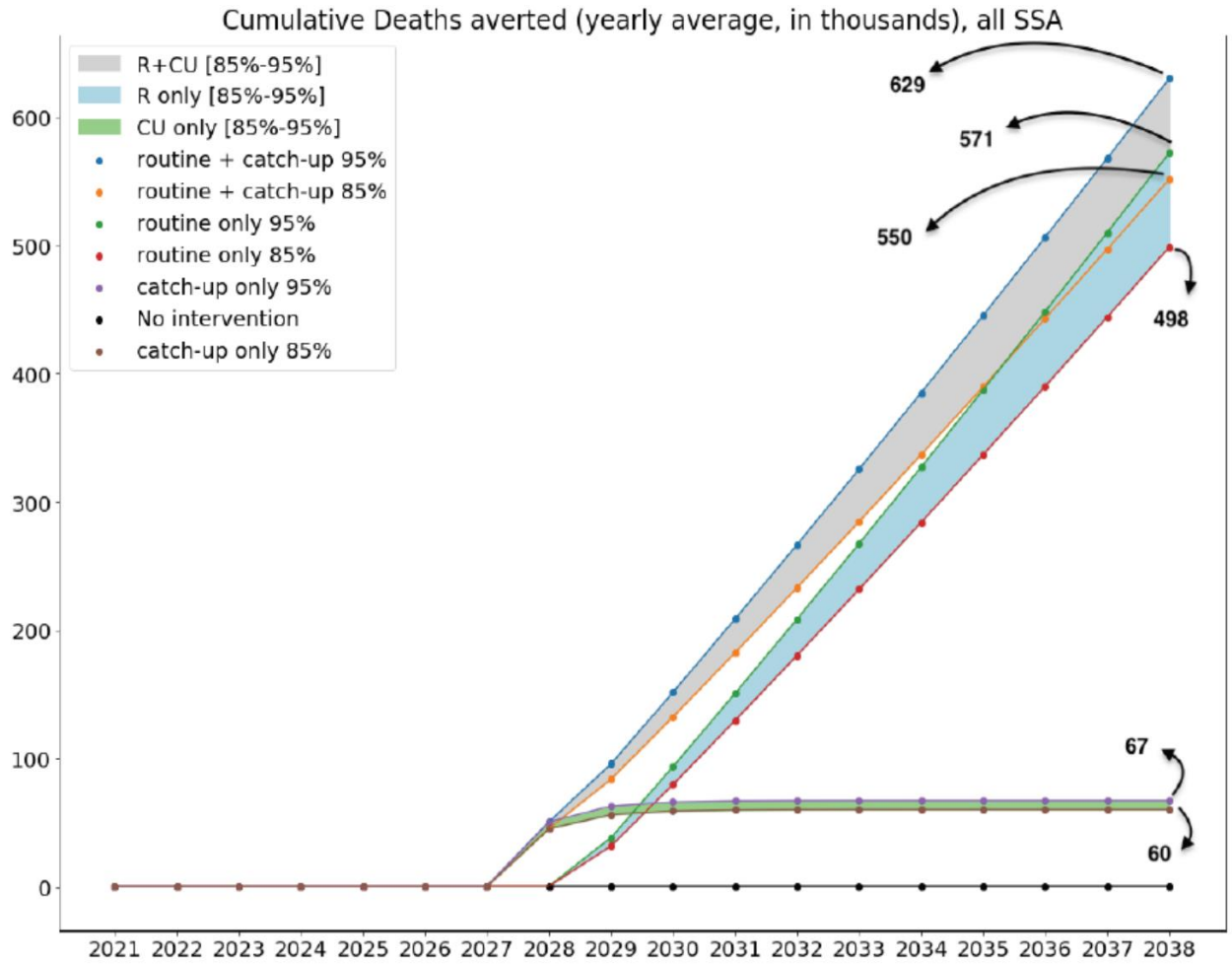


The impact of a catch-up campaign in sSA in age classes 1 to 5 y.o.a. may be quantified in a reduction of ≈ 300,000 infections and ≈50,000 deaths in this age class increasing chances of success of the following routine immunization

2. Total cumulative cases prevented in SSA (left), deaths averted (right) 2028 - 2038

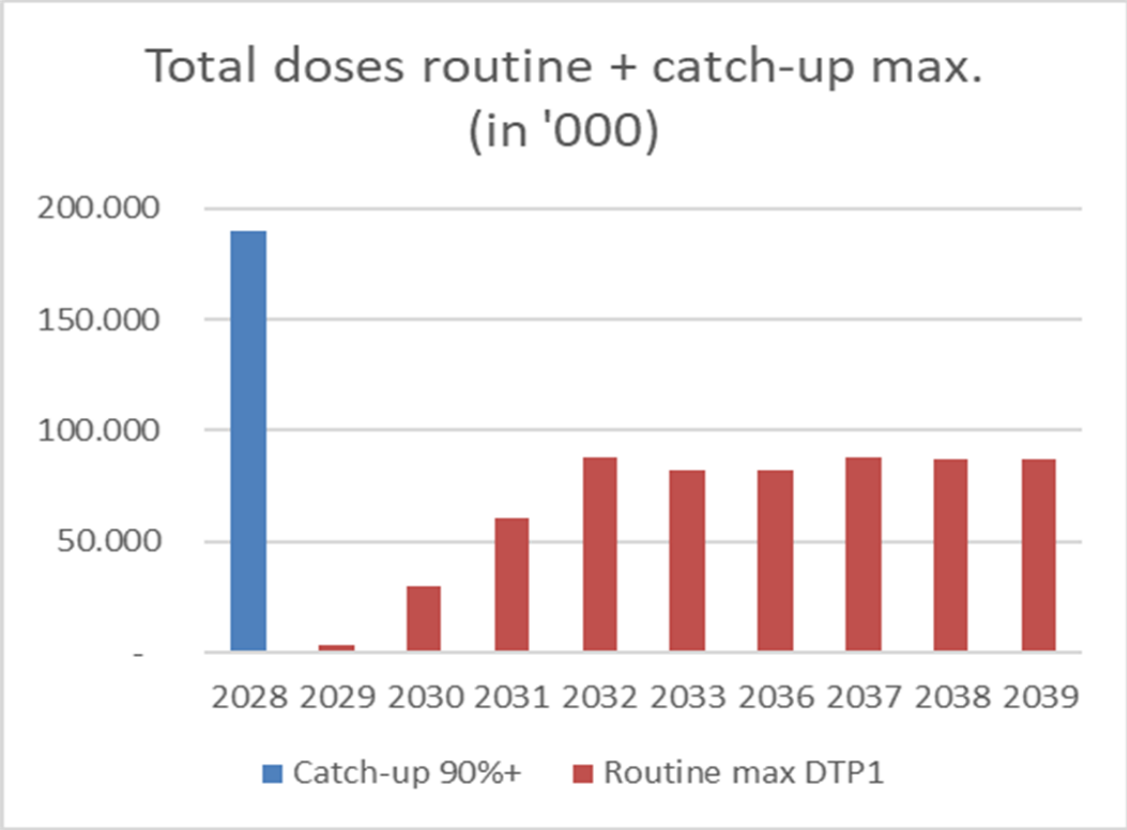
Significant impact on B.o.D. in SSA in the long run: 3 vaccination strategies + 2 vaccine efficacy rates projected

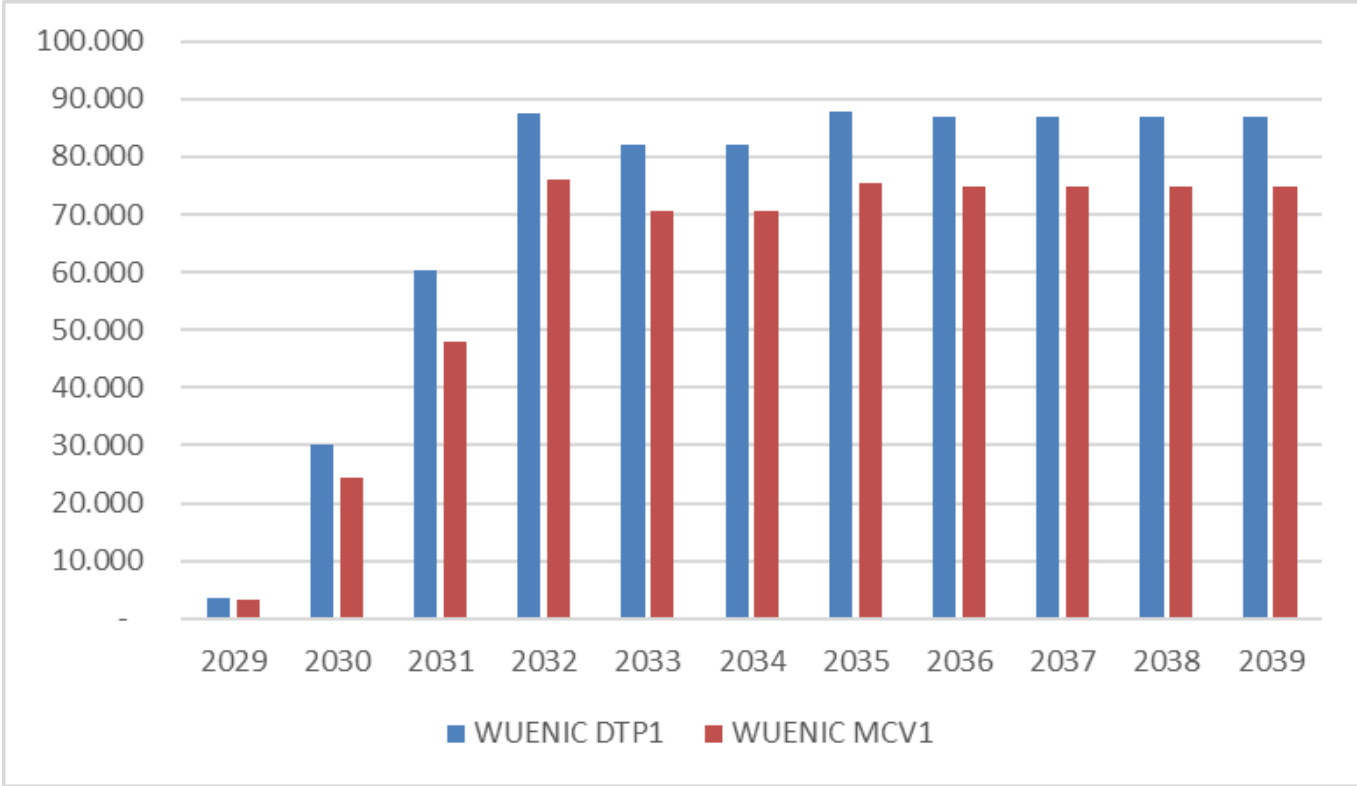




3. Total doses needed catch-up (assumed in 1 year) + routine immunizations DTP1 WUENIC)

Source for Coverage: WHO. Total doses: theoretical doses + WHO accepted wastage 15% + 10% stock



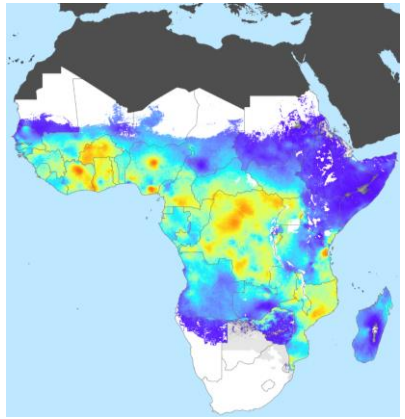


Probability of Occurrence Model IVI – University of Cambridge

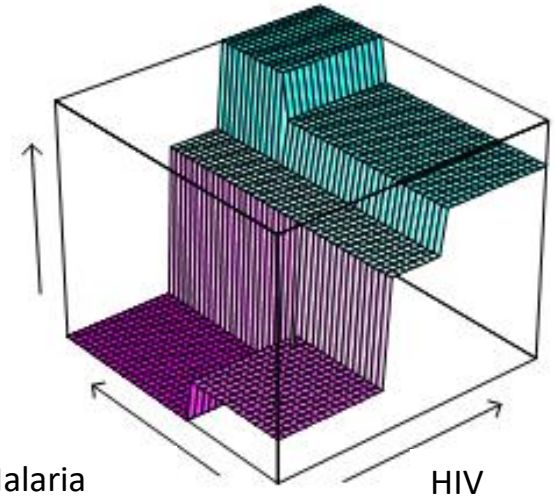
Input → Model → Output

iNTS occurrence

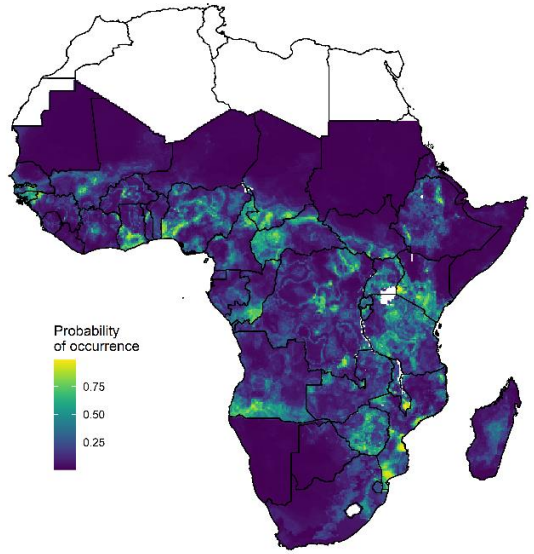
Geospatial covariates



Boosted Regression Tree method



iNTS risk



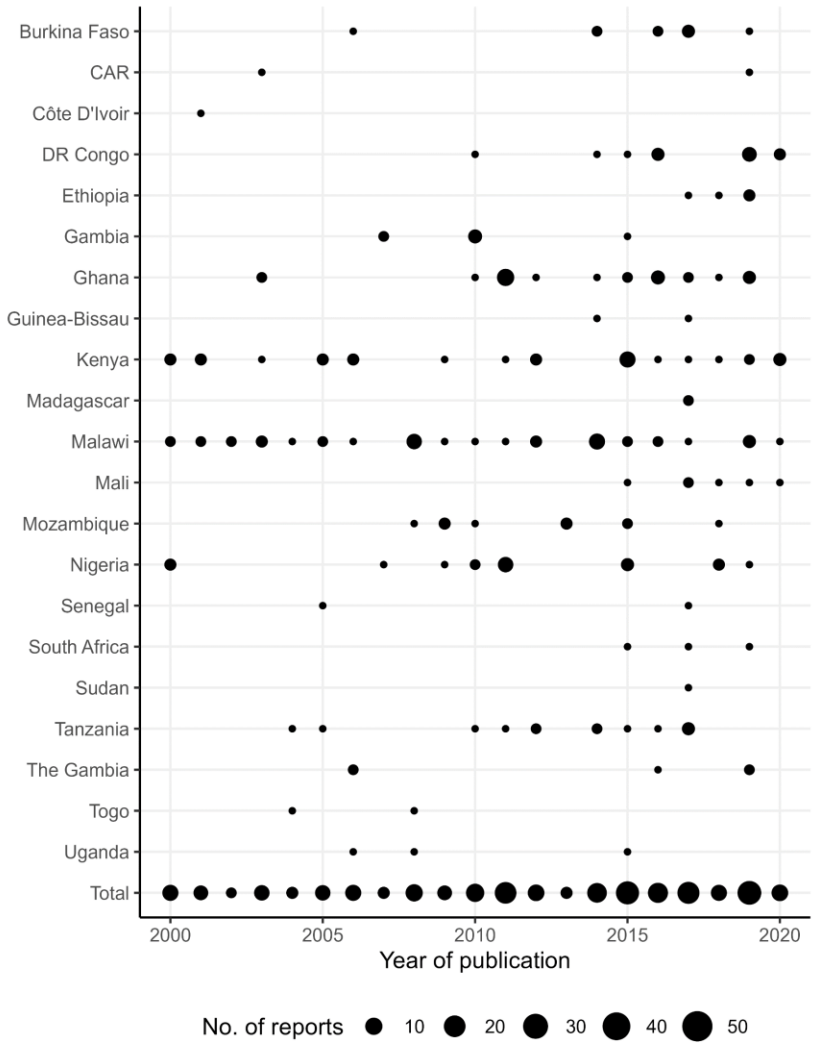
BRT is a machine-learning approach using data on iNTS occurrence, explanatory covariates and background data to predict probability of occurrence as an output. The model characterizes complex relationships by not assuming relationships, letting data suggest it

iNTS occurrence data extracted from Vacc-iNTS Epidemiological Reviews

Occurrence:

- 130 unique references reporting human iNTS infection
- 52,407 cases from 21 countries
- 227 occurrences standardized across year and location

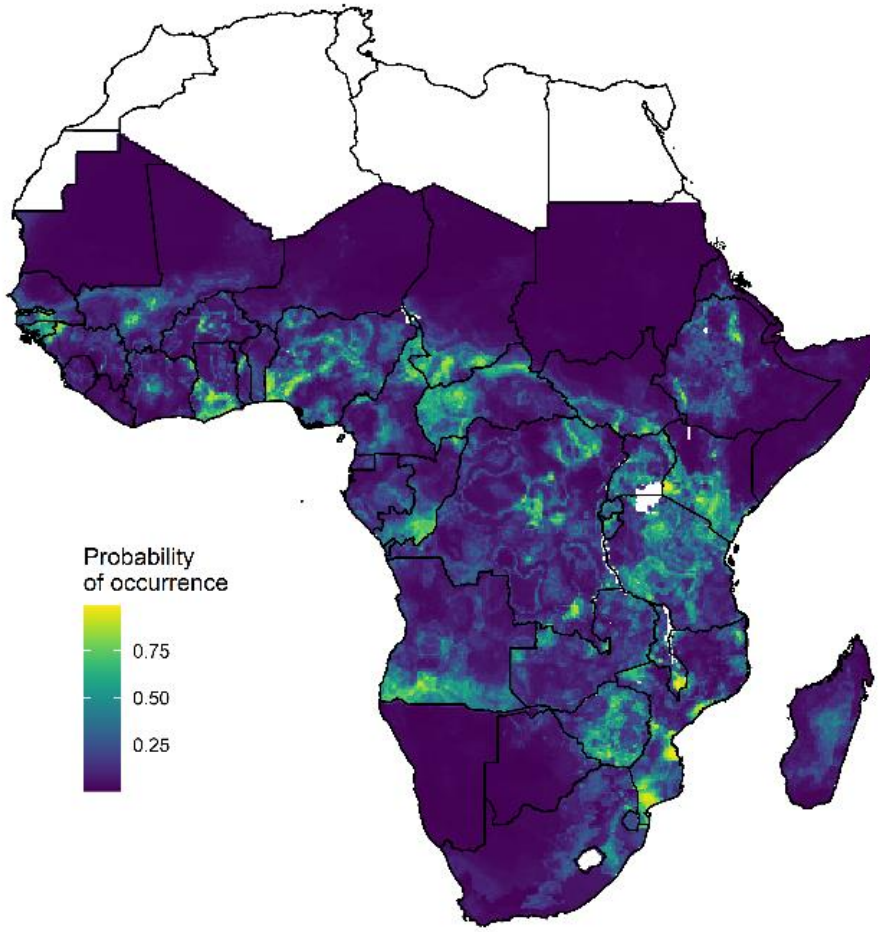
Covariates:
WaSH variables just as predictive as well-known risk factors (HIV, Malaria and wasting)



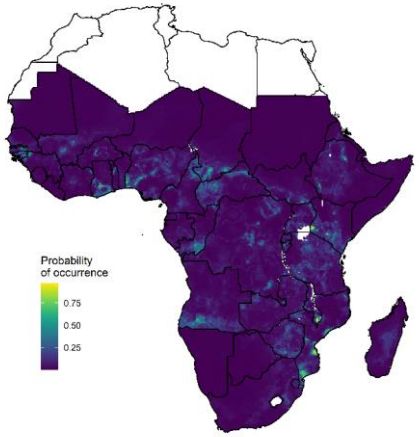
Probability of occurrence of human iNTS infection

- Probability of occurrence
  - Probability (varying from 0 to 1) of occurrence of human iNTS infection on 20 km by 20 km grid cells
  - Estimated by modeling association between occurrence and risk factors
  - Median value of 200 stochastic simulations of boosted regression tree models
  - Validation against external data necessary to validate methodology.

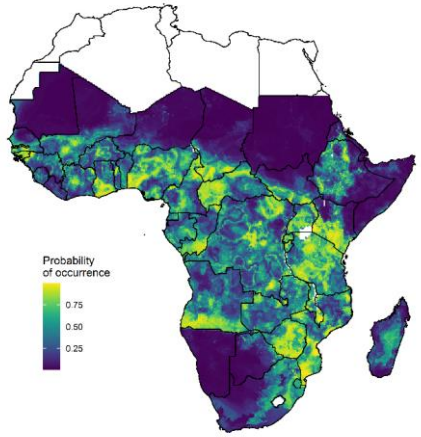
median



2.5th percentile



97.5th percentile



Conclusions on Modeling

- Flexible, expandable models based on current data to project/complete :
  - B.o.D. mapping and trends for sSA
  - vaccination impact
  - vaccine introduction scenarios
- Catch-up campaign appears to have a notable effect in decreasing B.o.D. in sSA
- Useful first-release tools that may be enhanced adding:
  - further parameters
  - new data on epidemiology and vaccines
- WP concluded: support needed to involve researchers and P.H. experts from epidemic areas

Key takeaways

1. The model projecting burden of disease and vaccination impact support a double immunization strategy in sSA: first a catch-up campaign to curb epidemic, followed by routine vaccination in EPI schedule
2. The model predicting iNTS occurrence with high accuracy will help identify high-risk sub-national sSA areas
3. Epidemiology data identified three potential target populations
   - Neonatal (maternal immunization)
   - Pediatric (6 -18 months), evidence of attribution from malaria (Class with highest mortality)
   - Adult (20 - 40 years), evidence of attribution from HIV.

Delivery strategies

- iNTS vaccine should be delivered in a national campaign, with routine immunization plus a catch-up
- Single iNTS vaccine may reduce GAVI costs and speed up approval/recommendations by SAGE vs. a combination, allowing a more efficient catch-up campaign saving more lives in sSAfrica, having the highest mortality
- Considerable C/B ratio exist with combination vaccines since main costs of introduction are delivery costs
- Evidence needs to be balanced with increasing unit costs and manufacturing complexity using a combination vaccine across Asia and Africa, vs. adopting a Regional Vaccines

Acknowledgements for the models

Probability of Occurrence:

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Florian Marks (Univ. of Cambridge)
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Stefano Malvolti (MMGGH Consulting)
Laura Martin

THANK YOU FOR YOUR ATTENTION!

Funding:

Public health need and goals for iNTS vaccines for LMICs

Sam Kariuki
Kenya Medical Research Institute

What are the Key considerations for iNTS as a public health priority by regional and country stakeholders

- iNTS disease is an important cause of death in neonates, infants and young children. However, a crowded EPI immunization schedule is a key issue, especially if boosters are needed.
- Antimicrobial resistance in iNTS has required changes to empiric antimicrobial guidelines.
- Co-infection in persons living with HIV represents a secondary target group of interests.
- Co-infection in persons with recent or current malaria, as well as residual of iNTS disease following progress with malaria elimination is also of interest.
- Raising awareness and acceptability of the vaccine among population, decision/policy makers has been highlighted as a key issue. The case for vaccine will need to be made beyond the burden.

What are the knowledge/evidence gaps for policy makers and decision makers on future iNTS vaccine use

- There are currently plenty of age-occurrence data, but these could be summarized by country or region?
- A 6-month vaccine time point versus a time point earlier in life consideration; compromise over a crowded schedule early in life? combination with typhoid vaccine?
- Epidemiology of iNTS disease might change if malaria is eliminated. Observational data from malaria elimination in combination with invasive bacterial disease surveillance might provide some insights.
- What is the effectiveness of iNTS vaccines in those with or without co-morbidities?

What is the feasibility of introducing iNTS vaccine to routine vaccination (based on current knowledge)?

- Feasible given the burden of disease. Implementation will require careful planning, introduction before six months of age?
- Bring typhoid vaccines to 6 month age to match/optimize on iNTS vaccine introduction?
- Public engagement and policy makers need to get involved early on.

What are the anticipated broader health system benefits or added burden of iNTS?

- NTS has continued to be perceived as simply a foodborne disease and a cause of diarrhea. Confusing to some stakeholders; more appropriate explanatory narrative is to explain the similarity between typhoid and iNTS disease.
- Strong advocacy and clear communication to healthcare workers in LMICs who have been already overwhelmed by the incidence of typhoid fever and AMR will be needed.

What are the key considerations to best meet the public health needs of key and general populations through a vaccination program?

- Importance of having diagnostics available to meet the public health needs, this will support both the uptake and public health benefits.
- The manufacturers will need to consider affordable availability for use especially in countries with a high burden of disease.
- Meningitis as a complication of iNTS, leads to an even higher case fatality than invasive bloodstream disease. Allowing the vaccine in the early EPI to reduce deaths caused by meningitis might appeal to policymakers.

The key elements to be considered for a PPC for iNTS vaccines (Framework for a PPC).

- Ideally, children should be immunized at 4-6 months, in order to provide some immunity in readiness for the peak of iNTS incidence.
- If iNTS vaccine is to be administered at 6 months, combining with TCV would be feasible as there is precedence of use of TCV at 6 months and the vaccine may actually be increasingly administered at a lower age.
- Modelling delivery schedules on mortality helpful to assess tradeoffs between moving either on or both (iNTS and TCV) to the 4 months versus the 6 months window.

CONT'D

- Ideally, iNTS vaccine should be of one dose, as for TCV, where most data has been generated at 9 months. One or two doses of iNTS vaccine might be required, particularly if administered earlier in life.
- If the TCV and/or RTS,S vaccines are going to be co- administered, research is needed on the potential interference between the vaccines.
- For combination vaccines, schedule, route of administration and number of doses must be compatible.

What are the key end user perspectives and potential drivers and barriers to iNTS vaccine uptake in context of specific factors

- The key end users are mainly in-country vaccine decision makers e.g., Ministry of Health, public health officers, physicians and caregivers.
- Key driver will be the potential opportunity to integrate the vaccine at the 6-month time point as countries start to introduce RTS,S vaccine.
- Country- specific modeling for cost effectiveness may be required in order to convince decision makers.
- AMR will be be an important consideration for policymakers as most Salmonella spp are MDR.
- Resource burden considerations for cold chain logistics, but may leverage existing cold chains.

What are the key end user perspectives and potential drivers and barriers to iNTS vaccine uptake in context of specific factors

- Community engagement requires very practical strategy (e.g., What is iNTS in the local language? How do we differentiate between iNTS and typhoid?) and needs to start early.
- To prioritize iNTS vaccine against other products, communicating with NITAGs requires making a strong case with robust data in terms of burden, cost effectiveness and AMR significance.

LEARNINGS AND KEY TAKEAWAYS RELATED TO INTS PRODUCT DEVELOPMENT AND PIPELINE, CHIM STATUS, POTENTIAL COMBINATION STRATEGIES

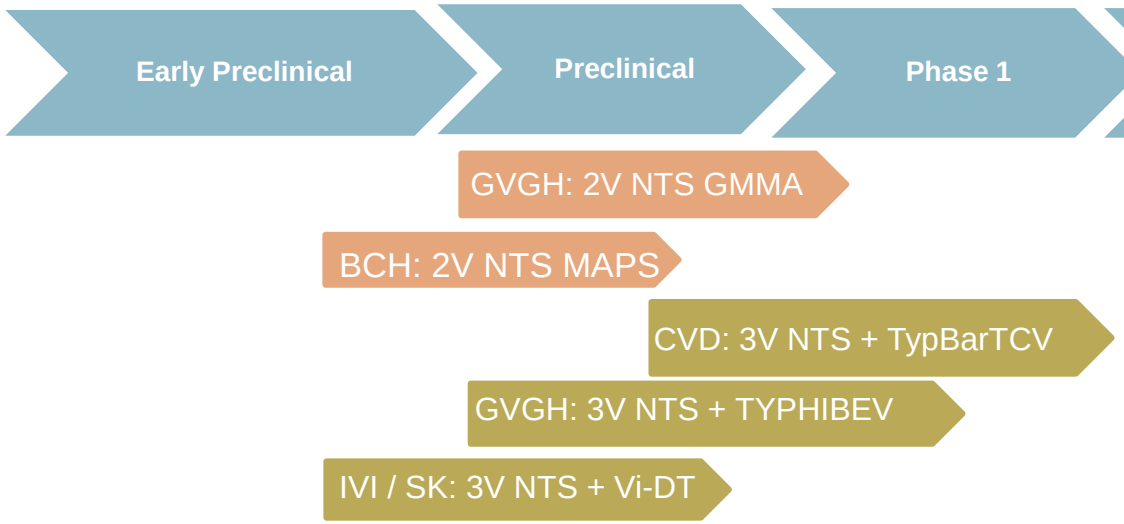
February 7, 2022

Cal MacLennan, Bill & Melinda Gates Foundation

PDVAC (virtual) meeting on invasive non-typhoidal Salmonella (iNTS) vaccines

NTS VACCINE DEVELOPMENT PIPELINE

NTS VACCINE DEVELOPMENT PIPELINE



- UMD/BBIL 3V vaccine with TypBar TCV (Vi-TT)
- In Phase 1 plans for Phase 2

- GVGH 2V vaccine to enter the clinic 1Q2022
- 3V vaccine with BioE's TYPHIBEV (Vi-CRM_{197})
- CARB-X support for 3V Phase 1

Key

2V: NTS

3V: NTS + TCV

LEAD CANDIDATE VACCINES

- All O-antigen based
- All contain Typhimurium and Enteritidis (bivalent) components
- Extensive body of evidence to support O-antigen as key target of protective immunity

UMD/BBIL

- Conjugates of O-antigen and flagellin – full dose: 25 ug O-antigen
- 15-17 months of follow up data available following single dose of half-dose vaccine
- Impressive GMTs for IgG to both O-antigen components, persisting elevated titers at 15-17 months

GVGH

- Outer membrane vesicles (OMV/GMMA) as delivery vehicle for O-antigen

- Both vaccines have industry involvement
- Both vaccine linked to PQ’ed TCV

LEARNINGS – NTS VACCINE DEVELOPMENT

Target serovars

- Agreement on Typhimurium and Enteritidis (note cross-protection of O:4,5 and O:9 to other serotypes)

Target group for an iNTS vaccine

- Young children (6 months to 36 months)
- Secondary groups – adults 20 to 40 years (n.b. HIV association); neonates (potential for maternal immunisation)

Age of introduction

- 6 months compatible with PQ'ed TCVs and possible RTS,S EPI time point
- **OR** early EPI (14 weeks possibly best option our of 6, 10 and 14 week time points)
- **NOT** 9 or 15 month TCV and measles-containing vaccine EPI time points

LEARNINGS - NTS VACCINE DEVELOPMENT

Clinical Trials

- Key need for clinical data in target population (young children) – immunogenicity & likely efficacy trials
- To inform combination vaccines – compatibility & non-interference
- Assessment of immune responses in ‘at risk’ groups (malaria & HIV)
- Clinical endpoints need to be established & correlates of protection would be valuable
- CHIM could provide valuable information

Delivery strategies

- National campaign & routine immunisation
- Modelling data needed
- Epidemiology suggests reduced age-window required for campaign in children compared with TCV

LEARNINGS – NTS VACCINE COSTS

- Cost-saving possibilities, particularly when combined with TCV
- Otherwise, low-cost options
- Favorable outcomes driven by
  - High disease burden
  - Relatively short time window of protection required for target population
  - Potential low COGs vaccine options – will need testing

CHIM STATUS

ROLE FOR AN NTS CHIM FOR VACCINE DEVELOPMENT

BMGF/Wellcome convening January 2021 followed by Wellcome funding call
Imperial College-led consortium - in early stages of development. PI Malick Gibani

To inform

- Pathogenesis (dNTS/iNTS)
- Correlates of protection
- Clinical endpoints for field efficacy
- Ultimately – key role to aid decision-making in product development

ROLE FOR AN NTS CHIM FOR VACCINE DEVELOPMENT

Current status – planning stage

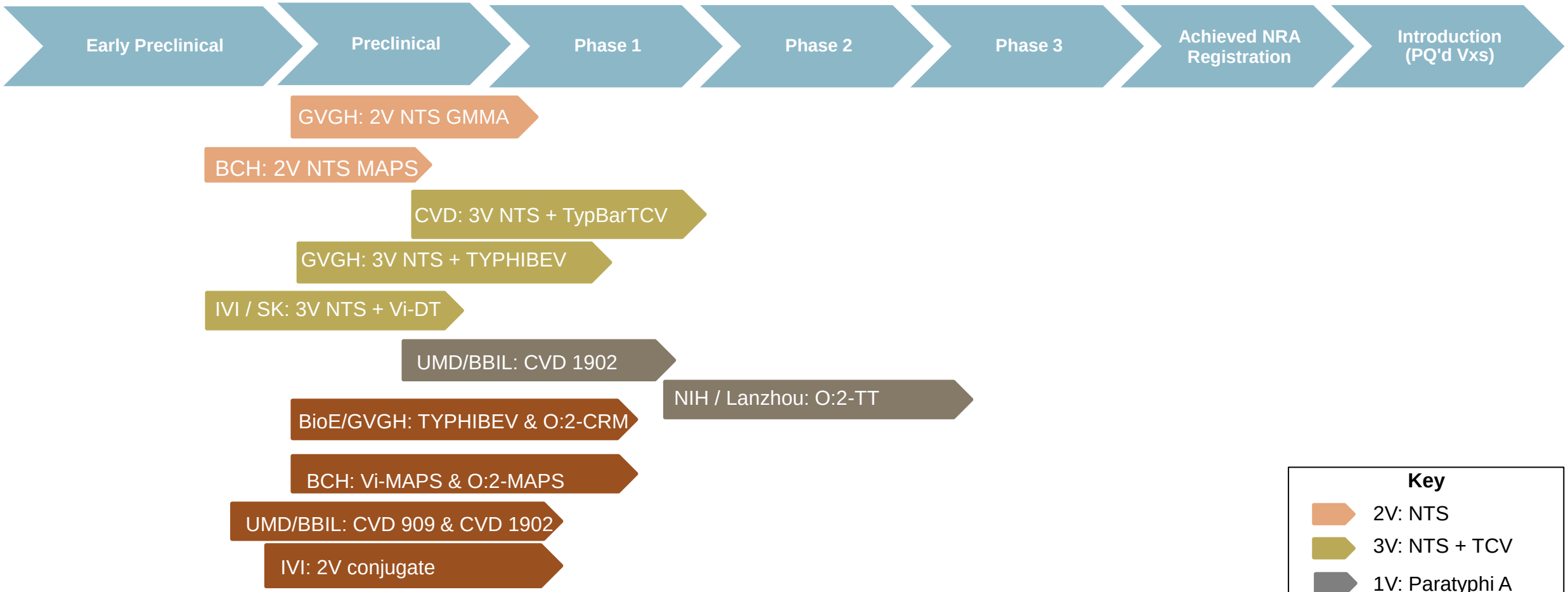
- Colonisation & gastrointestinal disease model
- Two Typhimurium challenge strains: ST19 (‘diarrheal’) and ST313 (‘invasive’)
- Initial safety and dose-escalation study to find dose giving a 60-75% Attack Rate

Composite primary endpoint

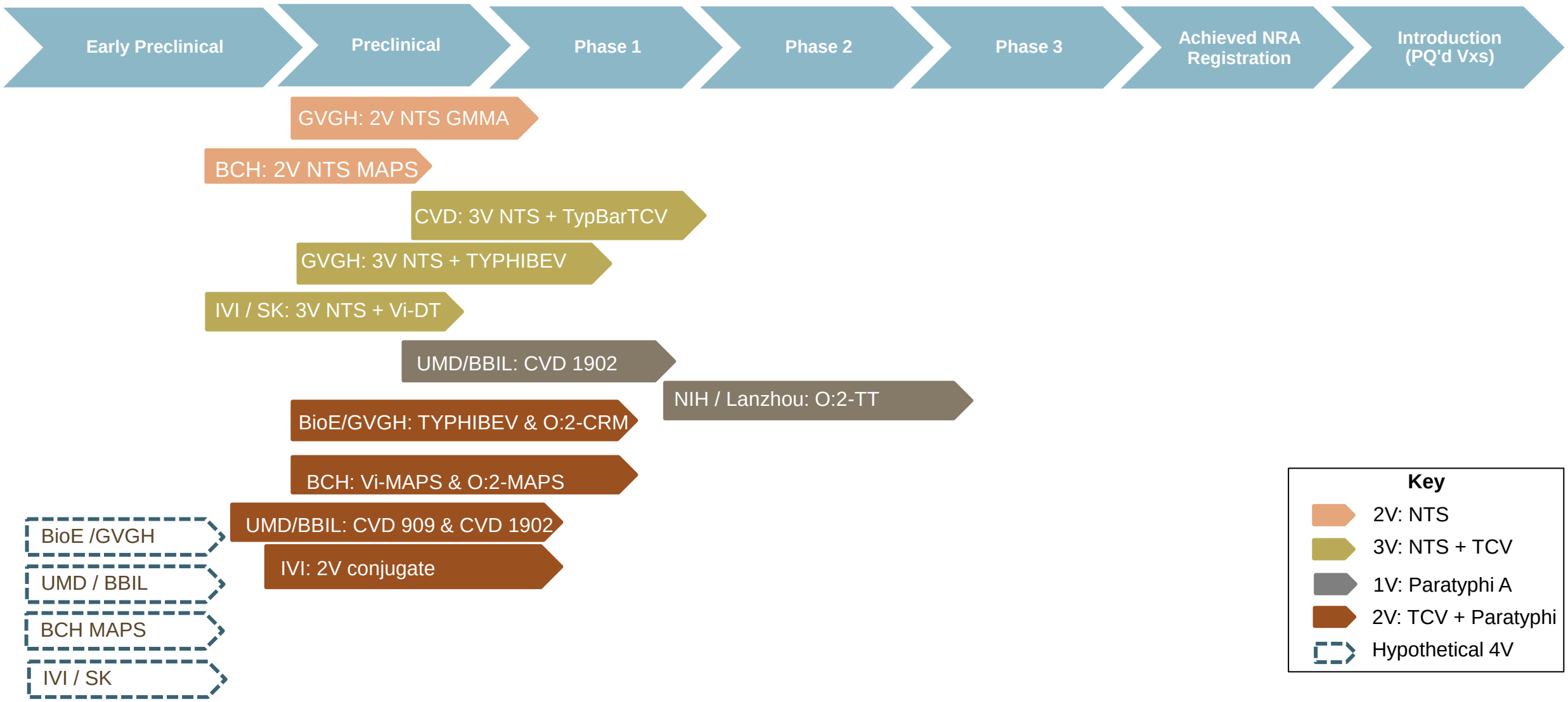
- Isolation of S. Typhimurium from stool on ≥2 occasions ≥after challenge **OR**
- Diarrhea **OR**
- S. Typhimurium bacteremia **OR**
- Fever ≥38ºC on ≥2 occasions ≥12 hours apart

COMBINATION STATEGIES

SALMONELLA VACCINE DEVELOPMENT PIPELINE



SALMONELLA VACCINE DEVELOPMENT PIPELINE



PAN-SALMONELLA VACCINE

- Covering 4 key serovars of invasive Salmonella disease
- Technically feasible
- Within reach of four partnerships between institutions & manufacturers
- Competitive advantage of combination vaccines – market share/geographical coverage

Universal and Regional Options

- A universal 4V combination vaccine
- A 2 or 3V vaccine (NTS +/- TCV) for Africa + 2V (Typhi/Paratyphi A) vaccine for Asia

PAN-SALMONELLA VACCINE

Considerations – Bill Hausdorff/PATH

- Learnings from meningococcal and pneumococcal conjugate vaccines

- Feasibility and acceptability – engagement with regional and national LMIC stakeholders
- Epidemiology and disease coverage
- Complexity of clinical testing
- Complexity/cost of manufacture

- Importance of value of vaccine assessment for different combinations

PAN-SALMONELLA VACCINE

Interim conclusion from further cost effectiveness analyses at BMGF

- The quadrivalent vaccine is a good $ / DALYs averted investment compared to other products in the portfolio and worth consideration as a future BMGF investment
- At the country-level, the quadrivalent vaccine is cost effective in most countries (85% when cost effectiveness is averaged across scenarios)
- The size of the dNTS burden estimate (ranging between the IHME reference and lower bound estimates) has a relatively small impact on total DALYs averted and is unlikely to change the investment decision *(note dNTS burden has been scaled down in GBD 2020 estimates)*
- Of the factors considered in the analysis, TPP is the biggest driver of impact and cost, followed by schedule and product introduction year

DEVELOPMENT PATHWAY

- Currently relatively unexplored – an area for attention

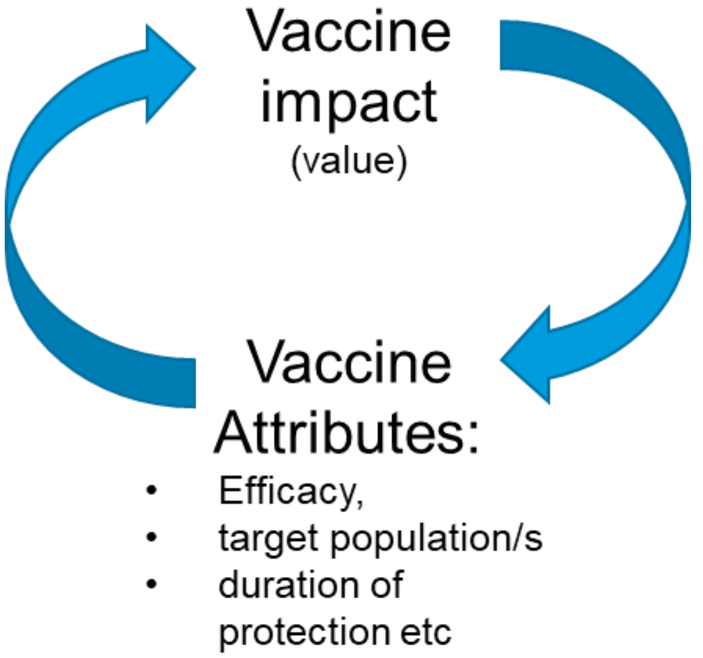
- Key to have data from clinical studies
- Need to move quickly into target population (young children in LMICs)
- Potential benefit from CHIMs for indication of efficacy. Will NTS CHIM be available in time?
- Likely need for field efficacy studies for NTS component
- Typhoid component has opportunity for immunobridging; paratyphoid A has CHIM

Preferred Product Characteristics for iNTS-containing vaccines

PDVAC 7th February 2022

Purpose of WHO PPCs

- Intended to encourage innovation and **promote development of vaccines** for use in settings most relevant to the global **unmet public health needs;**
- Describe preferred parameters pertaining to vaccine indications, **target populations, use case(s),** as well as data that should be collected for safety and efficacy evaluation with a view to policy consideration;
- PPCs are **pathogen-specific** and do not include minimally acceptable characteristics
- Developed when there are **early-stage clinical candidates** in the pipeline
- They are intended to provide early guidance to **inform subsequent candidate-specific target product profiles** (TPPs).



What are the desirable PRODUCT attributes? (in the context of what we know today…)

- Priority target and key populations:
  - Pediatric (6 -36 mo); malaria as an attributable risk factor
  - Neonatal (maternal immunization)
  - Adult (20 - 40 year olds), evidence of attribution from HIV.

➢ A key population for iNTS vaccination was defined as infants/young children from about four months to approximately 36 mo of age, i.e. the iNTS vaccine will need to offer approx. 2.5 years of protection

- A regimen of 1-2 doses is expected to be effective; potentially one in adults as for TCV, but potentially 2 will be needed for infants/young children

- Need to consider the delivery setting for each of these, and whether there is an existing platform that is compatible with the anticipated dose schedule:
  - Possible 6 mo timepoint for RTS,S could be leveraged. TCV is licensed from 6 mo of age, offering potential combination
  - Alternative of 9 mo with MCV1 is likely too late given the peak incidence
  - Inclusion in the early EPI (6, 10 or 14 weeks) will be challenging; tips the balance towards a combination, however TCV only licensed from 6 mo

Which of the target populations and potential combinations is a 'priority', since the product attributes (and therefore the PPC) will likely differ.

Many questions were identified in the consultations, that will impact PPC and R&D roadmap development

- What is the relative ‘full’ burden in each of these target populations (including co-morbidities)? How can these be addressed by the various iNTS vaccine permutations for combinations?
- What is the significance of transient, asymptomatic carriage for immunity and for vaccine impact?
- How can CHIM be used to identify potential end-points, correlates of protection and inform decision making related to product development?
- At what stage would populations with co-morbidities be included in clinical studies?
- What is the optimal case definition and clinical end-point/s?
- How can awareness of iNTS be developed at the country level, to partner with immunization stakeholders to develop a iNTS vaccine that meets country needs, i.e. appropriate combination with optimal product attributes.

These will be covered in detail, in future discussions and workstreams:

- PPC development
- Dedicated CHIM stakeholder consultations
- Clinical and regulatory pathway stakeholder consultations
- R&D technology roadmap

Next steps

1. **PDVAC closed session:**

- Discussion on public need for iNTS-specific and pan-Salmonella vaccines
- The short-, medium- and long-term goals for development of iNTS vaccine(s): standalone (bivalent) NTS vaccines versus combination vaccines (including trivalent or quadrivalent vaccines combination vaccines targeting iNTS serovars as well as *S. Typhi* and/or *S. Paratyphi A*)
- *Output*: PDVAC recommendations, to help inform the broader stakeholder alignment and strategic planning for iNTS and Salmonella vaccine development

2. **IVI/WHO/Wellcome Research Steering Group for the iNTS FVVA project** – 11th February

- Alignment on the priority NTS-containing vaccine target for the FVVA, including PPC and R&D roadmap development.

3. **Key stakeholder and funders meeting**, to be scheduled, potentially late February, including IVI, Wellcome, BMGF, PATH to map the broader NTS-vaccine value related activities, to align on gaps and activities to support other (non IVI/WHO) value assessments.

4. **Return to PDVAC** as part of annual meeting in September/October 2022 to provide an update of iNTS and other pan-Salmonella vaccine related product development landscape.