Non-typhoidal *Salmonella* vaccines against invasive disease

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Dr Kate Emary

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PDVAC meeting, 13 December 2023

Overview – Salmonella vaccines session

- Overview (5’)

- Review of draft NTS vaccine PPC – Part 1 (10’)

- Emerging data: presentation of TyVAC TCV longevity data (10’)

- Review of draft NTS vaccine PPC – Part 2 (10’)

- **Discussion and questions for PDVAC** (20’)

- Clinical development considerations (10’)

- Overview of R&D Roadmap (5’)

- Combination *Salmonella* vaccines strategy - key takeaways from Kigali meeting (10’)

- **Discussion and questions for PDVAC** (10’)

Overview of iNTS Full Value of Vaccine Assessment (FVVA)

- Funded by the Wellcome Trust (3-year grant extended to April 2024)
- 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** post-2021 expert consultations

FVVA partners

- IVI-WHO joint project
- Shift Health
- LSHTM
- Swiss TPH

Research Steering Group

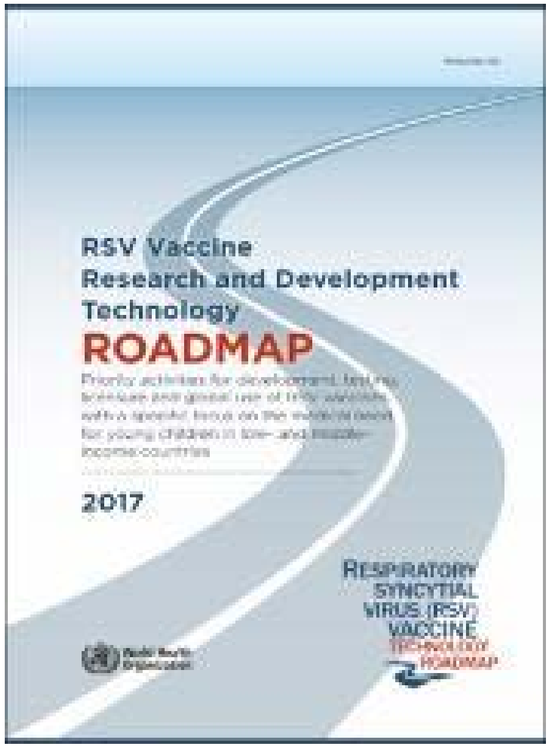
- Pierre Balard
- Martin Friede
- Jerome Kim
- Calman MacLennan
- Jean-Louis Excler (Project Lead)
- Adwoa Bentsi-Enchill (WHO Project Lead)

Overview of iNTS FVVA workstreams

- **Aims 1-3 (WHO lead)**
  - Aim 1 - **Landscape analysis** of iNTS (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 Vaccine 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)

Development of WHO Preferred Product Characteristics and R&D Roadmap for NTS vaccines against invasive disease (in draft)

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.

Can be R&D focused, or vaccine introduction focused.

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

Vision

- **Overarching vision of broadly protective vaccine(s) against invasive disease caused by *Salmonella* serovars**
- The R&D roadmap for a trivalent S. Typhi/S. Typhimurium/S. Enteritidis vaccine addresses a first potential combination *Salmonella* vaccine.

Development of a:

- safe,
- affordable, and
- broadly protective effective vaccine (or vaccines)
- to protect children against invasive disease
- caused by *Salmonella* serovars
- for use in low- and middle-income countries

Strategic goals

Near Term

To **demonstrate immunogenicity, safety, and efficacy** of a candidate iNTS vaccine against *Salmonella* serovars Typhimurium and Enteritidis

Medium Term

Licensure of a combination vaccine including TCV + iNTS components (*Salmonella* serovars Typhimurium and Enteritidis)

Long Term

Develop and license a safe and effective broadly protective vaccine(s) for the prevention of invasive disease caused by *Salmonella* serovars

Questions on the NTS vaccine PPC

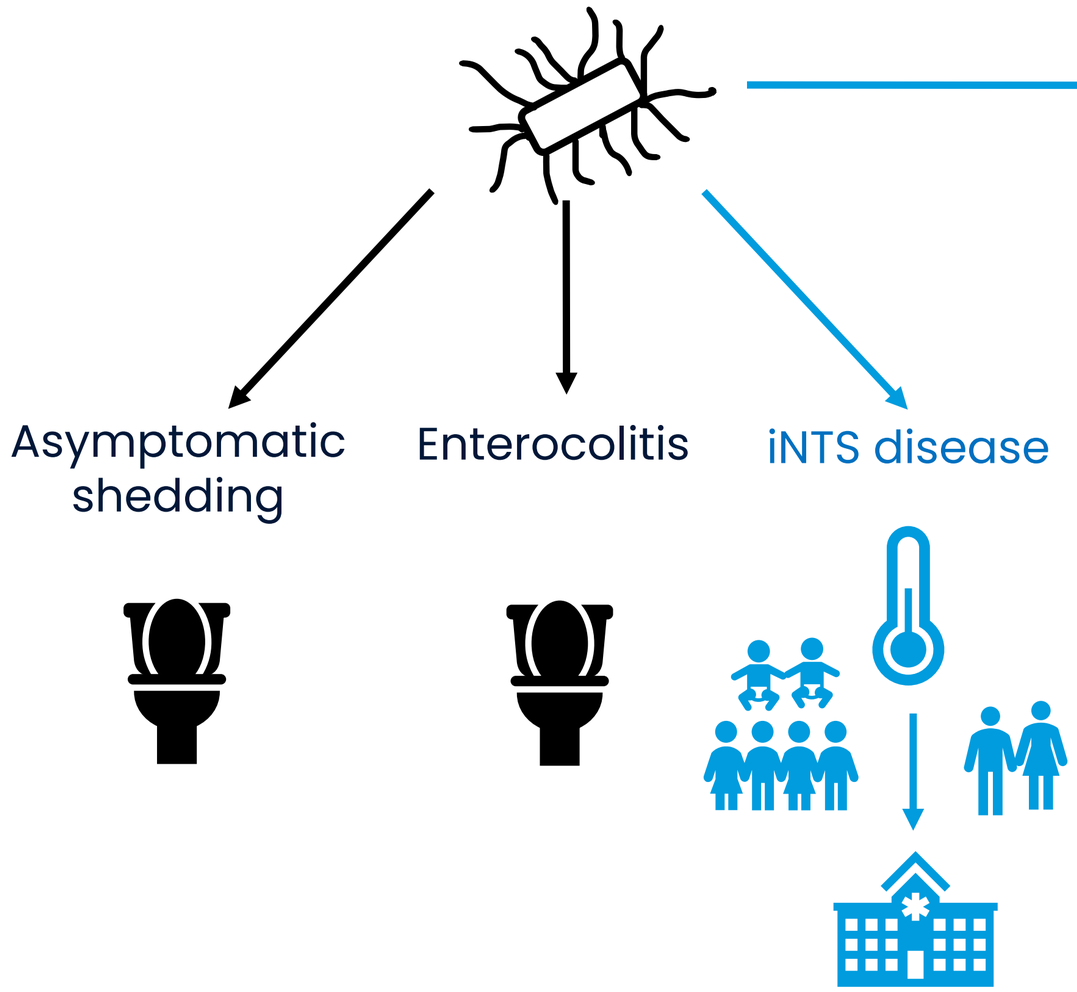
1. Should 6-36 months remain the target population in the PPC for vaccination against iNTS disease? And should 6 months be the target age at vaccination (1st dose)?

2. What is the advice of PDVAC as to whether the trivalent vaccine should remain the preferred strategy for NTS vaccination against invasive disease?

3. Should the current WHO PPC (versus a future PPC) also consider options for combination of Salmonella vaccines with other pathogens?

4. Has PDVAC identified any gaps or missing elements that should be in the R&D Roadmap?

Invasive NTS (iNTS) disease



Serogroups

Sero-group	n=24,253 (%)
O:4	15345 (63.3)
O:9	7386 (30.5)
O:7	1063 (4.4)
O:8	250 (1)

Serovars

Serovars	n=23,971 (%)
S. Typhimurium (O:4)	14314 (58)
S. Enteritidis (O:9)	6561 (27.3)
S. Dublin (O:9)	524 (2.2)
S. Heidelberg (O:4)	473 (2)
S. Choleraesuis (O:7)	225 (1)

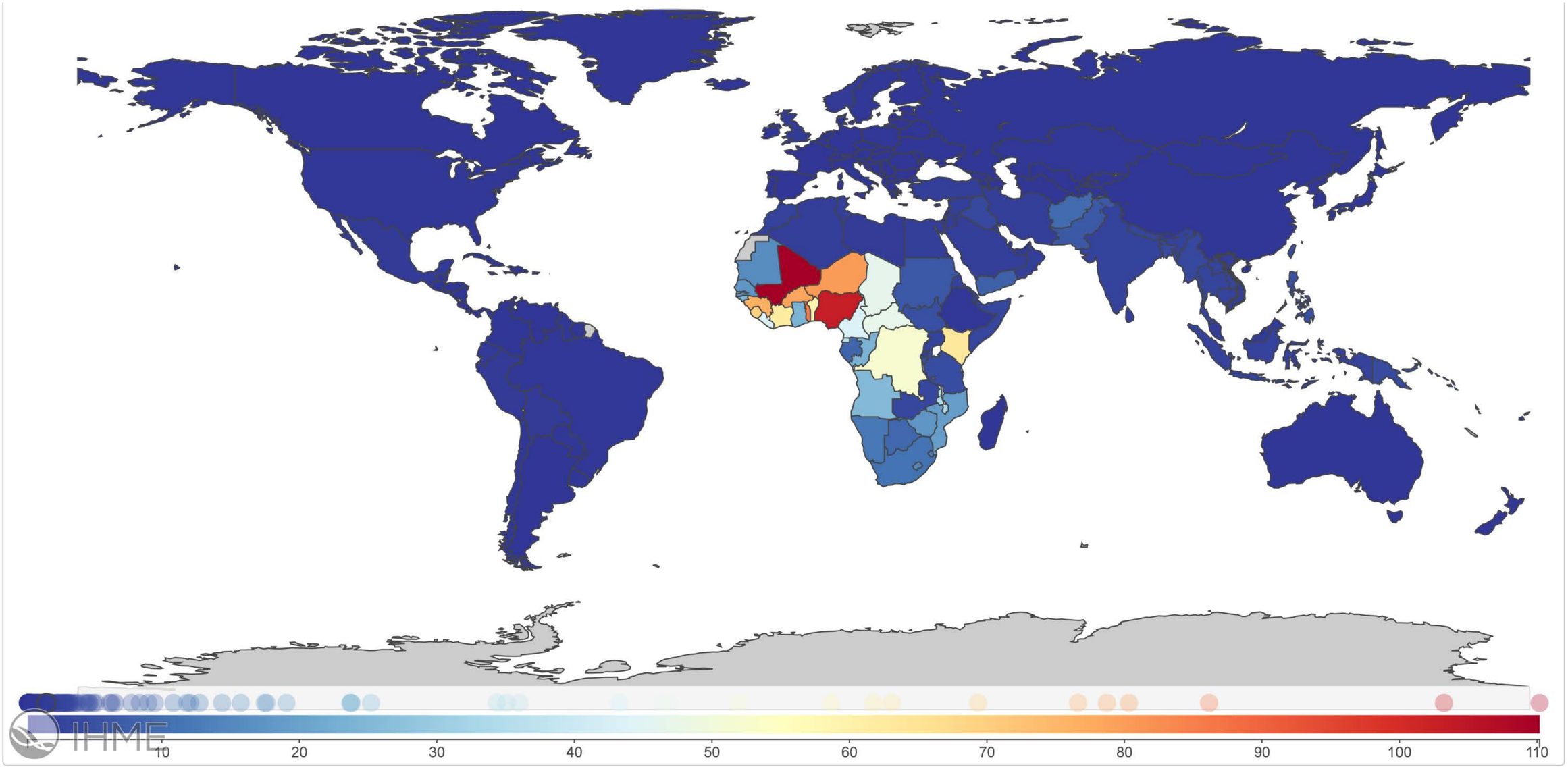
Haagedoorn et al., 2023

AMR is a major problem

Host risk factors

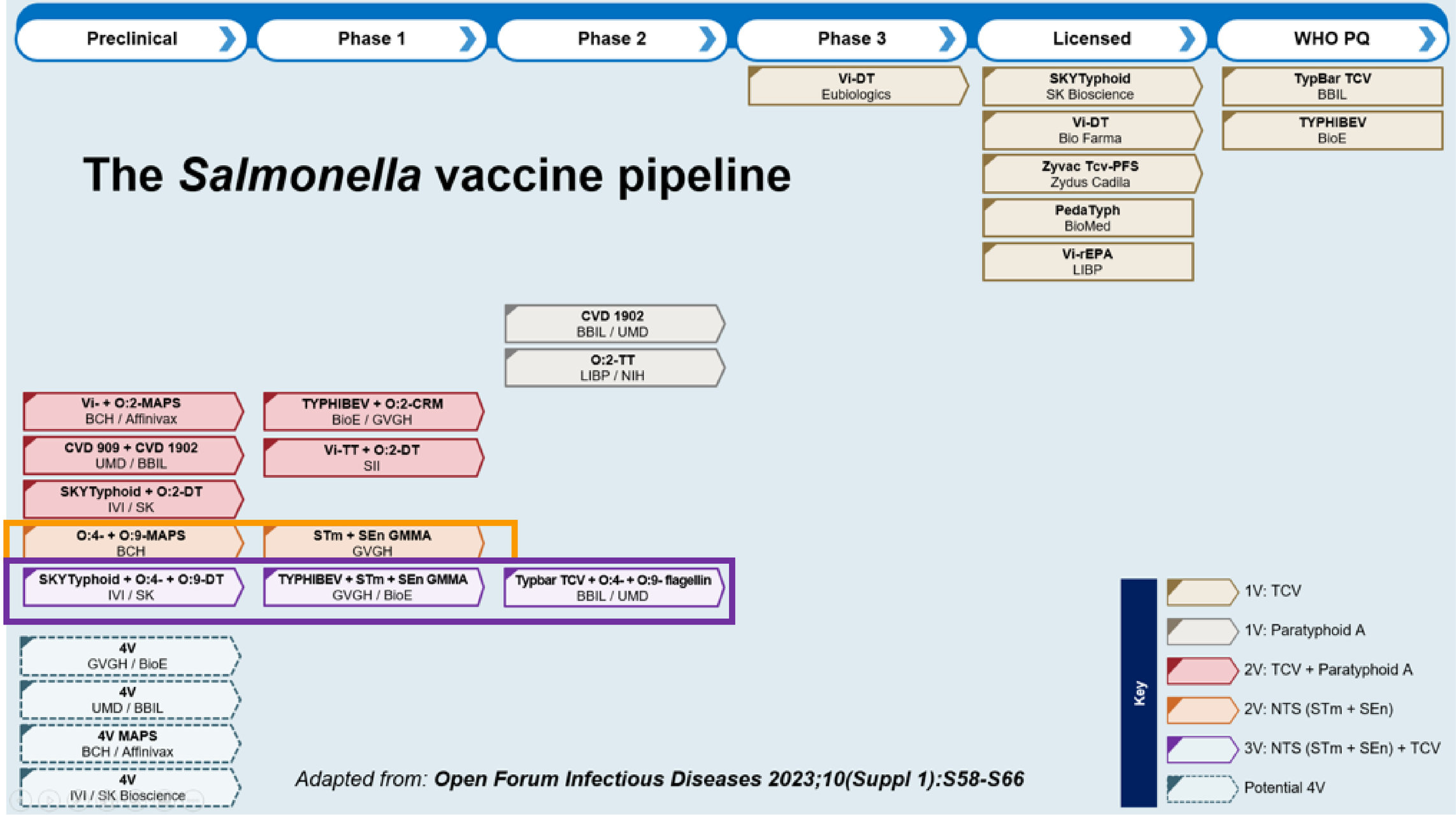
- Age
- Recent or current malaria
- Malnutrition
- Anaemia
- HIV

Global incidence of iNTS disease -All ages, new cases per 100,000



GBD 2019, *https://vizhub.healthdata.org/gbd-compare/*

The *Salmonella* vaccine pipeline



Adapted from: ***Open Forum Infectious Diseases 2023;10(Suppl 1):S58-S66***

Slide courtesy of Calman MacLennan

Key PPC parameters (current draft)

Indication	Prevention of invasive disease (infection in a normally sterile site for example, blood) caused by *Salmonella* serovars • Trivalent vaccine: *S.* Typhi/*S.* Typhimurium/*S.* Enteritidis • Bivalent vaccine: *S.* Typhimurium/*S.* Enteritidis.
Target population	Infants and young children 6 to 36 months of age.

Target age of vaccination	• Trivalent: 6 months is proposed (new data on duration of protection of TCV needs to be taken into account)
	• Alternative of early EPI schedule (e.g., 6 to 14-week timepoints).
	  o May not be feasible due to congested EPI schedule
	  o Confirmation of safety, immunogenicity, and efficacy of TCV in infants <6 months would be required
	• Bivalent: early EPI schedule should be considered.

Key PPC parameters (current draft)

Dose regimen and schedule

Trivalent: primary regimen may or may not require >1 dose to provide protection.

The main required window of protection for iNTS disease is until 3 years of age.

Bivalent: may be given to younger infants and therefore dosing schedule may differ from the trivalent.

Duration of protection

For NTS:
Minimum duration of protection for 24 months following the last vaccine dose in the primary series, with protection up to 3 years of age desirable.

For TCV:
non-inferiority with a prequalified TCV for the same duration of follow-up


Efficacy of Typhoid Conjugate Vaccine: Final Analysis of a Four-Year, Randomised Controlled Trial in Malawian Children

19 Pages • Posted: 7 Apr 2023

Priyanka D. Patel
Malawi-Liverpool-Wellcome Trust Clinical Research Programme

Yuanyuan Liang
University of Maryland - Department of Epidemiology and Public Health

More...

Patel et al. (2023), Lancet pre-print

Efficacy of 78.3% (all ages) 4yrs post-single dose
9 mths – 2 yr group efficacy of 70·6%

Target population: iNTS disease increases from 6 months of age

Single country data: Democratic Republic of Congo (Kisantu)

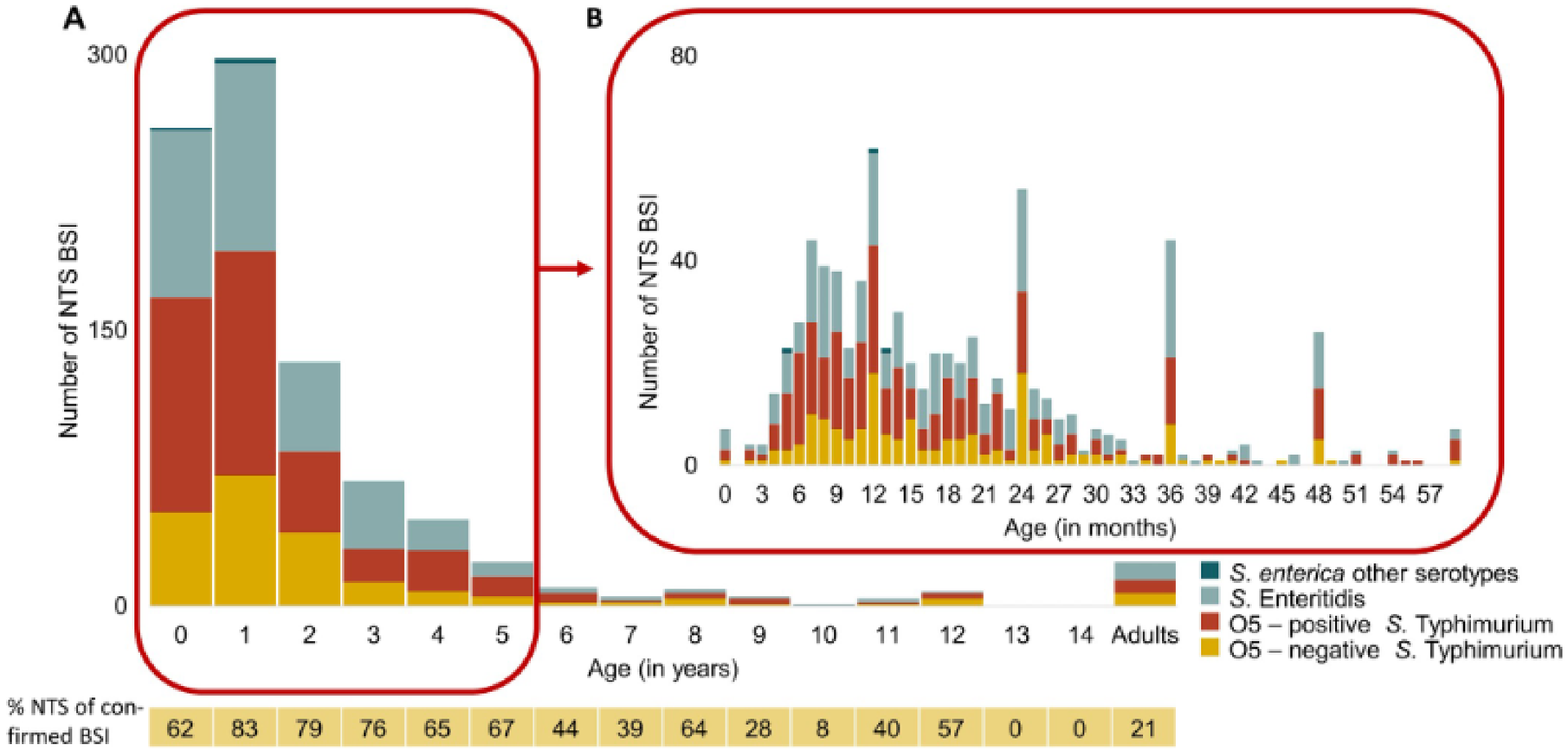
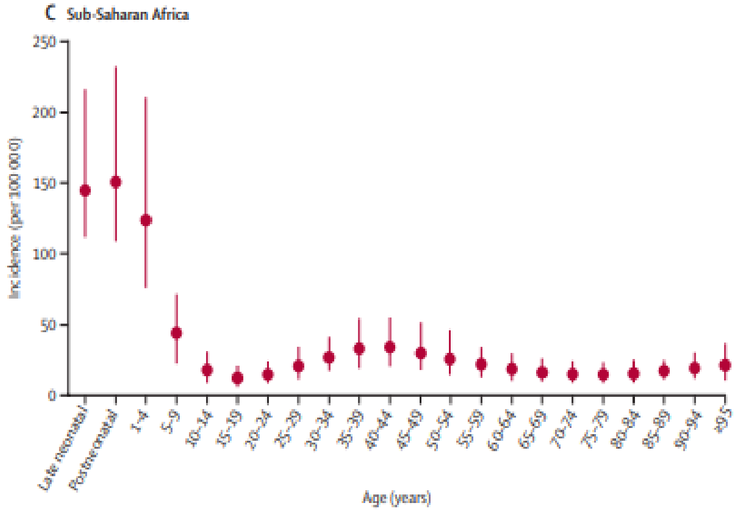


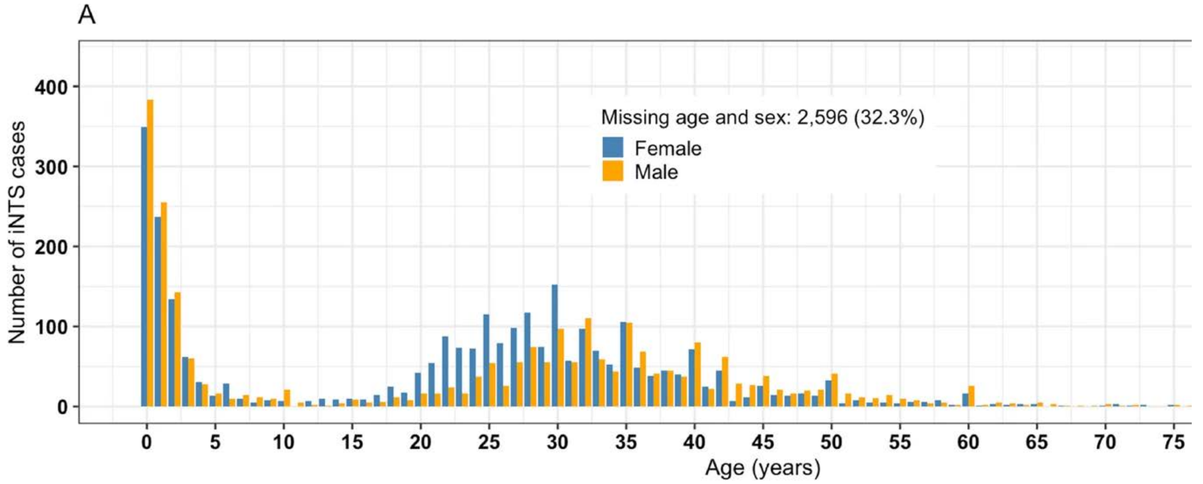
Fig 3. Age distribution of NTS bloodstream infections sampled at Kisantu general referral hospital from 2015–2017. A: Bars represent the number of NTS bloodstream infection (BSI) per age (in years). The proportion (%) of confirmed BSI episodes caused by NTS in the respective age group is displayed below the graph. **B:** Bars represent the number of NTS BSI per age (in months). During this period, 806/896 NTS BSI were obtained from children < 5 years old. The exact age in months was available for 770/806 NTS BSI from children < 5 years old. Poor knowledge and registration of the exact age in months resulted in artificial peaks of NTS on multiples of 12 months. Abbreviations: BSI: bloodstream infection.

Tack B, et al. (2020). PLoS Negl Trop Dis 2020 14(4):e0008121.

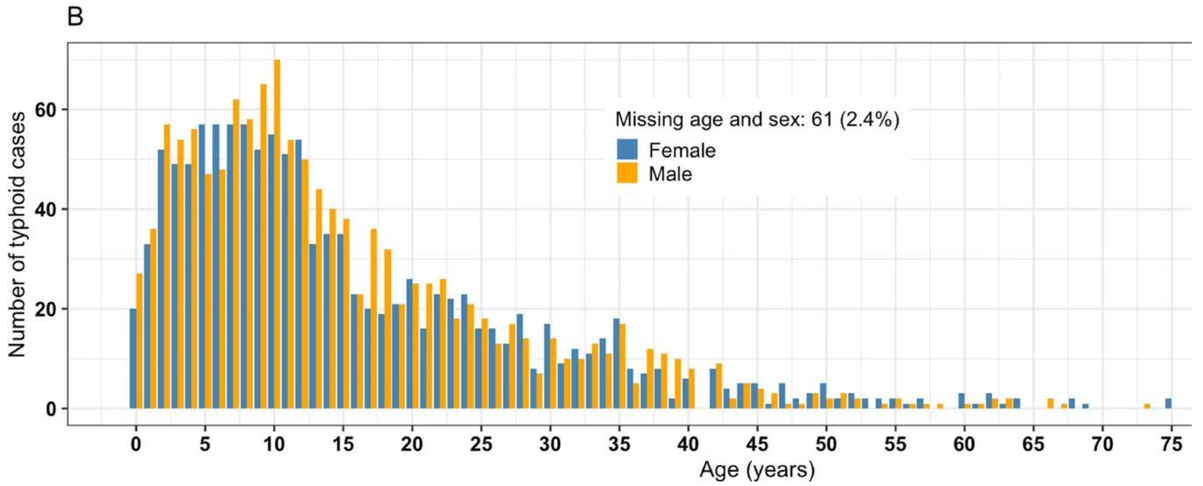
Comparison of the age distribution for iNTS cases and enteric fever cases – global estimates & single country data

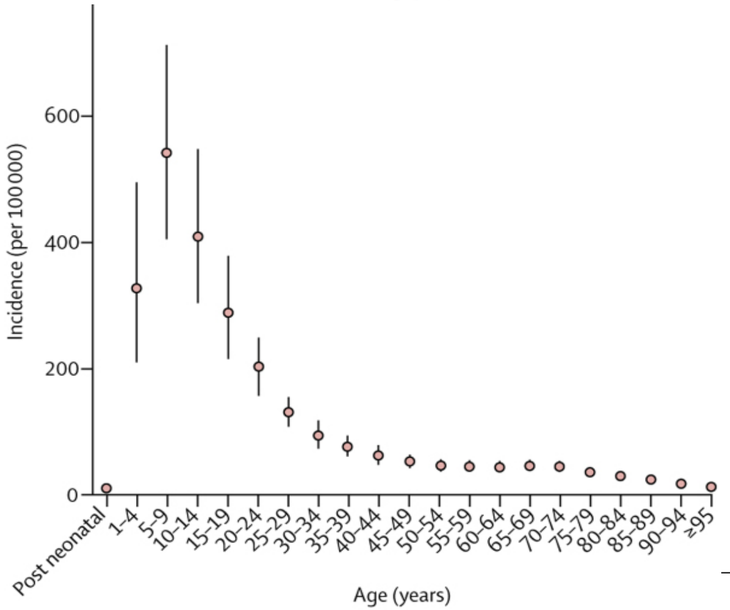


iNTS disease



Typhoid





Global estimate of enteric fever includes paratyphoid cases

GBD 2017, Lancet ID 2019 Apr;19(4):369-381.

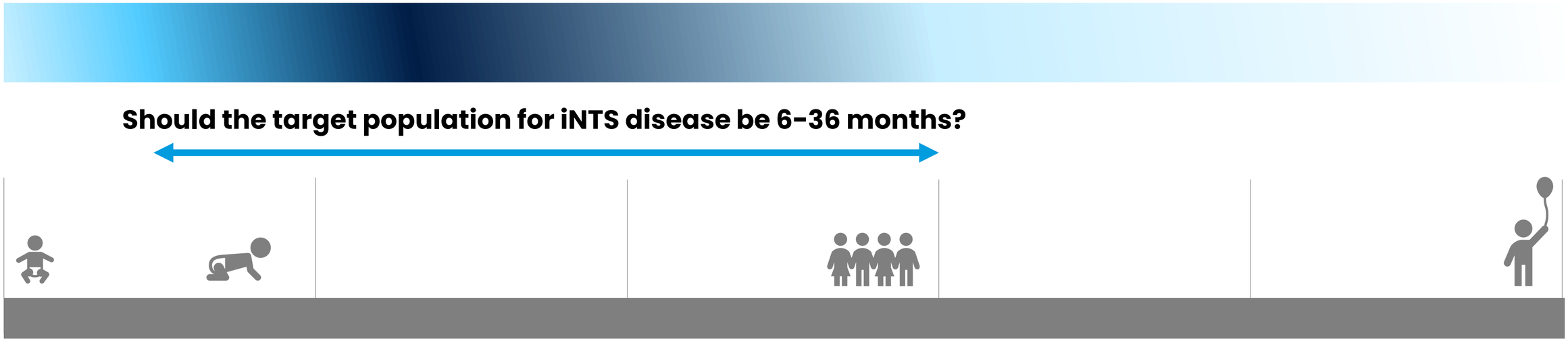
GBD 2017, The Lancet ID 2019 191312-1324DOI: (10.1016/S1473-3099(19)30418-9)

Thindwa et al., Sci Reports 2019 9(1):20310

Refer Prof Andy Pollard’s slides here

Summary

iNTS disease incidence



Waning of protection from typhoid in the youngest children after a single dose of TCV

Typhoid incidence

Considerations for bivalent and trivalent NTS vaccine approaches

	Bivalent	Trivalent (NTS+TCV)
Target population	If given early in EPI schedule, will achieve aim of protection by 6 months of age (or earlier)	If given at 6 months of age this concurs with current TCV licensure so no new TCV data required but NTS protection would not be achieved until >6 months of age If to be given before 6 months of age, data would be required for TCV safety and immunogenicity below this age
Immunogenicity and duration of protection	May require more than 1 dose as primary regimen in infancy +/- booster(s)	TCV likely to need a booster dose in some settings especially if given <9 months (TCV duration of protection may be shorter if given even earlier) NTS may require more than 1 dose but duration of protection required is shorter for NTS
Non-interference	If given in early EPI schedule, would require evidence of non-interference with multiple vaccines	
Programmatic considerations	Does not affect existing/planned TCV programmes or messaging around TCV	New malaria vaccine timepoints may provide opportunities for trivalent vaccine delivery Requirement and timing for booster doses may differ for NTS/TCV

Questions on the NTS vaccine PPC

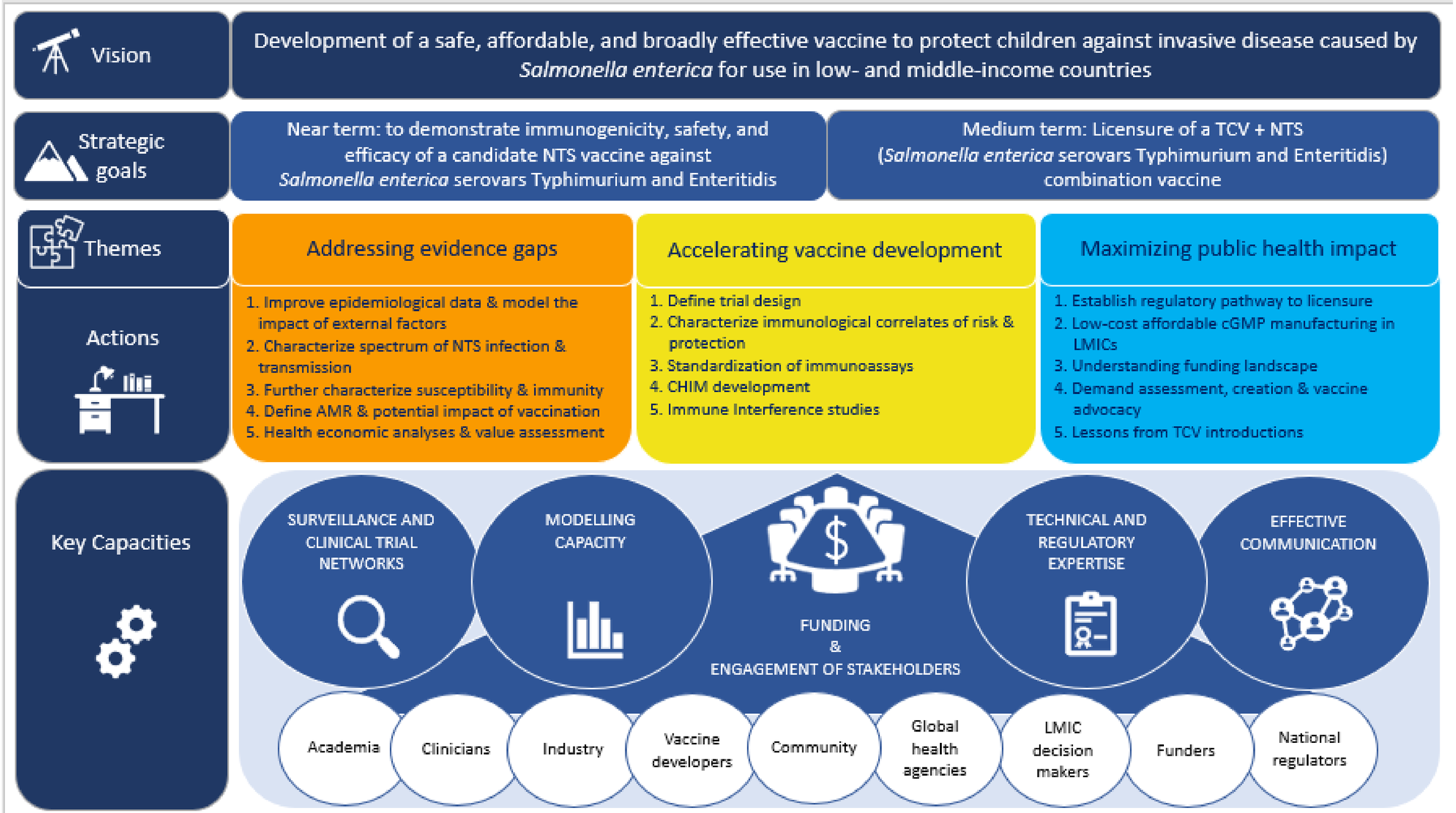
1. Should 6-36 months remain the target population in the PPC for vaccination against iNTS disease? And should 6 months be the target age at vaccination (1st dose)?

2. What is the advice of PDVAC as to whether the trivalent vaccine should remain the preferred strategy for NTS vaccination?

3. Should the current WHO PPC (versus a future PPC) also consider options for combination of Salmonella vaccines with other pathogens?

Overview of R&D Roadmap for NTS vaccines against invasive disease

Overview of the R&D Roadmap on NTS vaccines



Questions on the NTS vaccine R&D Roadmap

4. Has PDVAC identified any gaps or missing elements that should be in the R&D Roadmap?

Combination Salmonella vaccines strategy: Key takeaways from IVI-WHO meeting (Kigali, 04 Dec 2023)

3-hour think-tank meeting to:

- Gather opinions and perspectives on the **potential public health value for different *Salmonella* combination vaccines** to better inform developers, immunization policy decision-makers and donors on the best suitable way forward.
- Identify current **gaps in understanding the value** of and/or **needs for accelerating the development** of the most appropriate *Salmonella* combination vaccine(s) and define priorities to address those gaps

Formal (full) expert consultation being planned for 2024

Brief summary of invasive Salmonella diseases

Enteric fever

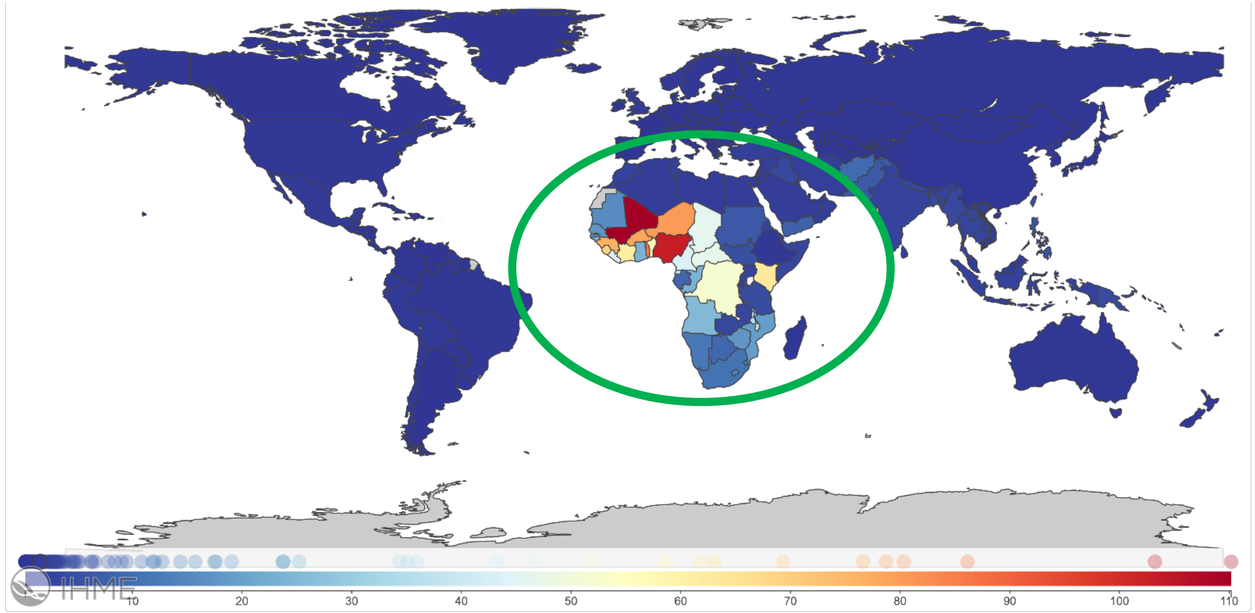
- Typhoid fever: burden very high in **South and South East Asia, and high in Africa and Oceania.**
- Paratyphoid fever: highest burden in **Asia.**
- Scarcity of data, notably pockets of sub-Saharan Africa, Oceania, Middle East, Latin America.
- Mostly affects **school aged children** extending into adulthood; **peak incidence overall in 5 to <15 year age group**

Invasive NTS disease

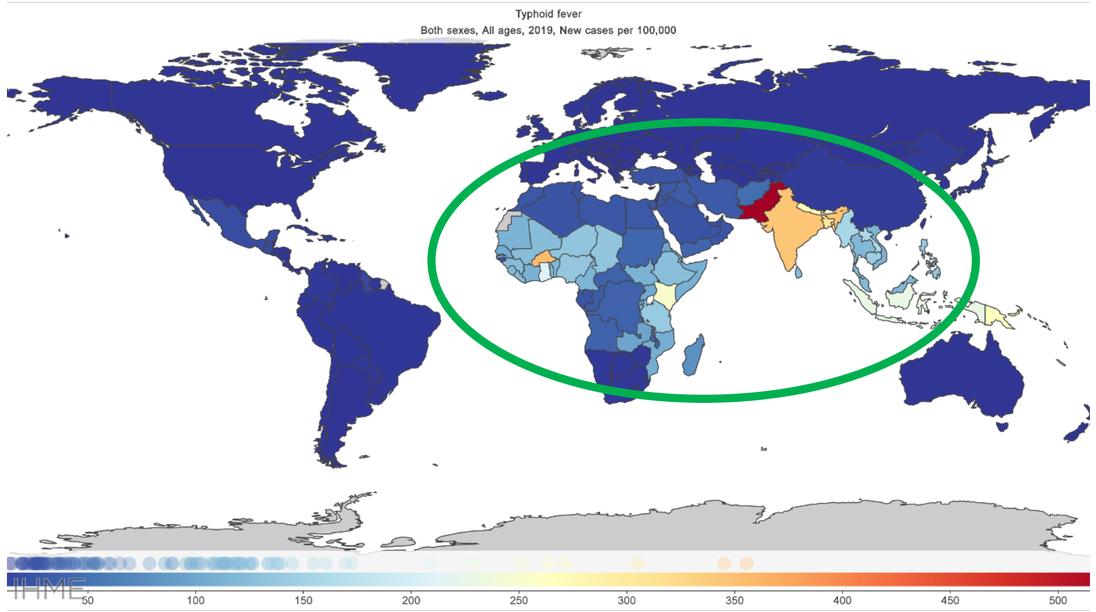
- Burden of disease concentrates in **sub-Saharan Africa.**
- Association with host risk factors (malaria, malnutrition, HIV)
- Reliable data from limited number of locations
- Disease predominantly in **infants and young children 6-36 months** of age; **peak 12-15 months** of age

Global estimates of incidence - All ages, new cases per 100,000

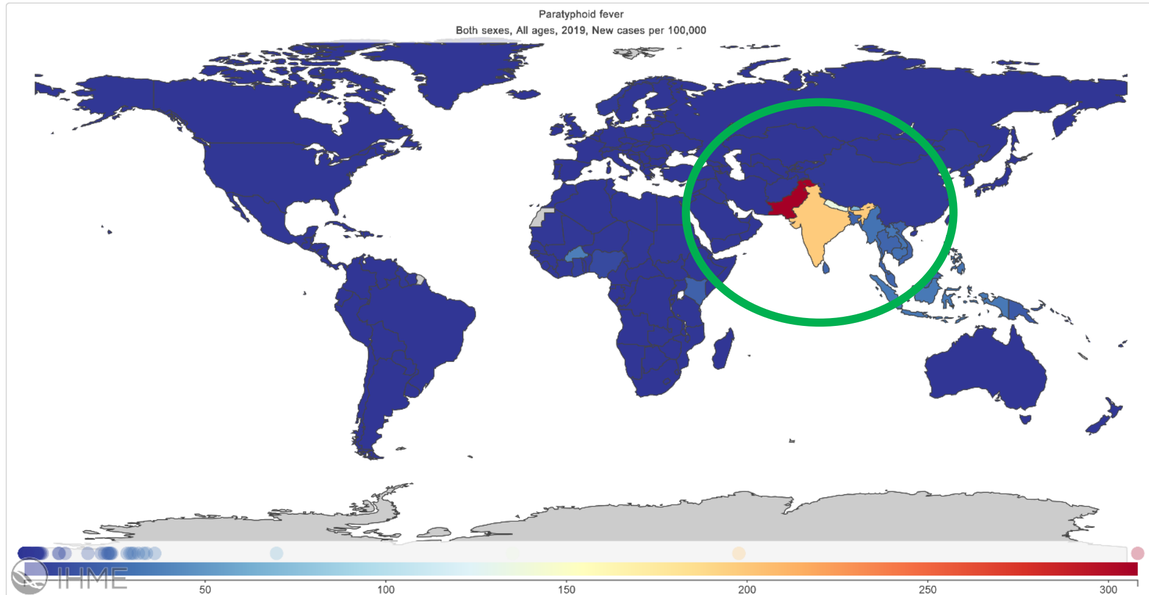
iNTS disease



Typhoid fever

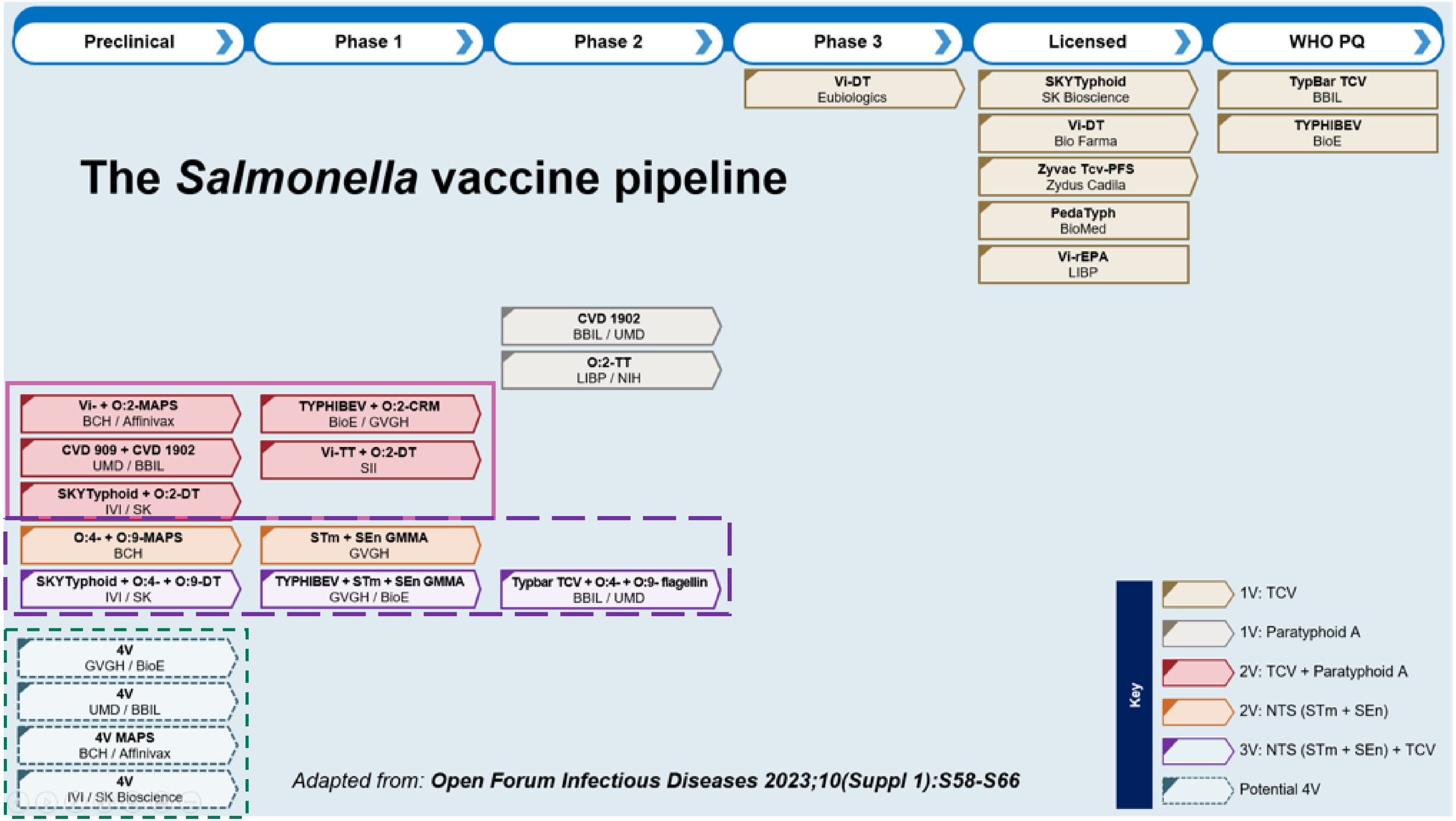


Paratyphoid fever



GBD 2019, *https://vizhub.healthdata.org/gbd-compare/*

The *Salmonella* vaccine pipeline



Adapted from: ***Open Forum Infectious Diseases 2023;10(Suppl 1):S58-S66***

Slide courtesy of Calman MacLennan

Combination vaccines … some key considerations

Impact	1.	Reduction in number of injections
“Must have” compatibility	**2.**	**Epidemiology (age group and geography of disease burden)**
	3.	Risk of immunologic interference (“clinically important” impact)
	4.	Route of administration (oral vs. injection)
Technical feasibility	**5.**	**CMC complexity (formulation compatibility, analytical testing burden, lot failure, live vs. non-live vaccines)**
	6.	Regulatory pathways (e.g. are efficacy studies feasible and if not, does an acceptable correlates of protection exist?)
Commercial feasibility	7.	Number of partners needed for collaboration
	8.	Commercial attractiveness of combination
	9.	Effect on market stability (e.g. supply risk, potential price increases)

Priority criteria

Slide courtesy of Calman MacLennan

IVI-WHO Consultation on Salmonella Combination Vaccines - Key takeaways

- **Regional vaccines** based on epidemiology need to be explored further with key stakeholders incl. LMICs.

- Combination vaccines should not be pursued for the sake of doing so, and **consideration should be given to combining *Salmonella* vaccines with other antigens if it makes sense to do so, e.g., by age group.**

- Concept of an iNTS **consortium to test multiple vaccine candidates within a single multi-centre efficacy trial** was raised as a potential way to accelerate identification of efficacious candidates and reduce cost.

Key takeaways (2)

- **Manufacturers need/want guidance** on combination products.
- There needs to be clear understanding of **data needs to support regulatory and policy pathways.**
- **Pricing and cost-effectiveness** of any combination vaccine is critical.
- Countries facing significant pressures with **multiple new vaccine introductions**.

DISCUSSION

Thank you

Immunity and Protection with TCV

TyVAC Typhoid Vaccine Acceleration Consortium

CENTER FOR VACCINE DEVELOPMENT • OXFORD VACCINE GROUP • PATH

Photo: PATH/Asad Zaidi

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Phase 3 Efficacy Analysis of a Typhoid Conjugate Vaccine Trial in Nepal

Mila Shakya, M.P.H., Rachel Colin-Jones, M.A., Katherine Theiss-Nyland, Ph.D., Merryn Voysey, D.Phil., Dikshya Pant, F.C.P.S., Nicola Smith, M.B., B.Chir., Xinxue Liu, Ph.D., Susan Tonks, B.Sc., Olga Mazur, B.Sc., Yama G. Farooq, M.Sc., Jenny Clarke, Ph.D., Jennifer Hill, Ph.D., Anup Adhikari, M.A., Sabina Dongol, D.Phil., Abhilasha Karkey, D.Phil., Binod Bajracharya, M.D., Sarah Kelly, M.Sc., Meeru Gurung, M.D., Stephen Baker, Ph.D., Kathleen M. Neuzil, M.D., Shrijana Shrestha, M.D., Buddha Basnyat, F.R.C.P.E., and Andrew J. Pollard, F.Med.Sci., for the TyVAC Nepal Study Team*

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Safety and Efficacy of a Typhoid Conjugate Vaccine in Malawian Children

Priyanka D. Patel, M.B., B.S., Pratiksha Patel, M.B., B.S., Yuanyuan Liang, Ph.D., James E. Meiring, Ph.D., Theresa Misiri, M.P.H., Felistas Mwakiseghile, M.Sc., J. Kathleen Tracy, Ph.D., Clemens Masesa, M.Sc., Harrison Msuku, B.Sc., David Banda, B.Sc., Maurice Mbewe, B.Sc., Marc Henrion, Ph.D., Fiyinfolu Adetunji, M.P.H., Kenneth Simiyu, Ph.D., Elizabeth Rotrosen, A.B., Megan Birkhold, M.D., Nginache Nampota, M.B., B.S., Osward M. Nyirenda, B.Sc., Karen Kotloff, M.D., Markus Gmeiner, M.Sc., Queen Dube, Ph.D., Gift Kawalazira, M.B., B.S., Matthew B. Laurens, M.D., Robert S. Heyderman, Ph.D., Melita A. Gordon, M.D., and Kathleen M. Neuzil, M.D., for the TyVAC Malawi Team

Protection by vaccination of children against typhoid fever with a Vi-tetanus toxoid conjugate vaccine in urban Bangladesh: a cluster-randomised trial

Firdausi Qadri, Farhana Khanam*, Xinxue Liu*, Katherine Theiss-Nyland, Prasanta Kumar Biswas, Amirul Islam Bhuiyan, Faisal Ahmmed, Rachel Colin-Jones, Nicola Smith, Susan Tonks, Merryn Voysey, Yama F Mujadidi, Olga Mazur, Nazmul Hasan Rajib, Md Ismail Hossen, Shams Uddin Ahmed, Arifuzzaman Khan, Nazia Rahman, Golap Babu, Melanie Greenland, Sarah Kelly, Mahzabeen Ireen, Kamrul Islam, Peter O'Reilly, Karin Sofia Scherrer, Virginia E Pitzer, Kathleen M Neuzil, K Zaman, Andrew J Pollard†, John D Clemens†*

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Summary

Background Typhoid fever remains a major cause of morbidity and mortality in low-income and middle-income countries. Vi-tetanus toxoid conjugate vaccine (Vi-TT) is recommended by WHO for implementation in high-burden countries, but there is little evidence about its ability to protect against clinical typhoid in such settings.

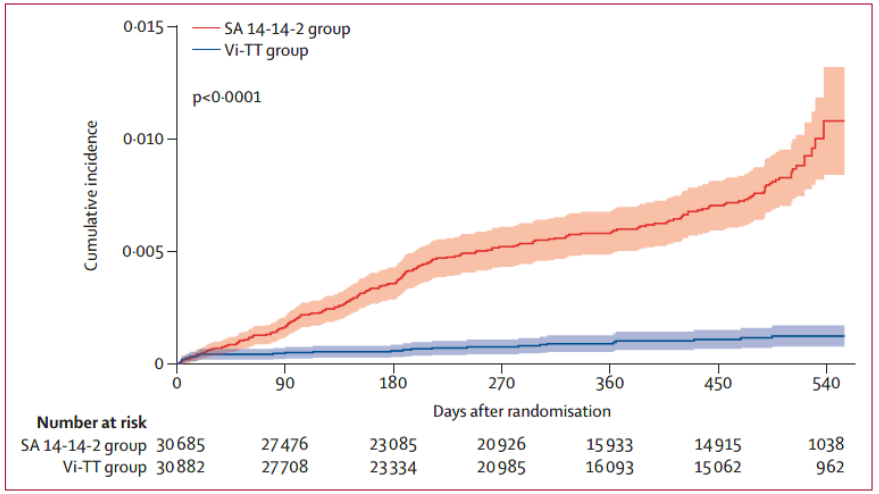
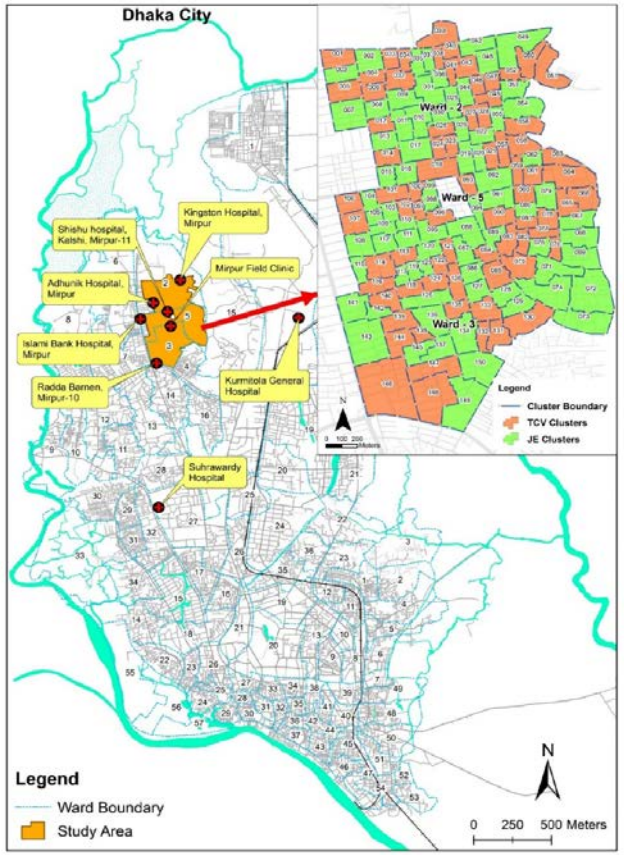


Figure 2: **The cumulative incidence of blood culture-confirmed typhoid fever among vaccinees by treatment group**
SA 14-14-2=Japanese encephalitis vaccine. Vi-TT=Vi-tetanus toxoid conjugate vaccine.

- Population of 205,760
- 150 geographic clusters
- Vi-TT or JE vaccine (75 clusters for each)
- 30,000 children vaccinated in each arm of the study = total 60,000

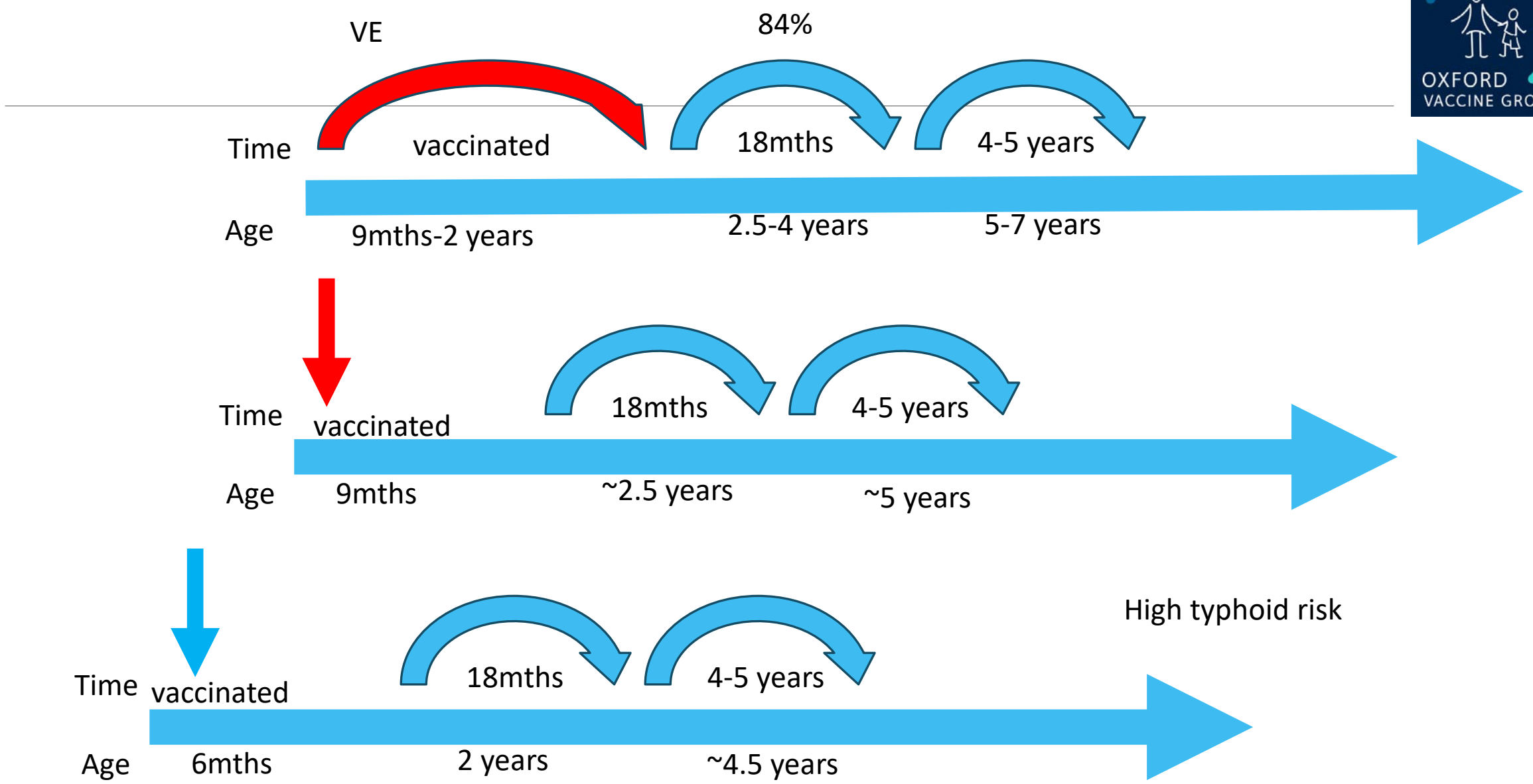


Study area: Mirpur (wards 2, 3 and 5), Dhaka

	Events/person-years†		Incidence, per 100 000 person-years		Protective effectiveness	p value	p value for interaction
	SA 14-14-2 group	Vi-TT group	SA 14-14-2 group	Vi-TT group			
Total vaccine protection							
9 months to <2 years	23/2804	4/2800	820 (520 to 1231)	143 (39 to 366)	81% (39 to 94)	0·0052	0·19
2 to 4 years	62/6413	12/6173	967 (741 to 1239)	194 (100 to 340)	80% (62 to 89)	<0·0001	..
5 to <16 years†	107/21 037	13/21 375	509 (417 to 615)	61 (32 to 104)	88% (78 to 93)	<0·0001	..
Overall vaccine protection							
<2 years	35/7779	13/7861	450 (313 to 626)	165 (88 to 283)	63% (20 to 83)	0·011	0·056
2 to 4 years	86/9295	34/9041	925 (740 to 1143)	376 (260 to 526)	59% (40 to 73)	<0·0001	..
5 to <16 years	141/32 316	50/32 462	436 (367 to 515)	154 (114 to 203)	65% (50 to 75)	<0·0001	..
≥16 years†	69/106 069	47/105 085	65 (51 to 82)	45 (33 to 59)	33% (−2 to 55)	0·061	..
Indirect vaccine protection							
<2 years	12/4846	8/4913	248 (128 to 433)	163 (70 to 321)	32% (−127 to 80)	0·53	0·38
2 to 4 years	24/2884	23/2880	832 (533 to 1238)	799 (506 to 1198)	6% (−78 to 51)	0·84	..
5 to <16 years	34/11 415	37/11 227	298 (206 to 416)	330 (232 to 454)	−13% (80 to 29)	0·60	..
≥16 years†	69/106 061	47/105 081	65 (51 to 82)	45 (33 to 59)	33% (−2 to 55)	0·060	..

Data are incidence rate/person-years, n (95% CI), or % (95% CI). SA 14-14-2=Japanese encephalitis vaccine. Vi-TT=Vi-tetanus toxoid conjugate vaccine. *Age at vaccination for the subgroup analyses of total vaccine protection, and age at date of residence for that of overall and indirect vaccine protection analyses; protective effectiveness, p values and CIs were adjusted for the stratifying variables for randomisation, including geographical ward, distance to study clinics, number of eligible children at baseline, and other baseline covariates prespecified in the statistical analysis plan, including age, sex, toilet type in the house, drinking water source, treatment of drinking water, handwashing before meals, and handwashing after defecation. †11 vaccinees were ≥16 years at vaccination and were included in the total vaccination analysis of the 5 to <16 years age group, resulting in a 12 person-years difference between overall and indirect vaccine protection analysis of the ≥16 years age group.

Table 3: **Incidence of blood culture-confirmed typhoid fever and protective effectiveness of Vi-TT by age group***


VE
84%
Time
vaccinated
18mths
4-5 years
Age
9mths-2 years
2.5-4 years
5-7 years
Time
vaccinated
18mths
4-5 years
Age
9mths
~2.5 years
~5 years
High typhoid risk
Time
vaccinated
18mths
4-5 years
Age
6mths
2 years
~4.5 years

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icddr,b

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Product Development for Vaccines Advisory Committee (PDVAC) Hybrid Consultation

Salmonella vaccines session

Invasive non-typhoidal Salmonella (iNTS) vaccines
Clinical Development Plan Considerations

Jean-Louis Excler
Program Director, New Initiatives

13 December 2023

International Vaccine Institute

CDP Considerations - Background

- There is no iNTS vaccine available for use in humans. Several potential candidate vaccines against iNTS and combination with TCV are being developed.

- Vaccine development considerations include a bivalent iNTS vaccine (*S.* Typhimurium and *S*. Enteritidis) or a trivalent vaccine (*S.* Typhi/iNTS). https://doi.org/10.1093/ofid/ofad041

- iNTS + TCV trivalent is considered a worthwhile endeavour (PDVAC Feb 2022)

- Following initial discussion with Wellcome Trust and other subject-matter experts, the project recently shifted from bivalent iNTS to a **trivalent (iNTS + S. Typhi CV) vaccine Full Value of Vaccine Assessment (FVVA).**

CDP Considerations for a Trivalent vaccine - 1

- TCV + iNTS vaccine
- Organize very early in the CDP a regulatory consultation on requirements for pathway to licensure and WHO PQ post licensure.
- Phase 1 and Phase 2a do not pose particular challenges:
  - Phase 1 FHI:
    - Dose exploration, Safety & Immunogenicity, randomized, placebo-controlled
    - Healthy participants aged 19-45yr in country of manufacturer and once preliminary safety and immuno data are available, expanded in endemic country with ML3 NRA
  - Phase 2a
    - Age de-escalation, Safety & Immunogenicity
    - Adult, (≥19yr), older children and adolescents (5-<19yr), young children (12mo-<5yr), infants (6-<12mo) in an endemic country

CDP Considerations for a Trivalent vaccine - 2

- Optimal age range of vaccination
  - 6 mo to 3 years of age (high incidence age range)
    - ✓ OK for 2b/3 efficacy study
    - ✓ However, envisage upfront 6 mo to 5 yrs with inflation of the sample size in the 6 mo -3 yrs age strata (preferred by manufacturers and policy makers): less restrictive, offer the possibility of late booster at 5 yrs
  - Lower age range (<6 mo) could be studied post licensure
- Regimen
  - primary series: 1 dose regimen at 6 mo
  - booster dose at 12 mo
  - In Phase 2a, 2b and 3, make provision of a follow-up for additional booster at 5 years
  - Intramuscular injection for trivalent when TCV administered IM; Oral administration

CDP Considerations for a Trivalent vaccine - 3

- Phase 2b and Phase 3 do pose challenges
  - Although there is no consensus yet as to whether efficacy could rely only on immunogenicity assessments and on immune correlates of protection in CHIM studies it is believed that clinical endpoint efficacy trials would have the preference for regulators and policy makers and would be feasible in highly endemic countries (high incidence).
  - CHIM is not considered as a gatekeeper to current clinical development plans but CHIM data may support clinical efficacy data and generate confidence.
    - ✓ What if the CHIM data are not supporting protection, what do we do?

CDP Considerations for a Trivalent vaccine - 4

- Phase 2b and Phase 3
  - Envisage a seamless Phase 2b/3 efficacy trial
  - Healthy children aged 6 mo to 5yrs in endemic countries
  - RCT, clinical efficacy & safety + L2L comparison
  - Trivalent iNTS/TCV vs Placebo - Non-enteric vaccine instead of placebo?
  - 1-year vs 2-year follow-up
  - Make provision for identification of immune correlates of protection with sufficient sample size of collected blood samples in vaccine recipients (micromethod for children)

CDP Considerations for a Trivalent vaccine - 5

- To support the CDP, consensus and alignments are needed on:
  - Clinical efficacy endpoints
  - Immunological endpoints
    - ✓ Standardization of assays
    - ✓ Primary immuno endpoints: ELISA
    - ✓ Secondary immuno endpoints: functional assays (bactericidal and systems serology)
  - Time points of assessments

CDP Considerations for a Trivalent vaccine - 6

- Effectiveness studies to assess the vaccine impact of iNTS burden of disease

- Envisage separate studies on the reciprocal impact of iNTS / trivalent vaccine and of malaria vaccine on iNTS and malaria immunogenicity and clinical burden of disease.

Non-prescriptive example of CDP to TCV/iNTS trivalent vaccine

Phase	Design	Target Population	Tentative Sample Size
I	Dose exploration, Safety & Immunogenicity FHI	Healthy participants aged 19-45yr in country of manufacturer and with preliminary safety and immuno data staggered in endemic country with ML3 NRA	~100 (TBC)
IIa	Age de-escalation, Safety & Immunogenicity	Adult, (≥19yr), older children and adolescents (5-<19yr), young children (12mo-<5yr), infants (6-<12mo) in an endemic country	~300 (TBC)
IIb	RCT, Efficacy & Safety + L2L Trivalent iNTS/TCV vs Placebo	Healthy children aged 6 months to 5yrs in endemic countries [80% power, 2:1 vaccine to placebo, alpha = 2.5% one-sided, 20% loss-to-follow-up, VE=60%, LB of 95% CI=0%]	~6000 /1 yr f/u ~3000 /2-yr f/u
III	RCT, Efficacy & Safety + L2L+ immuno of Trivalent iNTS/TCV vs Placebo	Healthy children aged 6 mo to 5 yrs in endemic countries [90% power, 2:1 vaccine to placebo, alpha = 2.5% one-sided, 20% loss-to-follow-up, VE=60%, LB of 95% CI=30%]	~20000 /1 yr f/u ~10500 /2-yr f/u
IV	RCT, Safety, immuno non-inferiority study of Trivalent iNTS/TCV vs Placebo	Healthy children < 6 mo in endemic countries	~1000 (TBC)
	Immune Non-Interference with EPI vaccines (including malaria-vaccinated)	Healthy children aged 6-12mo in an endemic country	~300 (TBC)
	Effectiveness Study /Mass Campaign	Healthy & HIV+, malaria-infected vs malaria-vaccinated participants aged <6mo to 45yr in an endemic countries	~100,000 (TBC)

CDP Considerations for a Trivalent vaccine - 7

- Regulatory consultation(s)
  - Engage as soon as possible with regulators by constituting a regulatory expert committee to discuss pathway to licensure with NRAs, WHO, developers, manufacturers, NITAGs, RITAGs, and donors
  - Some (preliminary) suggested questions:

a. Phase 2b/3 efficacy trial based on clinical endpoints in 6mo-5 years of age children with increase of sample size in the 6mo-3 yrs) (6mo-3yrs may suffice because of the highest incidence but regulators and manufacturers may prefer to give the opportunity of an extended age range of use upfront for licensure). Although an extension 3-5 yrs could also be envisaged post licensure, perhaps not the preferred pathway.
b. Since there is no iNTS vaccine as comparator, placebo remains the standard in efficacy trials. However, this may not be acceptable in children. Should an active non-enteric vaccine comparator be considered?
c. Would data of a human challenge study conducted in parallel to Phase 2b add value to licensure from a regulatory perspective?
d. TCV is licensed with one dose. It is assumed that conjugated iNTS would follow the same pattern, to be demonstrated though
e. Should 1 vs 2 doses as primary series be tested in a Phase 2a? If the second dose does not add to the first for iNTS abs, fine. If not, should a booster dose of the TCV+iNTS be considered after one dose a primary (e.g., 12 mo, 5 yrs)?


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