Salmonella vaccine development: Focus on TCVs and iNTS vaccines

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GVIRF 2021

International Vaccine Institute

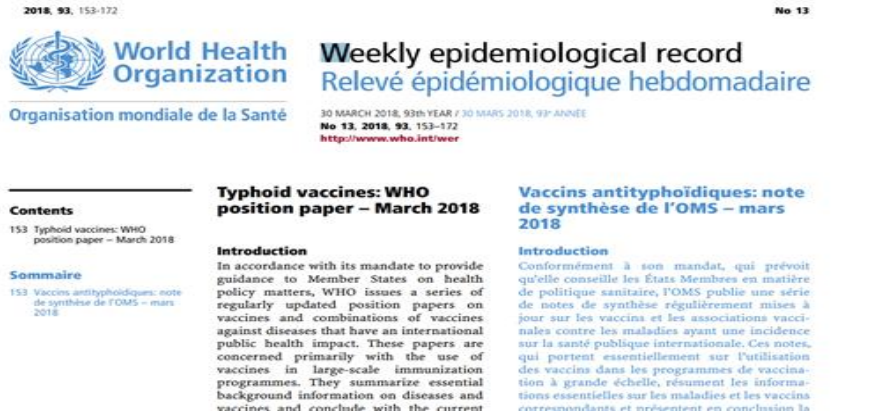
Agenda

- Landscape of TCVs
  - Vi-rEPA
  - BBIL
  - Biomed
  - Zidus
  - Biological E
  - SK Bioscience
  - Biofarma

- TCV: Next steps and challenges
- iNTS background and disease burden
- iNTS vaccines current status

Policy and Financing

- Policy:
  - WHO position paper: 2008; revised in 2018
  - Recommended use of TCV
- Vaccine supply:
  - 4 licensed in India
  - Typbar-TCV and TYPHIBEV prequalified by WHO
- Financing:
  - Gavi board has approved $85M for TCV and the call is open for eligible countries to apply


2018, 93, 153-172 No 13

World Health Organization

Organisation mondiale de la Santé

Weekly epidemiological record

Relevé épidémiologique hebdomadaire

30 MARCH 2018, 93th YEAR / 30 MARS 2018, 93e ANNÉE

No 13, 2018, 93, 153–172

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Typhoid vaccines: WHO position paper – March 2018

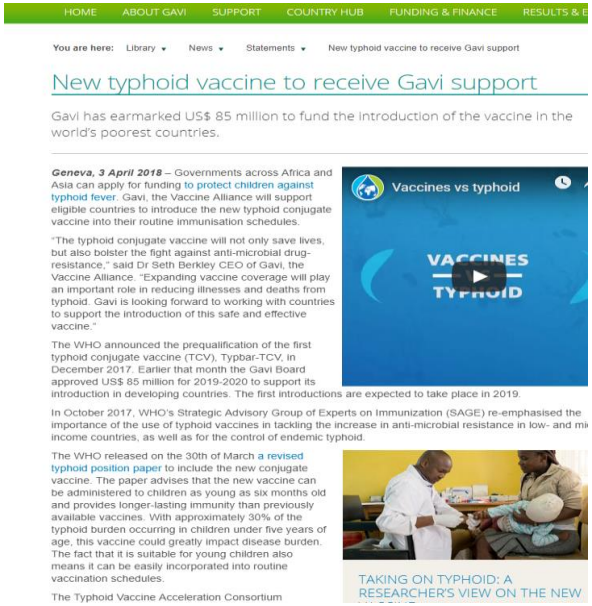
Introduction

In accordance with its mandate to provide guidance to Member States on health policy matters, WHO issues a series of regularly updated position papers on vaccines and combinations of vaccines against diseases that have an international public health impact. These papers are concerned primarily with the use of vaccines in large-scale immunization programmes. They summarize essential background information on diseases and

Vaccins antityphoïdiques: note de synthèse de l'OMS – mars 2018

Introduction

Conformément à son mandat, qui prévoit qu'elle conseille les États Membres en matière de politique sanitaire, l'OMS publie une série de notes de synthèse régulièrement mises à jour sur les vaccins et les associations vaccinales contre les maladies ayant une incidence sur la santé publique internationale. Ces notes, qui portent essentiellement sur l'utilisation des vaccins dans les programmes de vaccination à grande échelle, résument les informations essentielles sur les maladies et les vaccins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New typhoid vaccine to receive Gavi support

Gavi has earmarked US$ 85 million to fund the introduction of the vaccine in the world's poorest countries.

Geneva, 3 April 2018 – Governments across Africa and Asia can apply for funding to protect children against typhoid fever. Gavi, the Vaccine Alliance will support eligible countries to introduce the new typhoid conjugate vaccine into their routine immunisation schedules.

"The typhoid conjugate vaccine will not only save lives, but also bolster the fight against anti-microbial drug-resistance," said Dr Seth Berkley CEO of Gavi, the Vaccine Alliance. "Expanding vaccine coverage will play an important role in reducing illnesses and deaths from typhoid. Gavi is looking forward to working with countries to support the introduction of this safe and effective vaccine."

Vaccines vs typhoid

VACCINES TYPHOID

The WHO announced the prequalification of the first typhoid conjugate vaccine (TCV), Typbar-TCV, in December 2017. Earlier that month the Gavi Board approved US$ 85 million for 2019-2020 to support its introduction in developing countries. The first introductions are expected to take place in 2019.

In October 2017, WHO's Strategic Advisory Group of Experts on Immunization (SAGE) re-emphasised the importance of the use of typhoid vaccines in tackling the increase in anti-microbial resistance in low- and mi income countries, as well as for the control of endemic typhoid.

The WHO released on the 30th of March a revised typhoid position paper to include the new conjugate vaccine. The paper advises that the new vaccine can be administered to children as young as six months old and provides longer-lasting immunity than previously available vaccines. With approximately 30% of the typhoid burden occurring in children under five years of age, this vaccine could greatly impact disease burden. The fact that it is suitable for young children also means it can be easily incorporated into routine vaccination schedules.

The Typhoid Vaccine Acceleration Consortium

TAKING ON TYPHOID: A RESEARCHER'S VIEW ON THE NEW

Vi-rEPA clinical trials (First TCV developed)

phase I and II
- Safety and immunogenicity in adults, teenagers, and 2-4 year olds (Kossaczka 1999)
- 382 participants; 2 doses of Vi-rEPA1 and Vi-rEPA2

phase III
- Efficacy in 2 to 5 years old (Lin et al 2001)
- 12,008 children (at least 1 dose); 91% efficacy (89 at the end of 4 years)

Dose-ranging
- Dose (5, 12.5, 25 µg of Vi) study in 2-5 years old (Canh et al 2004)
- 241 children, 2 injections 6 weeks apart for all three doses; dose-related response observed, 25 was recommended for > 2 while for < 2, 12.5 and 25 were tested

Infant
- Concomitant administration with routine infant vaccines (Thiem et al 2011)
- 318 infants, suppressive effect of high levels of maternally-derived IgG antibody was observed

- US NIH transferred the technology to Lanzhou Institute of Biological Products (LIBP), part of the China National Biologics Group (CNBG)
- LIBP conducted additional trials and with the help from PATH, are working to get in-country licensure in China and eventual WHO PQ

Typbar-TCV

- First WHO Prequalified TCV (2018)
- Licensed in India plus multiple other countries
- Underwent human challenge study at Oxford University
- Being used in all efficacy, delivery campaigns and effectiveness studies as below:
  - Nepal: 25000 participants
  - Bangladesh: 50000 participants
  - Pakistan: 250000 participants
  - Malawi: 24000 participants
  - Navi Mumbai, India: 200000 participants
- Gavi supported vaccination campaigns started in Pakistan, Zimbabwe, Liberia
- Ongoing and additional campaigns are affected by COVID-19

Navi Mumbai Municipal Corporation launches the world's first public-sector typhoid conjugate vaccine campaign

Posted on September 17, 2018 by Dr. Kashmira Date, Medical Officer, Global Immunization Division, Center for Global Health, US Centers for Disease Control and Prevention

In Photos: A new vaccine to combat XDR typhoid in Pakistan

Posted on November 15, 2018 by Megan Carey, Bill & Melinda Gates Foundation

Drug resistance and typhoid in Zimbabwe: Using TCVs for outbreak control

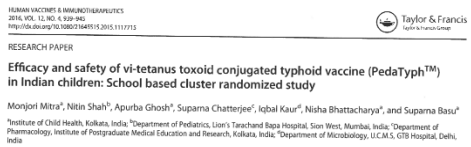
Posted on November 12, 2018 by Jessica Mooney, PATH

THECA
Typhoid conjugate vaccine introduction in Africa

TyVAC Typhoid Vaccine Acceleration Consortium

Pedatyph™: Vi-TT (Biomed)

- Licensed for more than 3 months of age in 2008 in India.
- Single dose of 0.5 ml, followed by booster at 2.5 to 3 years age



HUMAN VACCINES & IMMUNOTHERAPEUTICS
2016, VOL. 12, NO. 4, 939–945
http://dx.doi.org/10.1080/21645515.2015.1117715

Taylor & Francis

RESEARCH PAPER

Efficacy and safety of vi-tetanus toxoid conjugated typhoid vaccine (PedaTyph™) in Indian children: School based cluster randomized study

Monjori Mitra[a], Nitin Shah[b], Apurba Ghosh[a], Suparna Chatterjee[c], Iqbal Kaur[d], Nisha Bhattacharya[a], and Suparna Basu[a]

[a]Institute of Child Health, Kolkata, India; [b]Department of Pediatrics, Lion's Tarachand Bapa Hospital, Sion West, Mumbai, India; [c]Department of Pharmacology, Institute of Postgraduate Medical Education and Research, Kolkata, India; [d]Department of Microbiology, U.C.M.S, GTB Hospital, Delhi, India

Clinical Study

- Safety and immunogenicity in 169 subjects > 12 weeks with a comparison group (Vi) of 37 children > 2 years
- Four-fold or greater rise in antibody titer of each group on ELISA which was statistically equivalent to Vi-rEPA

- Effectiveness trial completed in Kolkata with 2000 children (6m to 12 years) http://ctri.nic.in/Clinicaltrials/showallp.php?mid1=4714&EncHid=&userName=Vi-TT
- 2 doses at 6 weeks interval in children 6 mths to 12 yrs
- Authors report 100% VE after 1 year of follow up
- No plans yet of WHO PQ application

ZYVAC TCV: Vi-TT (Zydus Cadila)

- Licensed in India (2018)
- Single dose 25ug from 6 months of age onwards
- Being marketed in the private market in India
- Plans to go for WHO PQ

Vi-CRM_{197} (GVGH): TYPHIBEV

- Developed by GSK Vaccines Institute for Global Health (GVGH, formerly NVGH)
- Have used CRM_{197} as carrier protein
- CRM_{197} is a non-toxic mutant of diphtheria toxin

Phase I
- Safety and Immunogenicity of Vi-CRM_{197} Vaccine Against S. Typhi in Adult (18-40 Years Old). Found safe and immunogenic
- completed in Belgium, 50 participants

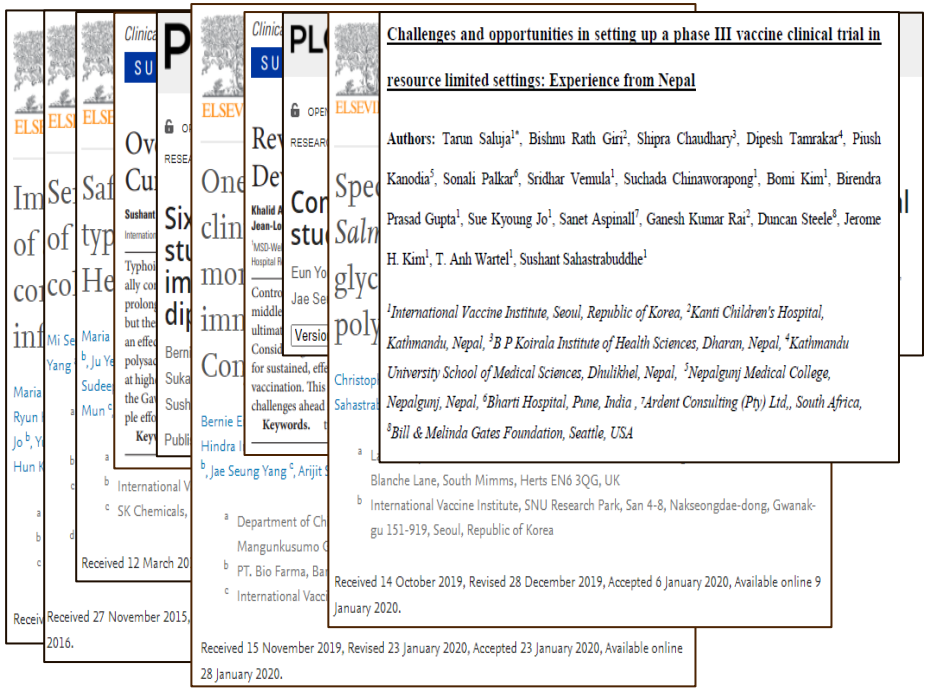
Phase II
- Safety and Immunogenicity of various Formulations (25, 12.5, 5, 1.25 µg) in Adults (18-40 Years Old).
- completed in Belgium, 88 participants

Phase II
- Safety, Reactogenicity and Immunogenicity of Vi-CRM197 Vaccine Against S. Typhi in Adults, Children, Older Infants (9 to 12 months) and Infants (6 weeks)
- 320 participants, studies completed in India, Philippines, and Pakistan

- Technology transferred to Biological E in 2013; BE further developed the vaccine, including manufacturing process optimization and scale-up; preclinical and clinical studies were completed in India
- After DCGI approval in March 2020, TYPHIBEV was prequalified by WHO in December 2020

Vi-DT: SK Bioscience

- Technology transfer completed in 2013 from IVI
- Preclinical studies completed in 2015
- Phase I and II clinical trials completed in the Philippines
- Concurrent phase III studies in Nepal and Philippines completed
- KMFDS submission done in Jan 2021, WHO PQ submission targeted for Sep 2021



Challenges and opportunities in setting up a phase III vaccine clinical trial in resource limited settings: Experience from Nepal

Authors: Tarun Saluja[1*], Bishnu Rath Giri[2], Shipra Chaudhary[3], Dipesh Tamrakar[4], Piush Kanodia[5], Sonali Palkar[6], Sridhar Vemula[1], Suchada Chinaworapong[1], Bomi Kim[1], Birendra Prasad Gupta[1], Sue Kyoung Jo[1], Sanet Aspinall[7], Ganesh Kumar Rai[2], Duncan Steele[8], Jerome H. Kim[1], T. Anh Wartel[1], Sushant Sahastrabuddhe[1]

[1]International Vaccine Institute, Seoul, Republic of Korea, [2]Kanti Children's Hospital, Kathmandu, Nepal, [3]B P Koirala Institute of Health Sciences, Dharan, Nepal, [4]Kathmandu University School of Medical Sciences, Dhulikhel, Nepal, [5]Nepalgunj Medical College, Nepalgunj, Nepal, [6]Bharti Hospital, Pune, India , [7]Ardent Consulting (Pty) Ltd., South Africa, [8]Bill & Melinda Gates Foundation, Seattle, USA

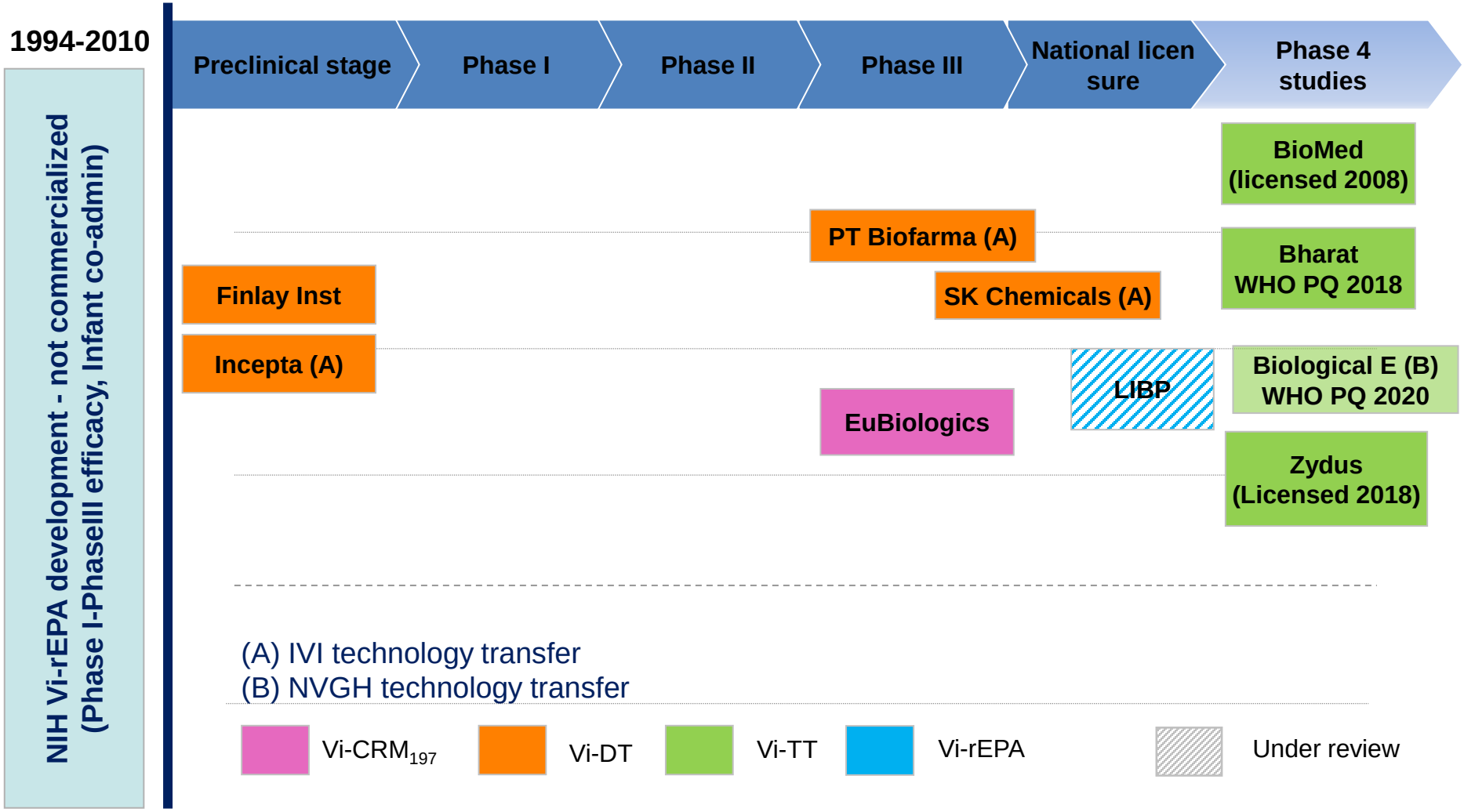
Brief overview of Vi-DT SK clinical trials

Phase	Study Design	Sample size	Test Vaccine /Comparator	Country	Status	Safety Database (test vaccine)
I	Safety & Immunogenicity	144 subjects (2-45 yrs)	Vi-DT, 25 µg/0.5 mL SD/ Typhim Vi®	Philippines	Completed	72 subjects
Obser-vational study	Phase I Long-term follow up study	144 subjects (2-45 yrs)	N/A	Philippines	Year 3 completed	-
II	Safety & Immunogenicity	285 subjects (6-23 months)	Vi-DT, 25 µg/0.5 mL SD/ Fluquadri/ Placebo	Philippines	Ongoing, pCSR available in Sep 2019	228 subjects
Obser-vational study	Phase II Long-term follow up study *(TBD)*	285 subjects (6-23 months)	N/A	Philippines	Target start (2021)	-
III	Immune Non-inferiority, L2L Consistency & Safety	1800 subjects (6 mths-45 yrs) 360 (MMR)	Vi-DT, 25 µg/0.5 mL MD/ Typbar TCV™	Nepal	Completed	Approx. 1350 (+180) subjects
III	Immune Equivalence & Safety	1800 subjects (6 mths-45yrs)	Vi-DT, 25 µg/0.5 mL SD/ MD	Philippines	Completed	Approx. 1500 subjects
					Total Safety Vi-DT database	**Approx. 3330**

Biofarma Vi-DT

- Phase I study (completed): To generate safety and immunogenicity data in adults and children (100 subjects; 2 to 5 years old age and 18 to 40 years old age)
  - Progress/result: 100% seroconversion (defined as four-fold rise in titer) after first dose in both adult and children Vi-DT group; while 88% in control group. No rise in GMT after the second dose; Data published in “PLoS One”.
- Phase II study (on-going): To generate safety and immunogenicity data in 6 months to 40 years of age participants (600 subjects; 6 months to 40 years old)
  - Progress/result: Satisfactory data in infants. Infants group shows highest response followed by adults and children groups per the GMT. 100% seroconversion is seen in adults and children groups and 98% in infants' group. Data published in “IJID”.
- Phase III study (on-going): To evaluate immunogenicity of Vi-DT compared to WHO PQ’ed vaccine in adults, children and infants (3,071 subjects; 6 months to 60 years old)
  - Initiated study in Jan 2020. Due to severe cases of COVID-19 in Indonesia, enrollment was on-hold till December 2020, restarted again.

Typhoid conjugate vaccine pipeline



Slide courtesy: Dr Adwoa Bentsi-Enchill

Next steps and Challenges

- There will be at least 2 more WHO PQed vaccines by 2022-23 with robust manufacturing capacity; however, the demand is uncertain
  - Lack of clarity of disease burden
  - Limited data from some regions (LatAm, North Africa, Middle-East)
  - Choice of vaccination strategy
  - Focal outbreaks of typhoid
- Lot of work is still needed around generating the potential health impact from TCVs
- A strong network of global and national partners, policy makers, and healthcare workers is needed to realize the dream of typhoid elimination

Steele et al 2020

Why iNTS?

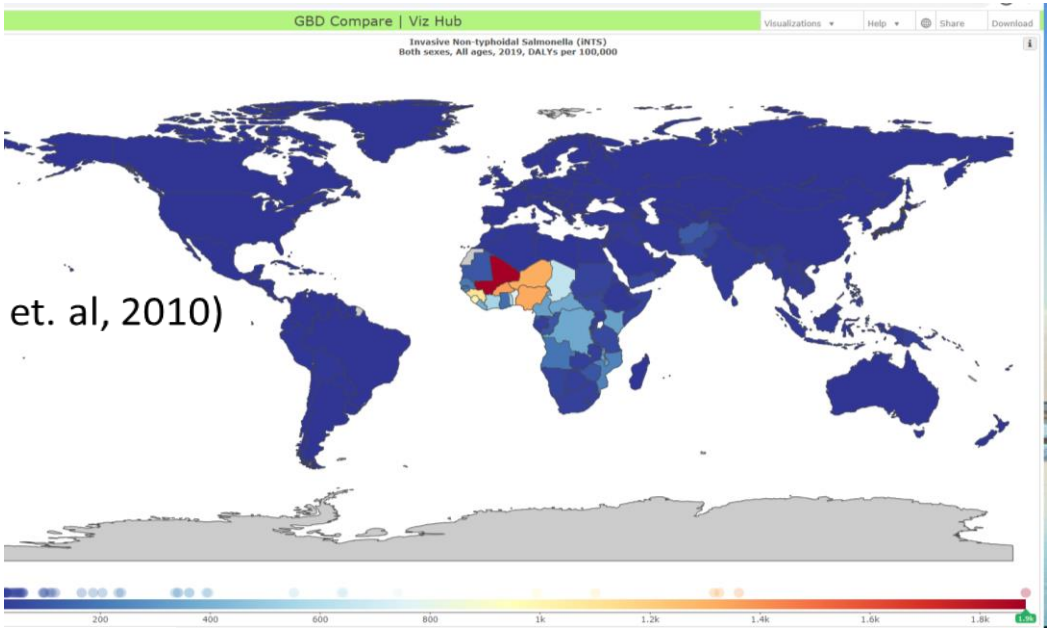
- The burden of iNTS disease, caused by Salmonella Typhimurium and Salmonella Enteritidis, is a serious public health concern in Sub-Saharan Africa
- 600,000 to 3.4M cases of iNTS disease occurred globally in 2010*. >50% of cases of iNTS disease occur in Sub-Saharan Africa. Case-fatality rates commonly reported at ~15-20%
- ~622,000 cases estimated in 2017 (490,000 – 800,000). ~68,000 deaths in 2017**
- High prevalence of iNTS disease seen in children under 3 years of age
- Clinical presentation is most commonly with fever alone: diagnosis not usually possible
- Diagnosis requires blood culture facilities that are uncommon in Sub-Saharan Africa
- Antimicrobial drug resistance to iNTS isolates, including MDR, is common. Emergence of fluoroquinolone and ceftriaxone resistance makes treatment increasingly difficult
- Effective methods for disease control as improvement to water supply and sanitation is lagging and cost prohibitive in endemic countries

*Ao et al, 2015; **GBD, 2017

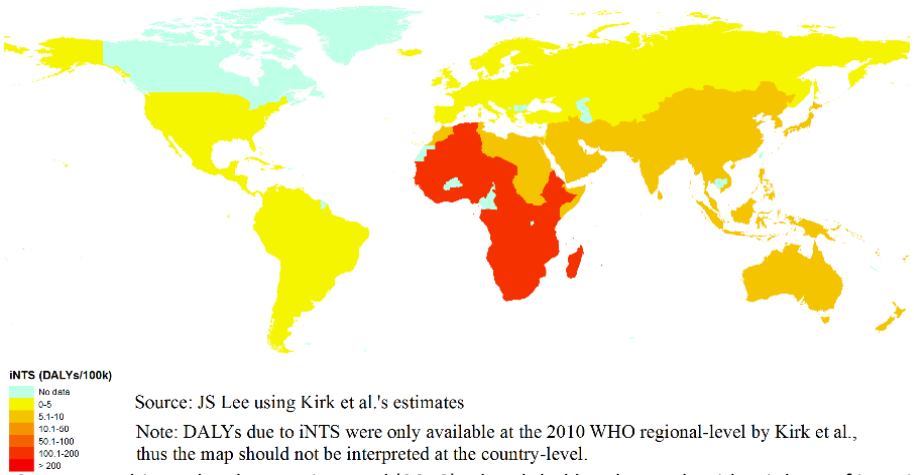
Slide courtesy: Cal McLennan and Duncan Steele, BMGF

iNTS burden: GBD 2019

Burden: mainly Sub-Saharan Africa
Incidence: 49.4 / 100k (Ao et al., 2010)
Deaths: 681,316[1] [415,165 – 1,301,520] (Ao et. al, 2010)
DALYs: 26 / 100k (Kirk et al., 2010)
*DALYs may be underestimated due to HIV
*Estimated at *region*, not *country* level



DALYs due to iNTS in 2010



Source: JS Lee using Kirk et al.'s estimates

Note: DALYs due to iNTS were only available at the 2010 WHO regional-level by Kirk et al., thus the map should not be interpreted at the country-level.

Source: Ruchita Balasubramanian et al (2018): The global burden and epidemiology of invasive non-typhoidal *Salmonella* infections, Human Vaccines & Immunotherapeutics, DOI: 10.1080/21645515.2018.1504717

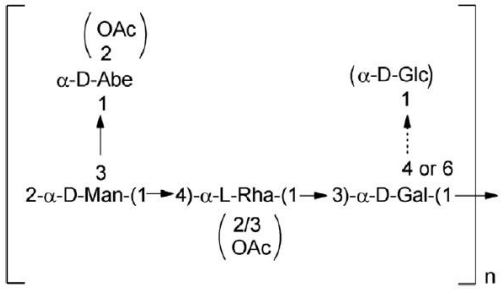
Global Landscape: iNTS vaccines

Name	Description	Developer	Stage of development	References
O:4,5/O:9-flagellin	O:4,5/O:9 Conjugate	University of Maryland	Preclinical	50,69
O:4,12-TT	O:4-TT Conjugate	NIH	Preclinical	51
Os-po	O:4-porin Conjugate	National Bacteriology Laboratory, Stockholm	Preclinical	146
O:4,5/O:9-CRM_{197}	O:4,5/O:9 Conjugate	NVGH	Preclinical	145
WT05	Live attenuated	Microscience, Wokingham Berkshire	Phase 1	147
CVD 1921 and CVD 1941	Live attenuated	University of Maryland	Preclinical	148
S. Typhimuirum ruvB mutant	Live attenuated	Seoul National University	Preclinical	149
Salmonella hfq deletion mutant	Live attenuated	Indian Institute of Science Bangalore	Preclinical	150
SA186	Live attenuated	Istituto Superiore di Sanità Roma	Preclinical	151
MT13	Live attenuated	KIIT University Odisha	Preclinical	152
Various	Live attenuated, DNA adenine methylase mutants	University of California, Santa Barbara	Preclinical	153,154
Various	Live attenuated, regulated delayed attenuation	Arizona State University	Preclinical	155-157
Porins	*S.* Typhimurium porins	National Bacteriology Laboratory, Stockholm	Preclinical	146
OmpD	Outer membrane protein	University of Birmingham, UK	Preclinical	73
S. Typhimurium and *S.* Enteritidis GMMA	Generalized Modules for Membrane Antigens	NVGH	Preclinical	65,158,159

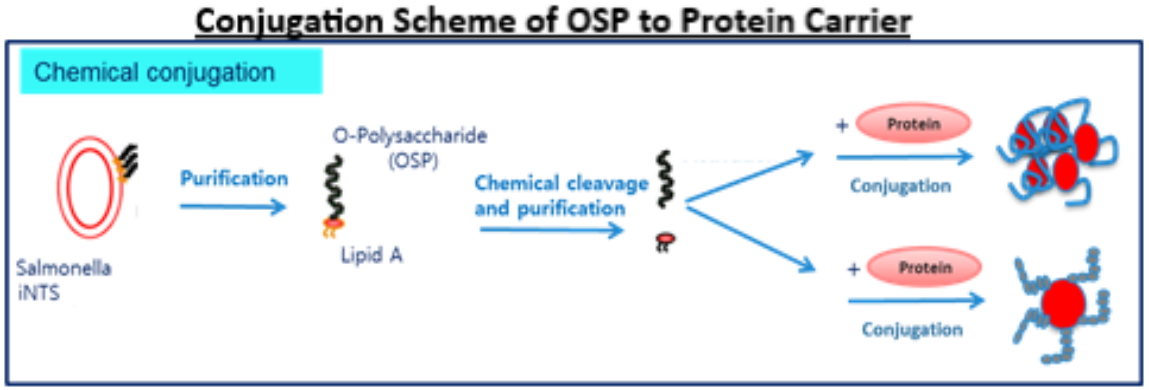
*an exhaustive list, particularly of all candidate vaccines in preclinical studies, is beyond the scope of this review

MacLennan CA, et al. Hum Vaccine Immunother 2014

IVI iNTS Vaccine Project - Current Status



Structure of the repeating unit of *S.* Typhimurium O-polysaccharide. The structural features that vary with the strain of origin are shown in curved brackets.



- POC of the trivalent vaccine concept (iNTS OSP conjugates, with Vi-conjugate) achieved, by demonstrating >90% seroconversion (defined as ≥4-fold increase of anti-OSP IgG over baseline) through immunogenicity testing in mice
- Process development to produce Purified O-Specific Polysaccharides of *S.* Typhimurium and *S.* Enteritidis through a scalable process completed at pilot scale
- Process development for producing conjugates of OSPs of ST and SE with carrier protein (Diphtheria Toxoid) through a scalable process completed at pilot scale
- Technology transfer to produce batches for Tox Study to be initiated in Mar 2021, with tox batches production planned in Q1-2022; Tox study completion & reporting expected by Q1-2023
- Work on Clinical Development Plan (CDP) and CDP initiation proposal in Q2-2022 for new grant submission to Funding Agencies to seamlessly move the project to the next stage upon completion of tox studies

Acknowledgements

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- SK bioscience
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- Incepta vaccines limited
- Bharat Biotech Ltd.
- Biomed
- Zydus Cadila
- Biological E
- Lanzhou Institute of Biological Products
- Finlay Institute
- Walvax
- Eubiologics

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- Olivier Lapujade
- Ivana Knezevic

Study sites

- Research Institute for Tropical Medicine, Philippines
- Dr. Cipto Mangunkusumo National General Hospital, Indonesia
- Sites in Nepal and Philippines

TyVAC Typhoid Vaccine Acceleration Consortium
CENTER FOR VACCINE DEVELOPMENT • OXFORD VACCINE GROUP • PATH

COALITION AGAINST TYPHOID a program of the Sabin Vaccine Institute

Regulatory Authorities

- Korean MFDS
- Philippines NRA
- Indonesia BPOM
- Nepal DDA
- Nepal NHRC

unicef

Gavi The Vaccine Alliance

ardent consulting

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IVI

THANK YOU

INTERNATIONAL VACCINE INSTITUTE