Typhoid Conjugate Vaccine Development: The Last mile?

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11th Typhoid conference

Hanoi, Vietnam

26th March 2019

International Vaccine Institute

What changed since Kampala 2017?

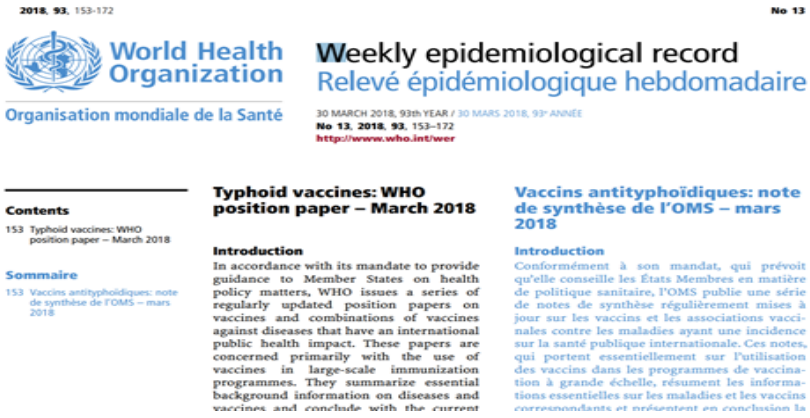
A lot….

In 2017,

- 2 TCVs licensed in India
- No TCV WHO Pqed
- WHO position paper 2008
- Gavi commitment, but pending WHO PQed TCV
- Unclear pathway for PQ
- No vaccine delivery projects

Policy and Financing (2019)

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



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Organisation mondiale de la Santé

Weekly epidemiological record

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

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Typhoid vaccines: WHO position paper – March 2018

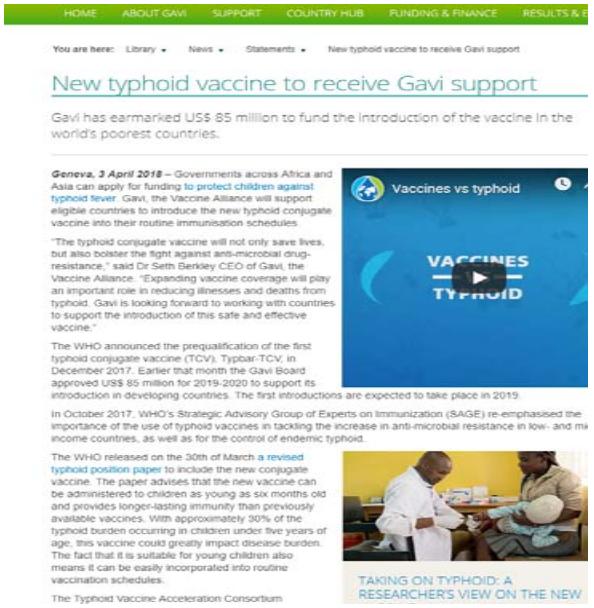
Introduction

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



HOME ABOUT GAVI SUPPORT COUNTRY HUB FUNDING & FINANCE RESULTS & I

You are here: Library News Statements New typhoid vaccine to receive Gavi support

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."

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.

Vaccines vs typhoid

VACCINES TYPHOID

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

Delivery

Three ongoing campaigns

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***

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

Posted on ***November 12, 2018*** *by* ***Jessica Mooney, PATH***

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

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

- Mumbai: 320,000 planned to be vaccinate d in 2 phases
- Pakistan: over 100,000 kids vaccinated
- Zimbabwe: more than 300,000 planned to be vaccinated

Effectiveness studies

- TyVAC consortium (Funded by BMGF):
  - 4 countries (Bangladesh, Nepal, Malawi, Burkina Faso)
  - Over 100,000 enrolled in the first 3 sites

- THECA consortium (Funded by EDCTP and BMGF):
  - 2 countries (Ghana and DRC)
  - Studies to initiate Q32019

These studies will collectively generate lot of data required by policymakers and will add to the existing knowledge gaps in TCV introduction

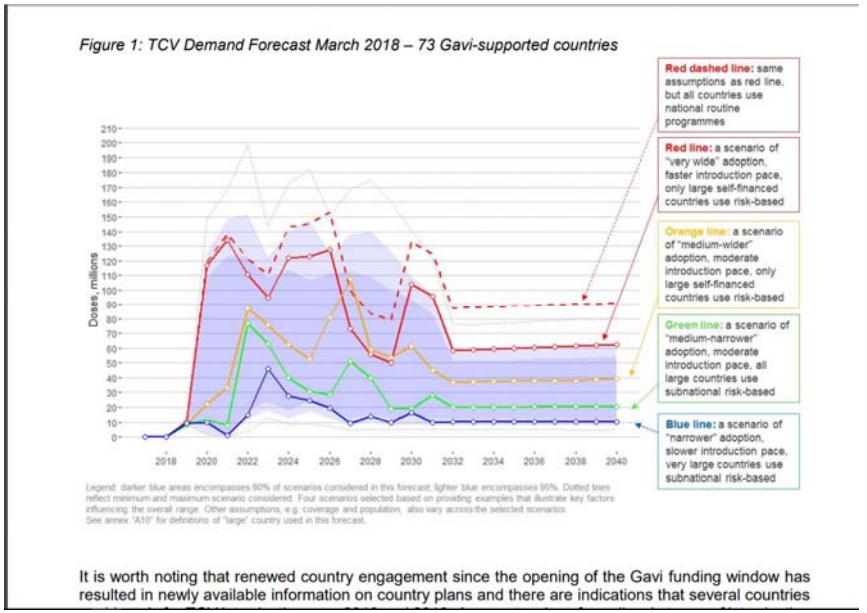
Road ahead….

- Lot of positives so far…..
  - Global typhoid community aligned
  - Major donors interested in typhoid prevention
  - Policy and financing pieces are moving well
  - Strong manufacturer with PQed vaccine
  - Multiple delivery and effectiveness studies

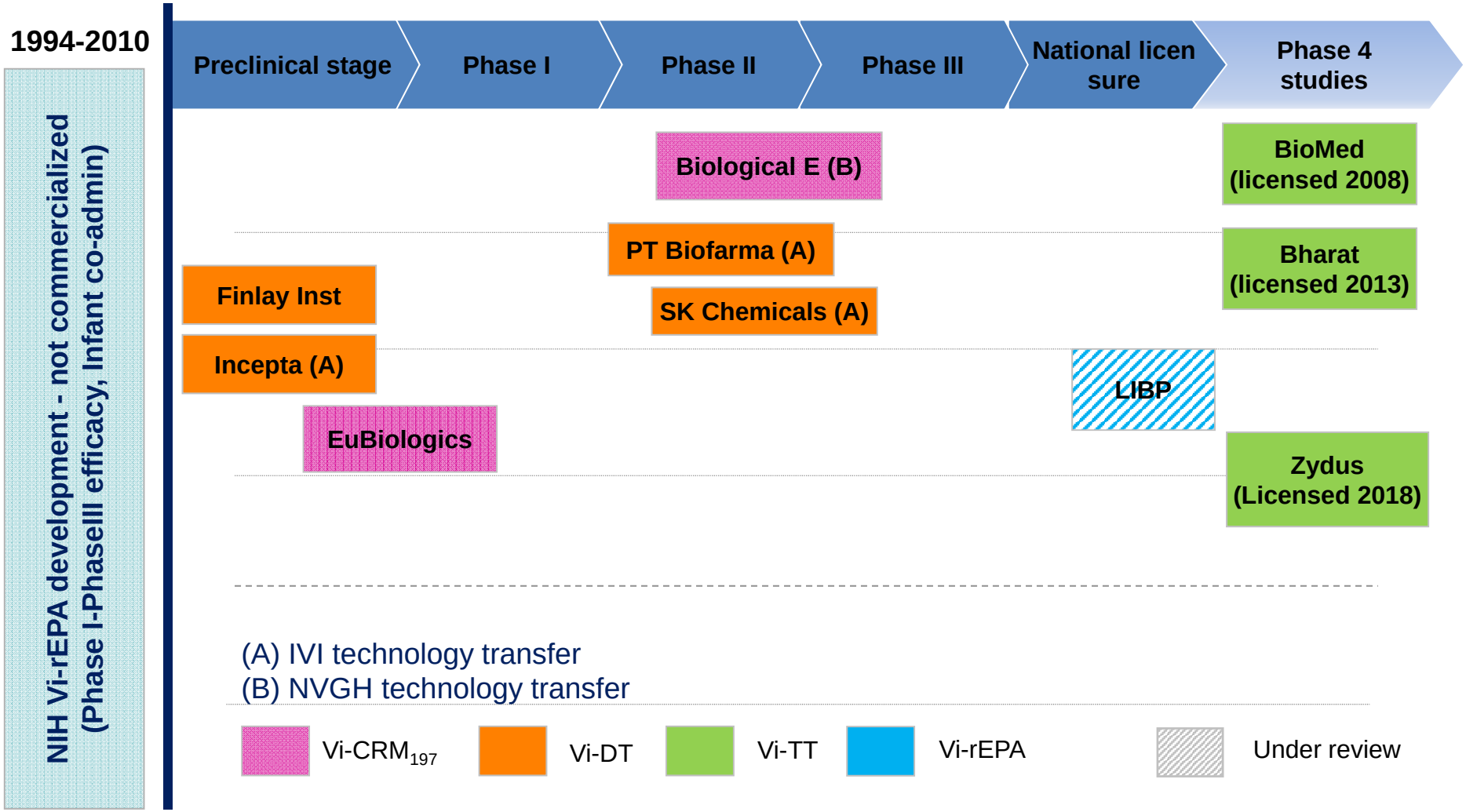
However, to keep the momentum, ***supply security*** will be a challenge…..

Vaccine Demand and Supply

- As for any new vaccine introductions, the demand is not clear and depends on various uptake scenario in the endemic countries
- Gavi's forecast:
  - Higher scenario: peaking at above 150 million doses in 2022, with a period of several years where demand could be well over 100 million doses per year, stabilizing later at levels above 70 million doses per year
  - Even with the lower scenario, demand is going to stabilize at >10M doses/year
- Multiple prequalified candidates will alleviate the supply insecurities and create healthy price competition

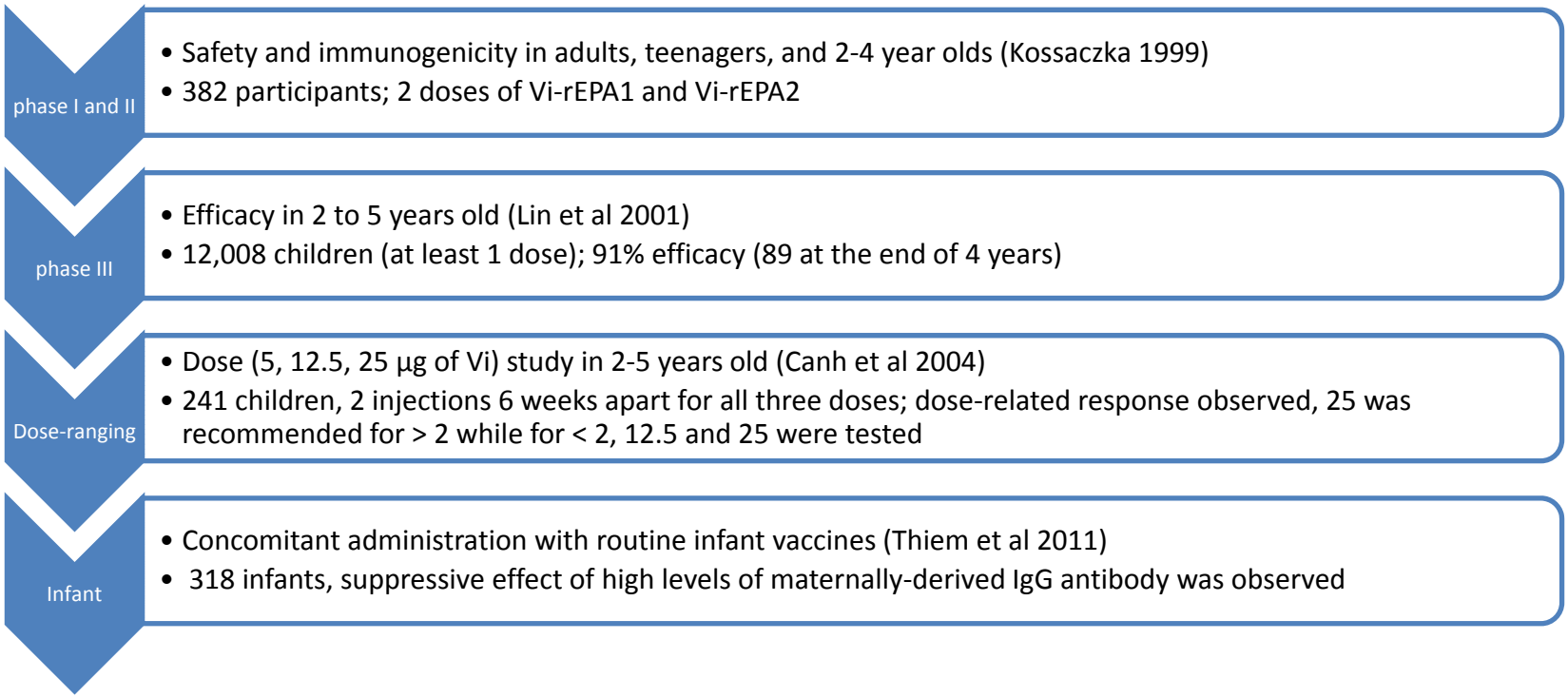


Typhoid conjugate vaccine pipeline



Slide courtesy: Dr Adwoa Bentsi-Enchill

Vi-rEPA clinical trials (First TCV developed)



- 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 have submitted for in-country licensure in China in 2013

Typbar-TCV

- First WHO Prequalified TCV (2018)
- Licensed in India plus 4 other countries
- Underwent human challenge study at Oxford University
- Being used in all delivery campaigns and effectiveness studies mentioned in the previous slides
- Only global public health market supplier of TCV for next 2 years

Vi-TT (Zydus Cadila)

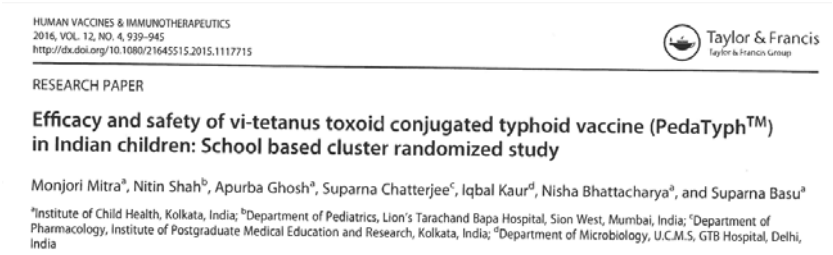
- Licensed in India (2018)
- Single dose 25ug from 6 months of age onwards
- Being marketed in the private market in India
- Plans to go for WHO PQ application in 2019

Vi-TT Pedatyph ™ (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

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



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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

- 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

Vi-CRM_{197} (GVGH)

- 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

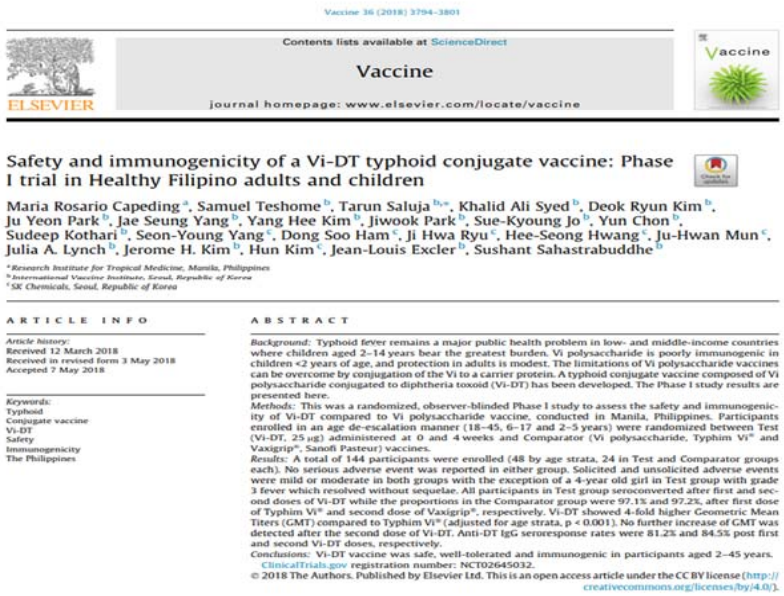
- Safety, Reactogenicity and Immunogenicity of Vi-CRM197 Vaccine Against S. Typhi in Adults, Children, Older Infants (9 to 12 months) and Infants (6 weeks)
- 320 participants, studies completed in India, Philippines, and Pakistan

Vi-CRM_{197} (GVGH)

- In summary,
  - Phase I and II in European adults → at least as immunogenic as ViPS *(van Damme et al. PLoS One 2011)*
  - Phase II in adults, children and infants in India, Pakistan and the Philippines (coadmin: msls 9 m, pentavalent & OPV at 6, 10, 14 wks) *(Bhutta et al. Lancet Infect Dis 2014)*
  - Anti-Vi IgG titers after 1 dose 5 µg Vi >= ViPS 25 µg (adults and children)
  - Immunogenic in 6-8 wk and 9-12 m infants (in latter, immune response equal or greater than 1 dose ViPS in children and adults).
  - **Antibody titers short-lived (~ 6 m); apparent lack of booster response.**
  - Technology transferred to Biological E, India and is currently in phase II/III clinical trial

Vi-DT: SK Bioscience

- Technology transfer completed in 2013 from IVI
- Preclinical studies completed in 2015
- Phase I clinical trial completed in the Philippines
- Phase II study ongoing in the Philippines
- Plans underway for phase III studies (Nepal and Philippines)



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Safety and immunogenicity of a Vi-DT typhoid conjugate vaccine: Phase I trial in Healthy Filipino adults and children

Maria Rosario Capeding [a], Samuel Teshome [b], Tarun Saluja [b,*], Khalid Ali Syed [b], Deok Ryun Kim [b], Ju Yeon Park [b], Jae Seung Yang [b], Yang Hee Kim [b], Jiwook Park [b], Sue-Kyoung Jo [b], Yun Chon [b], Sudeep Kothari [b], Seon-Young Yang [c], Dong Soo Ham [c], Ji Hwa Ryu [c], Hee-Seong Hwang [c], Ju-Hwan Mun [c], Julia A. Lynch [b], Jerome H. Kim [b], Hun Kim [c], Jean-Louis Excler [b], Sushant Sahastrabuddhe [b]

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ABSTRACT

Background: Typhoid fever remains a major public health problem in low- and middle-income countries where children aged 2–14 years bear the greatest burden. Vi polysaccharide is poorly immunogenic in children <2 years of age, and protection in adults is modest. The limitations of Vi polysaccharide vaccines can be overcome by conjugation of the Vi to a carrier protein. A typhoid conjugate vaccine composed of Vi polysaccharide conjugated to diphtheria toxoid (Vi-DT) has been developed. The Phase I study results are presented here.

Methods: This was a randomized, observer-blinded Phase I study to assess the safety and immunogenicity of Vi-DT compared to Vi polysaccharide vaccine, conducted in Manila, Philippines. Participants enrolled in an age de-escalation manner (18–45, 6–17 and 2–5 years) were randomized between Test (Vi-DT, 25 μg) administered at 0 and 4 weeks and Comparator (Vi polysaccharide, Typhim Vi® and Vaxigrip®, Sanofi Pasteur) vaccines.

Results: A total of 144 participants were enrolled (48 by age strata, 24 in Test and Comparator groups each). No serious adverse event was reported in either group. Solicited and unsolicited adverse events were mild or moderate in both groups with the exception of a 4-year old girl in Test group with grade 3 fever which resolved without sequelae. All participants in Test group seroconverted after first and second doses of Vi-DT while the proportions in the Comparator group were 97.1% and 97.2%, after first dose of Typhim Vi® and second dose of Vaxigrip®, respectively. Vi-DT showed 4-fold higher Geometric Mean Titers (GMT) compared to Typhim Vi® (adjusted for age strata, $p < 0.001$). No further increase of GMT was detected after the second dose of Vi-DT. Anti-DT IgG seroresponse rates were 81.2% and 84.5% post first and second Vi-DT doses, respectively.

Conclusions: Vi-DT vaccine was safe, well-tolerated and immunogenic in participants aged 2–45 years.

ClinicalTrials.gov registration number: NCT02645032.

Brief overview of the 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	Approx. 72 subjects
II	Safety & Immunogenicity	285 subjects (6-23 months)	Vi-DT, 25 µg/0.5 mL SD/ Fluquadri/ Placebo	Philippines	Ongoing, Interim report available in Nov 2018	Approx. 228 subjects
III	Immune Non-inferiority, L2L Consistency & Safety	1800 subjects (6 mths-45 yrs)	Vi-DT,25 µg/0.5 mL MD/ Typbar TCV™	Nepal (4 sites)	Target start (July 2019)	Approx. 1350 subjects
III	Immune Equivalence & Safety	1800 subjects (6 mths-45yrs)	Vi-DT, 25 µg/0.5 mL SD/ MD	Philippines	Target start (Dec 2019)	Approx. 1500 subjects
					Total Safety Vi-DT database	**Approx. 3150**

Vi-DT: Biofarma

- Technology transfer completed in 2013 from IVI
- Preclinical studies completed in 2015
- Phase I clinical trial completed in Jakarta, Indonesia
- Phase II study ongoing in Jakarta, Indonesia; interim report to be available end-March 2019
- Plans underway for phase III study (3 sites in Indonesia)

PLOS ONE

RESEARCH ARTICLE

Six-month follow up of a randomized clinical trial-phase I study in Indonesian adults and children: Safety and immunogenicity of *Salmonella typhi* polysaccharide-diphtheria toxoid (Vi-DT) conjugate vaccine

Bernie Endyarni Medise[1☯*], Soedjatmiko Soedjatmiko[1☯], Iris Rengganis[2☯], Hartono Gunardi[1☯], Rini Sekartini[1☯], Sukamto Koesno[2☯], Hindra Irawan Satari[1☯], Sri Rezeki Hadinegoro[1☯], Jae Seung Yang[3‡], Jean-Louis Excler[3‡], Sushant Sahastrabuddhe[3‡], Mita Puspita[4‡], Rini Mulia Sari[4‡], Novilia Sjafri Bachtiar[4‡]

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Abstract

Introduction

TCV Research Priorities (WHO)

- To generate data that will further support typhoid vaccination policy and immunization programs, particularly through research in the following areas:
  - Development of tools or methods to identify populations and individuals at risk of typhoid fever;
  - The risk of transmission from chronic carriers of S. Typhi and strategies to identify and treat carriers;
  - Correlate(s) of protection for typhoid vaccines;
  - Co-administration with other childhood vaccines (where not yet studied);
  - Safety and immunogenicity in special populations, including malnourished children, immunocompromised persons, and pregnant women;
  - Duration of protection after a single dose of TCV and the potential need for revaccination;
  - whether the tetanus toxoid carrier protein of the Vi-TT conjugate vaccine provides protection equivalent to a booster dose of tetanus vaccine; and
  - The impact of different TCV strategies including target age ranges for routine and catch-up vaccination as well as vaccination for outbreak control.

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INTERNATIONAL VACCINE INSTITUTE

SK Vi-DT Phase I Study

Purpose	Evaluate the safety of 25 µg of Vi-DT typhoid conjugate vaccine Assess the immunogenicity of 25 µg of Vi-DT typhoid conjugate vaccine Compare the safety and immunogenicity of Vi-DT and Vi-Polysaccharide typhoid vaccines
Country	Philippines
Study Design	Randomized, observer-blinded, age de-escalating, safety and immunogenicity study
Target Age	Adults 18 to 45 years of age; adolescents 6 to 17 years of age; children 2 to 5 years of age Total: 144 participants
Comparison	**Test Vaccine:** Vi-DT (25 µg of Diphtheria Toxin-conjugated Vi polysaccharide) typhoid vaccine **Comparator Vaccine**: Typhim Vi® (25 µg of Vi-polysaccharide) typhoid vaccine
Schedule	

Age groups (years)	N	Study arm	1st Vaccination (Week 0)	2nd Vaccination (Week 4)
18-45	24	Test	Vi-DT	Vi-DT
	24	Comparator	Typhim Vi®	VAXIGRIP®
6-17	24	Test	Vi-DT	Vi-DT
	24	Comparator	Typhim Vi®	VAXIGRIP®
2-5	24	Test	Vi-DT	Vi-DT
	24	Comparator	Typhim Vi®	VAXIGRIP®

Objectives

Primary

- To evaluate the safety of 25 µg of Vi-DT typhoid conjugate vaccine administered at 0 and 4 weeks

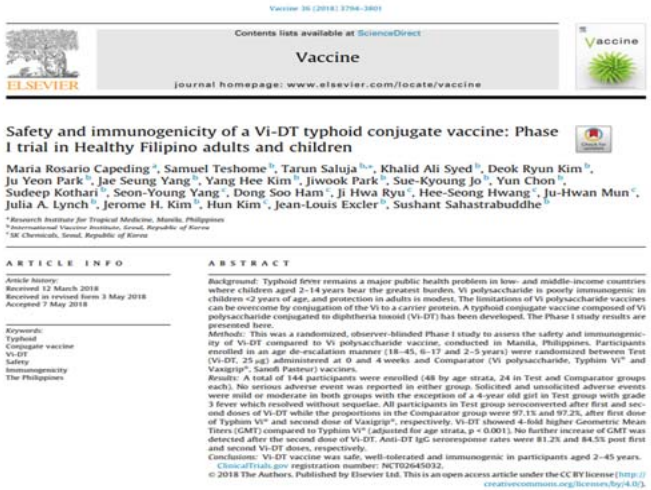
Secondary

- To assess the immunogenicity of 25 µg of Vi-DT typhoid conjugate vaccine administered at 0 and 4 weeks
- To compare the safety and immunogenicity of Vi-DT and Vi-Polysaccharide typhoid vaccines

Summary: Results

Vi-DT is safe, generally well tolerated and immunogenic

Phase I (in progress)	
Safety	• No subject was withdrawn from the study due to AE • AEs balanced between groups, mild and moderate - No SAE • Majority of solicited AE ✓ in adults are pain, tenderness and headache. ✓ In adolescent are pain and tenderness ✓ In young children are pain and fever



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Conclusions: Vi-DT vaccine was safe, well-tolerated and immunogenic in participants aged 2–45 years. ClinicalTrials.gov registration number: NCT02645032.

converted after the first dose
se does not increase GMT
are 4-fold higher than Typhim Vi

SK Vi-DT Phase II Study

Study Title:

A Phase 2, Randomized, Dose-scheduling, Observer-Blinded Study to Assess the Safety, Reactogenicity and Immunogenicity of Vi-DT Conjugate Vaccine in 6-23-Month old Healthy Infants and Toddlers

Number of participants: 285

Group	Number of Vaccinees	Vaccination Schedule (Weeks)		
		0	24	96***
A	114	VI-DT** 25 µg 0.5 mL	FluQuadri™ * 0.25 mL	VI-DT 25 µg 0.5 mL
B****	114	VI-DT** 25 µg 0.5 mL	VI-DT 25 µg† 0.5 mL	No VI-DT boost
C	57	Placebo**	FluQuadri™ * 0.25 mL	N/A

Primary Objectives:

- Assess and describe the safety and reactogenicity of Vi-DT
- Assess and compare anti-Vi seroconversion rate 4 weeks post dose one [of combined one and two-dose regimens] of Vi-DT to comparator group

Phase III considerations (continued)

- We have developed a two-pronged strategy for conduct of the phase III trial:
  1. We will conduct the non-inferiority study with Typbar-TCV along with the lot to lot consistency in Nepal (sample size ~1800)
  2. We will conduct another phase III study in the Philippines for additional safety data generation as well as to immune equivalence of single dose formulation (used in phase I and II) against multiple dose formulation (To be used in the phase III)