Update on Typhoid Vaccines
ARVAC 2023

Kathleen Neuzil, MD, MPH

Myron M. Levine Professor in Vaccinology
Director, Center for Vaccine Development and Global Health

June 7, 2023

PATH/Rocky Prajapati.

UNIVERSITY of MARYLAND
SCHOOL OF MEDICINE
CENTER FOR VACCINE DEVELOPMENT
AND GLOBAL HEALTH

"Not only is typhoid one of the leading causes of death in America, but the greater part of it is conveyed, directly or indirectly, through water."

ON THE RELATIVE IMPORTANCE OF PUBLIC WATER SUPPLIES AND OTHER FACTORS IN THE CAUSATION OF TYPHOID FEVER.

By W. T. SEDGWICK and C.-E. A. WINSLOW, Massachusetts Institute of Technology, Boston.

The rôle of public water supplies as vehicles of typhoid fever was early made apparent by the epidemic at Lausen, Switzerland, in 1872, and that at Caterham, England, in 1879. In this country evidence of a similar character was not long lacking; for in 1885 the thriving mining town of Plymouth, Pa., suffered one of the most disastrous water epidemics of which we have any record. The great epidemics at Lowell and Lawrence in 1890 added new emphasis to the old lessons; and only two years ago over 450 cases of typhoid fever at New Haven, due to a combination of circumstances nearly parallel with those of the Plymouth disaster, showed that the teach-

Sedgwick WT, Winslow CE.
Public Health Pap Rep. 1902;28:288-95.

THE ORIGIN AND DISSEMINATION OF TYPHOID FEVER.[1]

By Prof. W. T. SEDGWICK,

Boston, Mass.

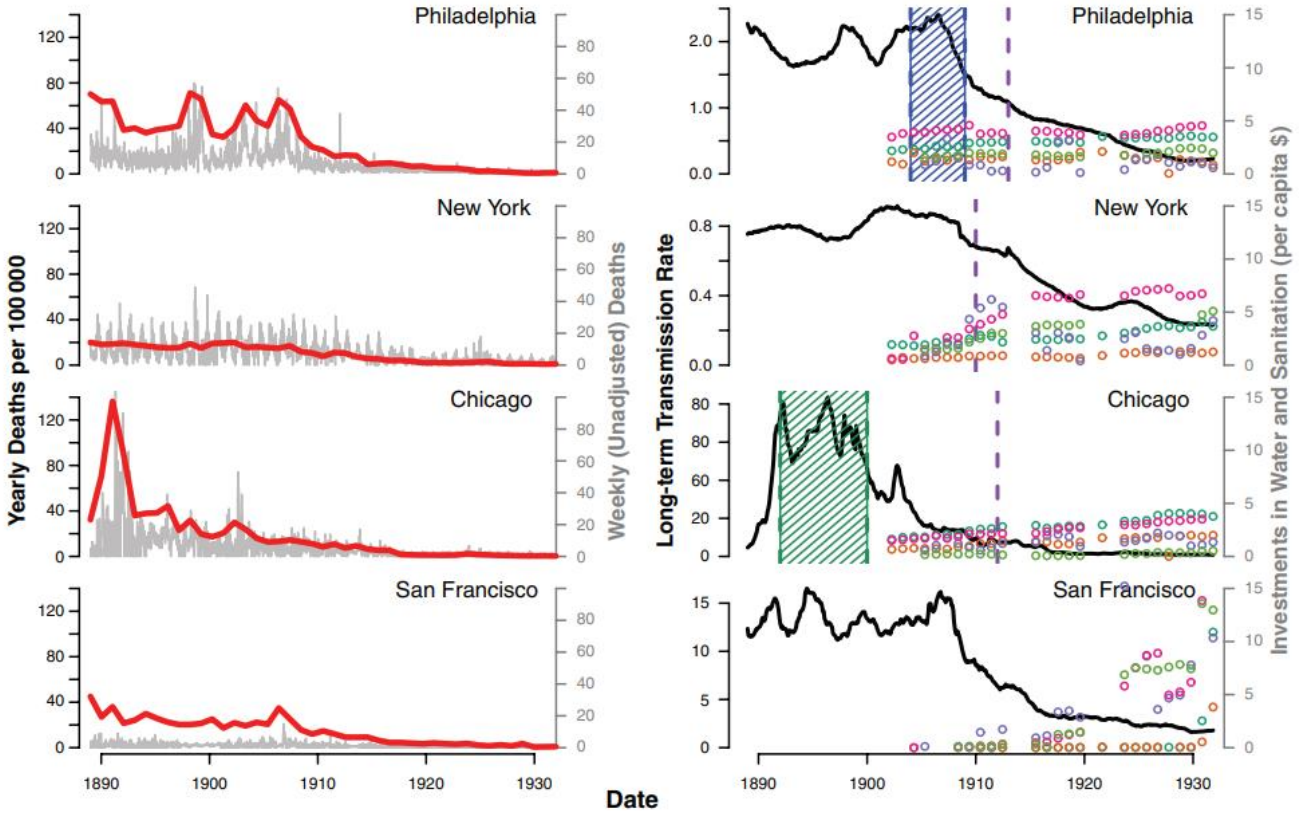
In 1886 the state board of health of Massachusetts was re-organized. It was placed under the able leadership of Dr. Henry P. Walcott, who certainly needs no introduction to this Association. It contained upon its membership-roll one of the most eminent sanitary engineers in the country, Hiram F. Mills; and as a medico-legal expert, Dr. Frank W. Draper, and others, well known either in medicine or in public health matters. I bid you mark the date—1886. It was at this time that the magnificent work of Koch and Pasteur was beginning to bear fruit. In 1884 we had the splendid paper of Gaffky, upon the Eberth bacillus, and soon after our attention was called to the Eberth-Gaffky bacillus the board began its

Sedgwick WT. The Origin and Dissemination of Typhoid Fever. Public Health Pap Rep. 1893;19:235-41.

Water and Filth: Reevaluating the First Era of Sanitary Typhoid Intervention (1840–1940)

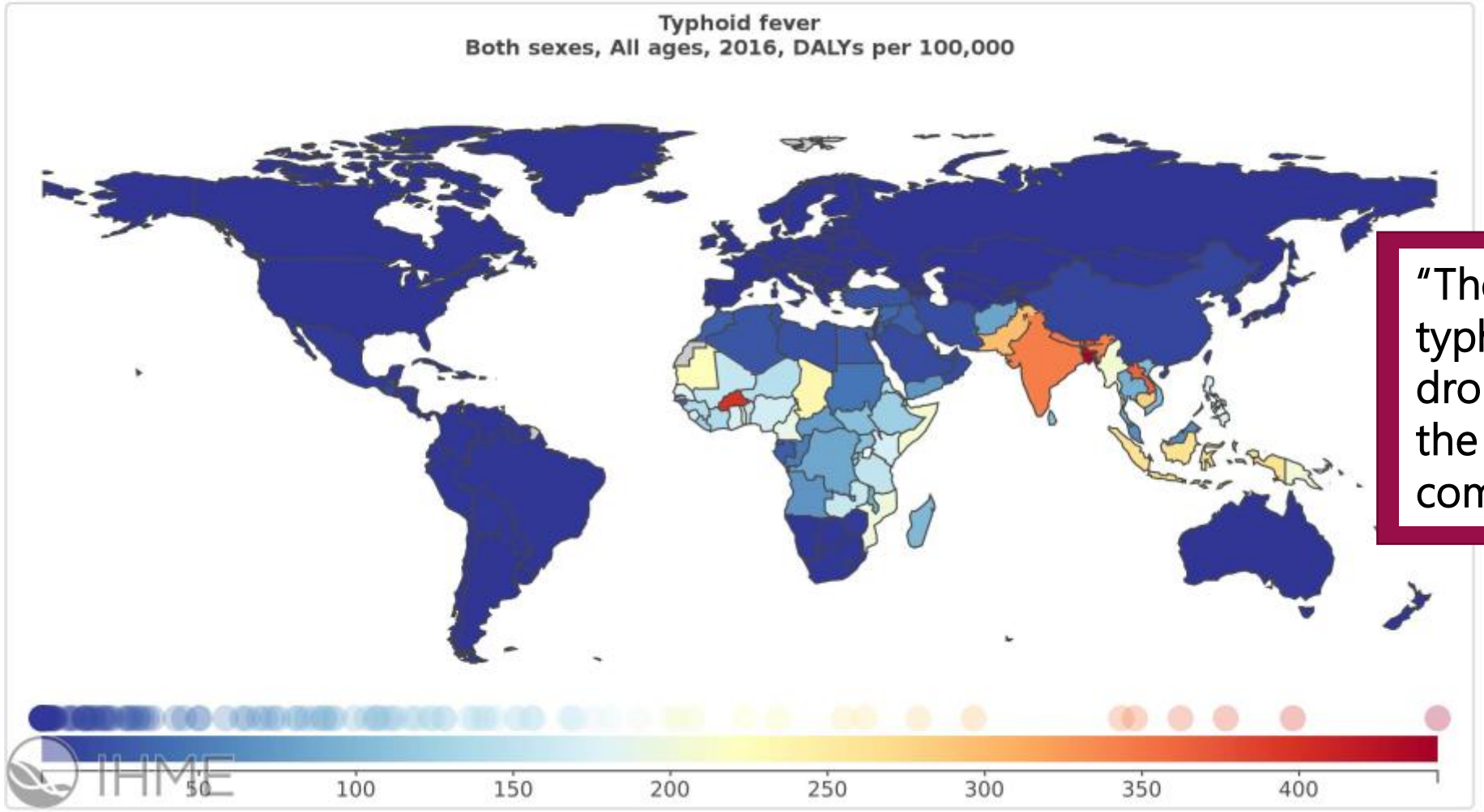
Samantha Vanderslott,[1] Maile T. Phillips,[2] Virginia E. Pitzer,[2] and Claas Kirchhelle[3]

[1]Oxford Vaccine Group/Oxford Martin School, University of Oxford, United Kingdom; [2]Department of Epidemiology of Microbial Diseases, Yale School of Public Health, Yale University, New Haven, Connecticut; and [3]Wellcome Unit for the History of Medicine/Oxford Martin School, University of Oxford, United Kingdom



Clinical Infectious Diseases® **2019;69(S5):S377–84**

Typhoid isn't a disease of the past; it's a disease of the poor

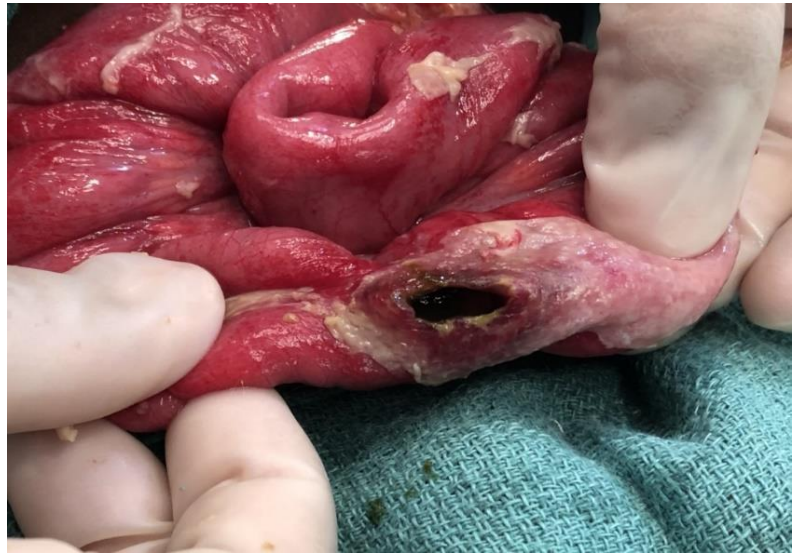


"The main problem with typhoid fever is that it has dropped out of the minds of the international health community…"

Source: The Lancet, www.thelancet.com, Volume 379, Feb 25, 2012.

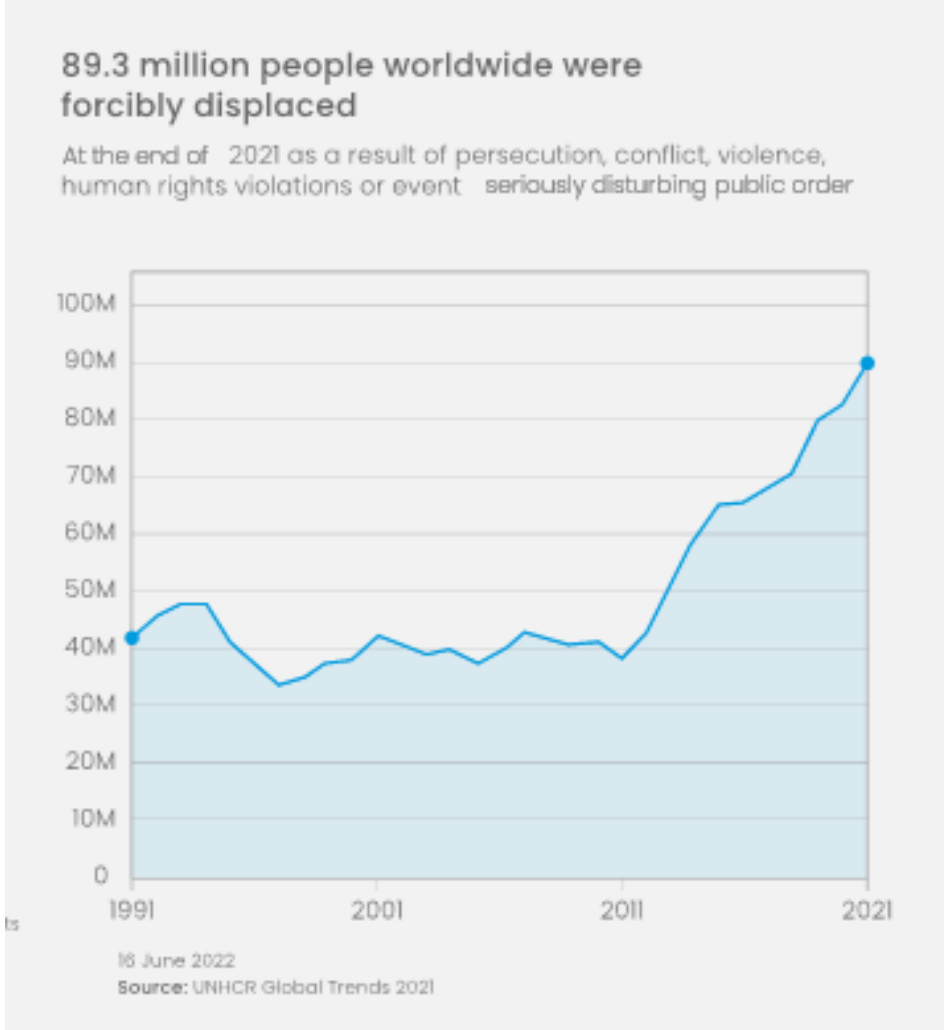
Typhoid: Where are we in 2023?

- Typhoid continues to be a substantial public health threat that disproportionately impacts children and marginalized populations in much of Asia, sub-Saharan Africa, and Oceania.
- The burden of typhoid is likely underestimated due to difficulties in surveillance and diagnostic challenges.
    - Current estimate is nearly 11 million cases and more than 116,000 deaths per year.
    - 1-4% fatality with treatment; 10-20% without.
    - Complications arise in 10-15% of untreated: intestinal perforation, hemorrhage, septic shock.

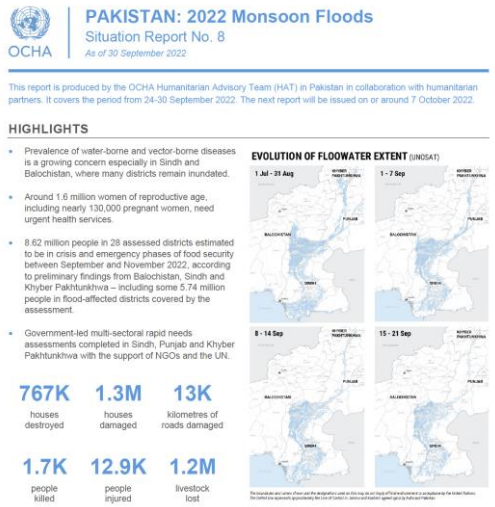


Enteric disease control is facing unprecedented challenges

- Competing health priorities
  - COVID-19 caused backsliding in immunization, including increases in number of zero-dose children
  - Polio, Ebola, Monkeypox, Dengue, Cholera outbreaks
- Increasing number of active State-based conflicts
- Economic stress on families and governments
- Climate change
- Antimicrobial resistance



Climate change: Pakistan and Nigeria under water



OCHA

PAKISTAN: 2022 Monsoon Floods
Situation Report No. 8
As of 30 September 2022

This report is produced by the OCHA Humanitarian Advisory Team (HAT) in Pakistan in collaboration with humanitarian partners. It covers the period from 24-30 September 2022. The next report will be issued on or around 7 October 2022.

HIGHLIGHTS

- Prevalence of water-borne and vector-borne diseases is a growing concern especially in Sindh and Balochistan, where many districts remain inundated.
- Around 1.6 million women of reproductive age, including nearly 130,000 pregnant women, need urgent health services.
- 8.62 million people in 28 assessed districts estimated to be in crisis and emergency phases of food security between September and November 2022, according to preliminary findings from Balochistan, Sindh and Khyber Pakhtunkhwa – including some 5.74 million people in flood-affected districts covered by the assessment.
- Government-led multi-sectoral rapid needs assessments completed in Sindh, Punjab and Khyber Pakhtunkhwa with the support of NGOs and the UN.

EVOLUTION OF FLOODWATER EXTENT (UNOSAT)

1 Jul - 31 Aug | 1 - 7 Sep | 8 - 14 Sep | 15 - 21 Sep

767K	1.3M	13K
houses destroyed	houses damaged	kilometres of roads damaged
1.7K	**12.9K**	**1.2M**
people killed	people injured	livestock lost

An inundated home in Sindh Province, Pakistan. Floods have killed more than 1,500 across the country. Asif Hassan/Agence France

The New York Times

By Ruth Maclean

Published Oct. 17, 2022 Updated Oct. 18, 2022, 1:05 a.m. ET

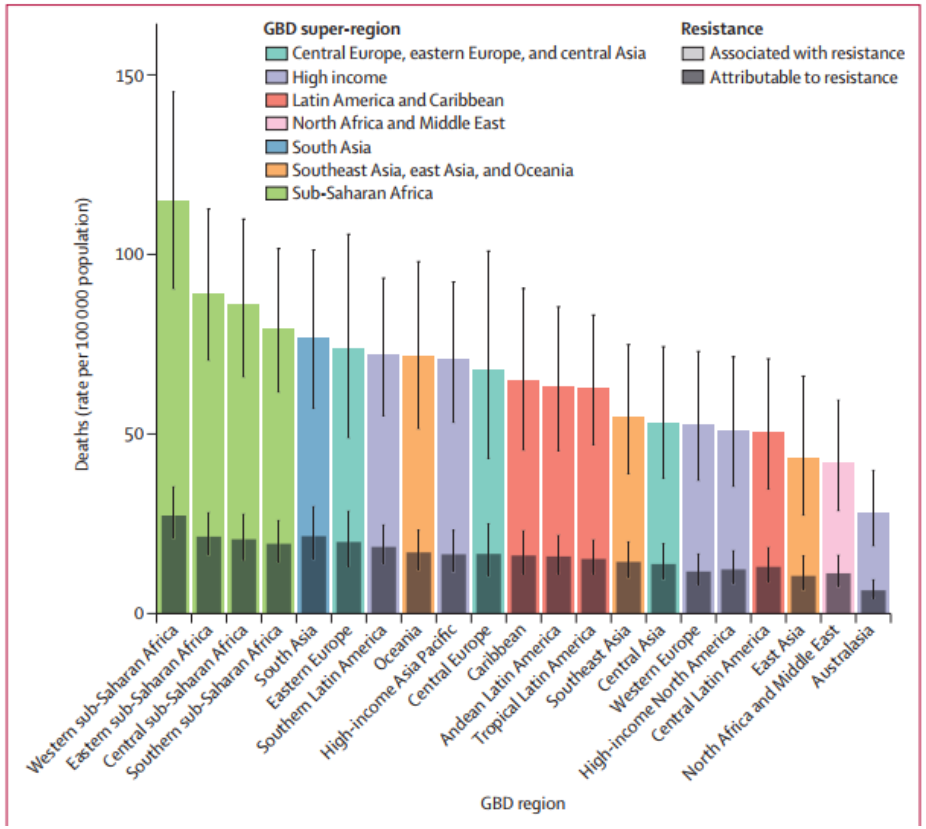
Nigeria Floods Kill Hundreds and Displace Over a Million

The country is experiencing its worst floods in years, damaging homes, infrastructure and vast sections of farmland.

Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis

*Antimicrobial Resistance Collaborators**

- Estimated deaths and DALYs attributable to and associated with bacterial AMR for 23 pathogens and 88 pathogen-drug combinations in 204 countries in 2019.
- Estimated 4.95 million (3.62-6.57) deaths associated with AMR, and 1.27 million attributable to bacterial AMR
- All-age death rate attributable to resistance was highest in sub-Sharan Africa
- Highest death rate in Western SSA at 27.3 deaths/100,000



https://doi.org/10.1016/S0140-6736(21)02724-0

Global antibiotic consumption and usage in humans, 2000-2018, a spatial modelling study.

Lancet Planet Health 2021; 5: 3893-904.

- Surveys done covering > 280,000 children with LRI.
- Large national and subnational variations of antibiotic usage in LMICs, with the lowest levels estimated in sub-Saharan Africa and the highest in eastern Europe a central Asia.
- Both inappropriate use of antibiotics, and lack of access to antibiotics are important public health problems.

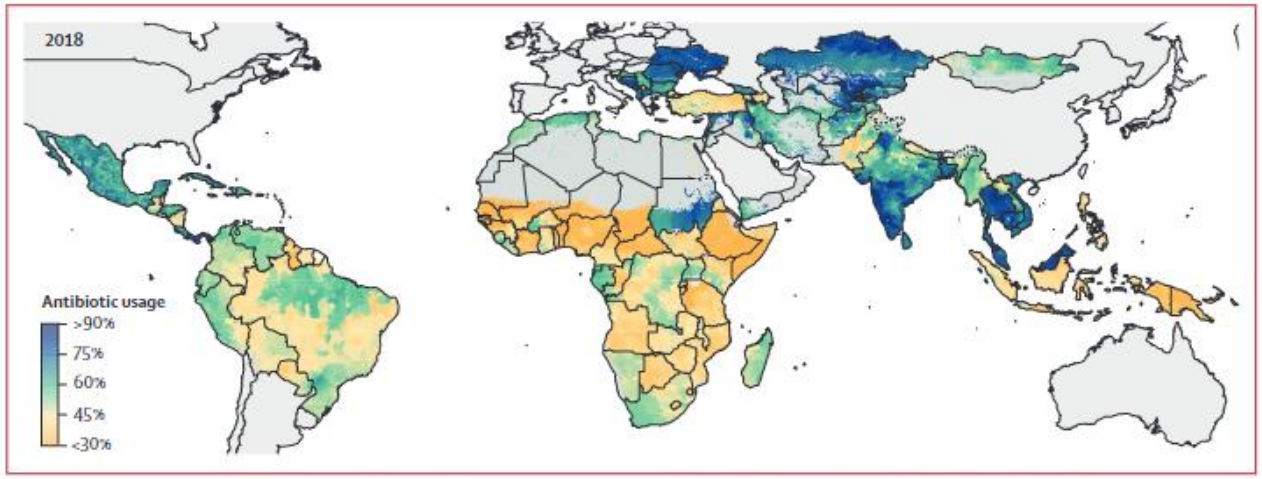
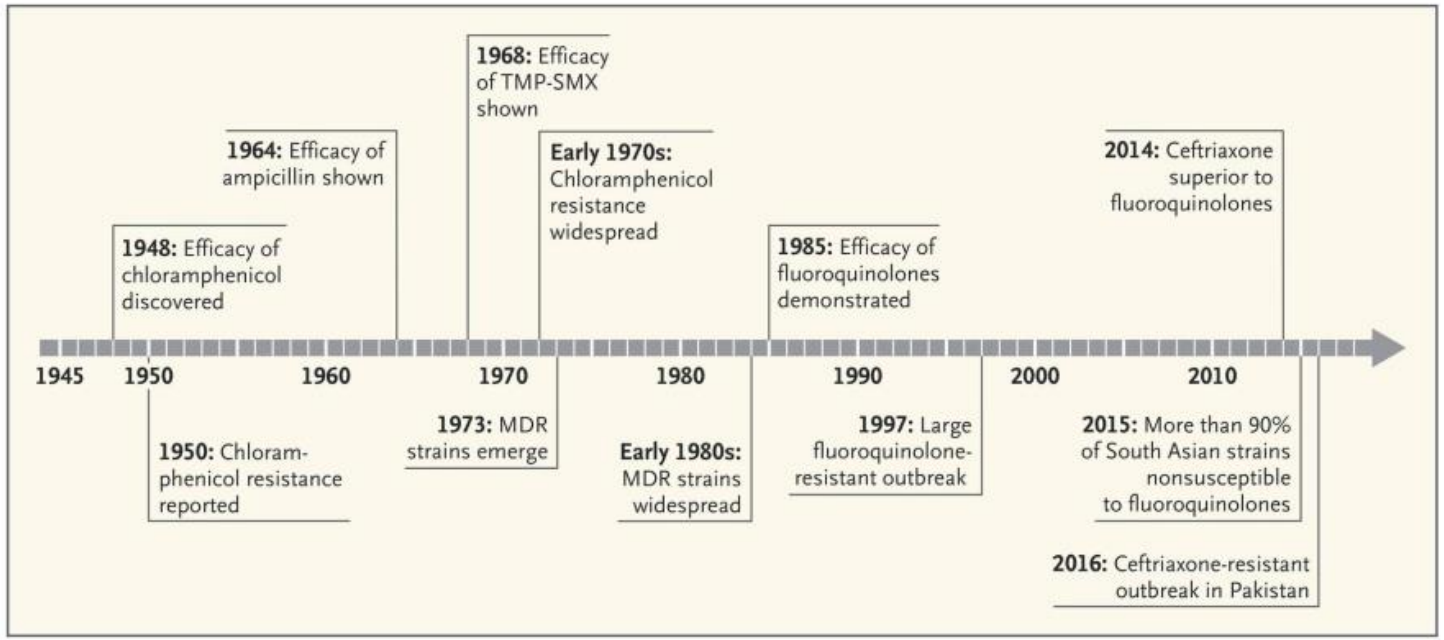


Figure 1: **The percentage of children (aged <5 years) with symptoms of lower respiratory tract infections with caregiver-reported antibiotic usage in low-income and middle-income countries, 2018**
Modelled estimates are shown by level two administrative divisions. High-income countries and pixels (1×1 km) with populations of less than ten people are shown in grey.

Lancet Planet Health 2021; 5: 3893-904.

The threat of drug resistant *S.* Typhi escalates



'We're Out of Options': Doctors Battle Drug-Resistant Typhoid Outbreak

Global Health

By EMILY BAUMGAERTNER APRIL 13, 2018

A baby believed to have contracted a drug-resistant strain of typhoid, hospitalized in Hyderabad, Pakistan in February. Nadeem Khawer/European Pressphoto Agency

Outbreak Reports

Extensively Drug-Resistant (XDR) *Salmonella* Typhi Outbreak by Waterborne Infection — Beijing Municipality, China, January–February 2022

Yu Wang[1,&]; Dan Lu[2,&]; Yingying Jin[2]; Huanxin Wang[2]; Bing Lyu[1]; Xin Zhang[1]; Ying Huang[1]; Gaolin Shu[2]; Baiwei Liu[1]; Changying Lin[1]; Hao Zhao[1]; Mingqiang Zhao[2]; Lingyu Shen[1]; Zhiyong Gao[1]; Daitao Zhang[1]; Quanyi Wang[1]; Mei Qu[1,#]; Lei Jia[1,#]

Source: Andrews et al. NEJM 2018; 379: 1493.

Safe and effective vaccines…

Vaccines to prevent typhoid fever					
Vaccination	Age (yr)	Dose, mode of administration	No of doses	Dosing interval	Boosting interval
Oral, live, attenuated Ty21a vaccine (Vivotif)[1]					
Primary series	≥6	1 capsule[2], oral	4	48 hrs	N/A
Booster	≥6	1 capsule[2], oral	4	48 hrs	Every 5 yrs
Vi capsular polysaccharide vaccine (Typhim Vi)					
Primary series	≥2	0.50 ml, intramuscular	1	N/A	N/A
Booster	≥2	0.50 ml, intramuscular	1	N/A	Every 2 yrs

[1]The vaccine must be kept refrigerated 35.6°F-46.4°F, 2°C-8°C
[2]Administer with cool liquid no warmer than 98.6°F (37°C)

Source: CDC Yellow Book on Typhoid Fever. https://wwwnc.cdc.gov/travel/yellowbook/2018/infectious-diseases-related-to-travel/typhoid-paratyphoid-fever.

Safe and effective vaccines…not fit for purpose for endemic settings

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Safe and efficacious typhoid conjugate vaccine….

VOLUME 344 APRIL 26, 2001 NUMBER 17

THE EFFICACY OF A *SALMONELLA TYPHI* Vi CONJUGATE VACCINE IN TWO-TO-FIVE-YEAR-OLD CHILDREN

FENG YING C. LIN, M.D., M.P.H., VO ANH HO, M.D., HA BA KHIEM, M.D., DANG DUC TRACH, M.D., PH.D., PHAN VAN BAY, M.D., TRAN CONG THANH, M.D., ZUZANA KOSSACZKA, PH.D., DOLORES A. BRYLA, M.P.H., JOSEPH SHILOACH, PH.D., JOHN B. ROBBINS, M.D., RACHEL SCHNEERSON, M.D., AND SHOUSUN C. SZU, PH.D.

TABLE 3. EFFICACY OF Vi-rEPA CONJUGATE VACCINE.

VARIABLE	VACCINE GROUP	PLACEBO GROUP	VACCINE EFFICACY (95% CI)*	P VALUE†
			%	
Children who received two correctly labeled injections — no.	5525	5566		—
Children with typhoid fever — no.	4	47	91.5 (77.1–96.6)	
Attack rate (cases/1000 children)	0.72	8.44		

Safe and efficacious typhoid conjugate vaccine….failed business model

VOLUME 344 APRIL 26 2001 NUMBER 17

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Typbar-TCV (Bharat Biotech Lmt)

- Vaccine consists of 25 µg of Vi polysaccharide conjugated to a nontoxic tetanus toxoid protein carrier.
- **Single dose** of Vi-TCV elicited seroconversion rates of 98%, 99%, 92% in persons 6-24 months, 2-15 years, 15-45 years
- Licensed in India in 2013 based on immunogenicity

Source: Mohan, CID 2015.

Efficacy and immunogenicity of a Vi-tetanus toxoid conjugate vaccine in the prevention of typhoid fever using a controlled human infection model of *Salmonella* Typhi: a randomised controlled, phase 2b trial

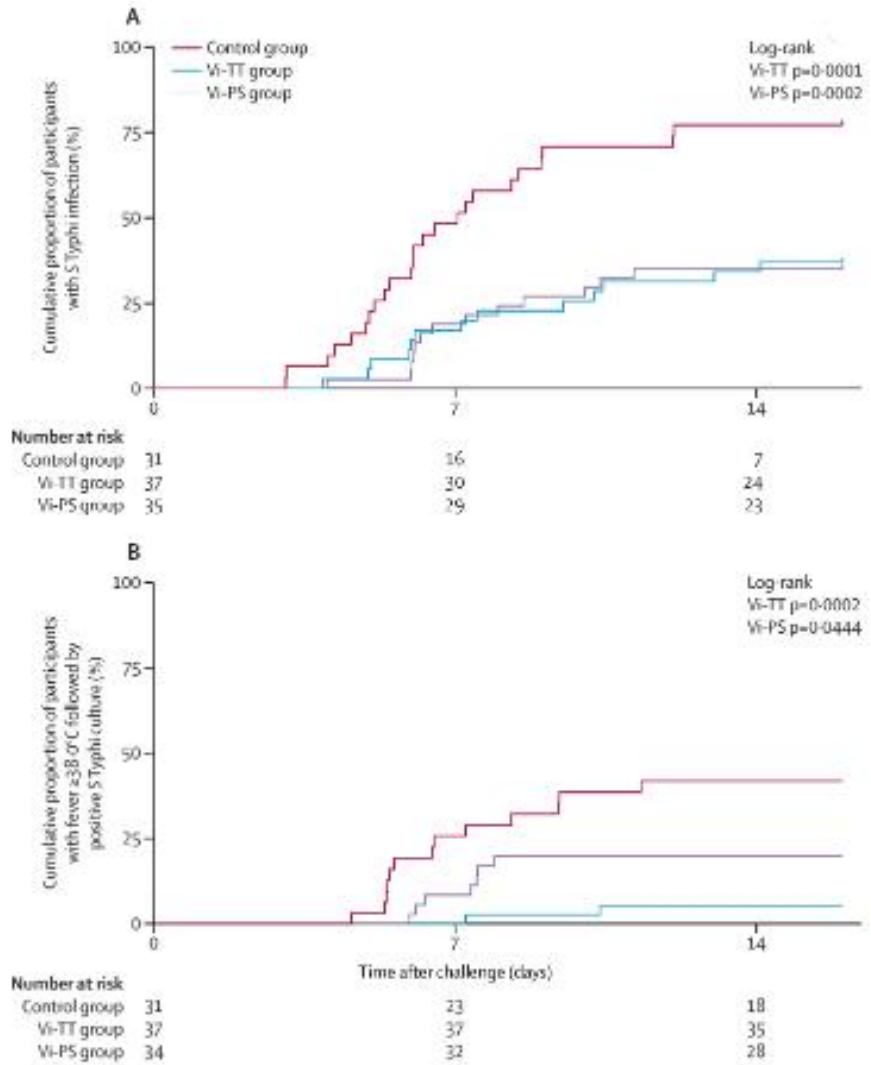
Celina Jin, Malick M Gibani, Maria Moore, Helene B Juel, Elizabeth Jones, James Meiring, Victoria Harris, Jonathan Gardner, Anna Nebykova, Simon A Kerridge, Jennifer Hill, Helena Thomaides-Brears, Christoph J Blohmke, Ly-Mee Yu, Brian Angus, Andrew J Pollard

Lancet 2017; 390: 2472–80
Published Online September 28, 2017
http://dx.doi.org/10.1016/S0140-6736(17)32149-9
See Comment page 2419

Summary

Background *Salmonella enterica* serovar Typhi (*S* Typhi) is responsible for an estimated 20 million infections and 200 000 deaths each year in resource poor regions of the world. Capsular Vi-polysaccharide-protein conjugate vaccines (Vi-conjugate vaccines) are immunogenic and can be used from infancy but there are no efficacy data for the leading candidate vaccine being considered for widespread use. To address this knowledge gap, we assessed the efficacy of a Vi-tetanus toxoid conjugate vaccine using an established human infection model of *S* Typhi.

	Control group (n=34)	Vi-TT group (n=41)	Vi-PS group (n=37)
Primary outcome			
Completed challenged	31	37	35
Total diagnosed (composite definition, clinical or microbiological typhoid diagnosis)	24/31 (77%)	13/37 (35%)	13/35 (37%)
Relative risk (95% CI)	..	0·45 (0·28–0·73)	0·48 (0·30–0·77)
Vaccine efficacy (%, 95% CI)	..	54·6% (26·8–71·8)	52·0% (23·2–70·0)
p value	..	0·0005	0·0010
Secondary outcomes			
Time to diagnosis (days)	6·0 (5·1–7·8)	6·5 (6·1–8·6)	7·2 (5·9–10·2)
Microbiological diagnosis	16/31 (52%)	12/37 (32%)	9/35 (26%)
Time to microbiological diagnosis (days)	6·0 (4·6–8·0)	6·3 (6·0–8·3)	6·1 (5·1–10·2)
Clinical diagnosis	8/31 (26%)	1/37 (3%)	4/35 (11%)



Typhoid Vaccine Acceleration Consortium (TyVAC)

Reduce the global burden of typhoid by accelerating the introduction of typhoid conjugate vaccines (TCVs) in low-resource countries.

University of Maryland School of Medicine
Center for Vaccine Development and Global Health

University of Oxford

PATH

COLLABORATING ORGANIZATIONS

Blantyre Malaria Project

Coalition Against Typhoid — a program of the Sabin Vaccine Institute

Groupe de Recherche Action en Santé

icddr,b

International Vaccine Institute

Malawi-Liverpool-Wellcome Clinical Research Programme

Johns Hopkins Bloomberg School of Public Health

oucru

University of Otago — Te Whare Wānanga o Otāgo New Zealand

Patan Academy of Health Sciences

THECA — Typhoid conjugate vaccine introduction in Africa

University of Antwerp

University of Cambridge

Yale School of Public Health

GALMI

TyVAC is funded by the Bill & Melinda Gates Foundation.

Oct 2017 WHO SAGE overview

- Noted the continued high burden of typhoid fever and the alarming increase in antimicrobial resistance in low- and middle-income countries.
- Recommended single dose in typhoid endemic countries for children over 6 months of age plus catch-up of up to 15 years of age.
    - Decision on preferred immunisation strategy should be based on disease burden, availability and quality of data, affordability and operational feasibility.
- Recommended prioritisation to countries with highest burden of disease or high burden of AMR *S.* Typhi.
- Data will be needed on co-administration of TCV and countries should strengthen surveillance and monitor occurrence of AMR.

Source: https://www.who.int/immunization/policy/sage/SAGE_oct_2017_meeting_summary.pdf?ua=1.

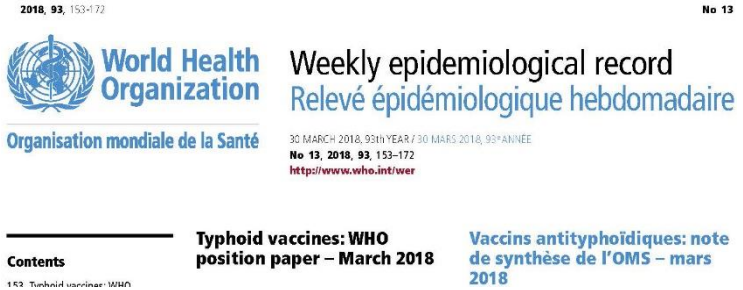
Policy milestones impacting TCV introduction

22 October 2017

Summary report for the SAGE meeting of October 2017

The summary report for the SAGE meeting of 17-19 October is now available.

– Summary report of the SAGE meeting of October 2017
pdf, 222kb



Oct 2017

Nov 2017

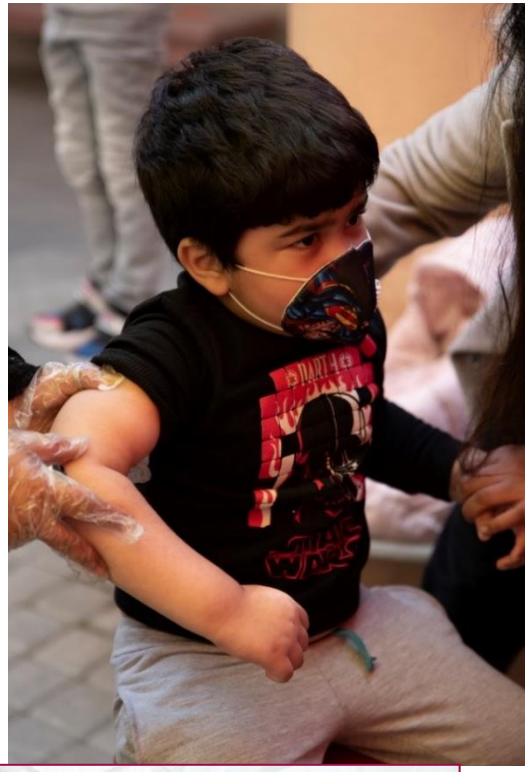
Dec 2017

Feb 2018

Mar 2018

Unique set of challenges for typhoid vaccines

- Variability in disease burden over time and place, AMR and health care utilization patterns across settings and over time.
- Laboratory-confirmed disease burden data lacking in many settings.
- No field efficacy data for newer TCVs; no established CoP in endemic populations



TyVAC trials designed to provide data on safety, immunogenicity, and efficacy of Typbar TCV® (Vi-TT) in diverse field settings

Location	Design	Control vaccine	Ages	Number vaccinated	Other
Lalitpur Metropolitan City, Kathmandu Valley, Nepal	Individually-randomized efficacy	Meningococcal A Conjugate Vaccine (MenA)	9 months-16 years	20,019	
Ndirande (urban township), Blantyre, Malawi	Individually-randomized efficacy	MenA	9 months-12 years	28,130	HIV prevalence ~18%
Mirpur (densely populated), Dhaka, Bangladesh	Cluster-randomized effectiveness	SA-14-14-2 JE vaccine	9 months-16 years	61,756	150 clusters of ~1350 residents

More than 100,000 children enrolled in RCT of single dose TCV

The NEW ENGLAND JOURNAL of MEDICINE
N ENGL J MED 381;23 NEJM.ORG DECEMBER 5, 2019

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*

Efficacy of typhoid conjugate vaccine in Nepal: final results of a phase 3, randomised, controlled trial

Mila Shakya, Merryn Voysey*, Katherine Theiss-Nyland*, Rachel Colin-Jones*, Dikshya Pant*, Anup Adhikari, Susan Tonks, Yama F Mujadidi, Peter O'Reilly, Olga Mazur, Sarah Kelly, Xinxue Liu, Archana Maharjan, Ashata Dahal, Naheeda Haque, Anisha Pradhan, Suchita Shrestha, Manij Joshi, Nicola Smith, Jennifer Hill, Jenny Clarke, Lisa Stockdale, Elizabeth Jones, [illegible] Abhilasha Karkey, Stephen Baker, Gordan Dougan, Virginia E Pitzer, Kathleen M Neuz for the TyVAC Nepal Team†*

Lancet Glob Health 2021; 9: e1561–68

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†*

Published online August 9, 2021 https://doi.org/10.1016/S0140-6736(21)01124-7

N ENGL J MED 385;12 NEJM.ORG SEPTEMBER 16, 2021

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

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

13 Pages • Posted: 7 Apr 2023

Preprints with THE LANCET

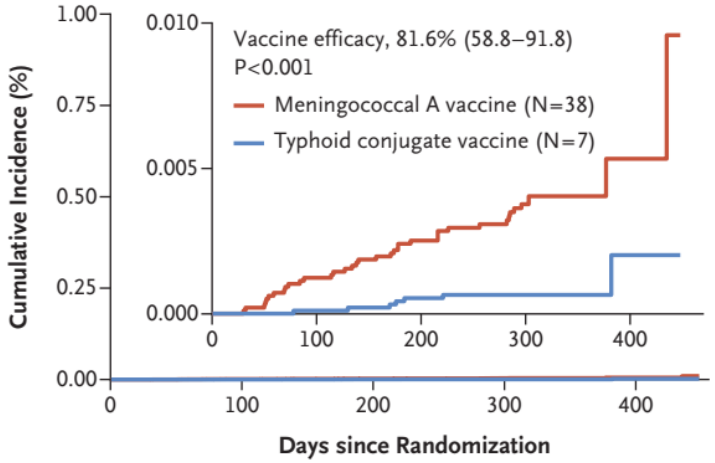
Priyanka Patel
Malawi-Liverpool-Wellcome Trust Clinical Research Programme

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

2019: First efficacy results from Nepal at 1 year follow-up

Table 1. Occurrence of Blood Culture–Confirmed Typhoid Fever and Protective Efficacy of Typhoid Conjugate Vaccine (TCV).*

Variable	TCV (N=10,005)		MenA Vaccine (N=10,014)		Efficacy of TCV (95% CI)	P Value†
	Cases	Incidence	Cases	Incidence		
	no.	*no. of cases/ 100,000 person-yr (95% CI)‡*	*no.*	*no. of cases/ 100,000 person-yr (95% CI)‡*	*percent*	
Confirmation of typhoid fever on blood culture						
First 14 days after vaccination			1			
After 14 days§	7	79 (37–165)	38	428 (311–588)	81.6 (58.8–91.8)	<0.001
Detection						
At clinic	5		27			
Through active follow-up and medical-record review	2		11			
Blood culture–confirmed typhoid fever in participants with at least 3 days of fever before blood culture¶	3	34 (11–105)	20	226 (146–350)	85.1 (49.7–95.6)	<0.001



No. at Risk

Meningococcal A vaccine	10,013	9536	9072	7233	649
Typhoid conjugate vaccine	10,005	9541	9120	7316	645

Figure 1. Kaplan–Meier Estimates of the Cumulative Incidence of Blood Culture–Positive Typhoid Fever, According to Trial Group.

Blood culture–positive typhoid fever was the primary outcome. The inset shows the same data on an enlarged y axis.

Incidence of blood culture-confirmed typhoid fever and protective effectiveness of Vi-TT by age group, Bangladesh

	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 (520–1231)	143 (39–366)	81% (39 to 94)	0·0052	0·49
2 to 4 years	62/6413	12/6173	967 (741–1239)	194 (100–340)	80% (62 to 89)	<0·0001	..
5 to <16 years†	107/21 037	13/21 375	509 (417–615)	61 (32–104)	88% (78 to 93)	<0·0001	..
Overall vaccine protection							
<2 years	35/7779	13/7861	450 (313–626)	165 (88–283)	63% (20 to 83)	0·011	0·056
2 to 4 years	86/9295	34/9041	925 (740–1143)	376 (260–526)	59% (40 to 73)	<0·0001	..
5 to <16 years	141/32 316	50/32 462	436 (367–515)	154 (114–203)	65% (50 to 75)	<0·0001	..
≥16 years†	69/106 069	47/105 085	65 (51–82)	45 (33–59)	33% (−2 to 55)	0·061	..
Indirect vaccine protection							
<2 years	12/4846	8/4913	248 (128–433)	163 (70–321)	32% (−127 to 80)	0·53	0·38
2 to 4 years	24/2884	23/2880	832 (533–1238)	799 (506–1198)	6% (−78 to 51)	0·84	..
5 to <16 years	34/11 415	37/11 227	298 (206–416)	330 (232–454)	−13% (80 to 29)	0·60	..
≥16 years†	69/106 061	47/105 081	65 (51–82)	45 (33–59)	33% (−2 to 55)	0·060	..

Single dose TCV 79-85% protective vs typhoid fever in endemic pediatric populations

Country	TCV product	Number doses	Control vaccine	AGES	Study period (Participant follow-up)	Total number vaccinated	Blood culture-confirmed typhoid fever, n		Cases/100,000 person–yr		Vaccine efficacy (95% CI)
							TCV	Control	TCV	Control	
Individual-Randomized Trials											
Nepal[3]	Vi-TT	1	Meningococcal serogroup A conjugate	9 months-<16 years	24 months	20,019	13	62	72	342	79.0% (61.9, 88.5)[4]
Malawi[5]	Vi-TT	1	Meningococcal serogroup A conjugate	9 months-<13 years	18 months	28,130	10	61	40	260	83.7% (68.1,91.6)[6]
Cluster-randomized trials											
Country	TCV product	Number doses	Control vaccine	Ages	Study period (Participant follow-up)	Total number vaccinated	Blood culture-confirmed typhoid fever, n		Cases/100,000 person–yr		Total effectiveness (CI)
							TCV	Control	TCV	Control	
Bangladesh[9]	Vi-TT	1	Live attenuated Japanese encephalitis	9 months-<16 years	25 months	67,395	29	192	96	635	85.0% (97.5% CI: 76, 91)[8]

Efficacy of typhoid conjugate vaccine: final analysis of a four-year, randomised controlled trial in Malawian children

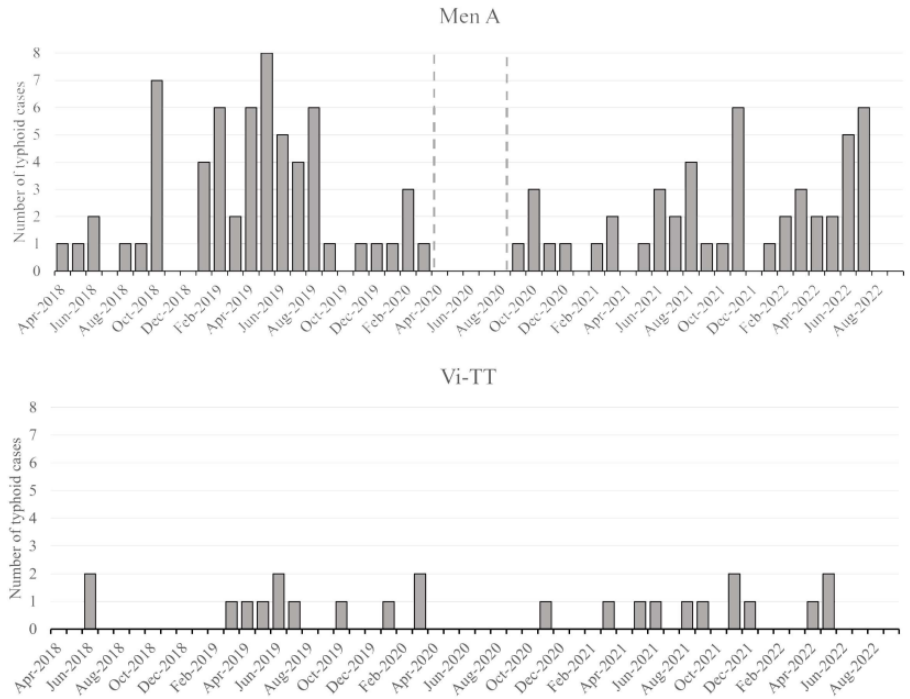
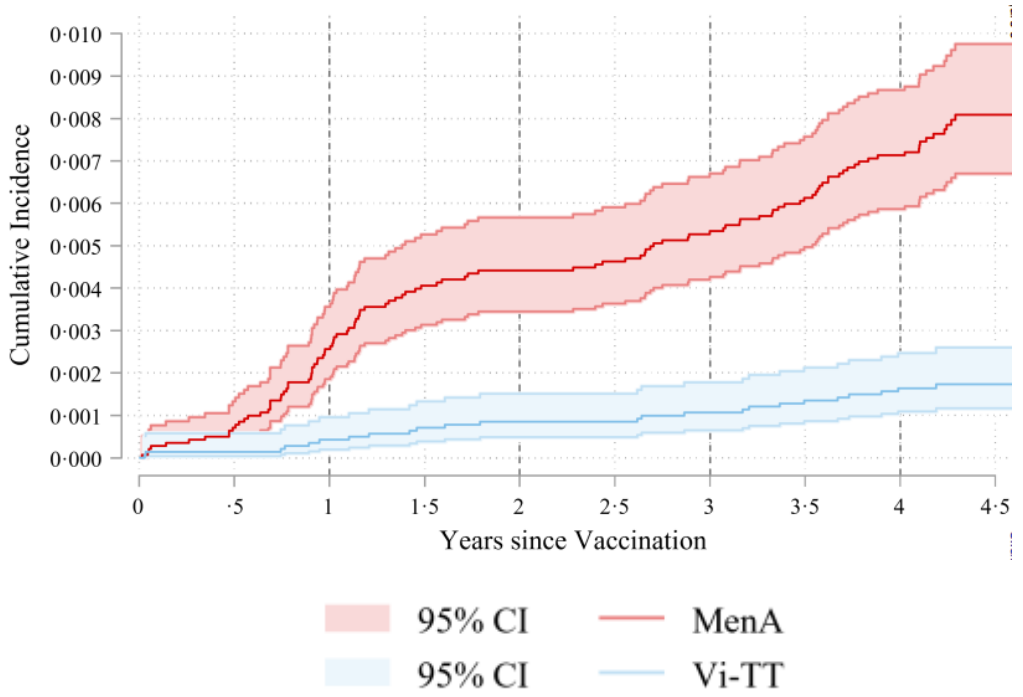


Figure 2: Number of blood-culture positive typhoid cases in the intention-to-treat population, by date and vaccine group. Dates of COVID-19 surveillance interruptions are shown with dotted vertical lines. MenA = meningococcal capsular group A conjugate vaccine; Vi-TT = Vi polysaccharide tetanus toxoid typhoid conjugate vaccine.



https://papers.ssrn.com/sol3/papers.cfm?abstract_id=4411421

International Journal of Infectious Diseases 108 (2021) 465–472

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International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Safety and immunogenicity of Vi-typhoid conjugate vaccine co-administration with routine 9-month vaccination in Burkina Faso: A randomized controlled phase 2 trial

Sodiomon B. Sirima[a], Alphonse Ouedraogo[a], Nouhoun Barry[a], Mohamadou Siribie[a], Alfred Tiono[a], Issa Nébié[a], Amadou Konaté[a], Gloria Damoaliga Berges[a], Amidou Diarra[a], Moussa Ouedraogo[a], Edith C. Bougouma[a], Issiaka Soulama[a], Alimatou Hema[a], Shrimati Datta[b], Yuanyuan Liang[b], Elizabeth T. Rotrosen[b], J. Kathleen Tracy[b], Leslie P. Jamka[b], Jennifer J. Oshinsky[b], Marcela F. Pasetti[b], Kathleen M. Neuzil[b], Matthew B. Laurens[b,*]

- Immunogenicity results comparable to settings where efficacy has been demonstrated.
- Co-administration studies facilitate integration into routine EPI and dual antigen campaigns.

International Journal of Infectious Diseases 102 (2021) 517–523

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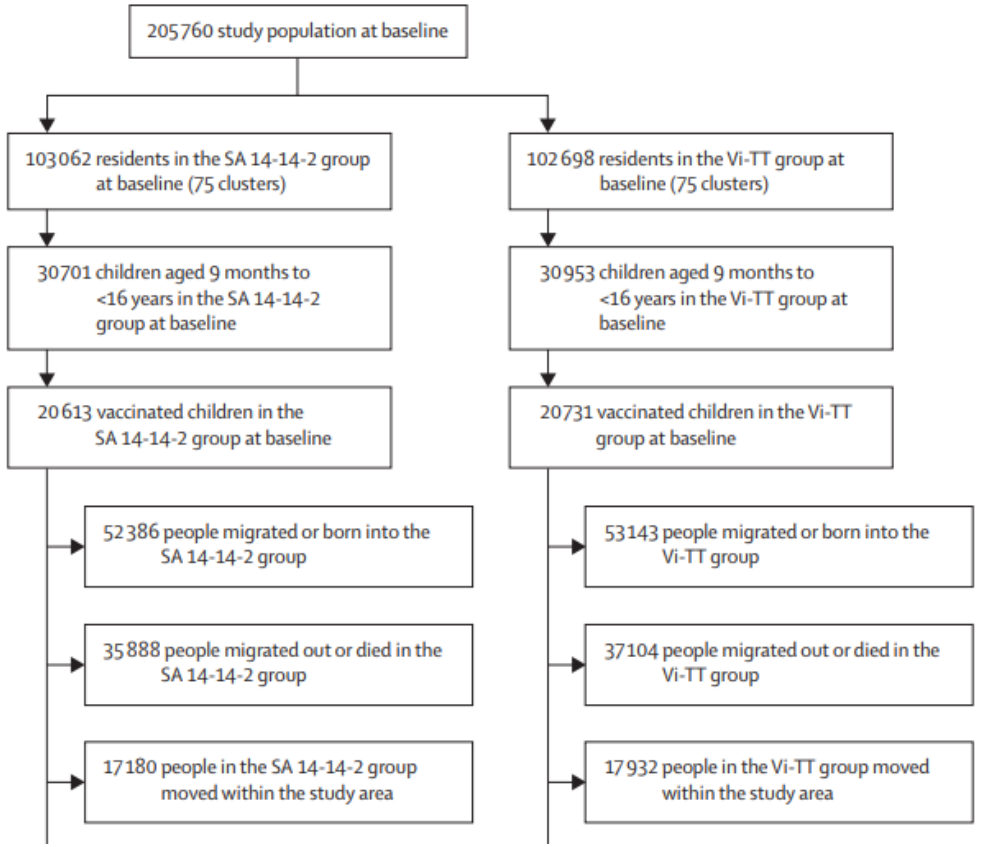
journal homepage: www.elsevier.com/locate/ijid

Safety and immunogenicity of co-administration of meningococcal type A and measles–rubella vaccines with typhoid conjugate vaccine in children aged 15–23 months in Burkina Faso

Sodiomon B. Sirima[a], Alphonse Ouedraogo[a], Nouhoun Barry[a], Mohamadou Siribie[a], Alfred B. Tiono[a], Issa Nébié[a], Amadou T. Konaté[a], Gloria Damoaliga Berges[a], Amidou Diarra[a], Moussa Ouedraogo[a], Issiaka Soulama[a], Alimatou Hema[a], Shrimati Datta[b], Yuanyuan Liang[b], Elizabeth T. Rotrosen[b], J. Kathleen Tracy[b], Leslie P. Jamka[b], Kathleen M. Neuzil[b], Matthew B. Laurens[b,*]

Highly mobile populations: Bangladesh and migration!

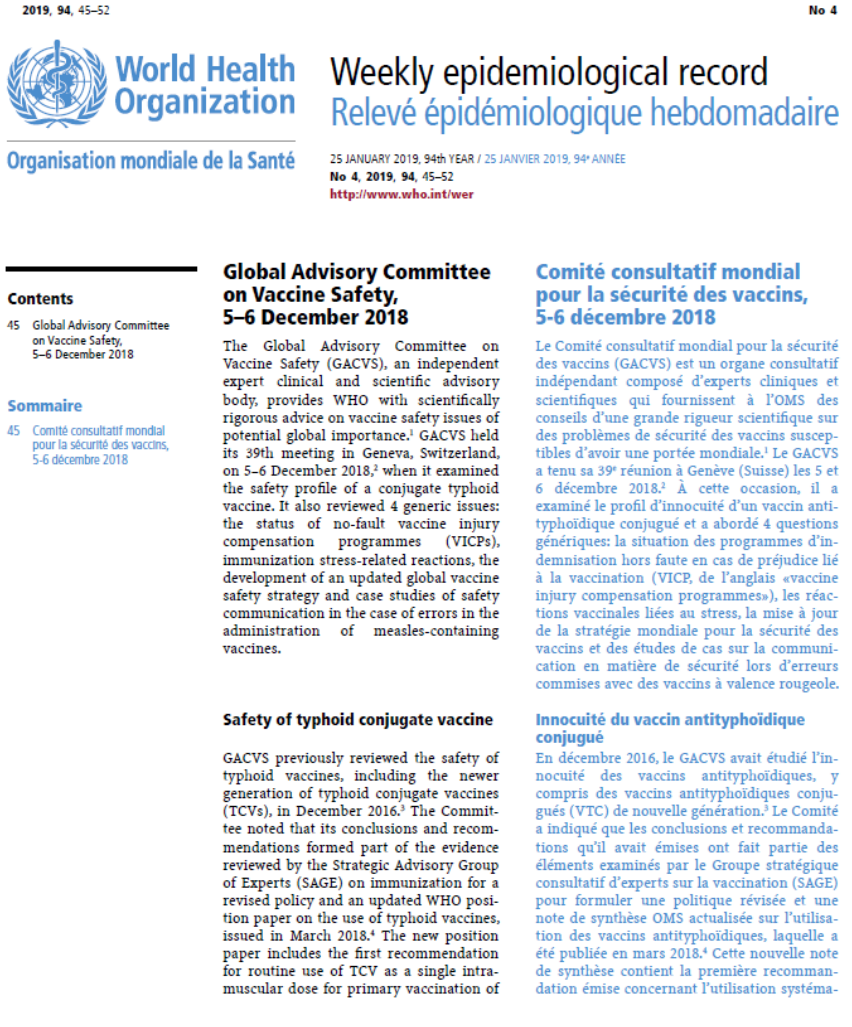
- During an average of 17.1 months of follow-up of the study population:
  - 150,529 births and in-migrations
  - 71,846 out-migrations
  - 35,112 people moved within the study area
- "Catch-up campaigns in 6-month intervals are unlikely to be feasible in routine public health practice"



Published online August 9, 2021 https://doi.org/10.1016/S0140-6736(21)01124-7

GACVS has reviewed the safety of TCV

- **December 2018:** The Global Advisory Committee on Vaccine Safety (GACVS) examined the safety profile of TCV.
- GACVS concluded "**safety profile of the Typbar-TCV™ vaccine is reassuring, and no signals of serious adverse events were presented**."
- GACVS recommends that **countries that introduce TCV into their routine immunization schedule or into campaigns make every effort to ensure robust monitoring of safety (as for any new vaccine)**
- Additional trial data since 2018:
  - No safety signals (full DSMB reviews)
  - Vaccine well-tolerated
  - Reactogenicity profile similar to control vaccines
- Millions of doses administered in campaigns and routine programs



2019, 94, 45–52 No 4

World Health Organization
Organisation mondiale de la Santé

Weekly epidemiological record
Relevé épidémiologique hebdomadaire

25 JANUARY 2019, 94th YEAR / 25 JANVIER 2019, 94e ANNÉE
No 4, 2019, 94, 45–52
http://www.who.int/wer

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Global Advisory Committee on Vaccine Safety, 5–6 December 2018

The Global Advisory Committee on Vaccine Safety (GACVS), an independent expert clinical and scientific advisory body, provides WHO with scientifically rigorous advice on vaccine safety issues of potential global importance.[1] GACVS held its 39th meeting in Geneva, Switzerland, on 5–6 December 2018,[2] when it examined the safety profile of a conjugate typhoid vaccine. It also reviewed 4 generic issues: the status of no-fault vaccine injury compensation programmes (VICPs), immunization stress-related reactions, the development of an updated global vaccine safety strategy and case studies of safety communication in the case of errors in the administration of measles-containing vaccines.

Comité consultatif mondial pour la sécurité des vaccins, 5-6 décembre 2018

Le Comité consultatif mondial pour la sécurité des vaccins (GACVS) est un organe consultatif indépendant composé d'experts cliniques et scientifiques qui fournissent à l'OMS des conseils d'une grande rigueur scientifique sur des problèmes de sécurité des vaccins susceptibles d'avoir une portée mondiale.[1] Le GACVS a tenu sa 39e réunion à Genève (Suisse) les 5 et 6 décembre 2018.[2] À cette occasion, il a examiné le profil d'innocuité d'un vaccin antityphoïdique conjugué et a abordé 4 questions génériques: la situation des programmes d'indemnisation hors faute en cas de préjudice lié à la vaccination (VICP, de l'anglais «vaccine injury compensation programmes»), les réactions vaccinales liées au stress, la mise à jour de la stratégie mondiale pour la sécurité des vaccins et des études de cas sur la communication en matière de sécurité lors d'erreurs commises avec des vaccins à valence rougeole.

Safety of typhoid conjugate vaccine

GACVS previously reviewed the safety of typhoid vaccines, including the newer generation of typhoid conjugate vaccines (TCVs), in December 2016.[3] The Committee noted that its conclusions and recommendations formed part of the evidence reviewed by the Strategic Advisory Group of Experts (SAGE) on immunization for a revised policy and an updated WHO position paper on the use of typhoid vaccines, issued in March 2018.[4] The new position paper includes the first recommendation for routine use of TCV as a single intramuscular dose for primary vaccination of

Innocuité du vaccin antityphoïdique conjugué

En décembre 2016, le GACVS avait étudié l'innocuité des vaccins antityphoïdiques, y compris des vaccins antityphoïdiques conjugués (VTC) de nouvelle génération.[3] Le Comité a indiqué que les conclusions et recommandations qu'il avait émises ont fait partie des éléments examinés par le Groupe stratégique consultatif d'experts sur la vaccination (SAGE) pour formuler une politique révisée et une note de synthèse OMS actualisée sur l'utilisation des vaccins antityphoïdiques, laquelle a été publiée en mars 2018.[4] Cette nouvelle note de synthèse contient la première recommandation émise concernant l'utilisation systéma-

Gavi supports TCV introduction

Photo: Bill & Melinda Gates Foundation/Sam Reinders

Single dose routine

- Co-financed
- Vaccine introduction grant
- Gavi recommends routine immunization at 9 months old

Photo: PATH/Asim Hafeez

One time single dose catch-up campaign

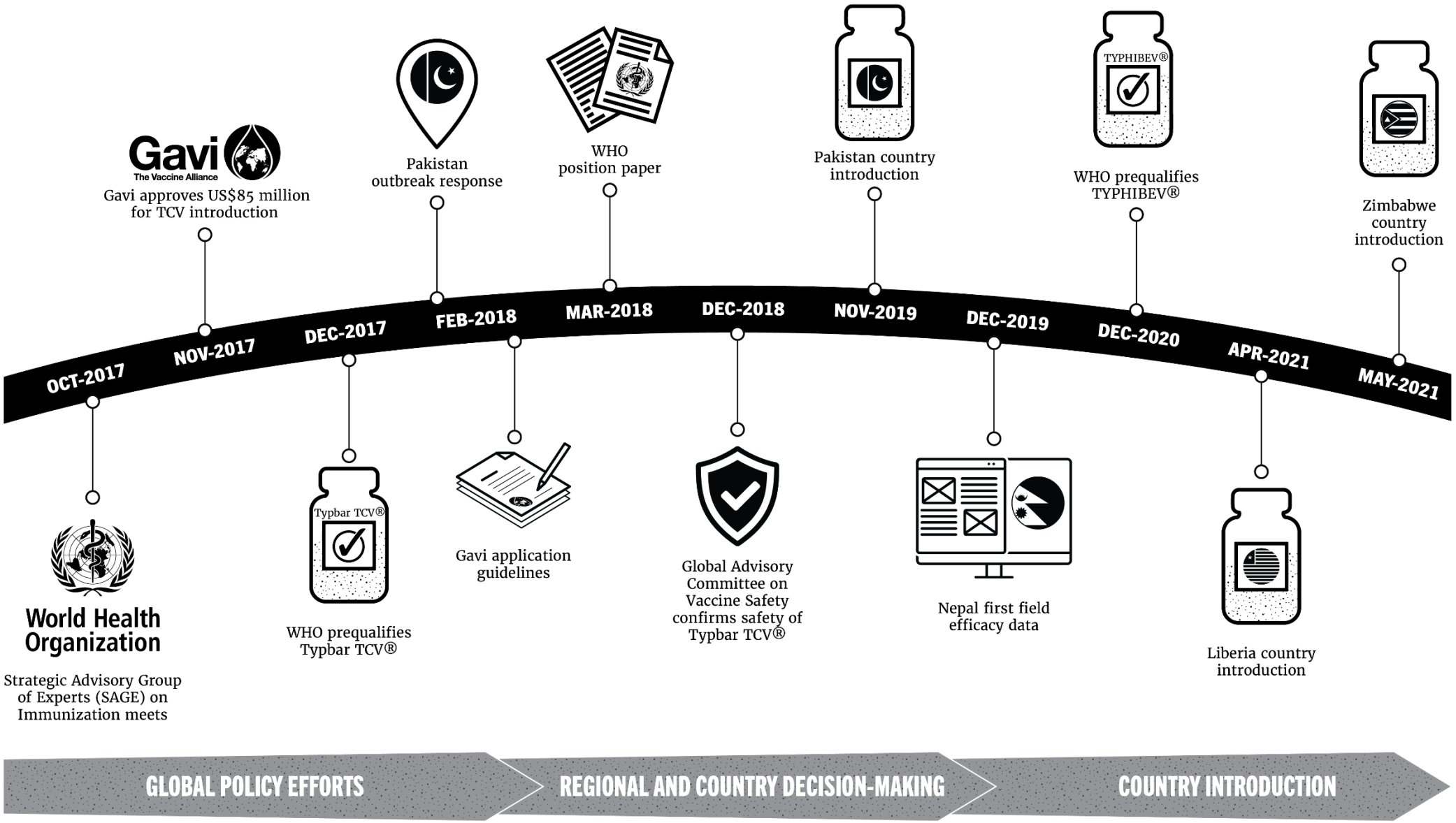
- Financed by Gavi
- Operational cost support
- Up to 15 years of age

Programmatic characteristics of WHO prequalified TCVs

	Typbar TCV®	TYPHIBEV®
MANUFACTURER	Bharat Biotech, India	Biological E, India
VACCINE TYPE	Vi polysaccharide from *Salmonella* Typhi conjugated to tetanus toxoid carrier protein	Vi polysaccharide from *Citrobacter freundii* conjugated to CRM197 carrier protein*
FORMULATION	Liquid: ready to use	
ADMINISTRATION	Intramuscular injection	
AGES	≥6 months to ≤65 years	≥6 months to ≤45 years
NUMBER OF DOSES REQUIRED	1	
WHO-PREQUALIFIED PRESENTATION(S) AVAILABLE WITH GAVI SUPPORT	5-dose vial	
COLD CHAIN VOLUME	5-dose vial: 2.9 cm3/dose	5-dose vial: 2.9 cm3/dose
SHELF LIFE	36 months at storage temperature: 2-8°C	24 months at storage temperature: 2-8°C
VACCINE VIAL MONITOR (VVM) TYPE	Type 30	
USE IN ROUTINE IMMUNIZATION PROGRAMS	India (Navi Mumbai only), Liberia, Pakistan, Samoa, Zimbabwe	Nepal

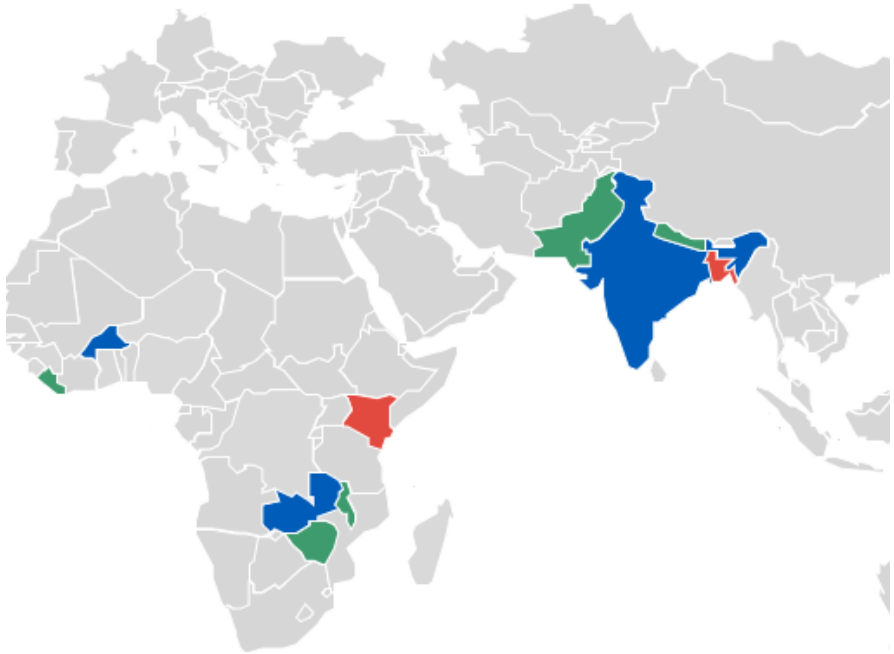
[Take on Typhoid (coalitionagainsttyphoid.org)]

Global policy and TCV vaccine introduction milestones



Our ultimate goal: Getting TCV to kids who need it

- Pakistan became the first country to introduce TCV into its routine childhood immunization program in November 2019. The final provinces concluded their campaign in October 2022.
- Liberia, Zimbabwe, and Samoa introduced TCV in 2021.
- Nepal introduced TCV in April 2022.
- Malawi introduced in May 2023
- TCV has also been used safely and effectively as part of outbreak response efforts, both in Pakistan and in Zimbabwe.
- **Nearly 60 million children** have been vaccinated during TCV campaigns.
- Other countries are in various stages of preparing applications and/or planning for TCV introduction into their routine immunization programs.



TCV introduced or approved	*TCV applications under review*	*TCV recommended by NITAG but not yet applied*
Liberia, Nepal, Pakistan, Zimbabwe; Malawi (planned Q2 2023)	Bangladesh, Kenya	Burkina Faso, India, Zambia

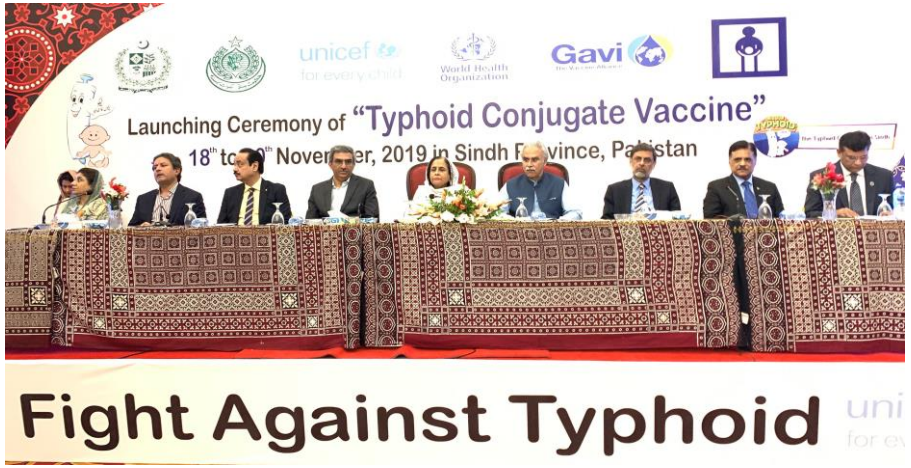
Pakistan becomes first country to introduce new typhoid vaccine into routine immunisation program

Gavi-supported introduction of new and improved typhoid conjugate vaccine to offer protection against increasingly drug-resistant disease

Karachi, 15 November 2019 - Pakistan today became the first country in the world to introduce the World Health Organization (WHO)-recommended typhoid conjugate vaccine (TCV) into its routine immunization program. It is the first typhoid vaccine that can be given to children as young as 6 months of age and confers longer term protection against typhoid. The government of Pakistan is launching the vaccine introduction with a campaign in Sindh Province, which is the center of an ongoing extensively drug-resistant (XDR) typhoid outbreak that began in November 2016.

"Children are disproportionately affected by typhoid and its associated complications, and we strongly

A man with his son during a vaccination session in Punjab Province, Pakistan. Credit: Gavi/2017/Asad Zaidi.

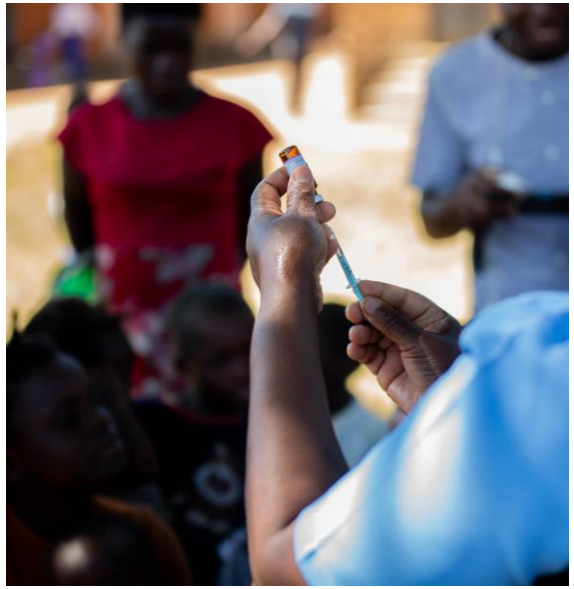


Celebrating Nepal's typhoid conjugate vaccine introduction

*Posted on **April 8, 2022** by **Mr. Sagar Dahal, Immunization Manager, Family Welfare Division, Nepal***

Credit: Nurudeen Sanni

Credit: Kudzai Tinago



Vaccine effectiveness against culture-confirmed *S.* Typhi and XDR *S.* Typhi, Pakistan

	Number of participants (n)	At-risk population (n)	Total person-time at risk, years*	S Typhi incidence; number of cases per 100 000 population (95% CI)	S Typhi incidence; number of cases per 100 000 person-years (95% CI)	S Typhi incidence rate ratio (95% CI)	Vaccine effectiveness* (95% CI)
Culture-confirmed S Typhi cases							
Age 6–59 months							
Vaccinated	22	5521	8646	398·5 (232·3–564·7)	254·5 (249·1–259·8)	0·06 (0·03–0·09)	94·5 (91·5–96·6)
Unvaccinated	349	4647	7599	7510·2 (6752·4–8268·0)	4592·5 (4489·3–4695·8)	..	..
Age ≥5 years							
Vaccinated	25	7915	12 103	315·9 (192·2–439·5)	206·6 (202·9–210·2)	0·05 (0·03–0·07)	95·2 (92·9–97·0)
Unvaccinated	379	5324	8722	7118·7 (6428·0–7809·4)	4345·1 (4253·9–4436·3)	..	..
Overall							
Vaccinated	47	13436	20 749	349·8 (250·0–449·6)	226·5 (223·4–229·6)	0·05 (0·04–0·07)	94·9 (93·2–96·3)
Unvaccinated	728	9971	16 322	7301·2 (6790·5–7811·8)	4460·3 (4391·9–4528·8)	..	..
XDR S Typhi cases							
Age 6–59 months							
Vaccinated	14	5521	8646	253·6 (120·9–386·2)	161·9 (158·5–165·3)	0·06 (0·03–0·10)	94·4 (90·4–97·0)
Unvaccinated	220	4647	7599	4734·2 (4123·6–5344·8)	2895·0 (2829·9–2960·1)	..	..
Age ≥5 years							
Vaccinated	4	7915	12 103	50·5 (1·0–100·1)	33·1 (32·5–33·6)	0·01 (0·00–0·04)	98·6 (96·4–99·6)
Unvaccinated	206	5324	8722	3869·3 (3351·2–4387·3)	2361·7 (2312·2–2411·3)	..	..
Overall							
Vaccinated	18	13 436	20 749	134·0 (72·1–195·8)	86·8 (85·6–87·9)	0·03 (0·02–0·05)	96·7 (94·7–98·0)
Unvaccinated	426	9971	16 322	4272·4 (3875·4–4669·3)	2610·0 (2570·0–2650·1)	..	..

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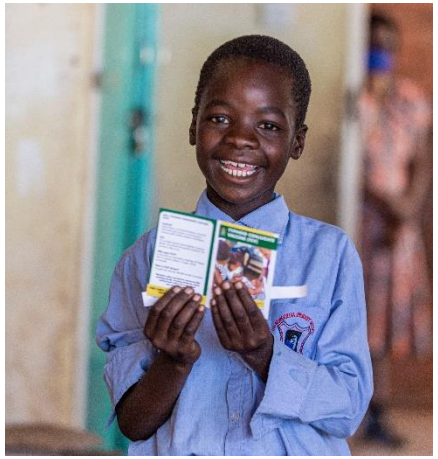
It's time to start making typhoid a disease of the past

- *S.* typhi is a substantial public health threat in low resource settings.
  - Numbers could increase, not decrease, in coming years
  - Need for simple, low-cost diagnostics
- A single dose of TCV is safe, well-tolerated, and efficacious in children as young as 9 months of age across diverse settings.
  - Understanding the duration of protection, and the need for, and timing, of booster doses of TCV are critical next steps.
- Need to ensure the most disadvantaged children have access to vaccine:
  - A broad rather than narrow population use of TCV to ensure no child is left behind
  - Innovation and flexibility in defining disease burden.
  - Multi-antigen campaigns
- Improvements in water, sanitation and hygiene are critical.

Credit: PHC Global



Credit: Kudzai Tinago

Thanks to the Global TyVAC Team