

# Update on Typhoid Vaccines

## ARVAC 2023

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June 14, 2023



“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.<sup>1</sup>

By PROF. W. T. SEDGWICK,  
*Boston, Mass.*

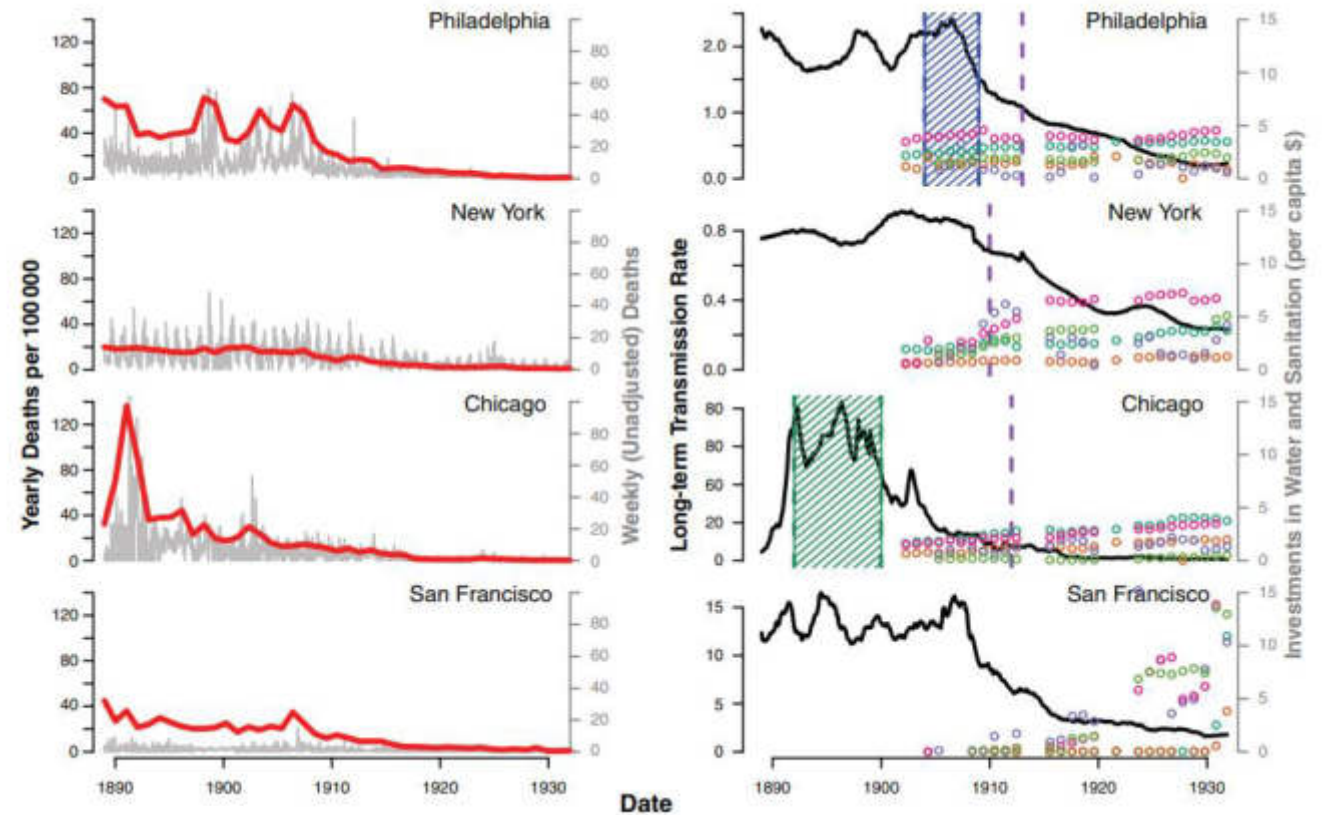
In 1886 the state board of health of Massachusetts was re-organized. It was placed under the able leadership of Dr. Henry P. Walcott, who certainly needs no introduction to this Association. It contained upon its membership-roll one of the most eminent sanitary engineers in the country, Hiram F. Mills; 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,<sup>1</sup> Maile T. Phillips,<sup>2</sup> Virginia E. Pitzer,<sup>2</sup> and Claas Kirchhelle<sup>3</sup>

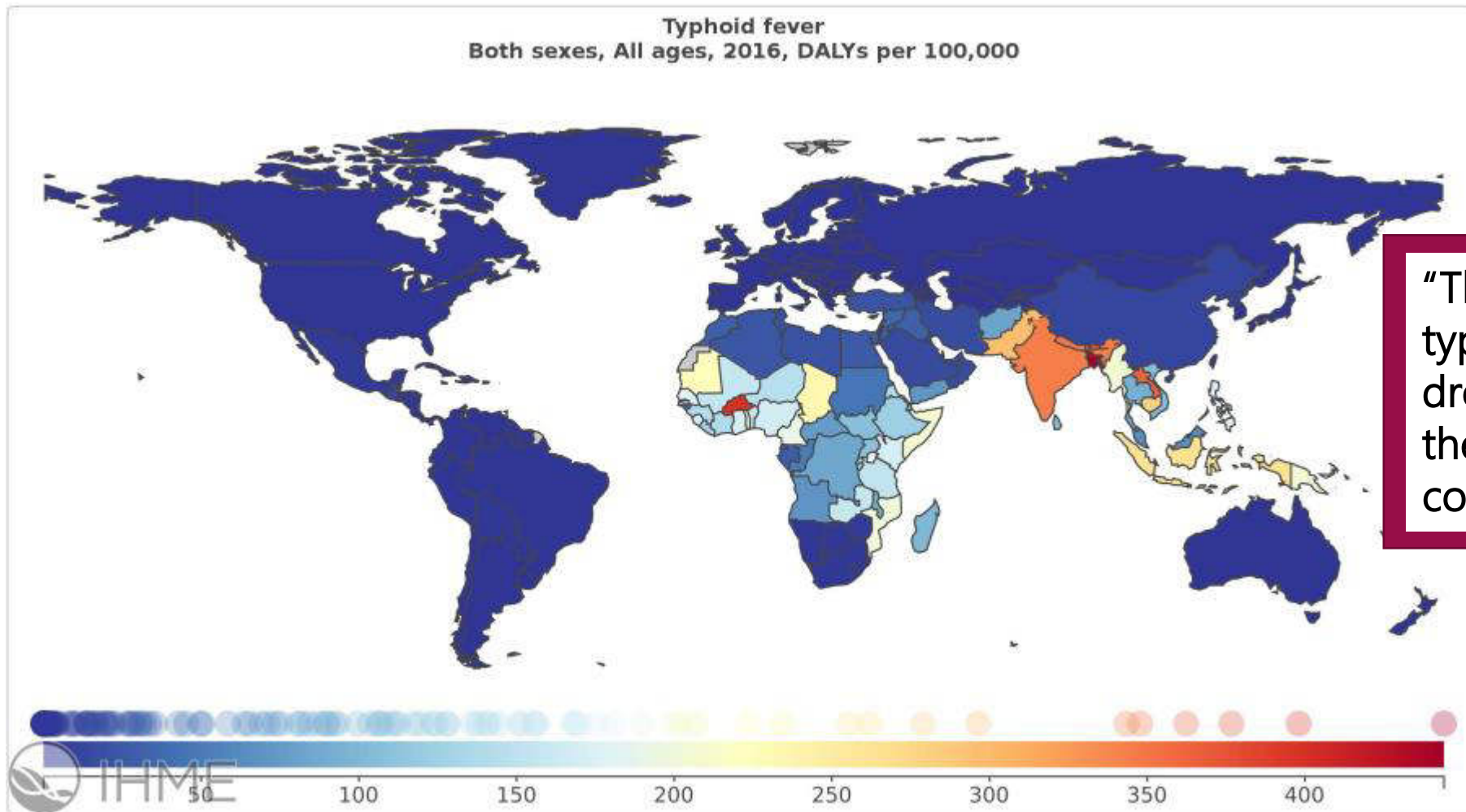
<sup>1</sup>Oxford Vaccine Group/Oxford Martin School, University of Oxford, United Kingdom; <sup>2</sup>Department of Epidemiology of Microbial Diseases, Yale School of Public Health, Yale University, New Haven, Connecticut; and <sup>3</sup>Wellcome Unit for the History of Medicine/Oxford Martin School, 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](http://www.thelancet.com), Volume 379, Feb 25, 2012.

GBD 2016. <https://vizhub.healthdata.org/gbd-compare/>

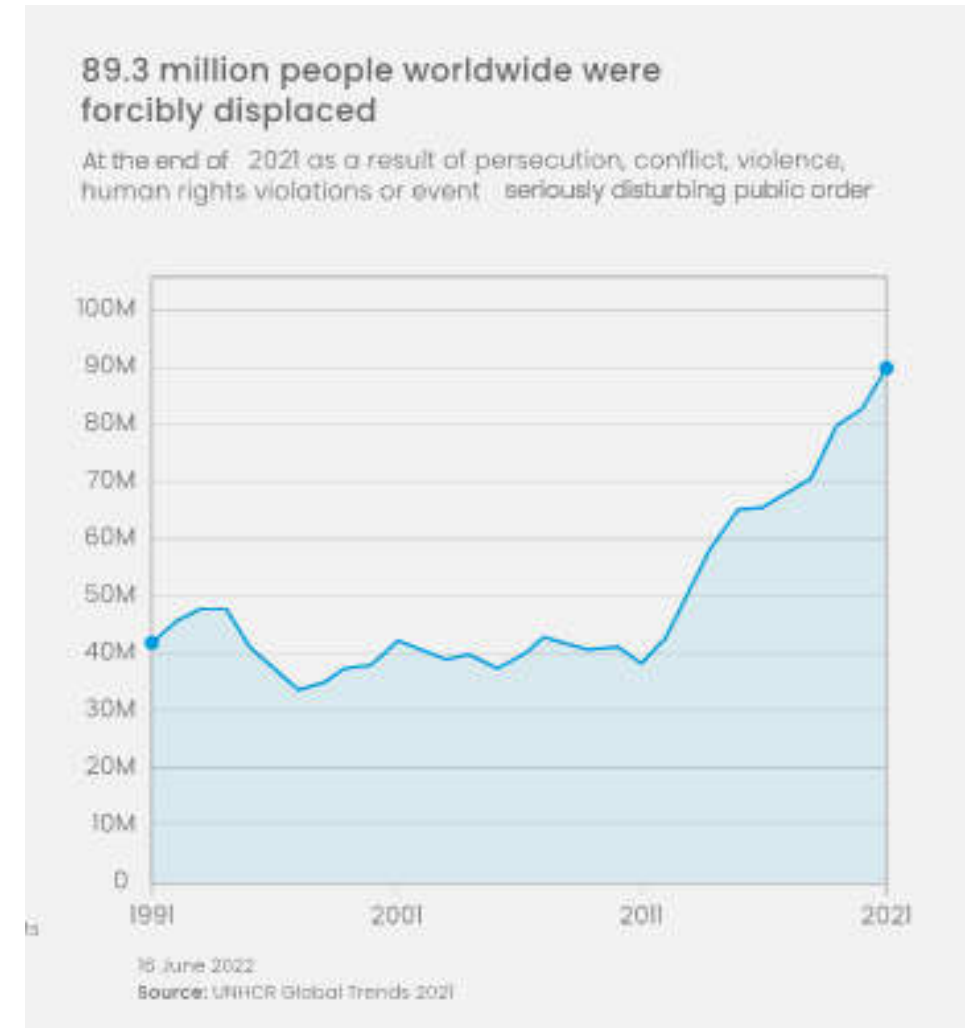
# Typhoid: Where are we in 2023?

- 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.

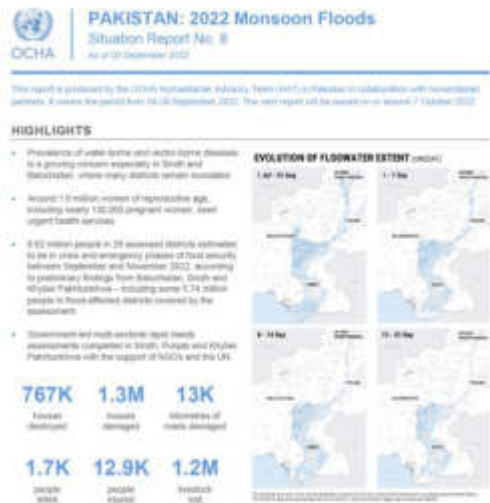


# Enteric disease control is facing unprecedented challenges

- 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



An elevated view of a flooded area in South Punjab, Pakistan. Floods have killed more than 1,000 people across the country, with thousands more injured.



## The New York Times

By **Ruth Maclean**

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

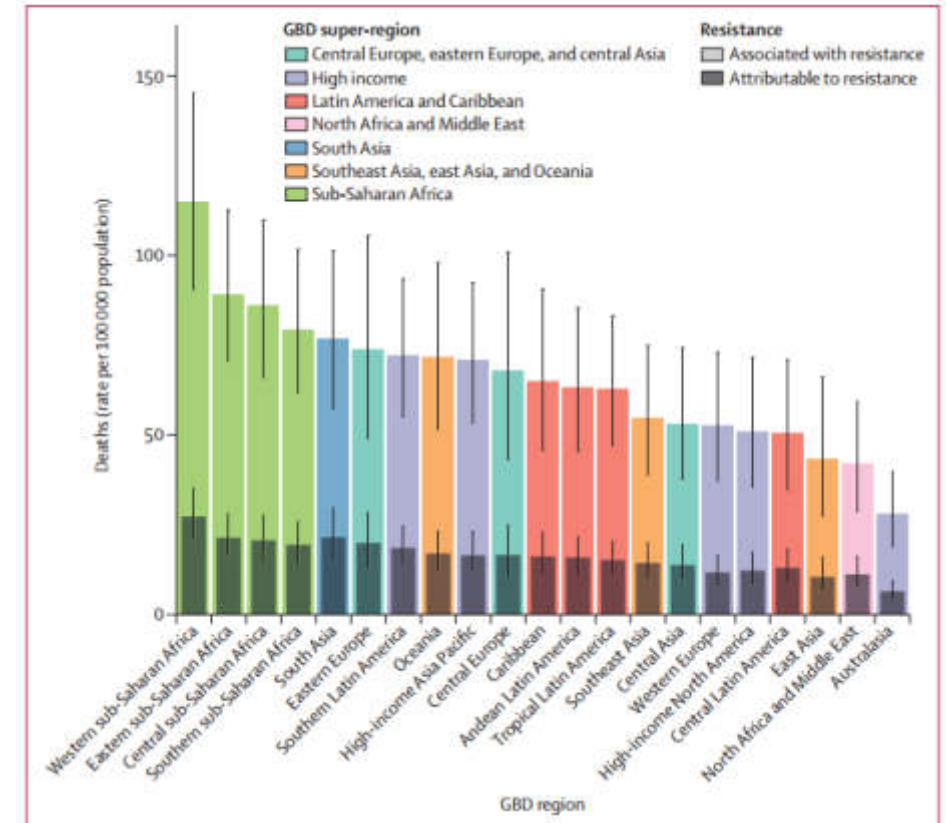
### *Nigeria Floods Kill Hundreds and Displace Over a Million*

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-Saharan Africa
- Highest death rate in Western SSA at 27.3 deaths/100,000



[https://doi.org/10.1016/S0140-6736\(21\)02724-0](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 and central Asia.
- Both inappropriate use of antibiotics, and lack of access to antibiotics are important public health problems.

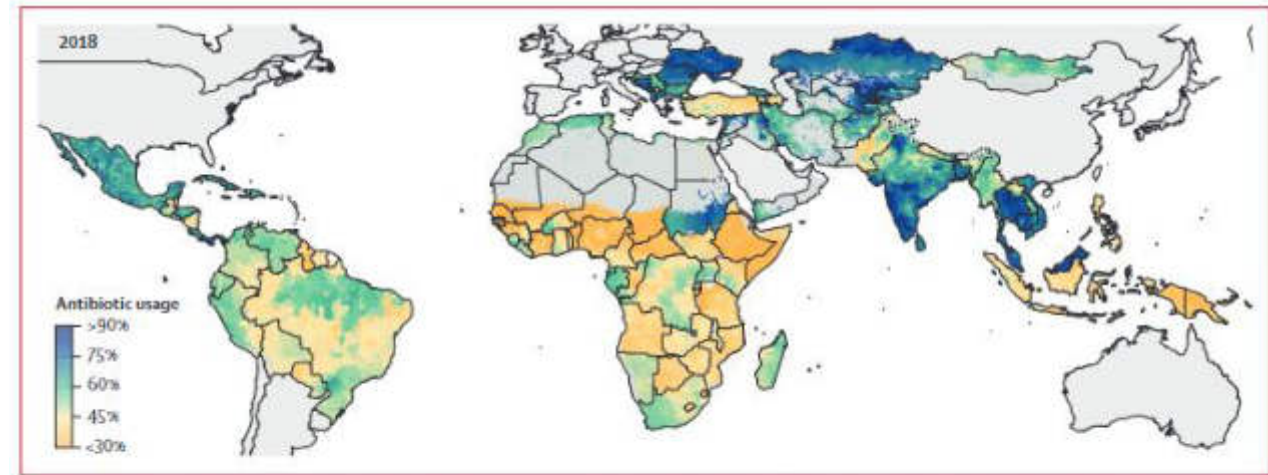
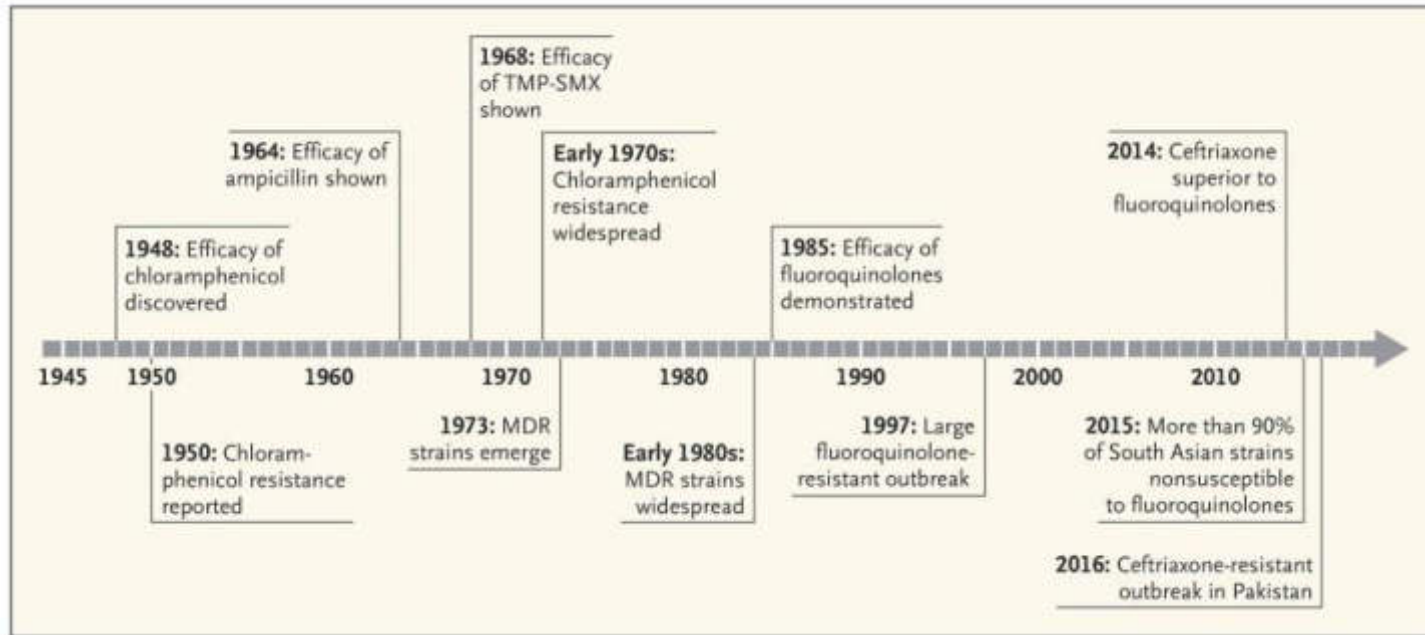


Figure 1: The percentage of children (aged <5 years) with symptoms of lower respiratory tract infections with caregiver-reported antibiotic usage in low-income and middle-income countries, 2018. Modelled estimates are shown by level two administrative divisions. High-income countries and pixels (1x1 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

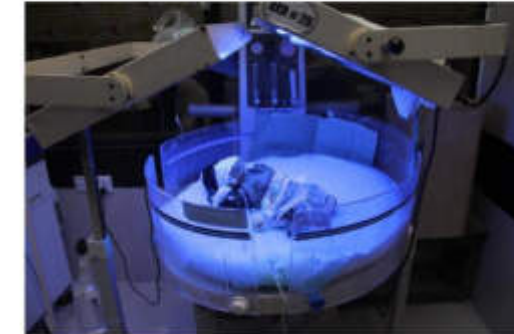


Source: Andrews et al. NEJM 2018; 379: 1493.

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

Global Health

By SEBASTIAN HARRIS | APRIL 12, 2018



A baby believed to have contracted a drug-resistant strain of typhoid, hospitalized in Hyderabad, Pakistan in February. Typhoid fever is a dangerous tropical disease.

## Outbreak Reports

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

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

# 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) <sup>1</sup>					
Primary series	≥6	1 capsule <sup>2</sup> , oral	4	48 hrs	N/A
Booster	≥6	1 capsule <sup>2</sup> , 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

<sup>1</sup>The vaccine must be kept refrigerated 35.6°F-46.4°F, 2°C-8°C

<sup>2</sup>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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Source: CDC Yellow Book on Typhoid Fever. <https://wwwnc.cdc.gov/travel/yellowbook/2018/infectious-diseases-related-to-travel/typhoid-paratyphoid-fever>.

# 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

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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

## 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.

Lancet 2017; 390: 2472–80

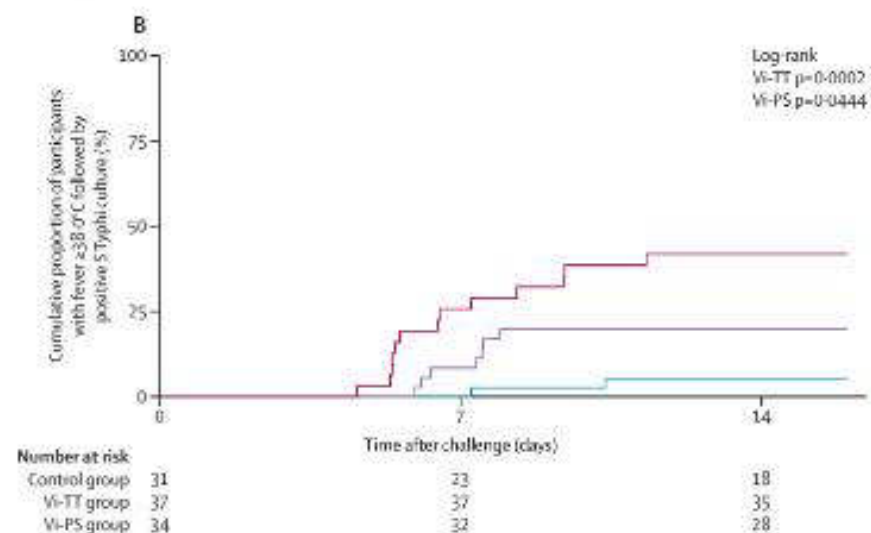
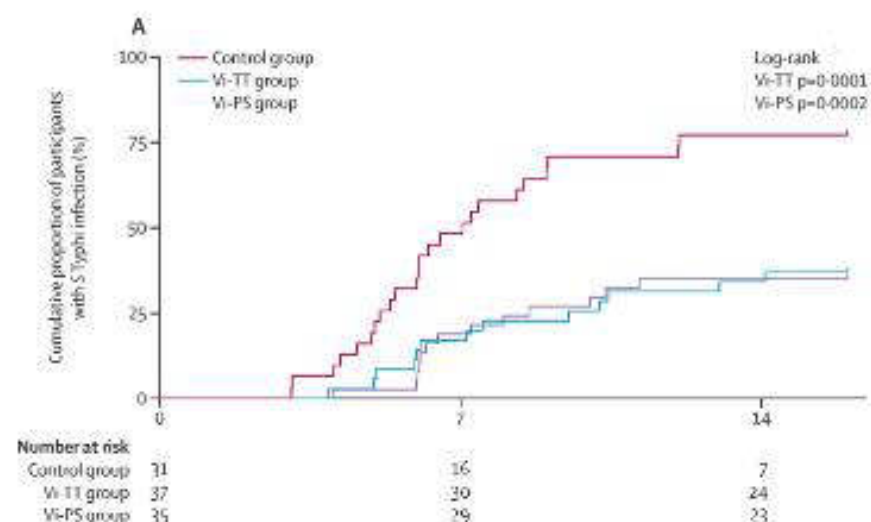
Published Online

September 28, 2017

[http://dx.doi.org/10.1016/S0140-6736\(17\)32149-9](http://dx.doi.org/10.1016/S0140-6736(17)32149-9)

See Comment page 2419

	Control group (n=34)	Vi-TT group (n=41)	Vi-PS group (n=37)
<b>Primary outcome</b>			
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
<b>Secondary outcomes</b>			
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.



## COLLABORATING ORGANIZATIONS



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](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

Nov 2017



Feb 2018



Mar 2018

Oct 2017

Dec 2017



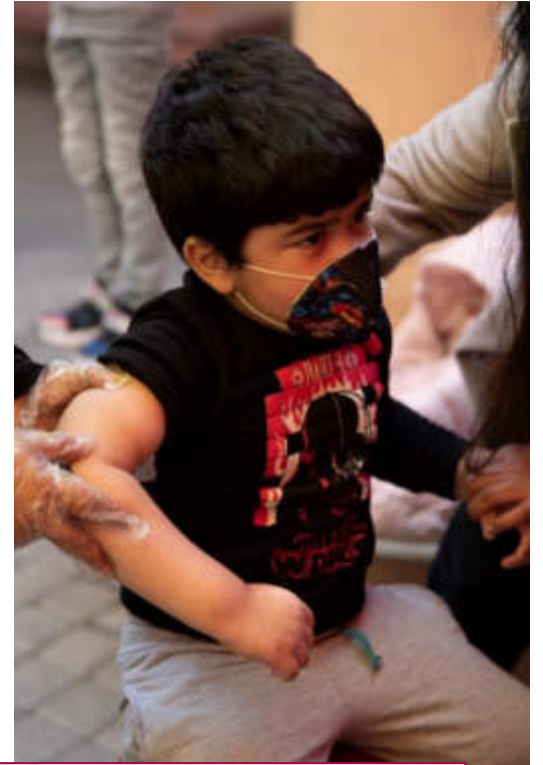
February, 2018  
(for applications in 2018)

## Application guidelines: Gavi's support to countries

Introduction .....	1
1. What types of support does Gavi provide to countries? .....	1
2. Core principles and requirements associated with Gavi support .....	3

# 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, Manoj Joshi, Nicola Smith, Jennifer Hill, Jenny Clarke, Lisa Stockdale, Elizabeth Jones, Abhilasha Karkey, Stephen Baker, Gordon Dougan, Virginia E Pitzer, Kathleen M Neuzil, 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, Aminul Islam Bhuiyan, Faisal Ahmed, Rachel Colin-Jones, Nicola Smith, Susan Tonks, Merryn Voysey, Yama F Mujadidi, Olga Mazur, Nazmul Hasan Rajib, Md Ismail Hossain, Shams Uddin Ahmed, Arifuzzaman Khan, Nazia Rahman, Golap Babu, Melanie Greenland, Sarah Kelly, Mahzabeen Ireen, Kamrul Islam, Peter O'Reilly, Karin Sofia Scherer, Virginia E Pitzer, Kathleen M Neuzil, K Zaman, Andrew J Pollard†, John D Clemens†

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., Ngina Nampota, M.B., B.S., Oswald 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

Priyanka Patel

Malawi-Liverpool-Wellcome Trust Clinical Research Programme

Yuanyuan Liang

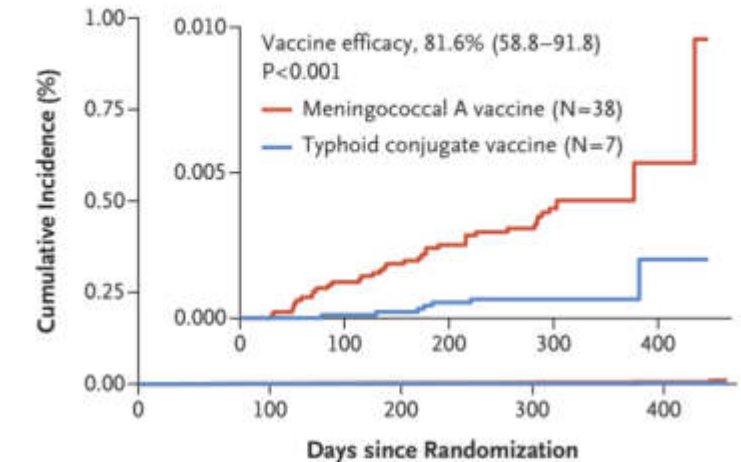
University of Maryland - Department of Epidemiology and Public Health

Preprints with THE LANCET

# 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)‡		
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



<b>No. at Risk</b>					
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			
<b>Total vaccine protection</b>							
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	..
<b>Overall vaccine protection</b>							
<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	..
<b>Indirect vaccine protection</b>							
<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 <sup>3</sup>	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) <sup>4</sup>
Malawi <sup>5</sup>	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) <sup>6</sup>
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 <sup>9</sup>	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) <sup>8</sup>

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

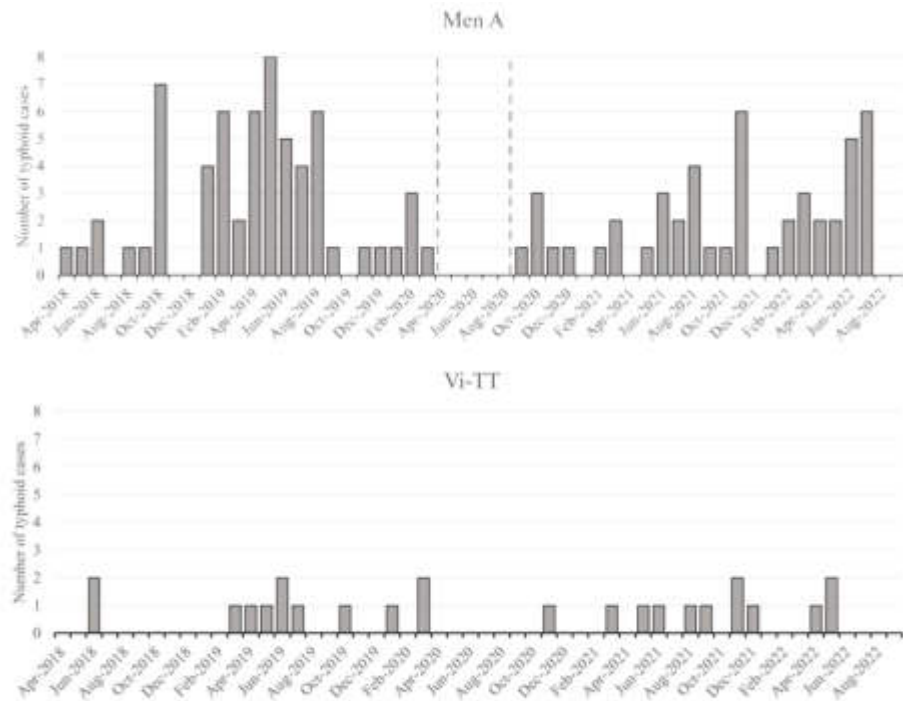
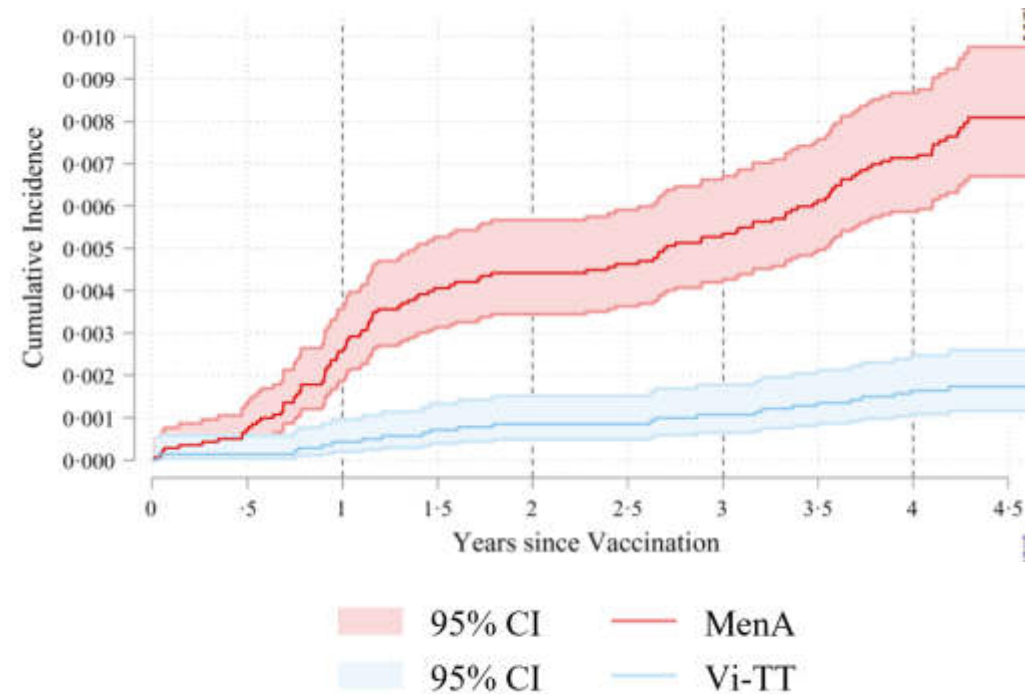


Figure 2: Number of blood-culture positive typhoid cases in the intention-to-treat population, by date and vaccine group. Dates of COVID-19 surveillance interruptions are shown with dotted vertical lines. MenA = meningococcal capsular group A conjugate vaccine; Vi-TT = Vi polysaccharide tetanus toxoid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



[https://papers.ssrn.com/sol3/papers.cfm?abstract\\_id=4411421](https://papers.ssrn.com/sol3/papers.cfm?abstract_id=4411421)



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

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



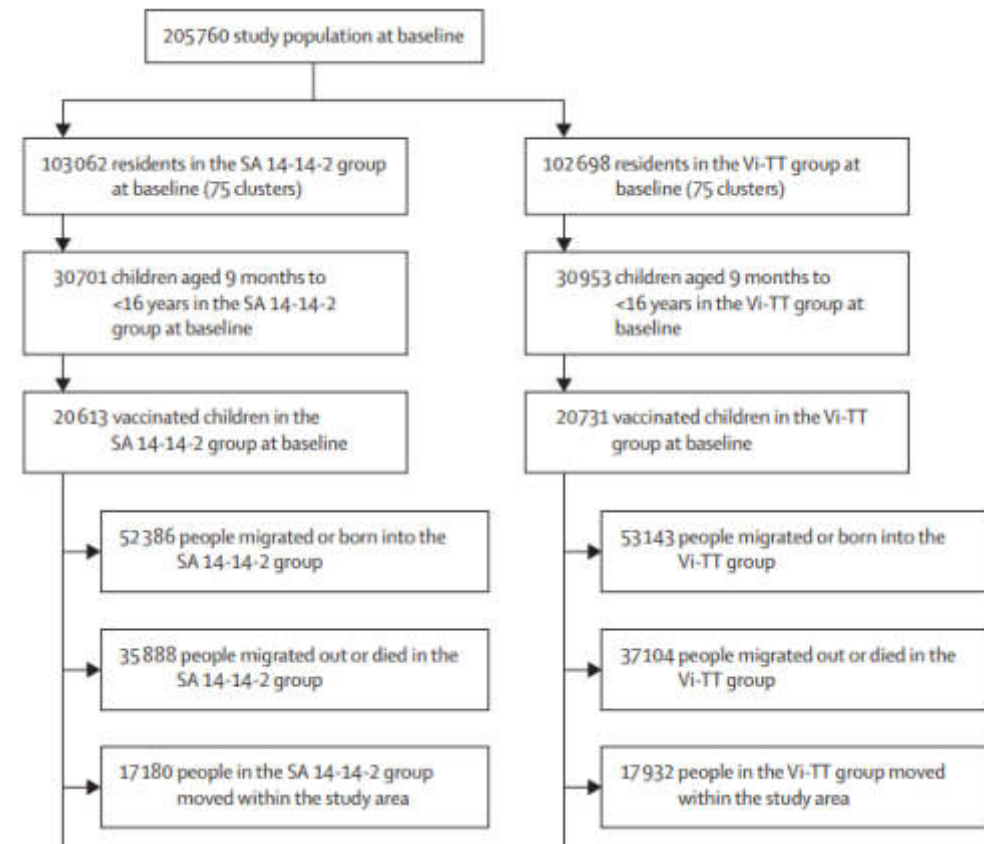
## Safety and immunogenicity of co-administration of meningococcal type A and measles–rubella vaccines with typhoid conjugate vaccine in children aged 15–23 months in Burkina Faso



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

# 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”



# 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



# 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

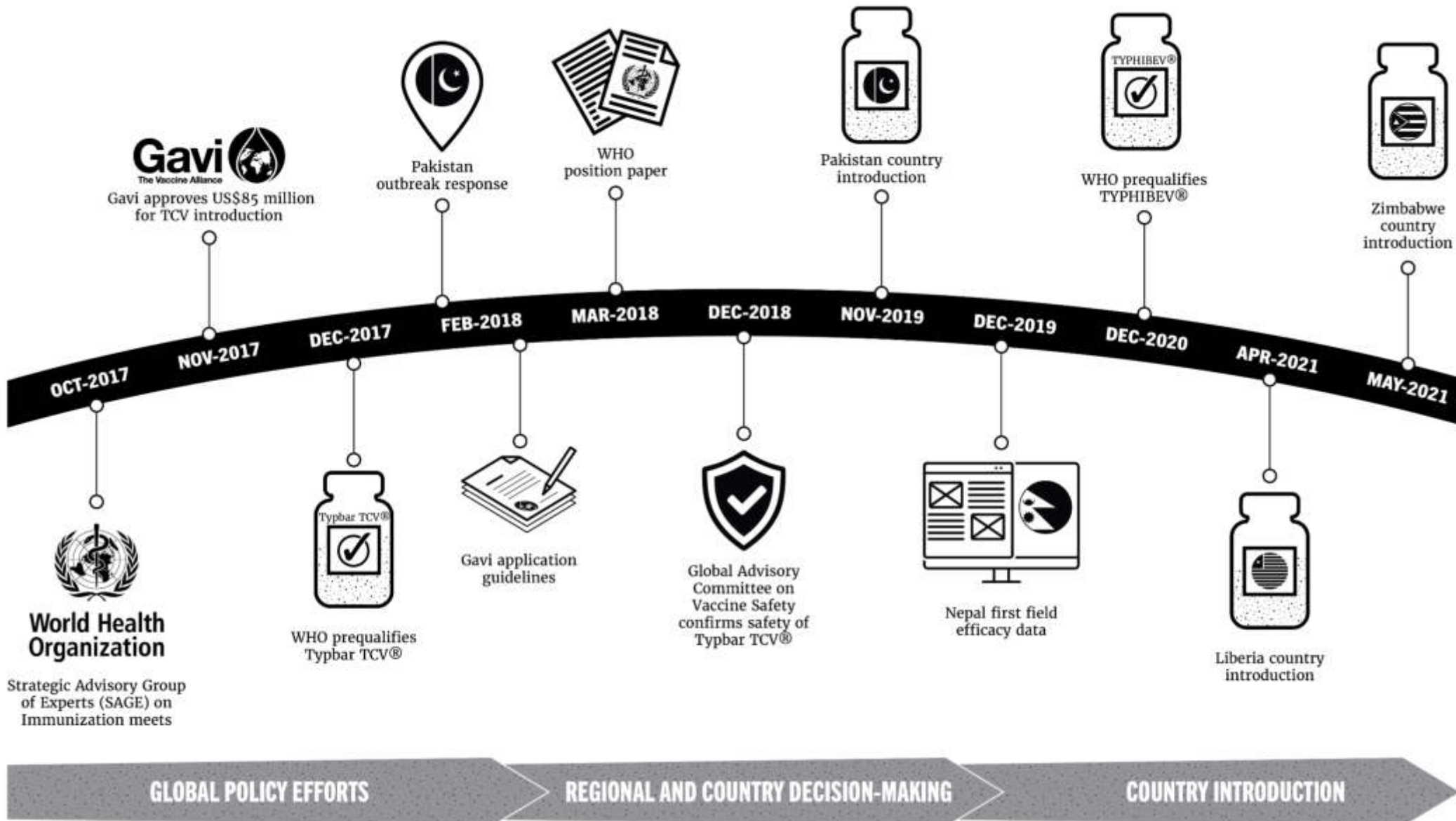
- Financed by Gavi
- Operational cost support
- Up to 15 years of age

# Programmatic characteristics of WHO prequalified TCVs

	Typbar TCV®	TYPHIBEV®
 <b>MANUFACTURER</b>	Bharat Biotech, India	Biological E, India
 <b>VACCINE TYPE</b>	Vi polysaccharide from <i>Salmonella</i> Typhi conjugated to tetanus toxoid carrier protein	Vi polysaccharide from <i>Citrobacter freundii</i> conjugated to CRM197 carrier protein*
 <b>FORMULATION</b>	Liquid: ready to use	
 <b>ADMINISTRATION</b>	Intramuscular injection	
 <b>AGES</b>	≥6 months to ≤65 years	≥6 months to ≤45 years
 <b>NUMBER OF DOSES REQUIRED</b>	1	
 <b>WHO-PREQUALIFIED PRESENTATION(S) AVAILABLE WITH GAVI SUPPORT</b>	5-dose vial	
 <b>COLD CHAIN VOLUME</b>	5-dose vial: 2.9 cm <sup>3</sup> /dose	5-dose vial: 2.9 cm <sup>3</sup> /dose
 <b>SHELF LIFE</b>	36 months at storage temperature: 2-8°C	24 months at storage temperature: 2-8°C
 <b>VACCINE VIAL MONITOR (VVM) TYPE</b>	Type 30	
 <b>USE IN ROUTINE IMMUNIZATION PROGRAMS</b>	India (Navi Mumbai only), Liberia, Pakistan, Samoa, Zimbabwe	Nepal

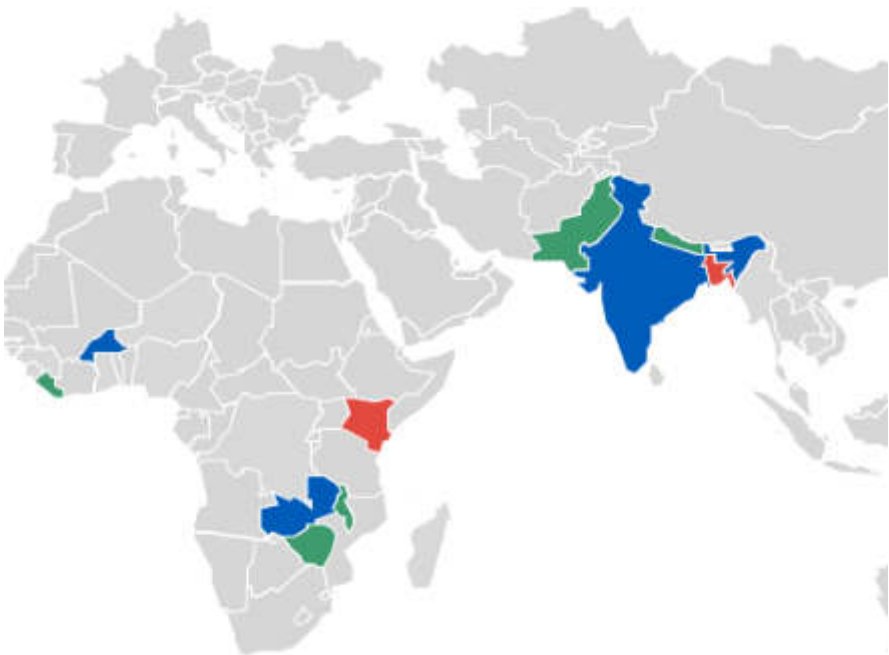
[Take on Typhoid \(coalitionagainststtyphoid.org\)](http://coalitionagainststtyphoid.org)

# 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.



# Fight Against Typhoid





# 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*	<i>S Typhi</i> incidence; number of cases per 100 000 population (95% CI)	<i>S Typhi</i> incidence; number of cases per 100 000 person-years (95% CI)	<i>S Typhi</i> incidence rate ratio (95% CI)	Vaccine effectiveness* (95% CI)
<b>Culture-confirmed <i>S Typhi</i> cases</b>							
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	20749	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)	..	..
<b>XDR <i>S Typhi</i> cases</b>							
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	20749	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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	Number of participants (n)	At-risk population (n)	Total person-time at risk, years*	<i>S. Typhi</i> incidence; number of cases per 100 000 population (95% CI)	<i>S. Typhi</i> incidence; number of cases per 100 000 person-years (95% CI)	<i>S. Typhi</i> incidence rate ratio (95% CI)	Vaccine effectiveness* (95% CI)
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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