

Typhoid Conjugate Vaccines

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CENTER FOR VACCINE DEVELOPMENT
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“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-

THE ORIGIN AND DISSEMINATION OF TYPHOID FEVER.¹

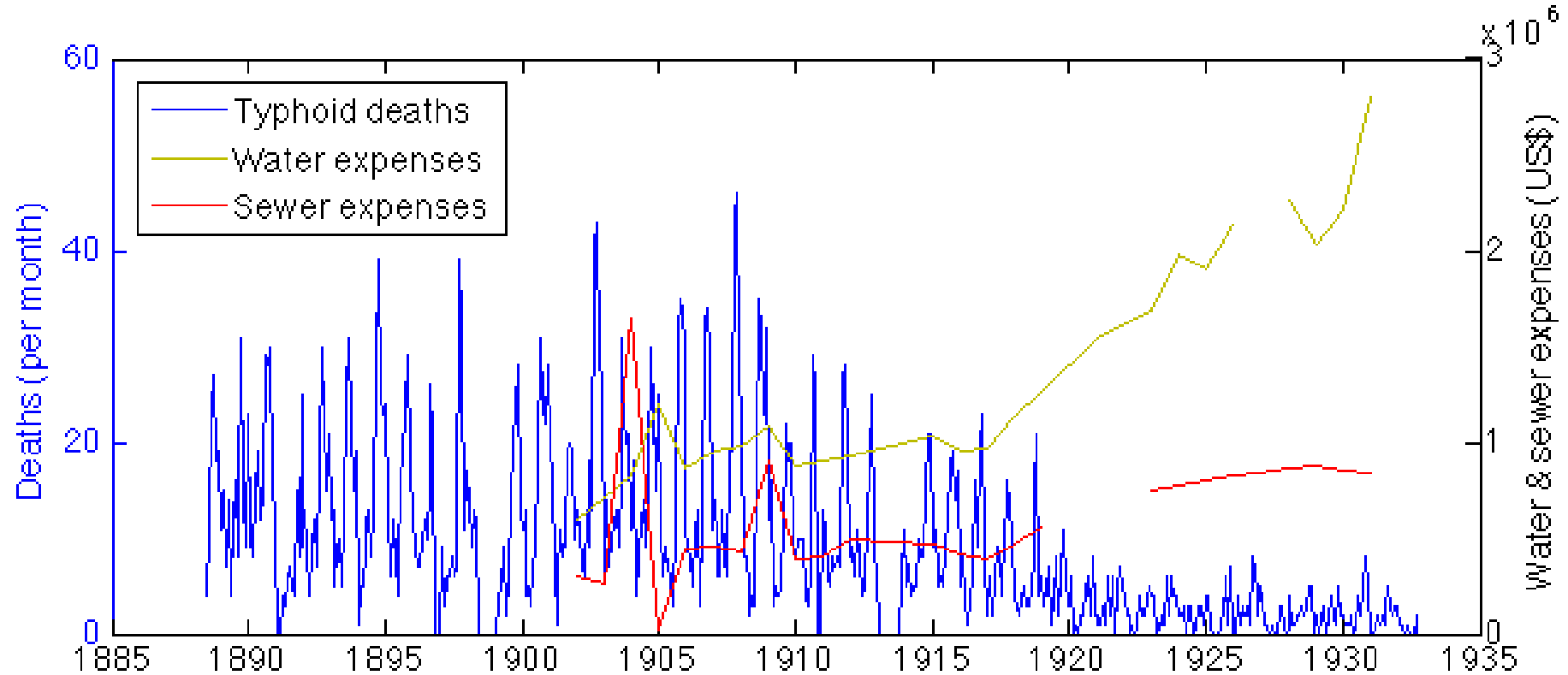
BY PROF. W. T. SEDGWICK,
Boston, Mass.

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

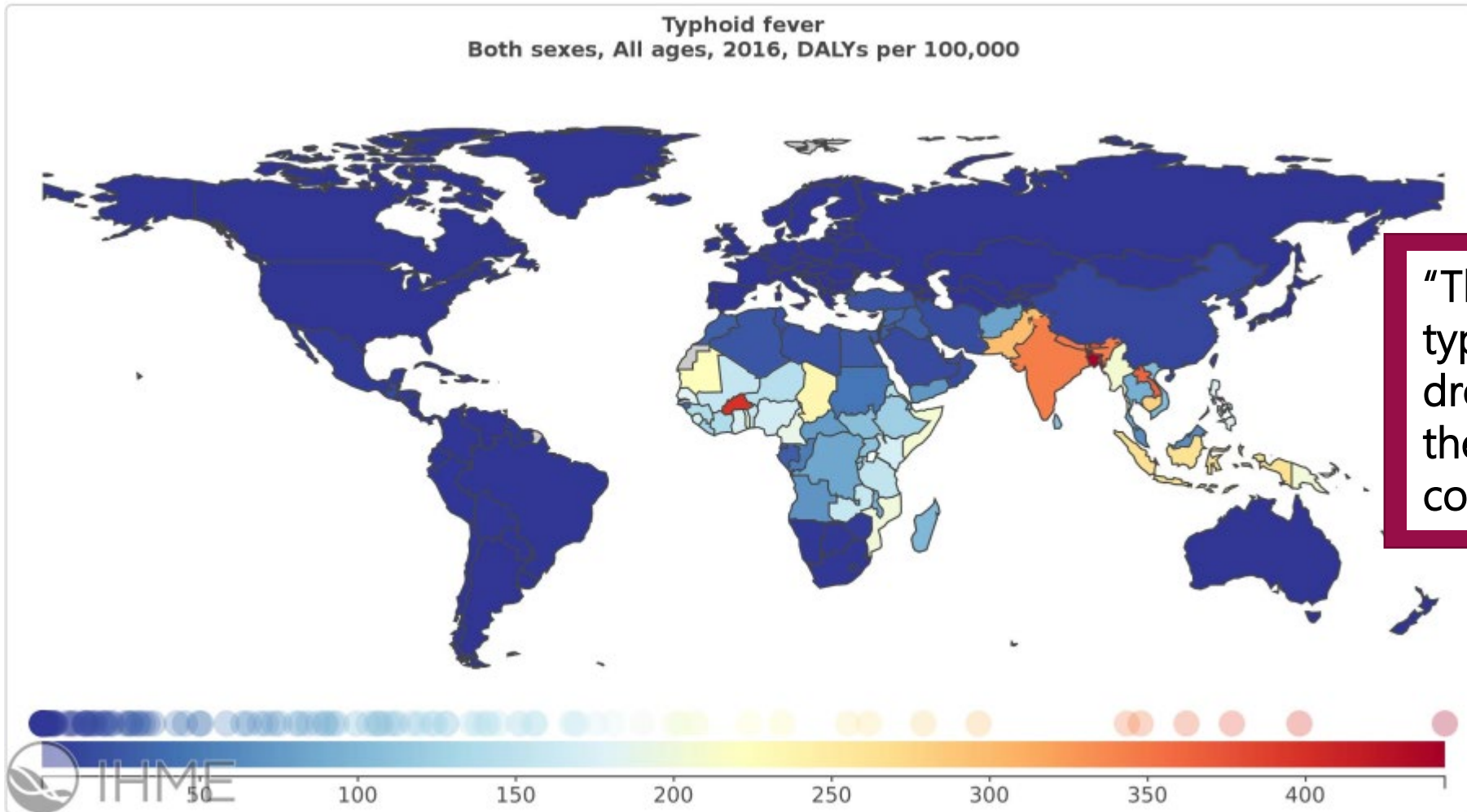
Sedgwick WT. The Origin and Dissemination of Typhoid Fever. Public Health Pap Rep. 1893;19:235-41.

Baltimore 1885-1935: Typhoid deaths in relation to water and sewage expenditures



Courtesy of V. Pitzer, Yale University.

Typhoid fever, DALYS per 100,000

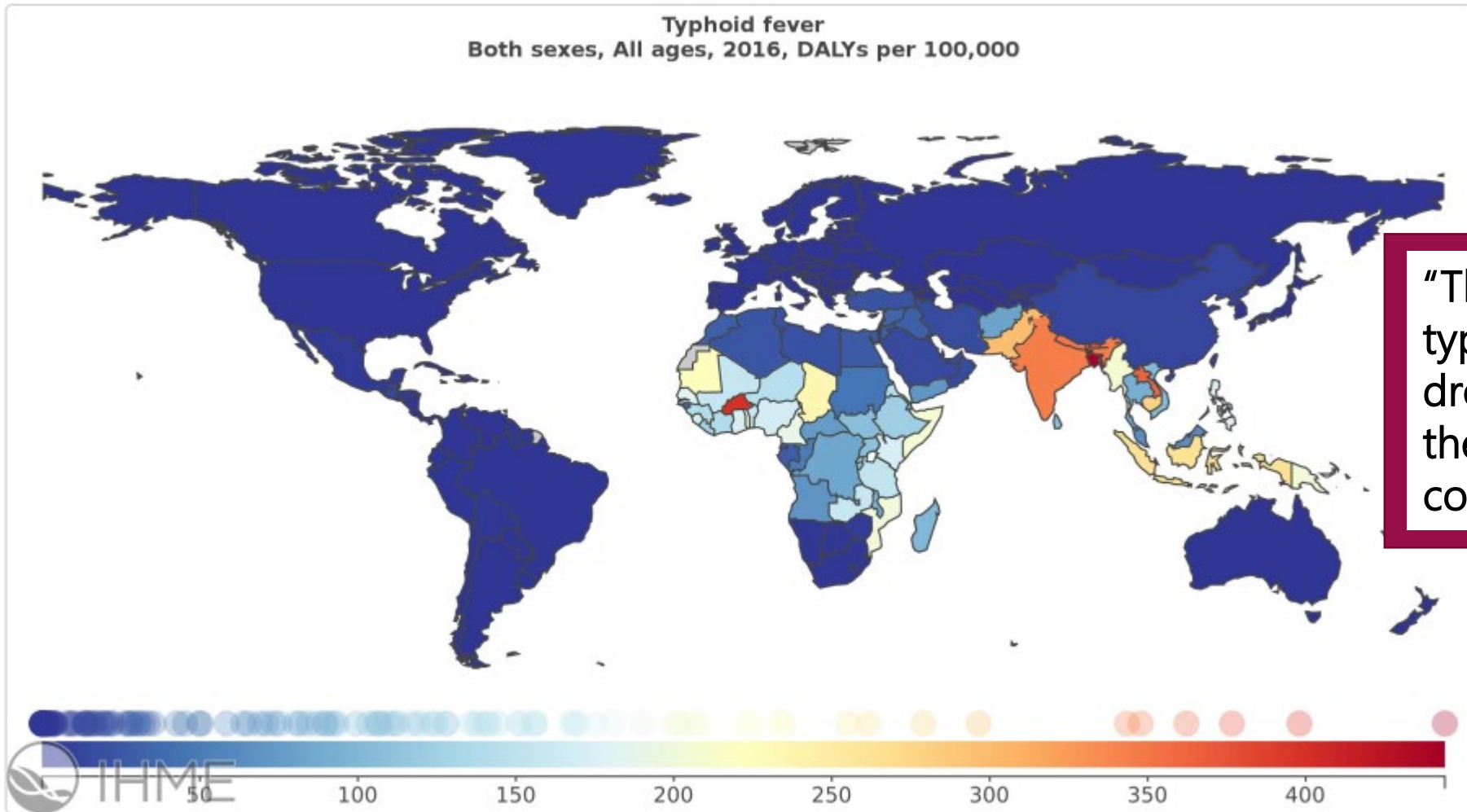


“The main problem with typhoid fever is that it has dropped out of the minds of the international health community...”

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

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

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

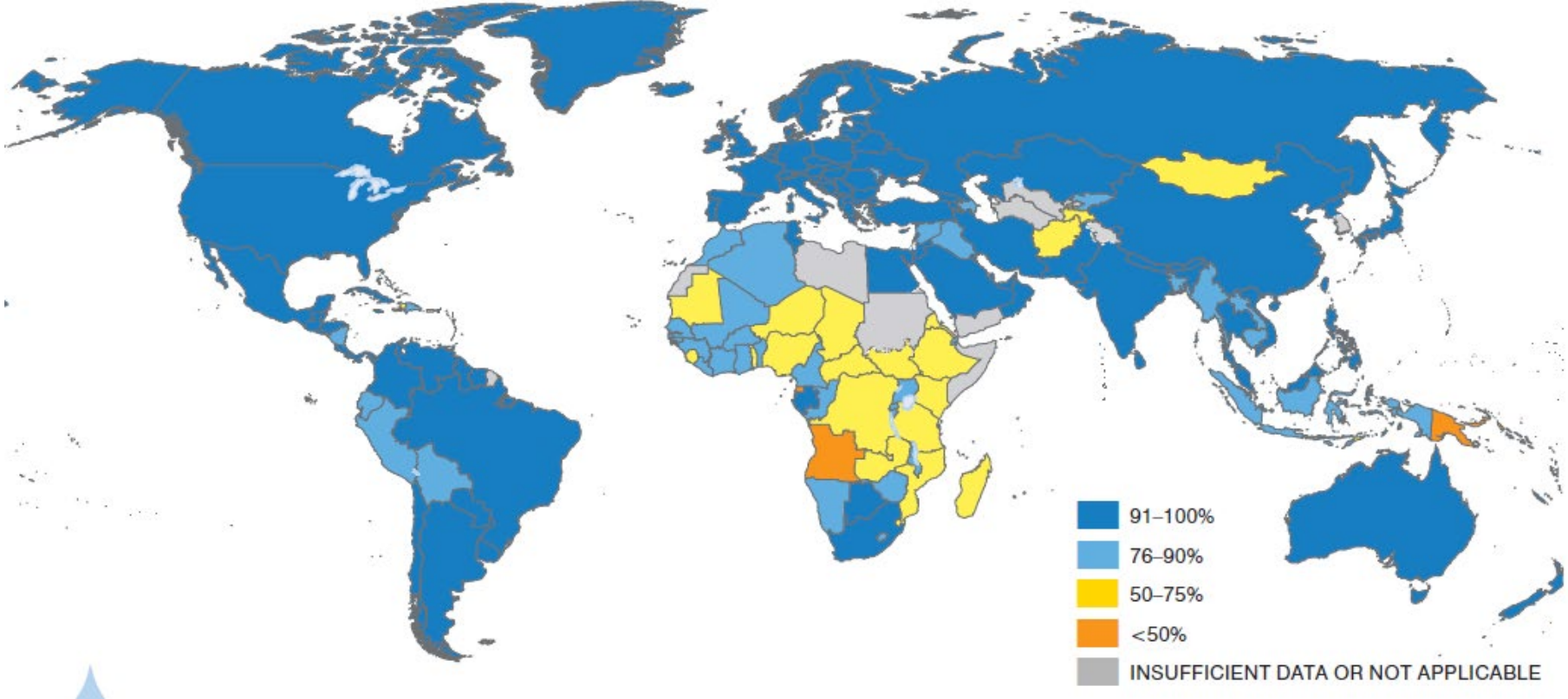


"The main problem with typhoid fever is that it has dropped out of the minds of the international health community..."

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

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

Improvements in water, sanitation and hygiene continue to lag in many parts of the world



Percent of population with improved drinking water sources, 2015.

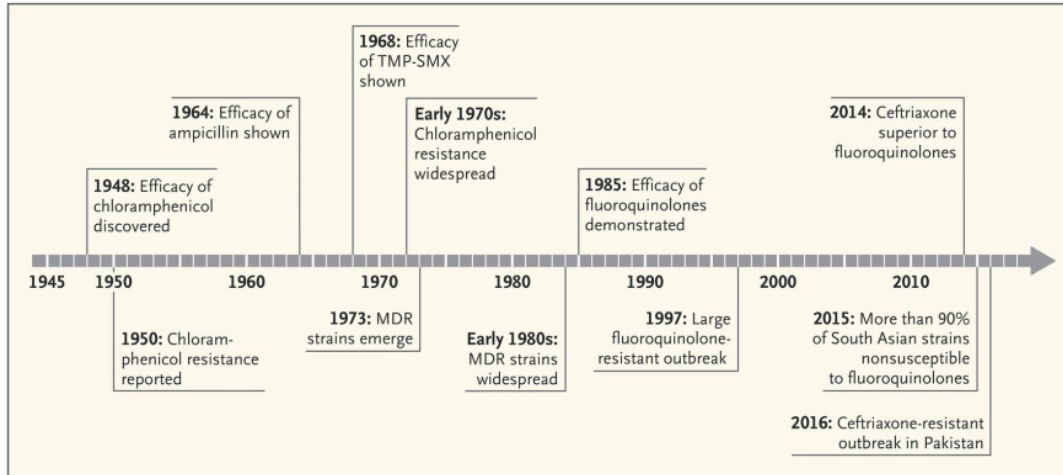
Source: UNICEF and WHO, 2015.

Typhoid: Where are we in 2019?

- 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.



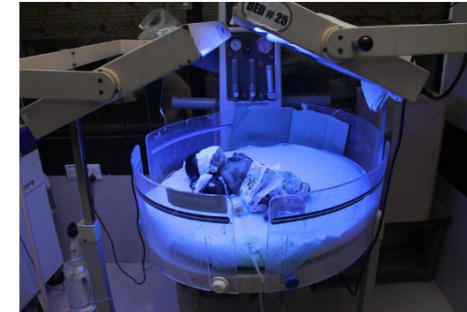
Where are we in 2019: The threat of drug resistant S. Typhi escalates



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

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

Global Health
By CHELY BAUMGAERTNER APRIL 13, 2018



A baby believed to have contracted a drug-resistant strain of typhoid, hospitalized in Hyderabad, Pakistan in February. Nadreen Khan/Reuters/Photograph Agency

The Gathering Storm: Is Untreatable Typhoid Fever on the Way?

Levine MM¹, Simon R².

Author information

Abstract

Klemm et al. (mBio 9:e00105-18, 2018, <https://doi.org/10.1128/mBio.00105-18>) present comprehensive antibiotic sensitivity patterns and genomic sequence data on *Salmonella enterica* serovar Typhi blood culture isolates from typhoid fever cases during an epidemic in Pakistan. Microbiologic and genomic data pinpoint the identities and locations of the antimicrobial resistance genes and the outbreak strain's lineage. They propose that *Salmonella enterica* serovar Typhi be added to the list of bacterial pathogens of public health importance that have become extensively drug resistant (XDR). This paper portends possible dire scenarios for typhoid fever control if XDR strains disseminate globally. Since the outbreak strain is of the H58 haplotype, known for its ability to spread worldwide and displace endemic S Typhi, this concern is well-founded. The report of Klemm et al. forewarns the global community to address control of typhoid fever more aggressively through prevention, should therapeutic options disappear. This Commentary frames the Klemm et al. findings within a historic perspective.

KEYWORDS: ceftriaxone resistance, chloramphenicol, typhoid fever


AMR adds to urgency to control typhoid fever through prevention - why typhoid conjugate vaccines (TCVs)?

- Ty21a and typhoid polysaccharide vaccines are underutilized in high-burden countries despite typhoid's substantial and detrimental impact and WHO recommendation for their use.
- New TCVs have the potential to overcome certain challenges that have impeded the uptake of earlier vaccines through:
 - Single dose.
 - Suitability for children under the age of two.
 - Inclusion in routine immunization programs.
 - Longer lasting protection.

Perspective

Extensively Drug-Resistant Typhoid — Are Conjugate Vaccines Arriving Just in Time?

Jason R. Andrews, M.D., Farah N. Qamar, F.C.P.S., Richelle C. Charles, M.D., and Edward T. Ryan, M.D.

 The NEW ENGLAND
JOURNAL of MEDICINE

October 18, 2018

N Engl J Med 2018; 379:1493-1495

DOI: 10.1056/NEJMp1803926

Article Figures/Media

Metrics

5 References 1 Citing Article

IN HYDERABAD, PAKISTAN, AN OUTBREAK OF EXTENSIVELY DRUG-resistant (XDR) *Salmonella enterica* ssp. *enterica* serovar Typhi, resistant to chloramphenicol, ampicillin, trimethoprim-sulfamethoxazole, fluoroquinolones, and third-generation cephalosporins, was recognized in November 2016 and has now spread to Karachi, home to more than 14 million people. More than 1000 cases have been confirmed by blood culture; since most typhoid cases are treated empirically, however, the true number of cases is probably many times greater. The outbreak is being caused by the H58 clade, a multidrug-resistant haplotype of S. Typhi that is common in Asia and areas of Africa. The H58 S. Typhi involved in the



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		

AMR adds to urgency to control typhoid fever through prevention - why typhoid conjugate vaccines (TCVs)?

- Typbar-TCV, Bharat Biotech
 - 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 based on immunogenicity
 - Efficacy shown in volunteer challenge study in UK
- Other TCVs in various stages of development



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



2018, 93, 153-172

No 13



Weekly epidemiological record Relevé épidémiologique hebdomadaire

30 MARCH 2018, 93th YEAR / 30 MARS 2018, 93^{ème} ANNÉE
No 13, 2018, 93, 153-172
<http://www.who.int/wer>

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Typhoid vaccines: WHO position paper – March 2018

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

Nov 2017

Feb 2018

Oct 2017

Dec 2017

Mar 2018




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

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.

The Typhoid Vaccine Acceleration consortium (TyVAC)
Mission: To reduce the global burden of typhoid by accelerating the introduction of typhoid conjugate vaccines (TCVs), particularly in low resource countries.



COLLABORATING ORGANIZATIONS



TyVAC trials will provide data on safety, immunogenicity, and impact of Typbar-TCV in field settings to inform country-level decision-making

Country	Design	Control vaccine	Ages	Start date	Duration	Number vaccinated
Nepal	Individually-randomized efficacy	Meningitis A	9 months- 16 years	Nov 2017	2 years	20,019
Malawi	Individually-randomized efficacy	Meningitis A	9 months-12 years	Feb 2018	2 -3 years (30 cases)	28,142
Bangladesh	Cluster-randomized	Japanese enceph.	9 months- 16 years	Apr 2018	2 years	53,692
Burkina Faso	Individually-randomized	IPV	9-23 months	Nov 2018	9 months	250



Current studies and vaccine introduction efforts



Number vaccinated

- TyVAC Malawi: 28,142
- TyVAC Burkina Faso: 242 (Goal 250)




Number vaccinated

- TyVAC Bangladesh: 41,344
- TyVAC Nepal: 20,015
- Navi Mumbai India: ~ 113,000
- Pakistan (outbreak response): Goal 250,000

WHO 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) in order to add data on co-administration of TCV with other routine childhood vaccines or in special populations, to detect any signals that require further investigation and to maintain public confidence in the immunization programme.

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, 94^e 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.

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

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 39^e 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.

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-

Typhoid: Where are we in 2019?

- Strong WHO recommendation.
- Gavi application process and country planning activities underway.
- Experience with Typbar-TCV:
 - **Safety**
 - **Immunogenicity**
 - **Interim efficacy in Nepal**
 - **Co-administration data**
 - **Impact on multiple outcomes and in multiple settings**
 - **Indirect effects**

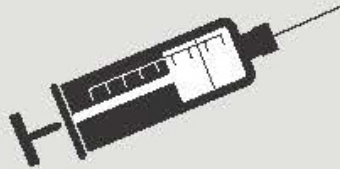


Photo: Asim Hafeez

An integrated solution

Prevention:

safe water, sanitation, hygiene, & vaccines*



* New typhoid conjugate vaccines have the potential to take on typhoid in the most vulnerable populations.

Learn more and join the effort at www.takeontyphoid.org.

#TakeOnTyphoid



Photo: Asim Hafeez



Summary

- *S. typhi* is a substantial public health threat in low resource settings.
- While integrated solutions are needed, the value of vaccination for typhoid is considerable:
 - Reduce morbidity and mortality.
 - Combat antibiotic resistance.
 - Outbreak control.
- Global policy and financing recommendations are supportive of TCV introduction.
- On-going efforts will provide additional data for decision-making by individual countries.
- Multidisciplinary, collaborative approach is necessary for success.



Photo: Asim Hafeez

