Typhoid Fever Vaccines

M. Imran Khan

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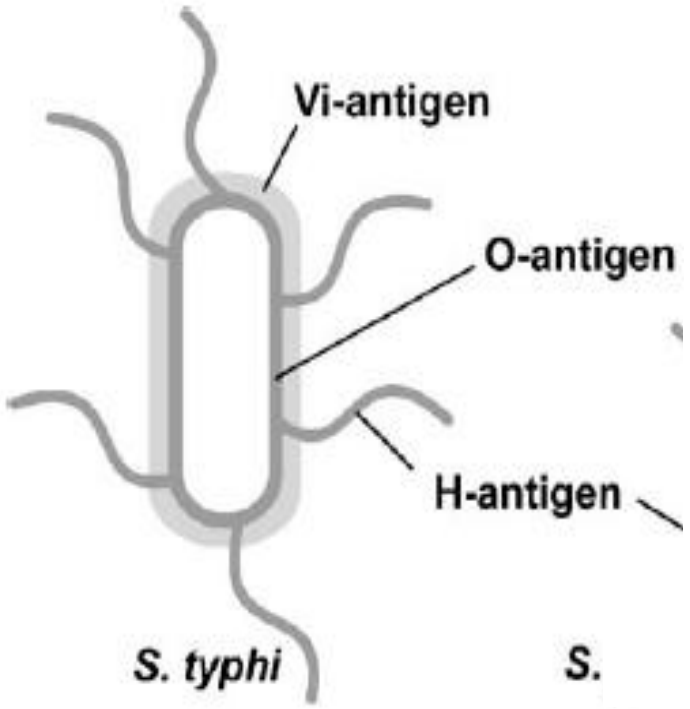
Bangkok, Thailand

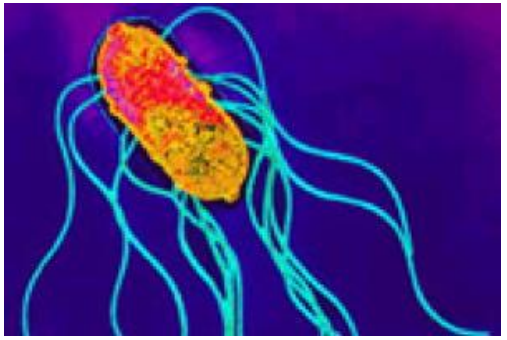
Outline

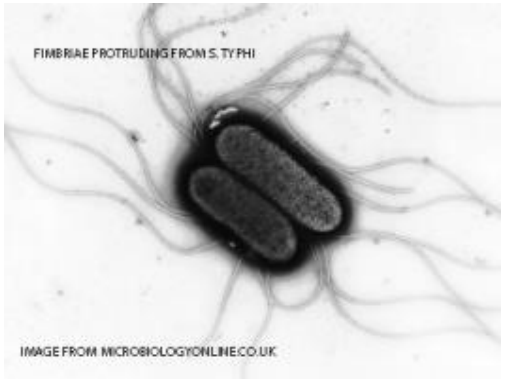
- Background: Typhoid disease burden estimates
- Background: Overview of typhoid vaccines
- Typhoid conjugate vaccine pipeline
- Knowledge gaps on typhoid conjugate vaccines
- Summary



Enteric fever: definition

- A systemic infection caused by *Salmonella enterica* serovar Typhi (Typhoid) or *Salmonella enterica* serovar Paratyphi A, B, and C (Paratyphoid)
- *Salmonella* belongs to the group of enterobacteriacae that are aerobic and Gram-negative
- *S.* Typhi is transmitted via the oral-faecal route through contaminated food or water.
- Usually associated with poor sanitation and hygiene practices





History of Typhoid:
Typhoid Fever has impacted populations since antiquity

430–424 BC: plague of Athens killed one third of the population, including their leader Pericles. The balance of power shifted from Athens to Sparta, ending the Golden Age of Pericles and Athenian dominance in the ancient world.

International Journal of Infectious Diseases (2006) 10, 206-14.
Image: http://www.pbs.org/empires/thegreeks/keyevents/430_c.html

Alexander the Great (356-323 BC) dies from typhoid fever in Babylon.

Oldach DW, Richard RE, Borza EN, Benitez RM. N Engl J Med. 1998 Jun 11;338(24):1764-9.
Alexander fighting the Persian king Darius III.
From Alexander Mosaic, Pompeii. Naples National Archaeological Museum. Naples, Italy.

History of Typhoid

S. Typhi is observed and cultured for the first time in the early 1880's

Philadelphia Water Department
Historical Collection
Downloaded from
www.phillyh2o.org/filtration.htm

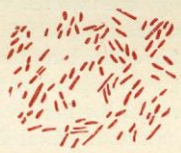
CHAPTER XX.

Typhoid fever—Study of the organism concerned in its production—Its morphological, cultural, and pathogenic properties—*Bacillus coli*—*Bacillus paratyphosus*—Its resemblance to *Bacillus typhosus*.

BACILLUS TYPHOSUS.

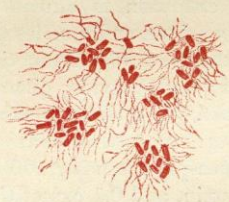
THE organism discovered in the tissues of typhoid cadavers microscopically by Eberth (1880–81), and subsequently isolated in pure culture and described by Gaffky (1884), is now generally recognized as the etiological factor in the production of typhoid fever. It may be described as follows:

FIG. 70.



Bacillus typhosus, from culture twenty-four hours old, on agar-agar.

FIG. 71.



Bacillus typhosus, showing flagella stained by Löffler's method.

It is a bacillus about three times as long as broad, with rounded ends. It may appear at one time as very short ovals, at another time as long threads, and both

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PWD Historical Collection, *from* The Principles of Bacteriology, *by A.C. Abbott, M.D. Seventh Edition. Philadelphia: Lea Brothers & Co., 1905.*

- The Widal agglutination test was described in 1896
- First used in municipal hospitals later that year (Johnston 1896) including the New York city Health Department (Guerard 1897)

http://www.applichaise.net/appl/article.php3?id_article=2038

General conclusions.—From an analysis of the results which have so far been obtained in the application of the Widal test, it would seem, in the first place, that the serum reaction is by no means specific, in the strict acceptation of the term. In the second place, it is evident that this test has certain limitations in its practical utility, and that unless properly applied with a due appreciation of these limitations, it is liable to lead to false conclusions. The chief

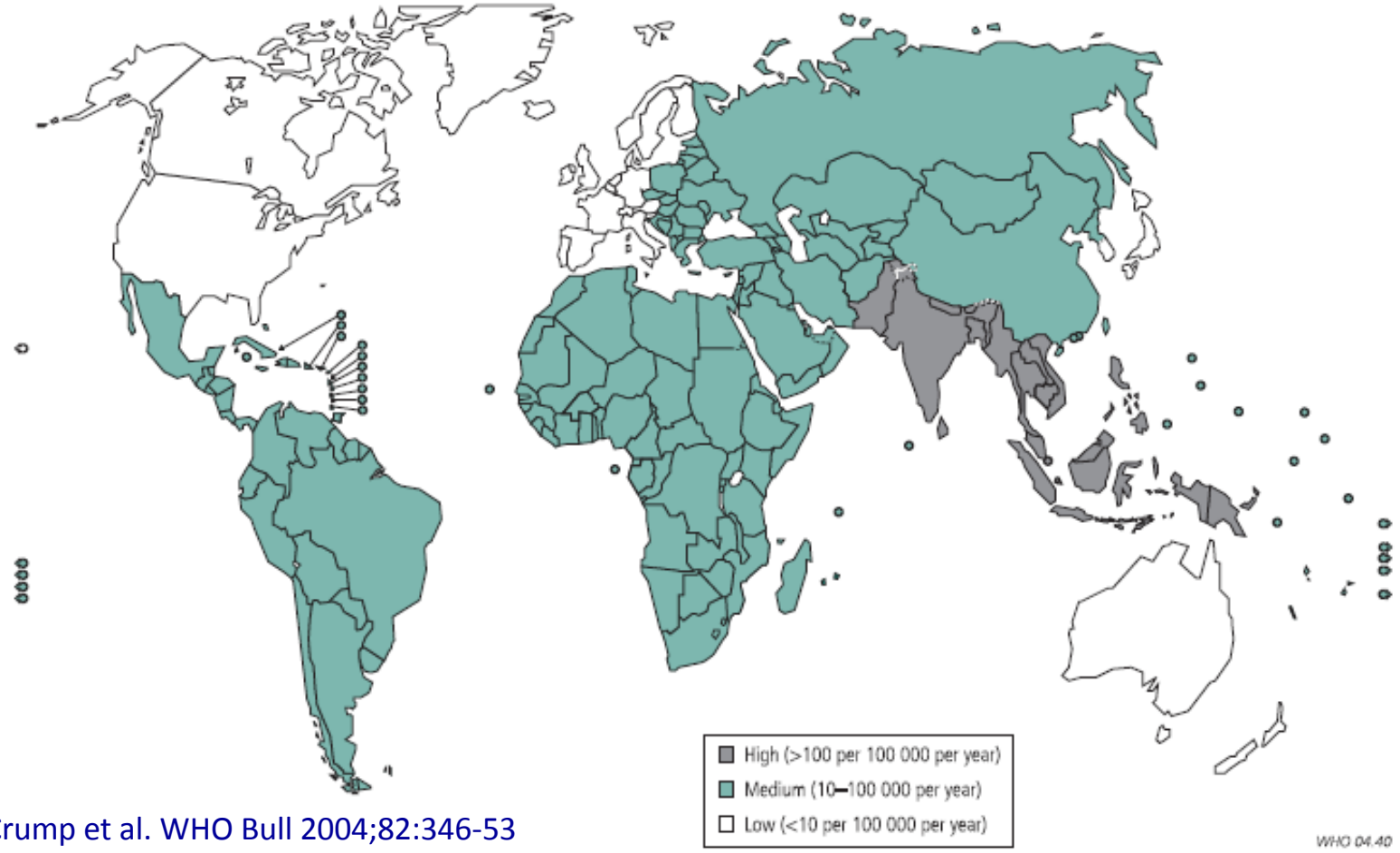
When the subject of the serum diagnosis of typhoid fever was first brought before the public, it was hoped that at last the long-sought infallible diagnostic test for typhoid fever had been discovered, which was at once rapid, simple and suitable for clinical use at the bedside. With the non-fulfillment of these hopes, some physicians have come to look upon Widal's test as practically useless for diagnostic purposes. But,

AR Guerard. JAMA. 29. 1897.

Typhoid fever burden estimates

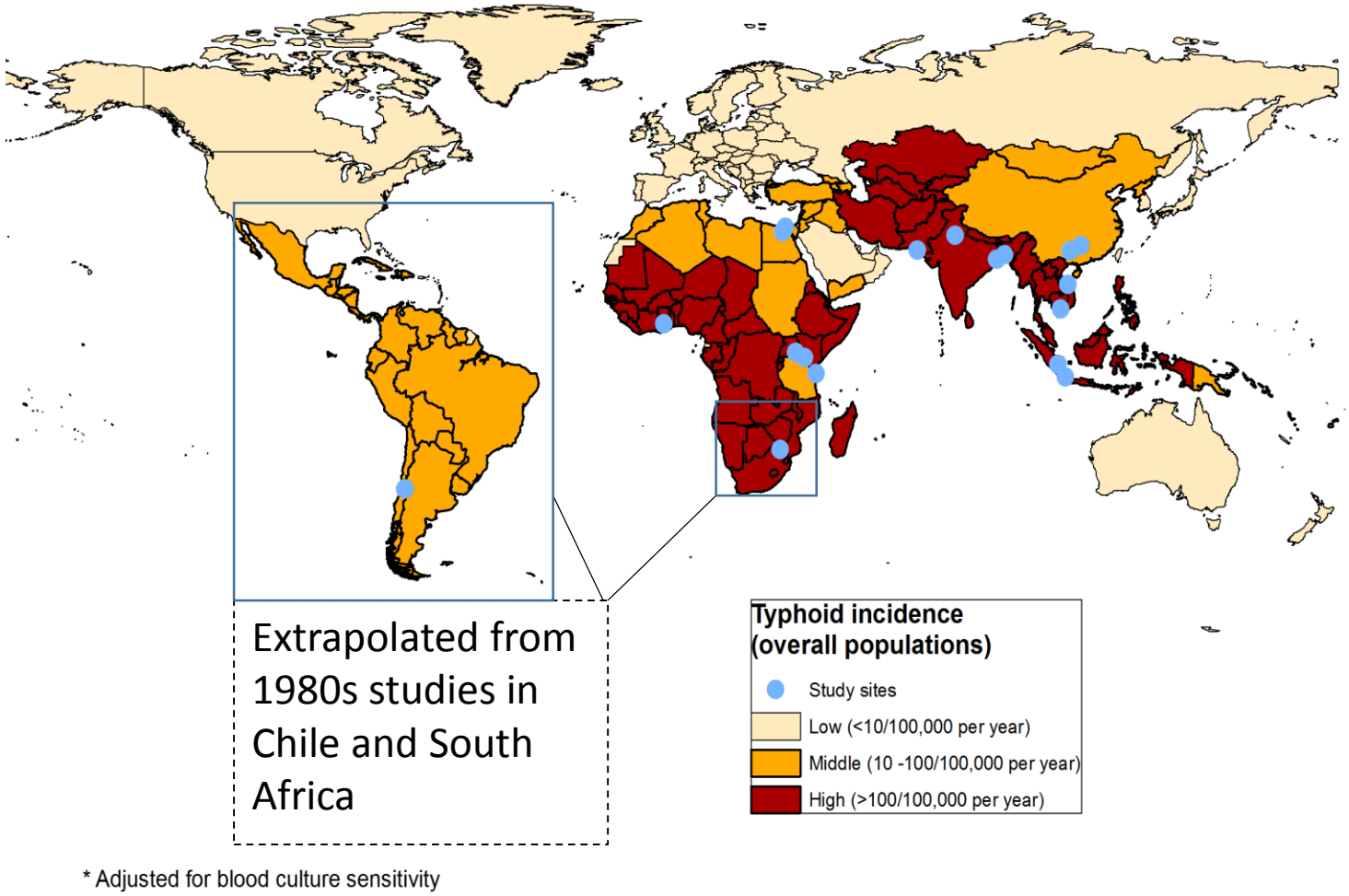
Ivanoff et al (1994)	• 16.6 million cases and 580,000 deaths
Crump et al (2004)	• 21.6 million cases, 216,000 deaths • Highest incidence (>100/100,000 per year) in south-central Asia and south-east Asia
Buckle et al (2012)	• 26.9 million cases (269,000 deaths) • Greatest increase in incidence in sub-Saharan Africa
Lozano et al (2012) Murray et al (2012) [IHME "GBD 2010”]	• 190,000 deaths (Typhoid and Paratyphoid), 12.2 million DALY lost
IHME "GBD 2013"	• 2014 publication pending
IVI estimates Adapted from Mogasale et al.	• 11.8-20.5 million cases and 129,000-223,000 deaths • 2014 publication under review (Lancet Global Health) • Review by WHO IVIR-AC scheduled for Sept 2014

Estimated global burden of typhoid fever (2000 data)



Crump et al. WHO Bull 2004;82:346-53

Global Burden of Typhoid: Revised Estimates



* Adjusted for blood culture sensitivity

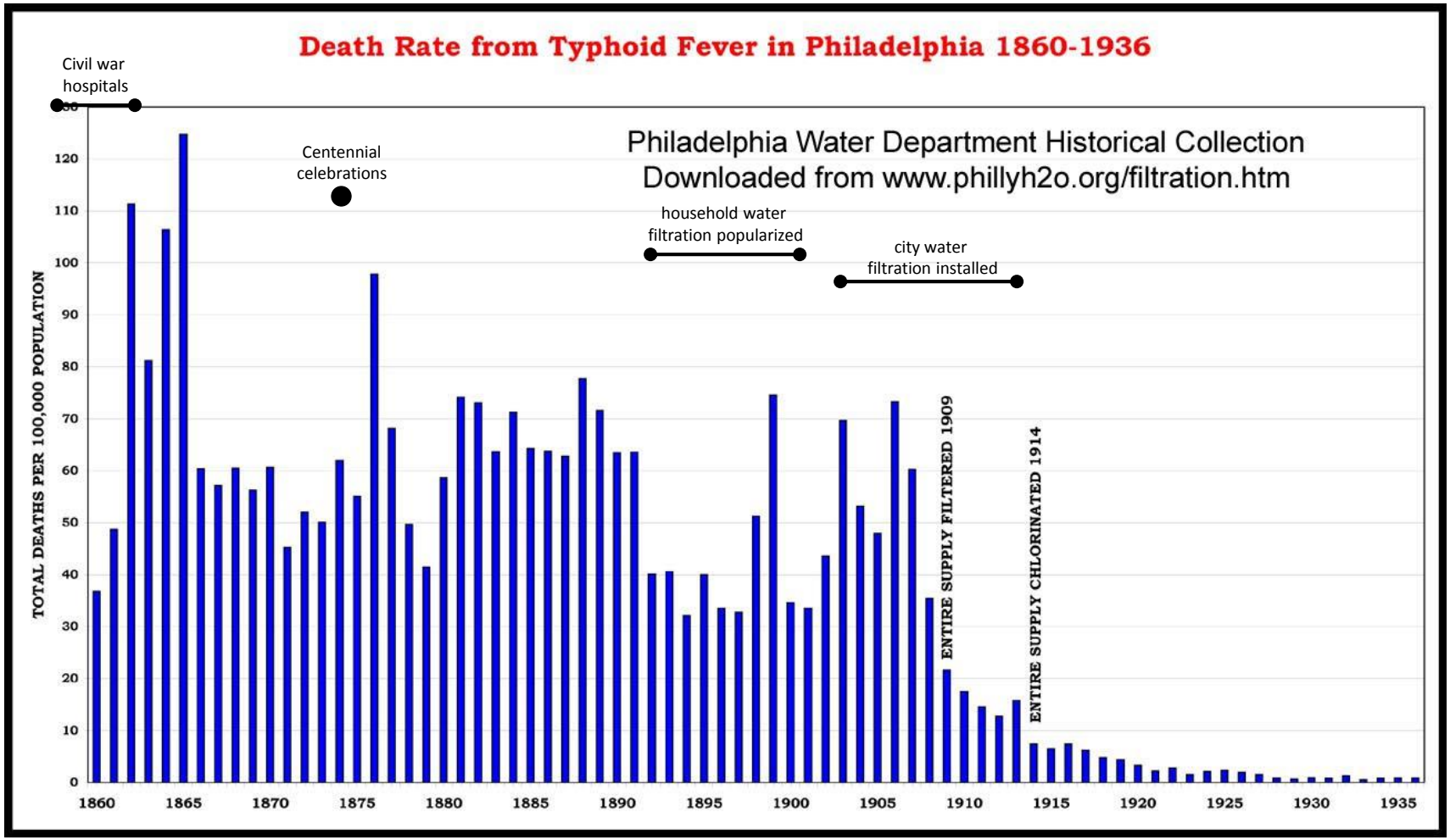
Mogasale V, Maskery B, Ochiai LR, et al. Revisiting global burden of typhoid for policy considerations (Lancet Global Health; Under revision)

Literature Review of Typhoid Risk Factors

Significant risk factors	Odds ratio	95% CI	Location/Sources
Piped water supply at home	**0.4**	0.2-0.9	Darjeeling, West Bengal, India (Sharma, et al. 2009)
Latrine at home	**0.5**	0.3-0.8	
No education	2	1.0-3.7	Son La province, northern Vietnam (Tran et al. 2005)
Drinking untreated water	3.9	2.0-7.5	
Low economic level	2.9	1.5-5.3	Mekong delta, southern Viet Nam (Luxemburger et al. 2001)
Drinking unboiled water	4.3	1.3-14.5	
Drinking unboiled water at home	12.1	2.2-65.6	Dhaka slum, Bangladesh (Ram et al. 2007)
Using foul-smelling water	7.5	2.1-25.4	
Drinking water from a community tap	**0.03**	0.003-0.331	Karachi, Pakistan (Luby et al. 1998)
No municipal water supply in house	29.18	2.12-400.8	Semarang, Indonesia (Gasem et al. 2001)
Open or without drainage system of house	7.19	1.33-38.82	
Unemployed or part time job	31.1	3.08-317.4	
No toilet in the household	2.2	1.06-4.55	Jakarta, Indonesia (Vollaard et al. 2004)
Consumption of unboiled surface water outside the home	3	1.1-8.2	Samarkand Oblast, Uzbekistan (Srikantiah et al. 2007)

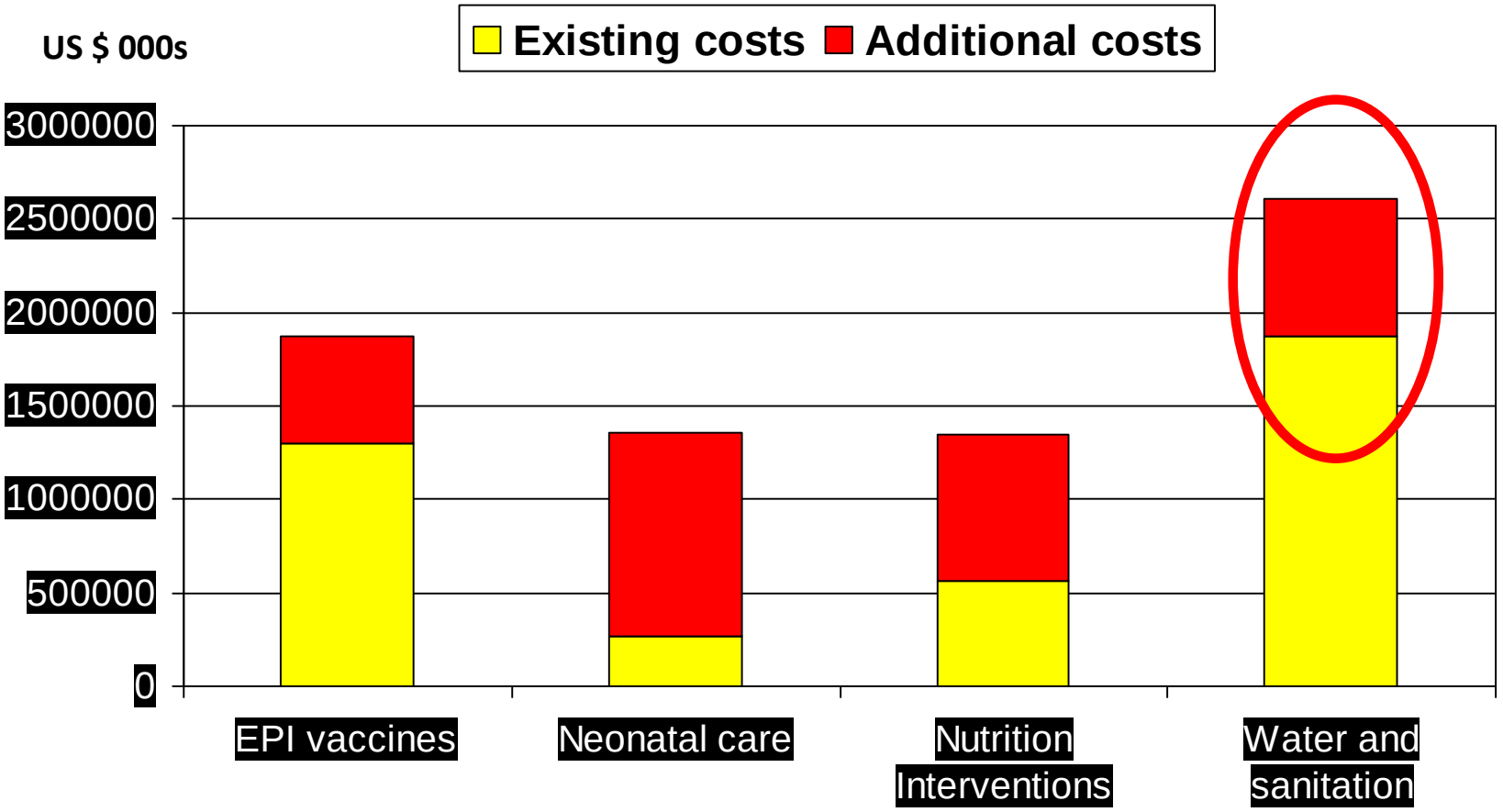
Control of Typhoid through Prevention

- Safe water
  - Typhoid fever is a waterborne disease and the main preventive measure is to ensure the access to safe water
- Food safety
  - Contaminated food is an important vehicle for typhoid fever transmission
- Sanitation
  - Proper sanitation contributes to reducing the risk of transmission of all diarrheal pathogens
- Health education
  - Health education is paramount to raise public awareness on all preventive methods
- Vaccination
  - Safe and efficacious vaccines are available



http://www.phillyh2o.org/filtration.htm

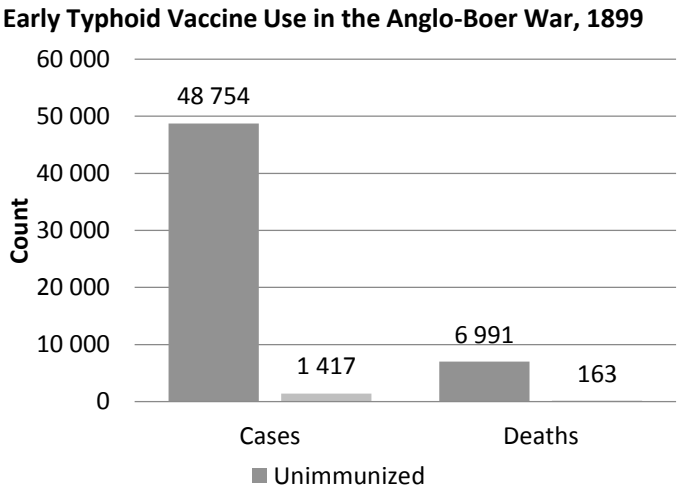
Global investments required for public health interventions

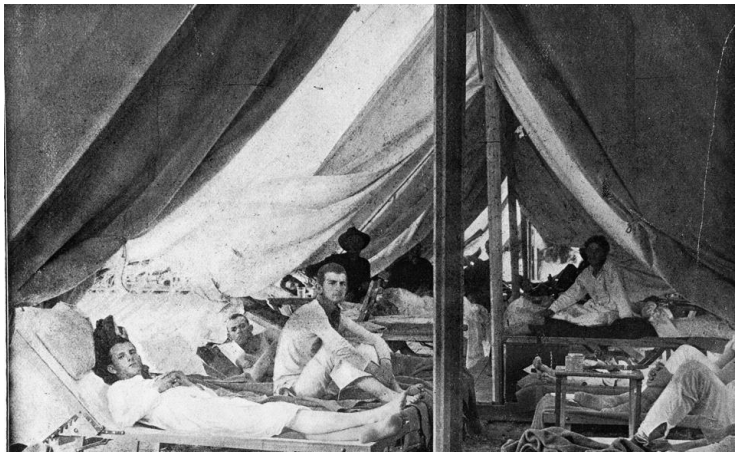


Typhoid Vaccine Use in UK

1897 English bacteriologist Almroth Wright introduces a killed (heat-inactivated, phenol-preserved, whole-cell) typhoid vaccine in Britain.

1898-9 Trials in the Indian army produced excellent results and typhoid vaccination was adopted for the use of British troops serving in the Second Boer War (1899).

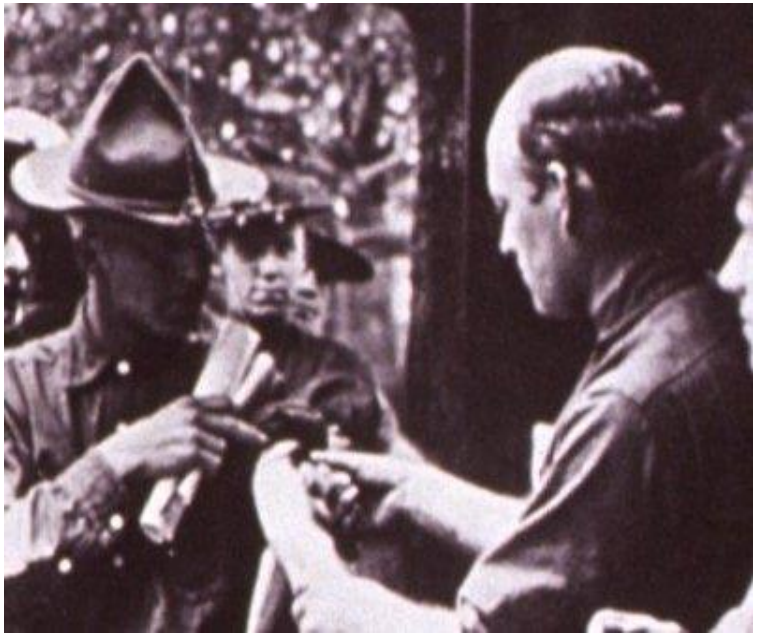




Cantlie N. History of the Army Medical Department, Vol. II. Edinburgh and London: Churchill Livingstone, 1974:230, 373.
NB: whole-cell inactivated vaccine, one dose regimen, soldiers.

Typhoid Vaccine Use in USA

- **1909** typhoid vaccination starts in US Army
- **1911** typhoid vaccination required for entire US Army and Navy

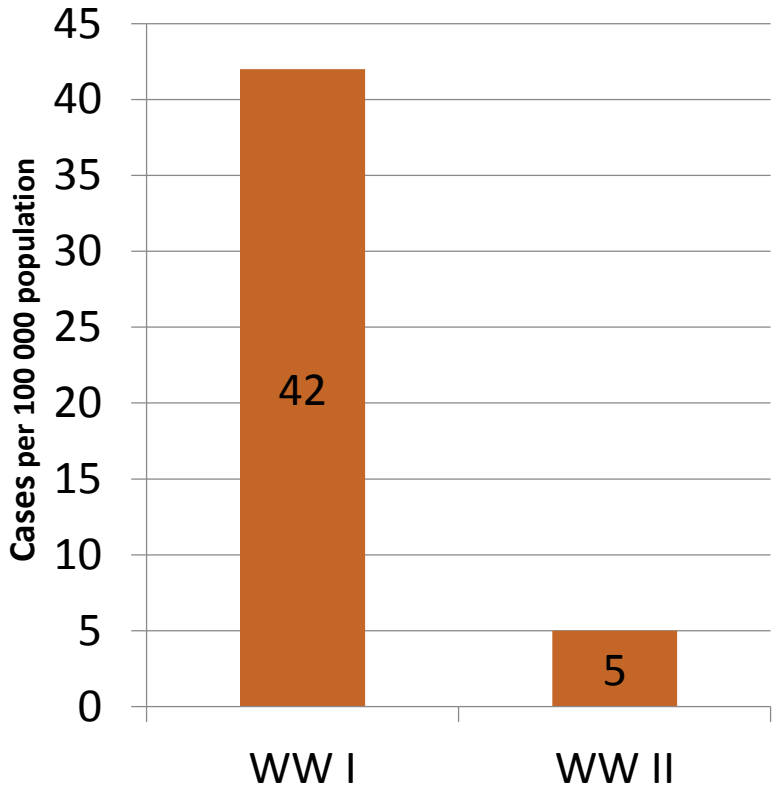


Grabenstein JD. et. al. Immunization to Protect the US Armed Forces: Heritage, Current Practice, and Prospects. Epidemiol Rev 2006;28:3–26. http://www.immunize.org/timeline/

Typhoid Vaccine Use in USA

The impact of typhoid vaccination in the US armed forces

- World War I, 1917–1918
  - 2 000 typhoid cases, 227 deaths (11.4% CFR)
  - 42 typhoid cases per 100 000 soldiers
- World War II, 1941–1945
  - 5 typhoid cases per 100 000 soldiers



Grabenstein JD. et. al. Immunization to Protect the US Armed Forces: Heritage, Current Practice, and Prospects. Epidemiol Rev 2006;28:3–26. http://www.immunize.org/timeline/

Typhoid Vaccine Use in USA

- **1914** Typhoid vaccine first licensed for the U.S. general population
- **July 16, 1952** Heat-phenol inactivated typhoid vaccine by Wyeth licensed in US.
- **Dec 15, 1989** A live, oral typhoid vaccine (Ty21a, *Vivotif Berna* by Swiss Serum Institute) licensed in US.
- **Nov 28, 1994** Typhoid Vi polysaccharide inactivated injectable polysaccharide vaccine (Typhim Vi by Aventis Pasteur) licensed in US.

Doctor administering a typhoid vaccination at a school in San Augustine County, Texas. Photograph by John Vachon, April 1943.

http://www.immunize.org/timeline/
Grabenstein JD. et. al. Immunization to Protect the US Armed Forces: Heritage, Current Practice, and Prospects. Epidemiol Rev 2006;28:3–26.

WHO Position Paper on Typhoid Fever

2008, 83, 49–60 No. 6

World Health Organization
Organisation mondiale de la Santé

Weekly epidemiological record
Relevé épidémiologique hebdomadaire

8 FEBRUARY 2008, 83rd YEAR / 8 FÉVRIER 2008, 83e ANNÉE

In view of the continued high burden of typhoid fever and increasing antibiotic resistance, and given the safety, efficacy, feasibility and affordability of 2 licensed vaccines (Vi and Ty21a), countries should consider the programmatic use of typhoid vaccines for controlling endemic disease. In most countries, the high-risk groups and populations. Given the epidemic potential of typhoid fever, and observations on the effectiveness of vaccination in interrupting outbreaks, typhoid fever vaccination is recommended also for outbreak control.

Decisions on whether or not to initiate programmatic use of typhoid vaccines should be based on knowledge of the local epidemiological situation. Important information includes data on subpopulations at particular risk and age-specific incidence rates, as well as on the sensitivity of the prevailing S. Typhi strains to relevant antimicrobial drugs. Ideally, cost-effectiveness analyses should be part of the planning process.

Immunization of school-age and/or preschool-age children is recommended in areas where typhoid fever in these age groups is shown to be a significant public health problem, particularly where antibiotic-resistant S. Typhi is prevalent. The selection of delivery strategy (school or community-based vaccination) depends on factors such as the age-specific incidence of disease, subgroups at particular risk and school enrolment rates, and should be decided by the concerned countries.

Typhoid fever vaccination may be offered to travellers to destinations where the risk of typhoid fever is high, especially to those staying in endemic areas for >1 month and/or in locations where antibiotic resistant strains of S. Typhi are prevalent.

All typhoid fever vaccination programmes should be implemented in the context of other efforts to control the disease, including health education, water quality and sanitation improvements, and training of health professionals in diagnosis and treatment.

Global vaccination policy: WHO Position Paper 2008

- Programmatic use for endemic disease & outbreak control
- Vaccination of high-risk groups and populations
- Immunization of school-age and/or preschool-age children if a significant public health problem in these age groups
- Local factors required for decisions on programmatic use
  - Sub-populations at risk (to support risk-based strategy)
  - Age-specific incidence rates
  - Sensitivity of prevailing strains to relevant antimicrobials
  - Cost-effectiveness analyses
  - School enrolment rates etc.

Typhoid vaccines (licensed) overview

- **Vi polysaccharide vaccine** (ViPS)
  - IM/SC, 1 dose, 55-72% efficacy; 3 yrs duration of protection
  - NOT licensed for <2 years of age;
  - WHO prequalification (Typhim – 2011)
- **Ty21a**
  - oral, 3-4 doses, 35-67% efficacy; 7 yrs duration of protection
  - NOT recommended for <5 yrs;
- Programmatic feasibility and impact of vaccination demonstrated in several SEAR & WPR countries (mostly ViPS)
  - school-based & routine immunization delivery strategies
  - outbreak control in China, Fiji (2010, ViPS in cyclone-affected areas)
- **Future Gavi funding of conjugate vaccine** expected (Board decision in 2008)

Diseases of Most Impoverished Program (DOMI) Vi Effectiveness Trials

- Large scale effectiveness trials were conducted in slums in Kolkata, India and Karachi, Pakistan using Vi polysaccharide vaccine
- Studies were standardized, except the target population
  - Kolkata: 2 years and above
  - Karachi: 2-16 years

Results of the Effectiveness Trials

- Results from the two effectiveness trials showed differences in clinical protection for children aged 2-5 years

	Kolkata Protective Effectiveness	**Karachi** Protective Effectiveness
2-4.9 years	82% (P<.001; 95%CI: 58%,92%)	- 30% (95%CI: -183%,40%)
5.0-14.9 (Kolkata) 5.0-16.0 (Karachi)	59% (P<.05; 95%CI:18%,79%)	59% (P<.05; 95%CI:9%,81%)

Results of the Effectiveness Trials

- Results on immunogenicity
  - For Kolkata, the small number of subjects under the age of 5 years bled at 6 weeks (N= 5) and 2 years (N= 3) after vaccination precluded meaningful analyses of this age group
  - For Karachi, results showed large number of children under the age of 5 showing no response after vaccination (7/41)

Summary

- Large clinical trial with a follow up period of 2 yrs
  - Difference in results based on clinical protection are unlikely to be different by chance
- Difference in design was the target population
  - Kolkata covered general population (2 and above) and attained 61% coverage
  - Karachi covered children (2 to 16) and attained 52% coverage
- Converted coverage (all age coverage)
  - Kolkata: 60%
  - Karachi: 22%

Summary

- The difference in the protection in the children less than 5 years of age is due to interruption of transmission (hence herd protection)
  - Potential mechanism of herd protection
    - Children under the age of 5 are usually at home under the care of parents
    - Children under the age of 5 usually consume food prepared at home and eat at home
    - If parents are protected, it is likely that the younger children are protected from transmission within household

Programmatic Use of Typhoid Vaccines

- Vi Vaccination Program for 2-5 Year Olds in **Delhi**, India
- Mass vaccination campaigns in several provinces and districts in **China** for school children and food handlers in mid-1990s
- Annual campaigns in **Vietnam** for 3-10 year old children in a limited number of high-risk districts since 1997
- **Pondicherry** and **Fiji** vaccination after outbreaks
- **Sri Lanka** vaccination campaigns for Internally Displaced people (IDPs) and food handlers
- Demonstration project in **Nepal, Pakistan**

Addressing the challenges: Typhoid conjugate vaccines

- Typhoid conjugate vaccine (ViCV): preparation of Vi polysaccharide covalently linked to a carrier protein
  - Vi antigen from *S.* Typhi or *C. freundii*
  - At least four carrier proteins
- Objectives of ViCV development (advantages over ViPS & Ty21a)
  - **higher efficacy** than the ViPS (>70% in endemic regions)
  - **longer lasting protection** (persisting > 3 years)
  - **broader age coverage** (i.e., immunogenic in infants)

Typhoid conjugate vaccine pipeline

No.	Manufacturer	Location	Technology Transfer Agreement	Product details	Clinical Dev't Status
1	Bharat Biotech Int. Ltd. (BBIL)	India	Own R&D (NIH technology)	Vi-TT	NRA Licensure in India
2	Shantha Biotechnics Ltd. (SBIL)	India	IVI	Vi-DT	Development stopped
3	Bio-Med Pvt. Ltd	India	Own R&D (NIH technology)	Vi-TT	NRA Licensure in India
4	PT BioFarma	Indonesia	IVI	Vi-DT	Phase I clinical trial to start in 3Q 2015
5	Finlay Institute	Cuba	Unknown	Vi-DT	Phase I to start
6	Lanzhou Institute (CNBG)	China	US NIH	Vi-rEPA	NRA Licensure application submitted

Typhoid conjugate vaccine pipeline

No.	Manufacturer	Location	Technology Transfer Agreement	Product details	Clinical Dev't Status
7	SK Chemicals	S. Korea	IVI	Vi-DT	Phase I clinical trial will start in 4Q 2015
8	Incepta	Bangladesh	IVI	Vi-DT	Preclinical studies to start
9	Biological E	India	NVGH	Vi-CRM	Phase I clinical trial will start
10	EuBiologics	S. Korea	Own R&D	Vi-CRM	Preclinical studies ongoing
11	DAVAC	Vietnam	Own R&D	Vi-DT	Preclinical stage
12	Walvax	China	Own R&D	Vi-TT	Preclinical stage

Vi-rEPA (Lanzhou Institute of Biological Products)

- Based on technology transfer from NIH
- Phase III data for adults, preschool and school aged children reviewed (not yet in public domain)
  - Data suggest immune response better in vaccine groups vs. controls
  - No efficacy trials in infants
- Licensure review by Chinese NRA ongoing (for use in persons >=2 y)
- Immunogenicity and safety studies planned in <2 years age group

Vi-CRM$_{197}$ (Biological E Limited)

- Early clinical testing by Novartis Vaccines Institute for Global Health (NVGH)
  - Phase I and II in European adults
    - As immunogenic as ViPS *(van Damme et al. PLoS One 2011)*
  - Phase II in adults, children and infants in India, Pakistan and the Philippines (coadmin: msls 9 m, pentavalent & OPV at 6, 10, 14 wks) *(Bhutta et al. Lancet Infect Dis 2014)*
  - Anti-Vi IgG titers after 1 dose 5 µg Vi >= ViPS 25 µg (adults and children)
  - Immunogenic in 6-8 weeks and 9-12 months infants (in latter, immune response equal or greater than 1 dose ViPS in children and adults).
  - Antibody titers short-lived (~ 6 m); apparent lack of booster response
- Technology licensed to Biological E
  - Full clinical development programme planned
  - Interest expressed to apply for WHO PQ

Vi-TT (Bharat Biotech International Limited)

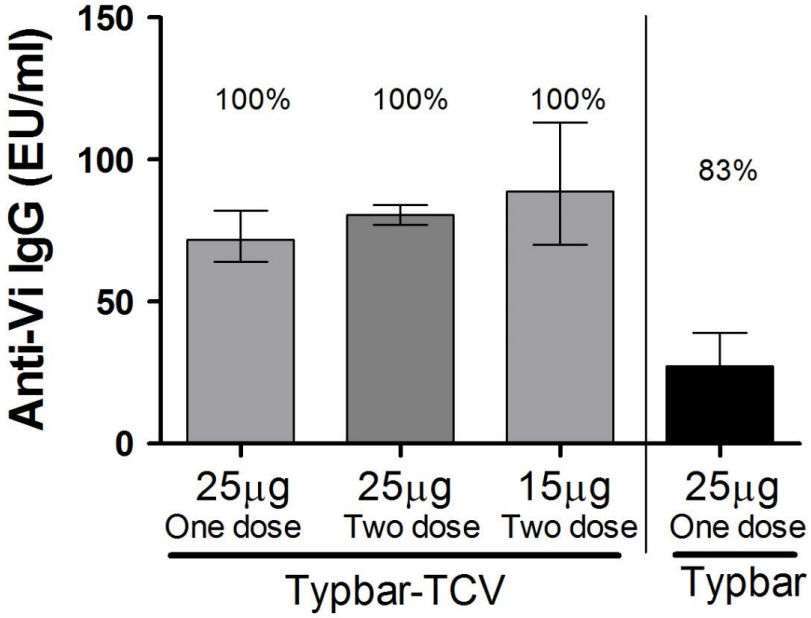
- Phase IIa/IIb study in 2-17 y: no difference in immune response in 1 vs 2 doses
- Phase III study
  - Cohort 1 >=6 months to <2 years (n = 327; no controls)
    - 98% protected (4-fold seroconversion)
  - Cohort 2 ≥2 years to ≤ 45 years (n ~340 per Vi-TT/ViPS arm)
    - 97% protection in Vi-TT arm vs 93% in ViPS arm (p=0.01).
- Licensed for single dose in >=6 m, children and adults
  - On average 30,000 doses per month sale in India, PMS safety evaluation (n ~3,000)
  - Interest expressed to apply for WHO PQ

Typbar-TCV Product Characteristics

Description	Presentation
Formulation	Liquid Vaccine
Storage	5ºC ± 3ºC
Dose volume	0.5 ml (Intramuscular injection)
Shelf life	24 months @ 5ºC ± 3ºC
O-Acetyl content (Hestrin)	NLT 0.085 ± 25% (25 µg of Vi Polysaccharide)
Vi Content	NLT 25 µg of Vi Polysaccharide
Free Vi-PS	NMT 20%

Typbar-TCV: phase IIa /IIb- Immunogenicity study data

- Single dose of 25µg Typbar-TCV is as immunogenic as two separated doses of 25µg or 15µg Typbar-TCV



Typbar-TCV: Immune presistance data

		Day 0	Day 42	Day 720
Open Label Trial	**Typbar-TCV**			
	No. of subjects	307	307	220
	GMT EU/ml (95% CI)	9.5 (9,10)	1937.4 (1785,2103)	48.7 (43,56)
	Fold change		205	5.2
Controlled Trial	**Typbar-TCV**			
	No. of subjects	332	332	243
	GMT EU/ml (95% CI)	10.4 (9.6,11.3)	1292.5 (1153,1449)	81.7 (73,92)
	Fold change		124	7.8
	Typbar			
	No. of subjects	305	305	197
	GMT EU/ml (95% CI)	11.6 (10.5,12.9)	411.1 (359,471)	45.8 (40,53)
	Fold change		35	3.8

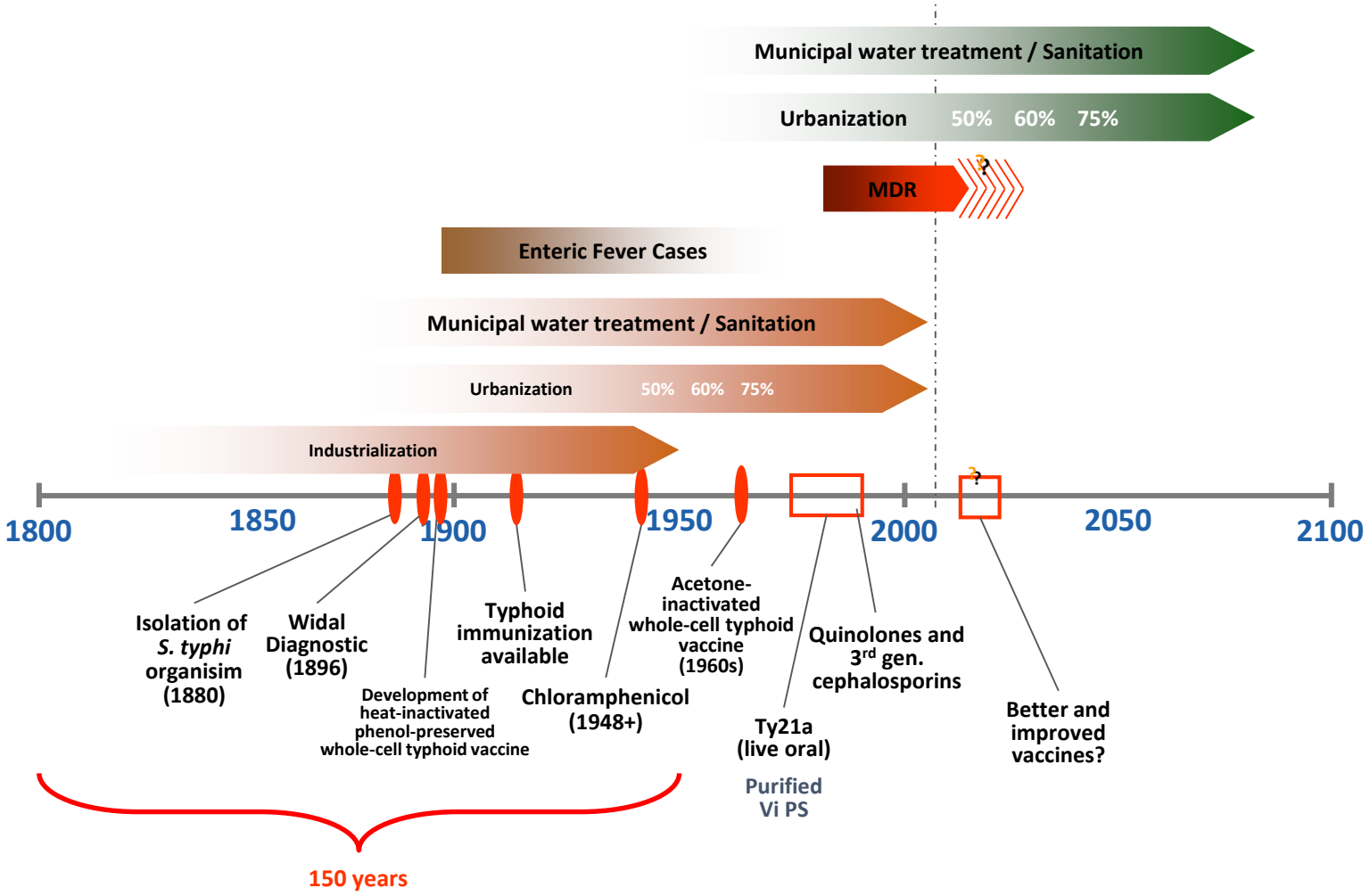
Research scope to advance access to typhoid conjugate vaccines

- Field evidence to support country vaccine introduction
  - Individual and herd protection
  - Feasibility, acceptance of multiple injections
  - Cost effectiveness of various vaccine delivery strategies
  - Impact of vaccination in context of other control strategies (WASH, appropriate diagnosis and antimicrobial treatment etc.)
- Understanding impact of long-term carriers on disease burden (serologic or microbiological studies)
- Potential demonstration studies under consideration
- There may be opportunities to evaluate ViCV performance where a licensed vaccine is being used

Summary

- Typhoid continues to be a significant burden, mainly in developing countries of Southeast and South Asia
- Antibiotics resistance continues to be a public health threat
- Economic development (investment in infrastructure development) will significantly reduce typhoid incidence, but progress is very slow
- Vaccination programs using existing licensed vaccines have demonstrated impact of vaccines
- Conjugate vaccine candidates are expected to be available for public sector use in the next five years
- Concrete efforts from global health community, especially typhoid endemic countries is critical

Typhoid Fever: Research and Control Journey



Thank you