Typhoid vaccine policy and practice: update from the Coalition against Typhoid (CaT)

Christopher B. Nelson, PhD MPH
Director, Coalition against Typhoid (CaT) Secretariat

www.COALITONagainstTYPHOID.org // CaT@sabin.org

1 March 2013
8th International Conference

Typhoid Fever and Other Invasive Salmonelloses

1-2 March 2013 • Dhaka, Bangladesh

typhoidconfernece.org

In Collaboration With Our Partners

COALITION AGAINST 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.


Image: http://www.pbs.org/empires/thegreeks/keyevents/430_c.html
Typhoid Fever has impacted populations since antiquity

Zhang Zhong-Jing (150 – 219 A.D.)

- compiled the “Shanghan Zabing Lun", or "Treatise on Febrile and Miscellaneous Diseases"
- addresses typhoid fever
- the work was later divided in two parts:
  1) "Shang han lun" or "Treatise on Febrile Diseases Caused by Cold“ (description of epidemic disease causing fever);
  2) “Jin kui yao lue" or “Synopsis of prescriptions of the golden chamber“ (compendium of clinical experience).

- in the preface the author notes that of the approximately 200 inhabitants in his village, more than two-thirds died within the course of 10 years and 70% of these deaths were due to typhoid.

THE URBAN PENALTY: TYPHOID FEVER
The widespread adoption of improved water (filtration +/- chlorination) by American cities in the early 20th century is followed by dramatic decreases in typhoid mortality.
After water filtration +/- chlorination, public health measures contributed to the control of typhoid fever: Pasteurization of milk, epidemiologic investigation of cases and outbreaks with hospitalization of cases, immunization of contacts, and occupational restrictions for carriers (pre-antibiotic era).
Typhoid Mary – a chronic carrier

- Mary Mallon worked as a cook for wealthy New York families.
- Families for whom Mallon had worked as a cook had fallen ill with typhoid fever.
- Was the first identified healthy carrier of typhoid: she carried the typhoid bacteria and spread them to others, but did not fall ill herself.
- In 1907, detained by the New York City Department of Health for three years.
- In 1915, while working under an assumed name, was associated with 25 typhoid cases, one of whom died.
- Detained at North Brother Island and remained there for the next 23 years until her death in 1938.
- At the time of her death in 1938, she was officially and directly linked to 10 outbreaks totaling 51 cases of typhoid fever, and three deaths from the disease.

http://www.historyofvaccines.org/
Erasing the Urban Penalty

During the early 20th century, the provision of clean water (filtration +/- chlorination) to major American cities led to:

- the near-elimination of typhoid fever (>90% reduction)
  - 26% almost immediately
  - Add’l 65% over 5 years
- a 74% decrease in infant mortality
- a 62% decrease in child mortality
POPULATIONS W/O ACCESS TO SAFE WATER AND BASIC SANITATION:
DEVELOPMENT, IMPLEMENTATION AND IMPACT OF THE FIRST TYPHOID VACCINES
S. Typhi is observed and cultured for the first time in the early 1880's.

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).

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 acceptance 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,
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).

NB: whole-cell inactivated vaccine, one dose regimen, soldiers.
Hx of Typhoid Vaccines: USA

Typhoid vaccination in the US armed forces
- **1909** starts in US Army
- **1911** required for entire US Army and Navy

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

http://www.immunize.org/timeline/
Hx of Typhoid Vaccines: USA

Typhoid vaccination in the general population

- **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.

http://www.immunize.org/timeline/
THE URBAN PENALTY: TYPHOID FEVER
A CONTINUING PROBLEM
IN LOWER AND LOWER MIDDLE INCOME COUNTRIES
Populations at Risk for Typhoid Fever

Typhoid fever is prevalent in populations with

– *inadequate* access to safe water
– *inadequate* access to basic sanitation

Estimated Global Burden of Typhoid Fever

- WHO estimates 21 million cases and 216,000 – 600,000 deaths are caused by S. Typhi, every year.
  - Ivanoff et al. (1994) 17 million cases and 600,000 deaths
  - Crump et al. (2004) 21.6 million cases and 216,000 deaths

Geographical distribution of typhoid fever
Estimated Global Burden of Typhoid Fever

Available burden estimates are limited by:
- Confounding with other febrile illness dx, e.g. malaria, dengue
  - Poor diagnostics
  - Lack of systematic surveillance
Typhoid is a global problem
Typhoid Fever Mortality is Similar to Other Vaccine Preventable (VP) Diseases

Estimated annual deaths (000s), worldwide:

- Typhoid: 600
- Rotavirus: 527
- Hib: 386
- HepB: 600
- Meningitis: 50
- HPV: 260
- DHF*: 20
- JE: 10
Typhoid Fever Morbidity and Mortality in Relation to Other VP Diseases

Morbidity (in thousand)

Mortality (in thousand)


Crump et al. Global Burden of Typhoid Fever, Bulletin of WHO (Typhoid*)

Parashar et al. Global Illness and Deaths Caused by Rotavirus Disease in Children, EID (Rotavirus)
POLICY & PRACTICE:
SOUTH AND SOUTHEAST ASIA
WHO recommends typhoid vaccines

**WHO Position Paper (2008)**
([http://www.who.int/wer/2008/wer8306.pdf](http://www.who.int/wer/2008/wer8306.pdf))

Countries should consider the programmatic use of typhoid vaccines for:

- controlling endemic disease (targeting high risk groups / high burden populations)
- outbreak control

WHO Regions and Countries: SEAR

WHO South East Asia (SEA) Regional Office
Immunization Technical Advisory Group (ITAG)

July 2008:
Recognizing that typhoid fever may be a significant cause of morbidity and mortality in the region, the ITAG encourages countries to identify their disease burden and at-risk populations in order to consider vaccines introduction as part of a comprehensive disease control package.

WHO South East Asia (SEA) Region Countries

May 2009:
Countries in WHO’s SEA region prioritize typhoid vaccines for ‘immediate’ introduction

WHO Regions and Countries: SEAR

WHO SEAR Immunization Technical Advisory Group (ITAG)

March 2011:

The ITAG recommends establishing sub-groups to review and make recommendations on specific issues such as health resource management and vaccine introduction (rubella, hepatitis B and typhoid) with each sub-group consisting of an ITAG member as a focal point, WHO staff as secretariat and invited experts from relevant areas.

- Second South-East Asia Regional Technical Advisory Group on Immunization (SEAR ITAG) Meeting. A Brief Report, 2-3 March 2011, New Delhi, India

- WHO-SEARO-ITAG chair: Professor Lalitha Mendis
- WHO-SEARO-ITAG Typhoid, Paratyphoid and Cholera working group chair: Dr Jacob John
- WHO-SEARO-ITAG Members: Professor Lalitha Mendis, Dr. Jacob John, Dr. Supamit Chunsuttiwat, Dr. Nyoman Kandun, Dr. A. M. Zakir Hussain, Dr. Lalit Kant., Dr. M. H. Maskey, Dr. N. K. Arora, Dr. Triono Soendoro, Dr. Khin Pyone Kyi, Dr. Brent Burkholder
Pediatric Associations recommend typhoid vaccines

the Indian Academy of Pediatrics Committee on Immunization (IAPCOI) recommends the use of ViPS typhoid vaccines in children 2-15y

the Indonesian Pediatric Society recommends the use of typhoid vaccines

Summary of typhoid vaccination programs: 1980-present

Despite a recognized need and WHO rec’s, few countries are using typhoid vaccines for prevention.
Summary of typhoid vaccination programs: 1980-present

Existing typhoid vaccination programs
- Food handlers
- Gen’t Population
  and
- in place many years
- started recently
WHAT HAS BEEN THE IMPACT?
Programmatic Effectiveness of existing Typhoid Vaccine

Old generation killed whole cell vaccine
- School-based vaccination program in Thailand
  - More than 5 million children vaccinated (1977-84)
  - Sharp decline in typhoid fever incidence (note: no formal assessment)

Live attenuated Ty21a vaccine
- School-based vaccination in Santiago, Chile
  - Half a million school aged children through large school-based, randomized, controlled vaccine trials
  - Conferred protection and decline in typhoid cases noted

Levine et al. Rev. Infect. Dis. 1989
Cuba Vaccine Impact

Vaccination Coverage and Rate of Typhoid Fever in Cuba, 1970 - 2007

(in 2002, Cuba switched from whole-cell inactivated vaccine to Vi PS, one dose regimen, 10-16y school children.)

Vaccine Coverage and Typhoid Incidence in Northwestern Region of Vietnam
Vaccine Coverage and Typhoid Incidence
Guilin, Guangxi Province, China
POLICY & PRACTICE: SOUTH AND SOUTHEAST ASIA
High Typhoid Burden Countries, without existing typhoid immunization programs

<table>
<thead>
<tr>
<th>Country</th>
<th>Country</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pakistan</td>
<td>Cambodia</td>
</tr>
<tr>
<td>Nepal</td>
<td>Laos</td>
</tr>
<tr>
<td>Bhutan</td>
<td>Indonesia</td>
</tr>
<tr>
<td>Bangladesh</td>
<td>Philippines</td>
</tr>
<tr>
<td>Sri Lanka</td>
<td>East Timor</td>
</tr>
<tr>
<td>India</td>
<td>Papua New Guinea</td>
</tr>
<tr>
<td>Myanmar</td>
<td>Pacific Island Countries</td>
</tr>
</tbody>
</table>
2009 - High Priority Countries: Progress with Recommendations, Policy and Practice

- Professional Society Recommendation
- NITAG Discussion
- NITAG Recommendation
- MoH operational costs in cMYP
- MoH vaccine costs in cMYP / program implementation

Pakistan
Nepal
Bhutan
Bangladesh
Sri Lanka
India
Myanmar
Cambodia
Laos
Indonesia
Philippines
East Timor
Papua New Guinea
Pacific Island Countries

WHO IVB Immunization surveillance, assessment and monitoring 2012
Coalition against Typhoid Secretariat
2012 - High Priority Countries: Progress with Recommendations, Policy and Practice

Pakistan
Nepal
Bhutan
Bangladesh
Sri Lanka
India
Myanmar
Cambodia
Laos
Indonesia
Philippines
East Timor
Papua New Guinea
Pacific Island Countries

- none
- Professional Society Recommendation
- NITAG Discussion
- NITAG Recommendation
- MoH operational costs in cMYP
- MoH vaccine costs in cMYP / program implementation
Goal - High Priority Countries: Progress with Recommendations, Policy and Practice

- Professional Society Recommendation
- NITAG Discussion
- NITAG Recommendation
- MoH operational costs in cMYP
- MoH vaccine costs in cMYP / program implementation

Pakistan
Nepal
Bhutan
Bangladesh
Sri Lanka
India
Myanmar
Cambodia
Laos
Indonesia
Philippines
East Timor
Papua New Guinea
Pacific Island Countries

WHO IVB Immunization surveillance assessment and monitoring 2012
Coalition against Typhoid Secretariat
TYPHOID VACCINES: CURRENT AND FUTURE
## Current Typhoid Vaccine Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Ty21a vaccine</th>
<th>Vi polysaccharide vaccine</th>
<th>Vi conjugate vaccine (future)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type</strong></td>
<td>Live attenuated</td>
<td>Subunit</td>
<td>Subunit</td>
</tr>
<tr>
<td><strong>Route of administration</strong></td>
<td>Oral</td>
<td>IM/SC</td>
<td>IM/SC</td>
</tr>
<tr>
<td><strong>Doses / regimen</strong></td>
<td>4 (USA)</td>
<td>1</td>
<td>1-3</td>
</tr>
<tr>
<td><strong>Revaccination</strong></td>
<td>5-7 years</td>
<td>3 years</td>
<td>never – 4y</td>
</tr>
<tr>
<td><strong>Efficacy</strong></td>
<td>35-67%</td>
<td>55-72%</td>
<td>90+%</td>
</tr>
<tr>
<td><strong>Duration of efficacy</strong></td>
<td>62% at 7 years</td>
<td>55% at 3 years</td>
<td>90+% at 4y –life</td>
</tr>
<tr>
<td><strong>Herd protection</strong></td>
<td>Yes</td>
<td>Yes</td>
<td>Likely</td>
</tr>
<tr>
<td><strong>Cross-protection against paratyphoid</strong></td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td>≥ 5 years (ex-USA; USA)</td>
<td>≥ 2 years (WHO; USA)</td>
<td>≥ 6 weeks / 9 months (TBD)</td>
</tr>
</tbody>
</table>

Current Typhoid Vaccines
WHO Pre-Qualification Status

Applied for WHO PQ
- Crucell-Vivotif (Ty21a)

WHO Pre-Qualified
- Sanofi Pasteur–Typhim Vi (June 2011)
# Future Typhoid Vaccines

**Vi Conjugate (ViCV) and Live Attenuated Vaccines**

<table>
<thead>
<tr>
<th>ViCV</th>
<th>Live Attenuated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vi-rEPA NIH (USA)</td>
<td>M01ZH09 Prokarium (July 2012)</td>
</tr>
<tr>
<td>Lanzhou Institute (China)</td>
<td></td>
</tr>
<tr>
<td>Vi-CRM197 NVGH (Italy)</td>
<td>Ty800 Avant Immunotherapeutics</td>
</tr>
<tr>
<td>Vi-TT Bharat Biotech (India)</td>
<td>CVD909 Center for Vaccine Development, UMD &amp; NIAID</td>
</tr>
<tr>
<td>Vi-DT * IVI/Shantha Biotechnics (India)</td>
<td></td>
</tr>
<tr>
<td>Vi-DT * IVI/SK Chemicals (S Korea)</td>
<td></td>
</tr>
<tr>
<td>Vi-DT * IVI/Biofarma (Indonesia)</td>
<td></td>
</tr>
<tr>
<td>Vi-DT DAVAC (Vietnam)</td>
<td></td>
</tr>
<tr>
<td>Vi-DT Finlay Institute (Cuba)</td>
<td></td>
</tr>
</tbody>
</table>
Development of WHO ECBS Guidelines for Prequalification of Typhoid Vi Conjugate Vaccines

• 5-7 September 2012
  – KFDA/WHO Joint Meeting of Working Group on Quality, Safety and Efficacy of Typhoid Vi Capsular Polysaccharide Conjugate Vaccine, Jeju, Republic of Korea

• 1-31 March 2013
  – first public consultation of the draft document through WHO website

• 29-30 April 2013
  – Follow-up meeting of Working Group on Quality, Safety and Efficacy of Typhoid Vi Capsular Polysaccharide Conjugate Vaccine, Geneva, WHO

• 28 June 2013
  – Submission of final draft for ECBS review

• August – September 2013
  – Second public consultation of the draft document through WHO website publication

• 21-25 October 2013
  – ECBS meeting and discussion, Geneva
Review and Discussion of Typhoid Models

• Disease Burden
• Transmission models
  – Interventions effectiveness
  – Cost-effectiveness
GAVI Supports Typhoid Vi Conjugate Vaccines

• In 2008, the GAVI Board approved the Vaccine Investment Strategy – GAVI’s strategic approach
  – 4 vaccines: Human Papillomavirus (cervical cancer), Japanese Encephalitis, Rubella, and Typhoid conjugate
  – Reflects a type and degree of commitment to countries, suppliers, and Alliance partners. (2010)

• In 2010 and 2011, the GAVI Programme and Policy Committee (PPC) recommended and the GAVI Alliance Board re stated their commitment to typhoid conjugate vaccines
  – Board-recommended Vaccine Investment Strategy (VIS) vaccines: Human Papillomavirus (cervical cancer), Japanese Encephalitis, Rubella, and Typhoid conjugate
THE COALITION AGAINST TYPHOID (CaT)
CaT’s aim is to expedite and sustain rational, evidence-based decisions regarding the use of typhoid vaccines.

Our aim is defined within the context of Enteric and Diarrheal Disease Control and specifically Enteric Fever Control

CaT’s success is based on the collective action of its membership. It is not a highly funded organization in the style of previous new vaccine initiatives.
ASTMH 61st Annual Meeting (2012)
November 11-15, 2012
Atlanta, Georgia USA
http://www.astmh.org/Home.htm

CaT symposium
Organizer: Chris Nelson, Coalition against Typhoid (CaT)/Sabin Vaccine Institute, Washington DC USA
Co-chair: Zulfi Bhutta, Founding Chair, Women and Child Health Division, the Aga Khan University, Karachi, Pakistan

Advances in typhoid fever epidemiology and control
• Non-malaria febrile illness, J Crump
• Enteric fevers: diseases in need of better diagnostics, G Vernet
• Progress with typhoid conjugate vaccines, S Szu
• Typhoid fever transmission models, I Longini
8th International Conference
Typhoid Fever and Other Invasive Salmonelloses
1-2 March 2013 • Dhaka, Bangladesh
typhoidconference.org
In Collaboration With Our Partners
COALITION AGAINST TYPHOID
ANNOUNCING THE SEVENTH INTERNATIONAL CONFERENCE ON:

VACCINES FOR ENTERIC DISEASES
6-8 November 2013, The Royal Orchid Sheraton Hotel & Towers, Bangkok, Thailand

ASTMH 62nd Annual Meeting
November 13-17, 2013
Marriott Wardman Park Hotel
Washington, DC USA

http://www.astmh.org/Home.htm
TYPHOID NEWS

AUGUST 05, 2011
Typhoid Epidemic Sweeps Philippines: Regional health officials declare typhoid incidence up 40%...

SEPTEMBER 25, 2011
Focus on Typhoid at ICID: The 15th International Congress on Infectious Diseases will feature...

OCTOBER 13, 2011
Indian Academy of Pediatrics Recommends Typhoid Vaccine Use: In a reversal of an earlier recommendation, the IAP COI recently...

MANY OF THOSE MOST AT RISK ARE THE LAST TO GET VACCINES...

CaT NEWS & EVENTS
Hyper-endemic Typhoid in Africa Takes Spotlight in Cannes
Important new evidence revealing hyper-endemic typhoid in Africa will be presented by global health experts and scientists...

RESOURCES
Community Acquired Bacteremia in Young Children from Central Nigeria: A Pilot Study
A team led by researchers from Michigan State University found similar typhoid infection rates...