

# Typhoid Fever and Typhoid Vaccines

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Typhoid Fever

# **BACKGROUND**

# Typhoid Fever

## Etiology and Transmission

- ❑ Caused by *Salmonella enterica* serotype Typhi
  - Humans are only reservoir
- ❑ Usually acquired from contaminated food or water



# Typhoid Fever Clinical Features

- ❑ Incubation period 6–30 days
- ❑ Insidious onset
- ❑ Typical symptoms include increasing
  - Fever
  - Malaise
  - Headache
  - Anorexia
- ❑ Life-threatening complications include septic shock, intestinal hemorrhage and perforation

# Typhoid Fever Treatment

## □ Antimicrobials

- Fluoroquinolone
- Beta-lactam
- Azithromycin
- Chloramphenicol
- Trimethoprim-sulfamethoxazole

□ Antibiotic resistance common and increasing<sup>1</sup>

□ Case-fatality ratio for untreated disease 10-20%,<sup>2</sup> but <1% with appropriate antimicrobial treatment<sup>3</sup>

1 Crump and Mintz. Clin Infect Dis. 2010

2 Stuart and Pullen. Arch Int Med. 1946

3 Bhan et al. Lancet. 2005

# Enteric Fever (Including Typhoid) Etiology

## ❑ Caused by *Salmonella enterica* serotypes

- Typhi → Typhoid Fever
  - Paratyphi A
  - Paratyphi B (tartrate negative)
  - Paratyphi C
- Paratyphoid Fever

## ❑ Paratyphoid fever clinically indistinguishable from typhoid fever<sup>1</sup>

## ❑ Current typhoid vaccines provide little or no protection against paratyphoid fever

# Enteric Fever Epidemiology—Global



- ❑ **Typhoid: Estimated ~20 million cases annually<sup>1</sup>**
  - ~200,000 deaths/year
- ❑ **Paratyphoid: Estimated ~5 million cases annually**
  - In some Asian countries, Paratyphi A accounts for half of enteric fever cases<sup>2</sup>
- ❑ **Multi-drug resistance (ampicillin, chloramphenicol, and TMP-SMX) common for Typhi<sup>2</sup>**
  - Emerging fluoroquinolone-resistance and extended-spectrum  $\beta$  lactamase
  - Increased importance of vaccination

1 Crump et al. Bull WHO. 2004

2 Crump and Mintz. Clin Infect Dis. 2010

# Typhoid Fever Epidemiology—United States



- ❑ ~400 cases per year 2007-2011<sup>1</sup>
  
- ❑ ~90% travel-associated<sup>1</sup>
  - ~80-85% involved travel to Bangladesh, India, or Pakistan
  - Low use of vaccine among travelers (eg, ~20% of travelers received typhoid vaccine in one study)<sup>2</sup>
  
- ❑ **Vaccine recommendations for travel (cdc.gov/travel)**
  - Travel to most countries in Africa, Asia, and Latin America
  - Since 2011, typhoid vaccine no longer recommended for travel to certain countries in Eastern Europe and the Middle East<sup>3</sup>

1 CDC Surveillance. [http://www.cdc.gov/nationalsurveillance/typhoid\\_surveillance.html](http://www.cdc.gov/nationalsurveillance/typhoid_surveillance.html)

2 Mahon et al. Vaccine. 2014

3 Johnson et al. J Trav Med. 2011



# **TYPHOID VACCINES**

# Typhoid Vaccines Available in U.S. in 2014

Vaccine	Vaccine type	Age	Mode of administration	No. of doses	Repeat dosing
Ty21a vaccine, Vivotif®	Live, attenuated	≥6 years	Oral	4	Every 5 years*
Vi capsular polysaccharide vaccine (ViCPS), Typhim Vi®	Subunit	≥2 years	Parenteral	1	Every 2 years*

\* No booster effect observed for either vaccine

Conjugate polysaccharide vaccines available in a few countries; not licensed in the United States

# Ty21a Vaccine Efficacy

- ❑ **Systematic review and meta-analysis of studies conducted in endemic countries:<sup>1</sup>**
- ❑ **2.5–3 year cumulative efficacy was 48% (95% CI 34–58%) based on single trial**
- ❑ **In 2 excluded trials that did not adjust for cluster design (and likely overestimated protective effect), efficacy was**
  - 79% (95% CI 65–87%) at 5 years
  - 62% (95% CI 48–73%) at 7 years

# ViCPS Vaccine Efficacy

- Systematic review and meta-analysis of studies conducted in endemic countries:<sup>1</sup>

	Efficacy	95% CI	No. trials included
Year 1	69%	63–74%	3
Year 2	59%	45–69%	4
Cumulative 2.5–3 years	55%	30–70%	1

# Typhoid Vaccination Effectiveness in travelers

- ❑ **No efficacy studies among US travelers**
- ❑ **80% (95% CI 66–89%) effectiveness of typhoid vaccination among US travelers<sup>1</sup>**
  - Estimate is for any typhoid vaccination—not able to differentiate between vaccines

# Typhoid Vaccines Safety Data

- **Both vaccines generally well-tolerated with low rates of adverse events**
  - Data from trials and post-marketing studies

# Ty21a Vaccine Safety Data

- ❑ **In meta-analysis of field trials, certain events more common in vaccinees than placebo recipients:<sup>1</sup>**
  - Fever (RR 1.8, 95% CI 1.0–3.1)
  - Combined any mild adverse event (RR 1.7, 95% CI 1.0–2.7)
  
- ❑ **Estimated 0.6 serious events reported per 100,000 doses distributed<sup>2</sup>**
  - Vaccine Adverse Events Reporting System (VAERS) data
  - Serious adverse events defined as reports of death, hospitalizations, prolongation of hospitalization, permanent disability, life-threatening illness, or congenital anomaly

\*

1 Anwar et al. Cochrane Database Syst Rev. 2014

2 Begier et al. Clin Infect Dis. 2004

# ViCPS Vaccine Safety Data

- ❑ **In meta-analysis of field trials, symptoms more common than placebo:<sup>1</sup>**
  - Pain (RR 8.0, 95% CI 3.7–17.2)
  - Swelling at injection site (RR 6.0, 95% CI 1.1–34.2)
  
- ❑ **Estimated 0.3 serious events reported per 100,000 doses distributed<sup>2</sup>**
  - Vaccine Adverse Events Reporting System (VAERS) data
  - Serious adverse events defined as reports of death, hospitalizations, prolongation of hospitalization, permanent disability, life-threatening illness, or congenital anomaly

<sup>1</sup> Anwar et al. Cochrane Database Syst Rev. 2014

<sup>2</sup> Begier et al. Clin Infect Dis. 2004



# Typhoid Vaccines Contraindications

- ❑ **Ty21a and ViCPS: hypersensitivity to any component of vaccine<sup>1,2</sup>**
  
- ❑ **Ty21a**
  - Live bacterial vaccines generally contraindicated in pregnant women<sup>3</sup>
  - Contraindicated in immunocompromised persons<sup>1</sup>
  - Should not be administered during acute febrile illness<sup>1</sup>

1 Vivotif Package Insert [www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM142807.pdf](http://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM142807.pdf)

2 Typhim Vi Package Insert [www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM142811.pdf](http://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM142811.pdf)

3 ACIP. General Recommendations on Immunization. 2011

# Typhoid Vaccines Precautions

- ❑ **Ty21a: Avoid antimicrobial agents, if possible, 3 days before and after vaccine administration<sup>1</sup>**
  - Certain anti-malarial prophylaxis medications can be taken at same time as vaccine<sup>1</sup>
  - Can be co-administered with other live vaccines<sup>2</sup>
  
- ❑ **ViCPS: Should be given to pregnant women only if clearly needed<sup>3</sup>**

1 Vivotif Product Monograph. [http://www.crucellvaccinescanada.com/pdf/vivotif\\_pm.pdf](http://www.crucellvaccinescanada.com/pdf/vivotif_pm.pdf)

2 ACIP. General Recommendations on Immunization. 2011

3 Typhim Vi Package Insert [www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM142811.pdf](http://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM142811.pdf)

Typhoid Vaccines

# **PROPOSED UPDATES TO RECOMMENDATIONS**

# Proposed Recommendation (1)

## Typhoid Vaccine Indicated For

- ***“Travelers to areas in which there is a recognized risk of exposure to Salmonella serotype Typhi (see [cdc.gov/travel/](http://cdc.gov/travel/))***
  - *“Risk is greatest for travelers to developing countries (e.g., countries in Latin America, Asia, and Africa) who have prolonged exposure to possibly contaminated food and drink, although short-term travelers are also at risk.*
  - *“Multidrug-resistant strains of Salmonella serotype Typhi have become common in many regions, and cases of typhoid fever that are treated with drugs to which the organism is resistant can be fatal.*
  - *“Travelers should be cautioned that typhoid vaccination is not a substitute for careful selection of food and drink. Typhoid vaccines are not 100% effective, and vaccine-induced protection can be overwhelmed by large inocula of Salmonella serotype Typhi.”*
- **No substantive changes to 1994 recommendation**

## Proposed Recommendation (2) Typhoid Vaccine Indicated For

- *“Persons with intimate exposure (e.g., household contact) to a documented Salmonella serotype Typhi chronic carrier (defined as excretion of Salmonella serotype Typhi in urine or stool for >1 year)”*
  
- **Change to 1994 recommendation**
  - Carrier specified as “chronic”
  - Chronic carriage defined (excretion >1 year)

## Proposed Recommendation (3) Typhoid Vaccine Indicated For

- ❑ *“Microbiologists and laboratory workers who work with cultures of Salmonella serotype Typhi or with specimens that contain this organism or who work in laboratory environments where these cultures or specimens are handled.”*
  
- ❑ **1994 recommendation**
  - *“Microbiology laboratorians who work frequently with S. typhi”*

## Proposed Recommendation Choice of Vaccine

- ❑ ***“Parenteral Vi polysaccharide and oral Ty21a vaccines are both acceptable forms of typhoid immunization”***
- ❑ **Consider**
  - Approved ages for use
    - ≥6 years for Ty21a
    - ≥2 years for ViCPS
  - Dosing
    - 4 oral capsules on alternating days for Ty21a
    - Single injection for ViCPS
  - Contraindications and precautions
- ❑ **The inactivated whole cell vaccine that is no longer available has been deleted from the recommendation**

## Summary

- ❑ **1994 ACIP typhoid vaccines statement outdated**
- ❑ **No substantive changes in recommendations proposed**
- ❑ **Updated statement reflects**
  - Change in vaccine availability (whole-cell vaccine discontinued)
  - Newer data on typhoid epidemiology
  - Newer data on vaccine efficacy and safety



# Questions and Discussion

**For more information please contact Centers for Disease Control and Prevention**

1600 Clifton Road NE, Atlanta, GA 30333

Telephone: 1-800-CDC-INFO (232-4636)/TTY: 1-888-232-6348

Visit: [www.cdc.gov](http://www.cdc.gov) | Contact CDC at: 1-800-CDC-INFO or [www.cdc.gov/info](http://www.cdc.gov/info)

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