Typhoid Fever in the U.S. Pediatric Population and the Potential Benefits of New Vaccines

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Background

Typhoid Fever in the United States

- Public health improvements in early 20th century
  - Municipal water and sewage treatment systems
  - Declines in typhoid fever incidence and mortality[1]
- 350 laboratory-confirmed *Salmonella* Typhi cases annually
  - ~80% acquired during international travel[2]
    - 2008-2012 CDC study[3] showed 87% decreased susceptibility or resistance to fluoroquinolones in travelers to South Asia

[1]Cutler D and Miller G. The Role of Public Health Improvements in Health Advances: The 20th century United States. Demography. 2005;42: 1-22
[2]Jackson, Brendan R., Shahed Iqbal, and Barbara Mahon. "Updated recommendations for the use of typhoid vaccine—Advisory Committee on Immunization Practices, United States, 2015." *MMWR. Morbidity and mortality weekly report* 64.11 (2015): 305
[3]Date, Kashmira A., et al. "Changing patterns in enteric fever incidence and increasing antibiotic resistance of enteric fever isolates in the United States, 2008–2012." Reviews of Infectious Diseases 63.3 (2016): 322-329.

Typhoid Vaccines Licensed in U.S.

Vaccine	Ty21a	ViCPS
Brand name	Vivotif	Typhim Vi
How given	Oral	IM injection
Age indication	≥ 6 years old	≥ 2 years old
Number of doses	Four doses	One dose
Booster frequency	q5 years 	q2 years 
Effectiveness	50% to 80%	50%-80%

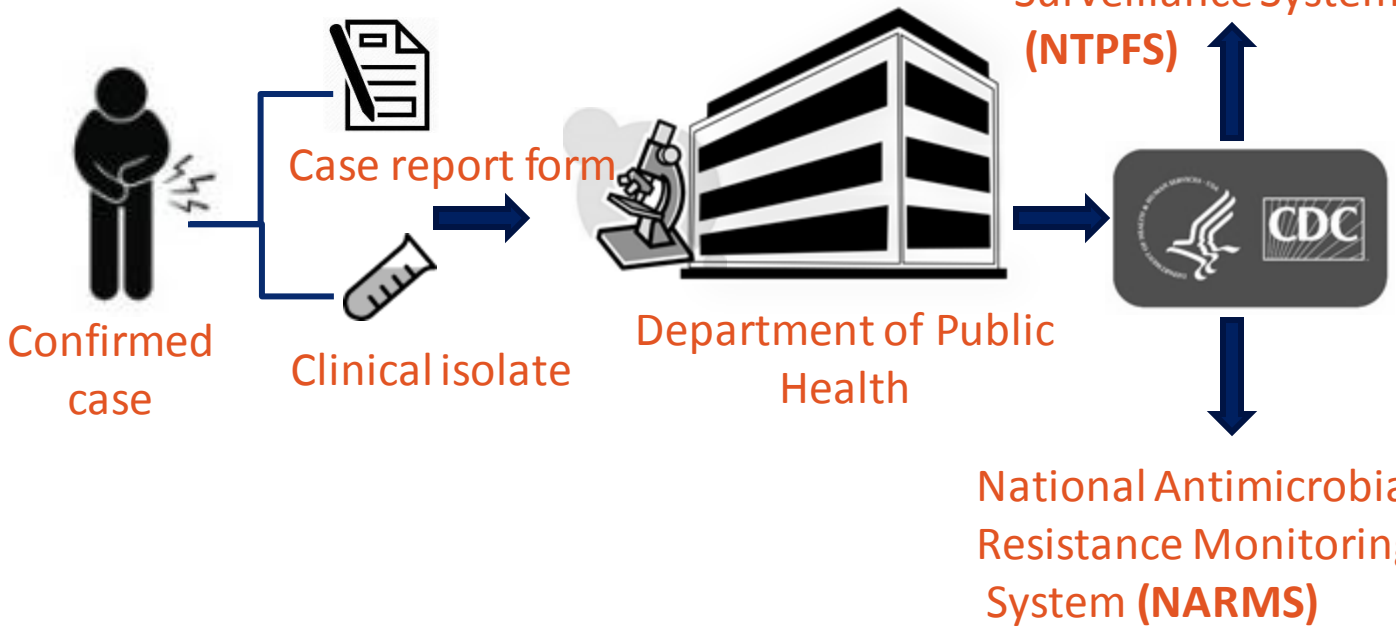
Modified from: http://www.coalitionagainsttyphoid.org/prevent-treat/typhoid-vaccines
*Ongoing studies; Estimated VE from adult challenge study

Typhoid Conjugate Vaccine (TCV)

Vaccine	TCV
Brand name	Typbar-TCV
How given	IM injection
Age indication	≥ 6 months old
Number of doses	One dose
Duration of protection	≥ 3 years*
Effectiveness	87%*

Modified from: http://www.coalitionagainsttyphoid.org/prevent-treat/typhoid-vaccines
*Ongoing studies; Estimated VE from adult challenge study

Surveillance for Typhoid Fever—United States

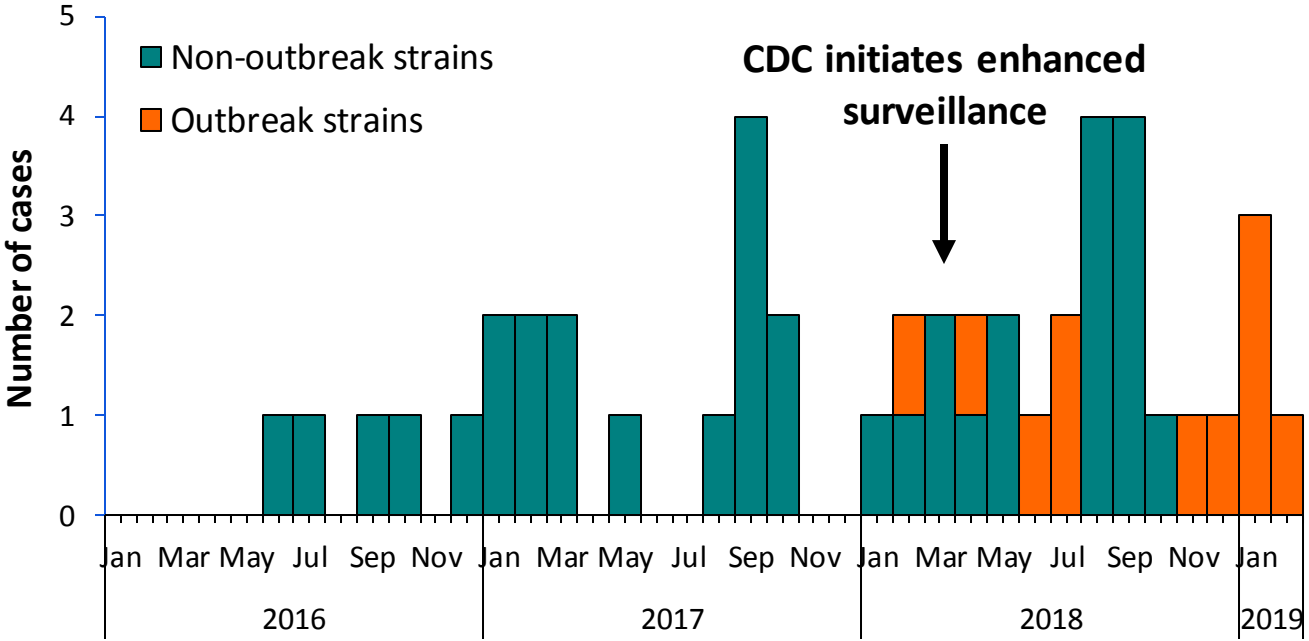


XDR Typhi in the United States, 2016–2019

- CDC enhanced surveillance for typhoid fever in travelers to or from Pakistan[1]
  - Retrospective review and prospective screening
- 46 patients with typhoid fever had travel to or from Pakistan
  - **11 travel-associated cases with XDR Typhi**
    - 9 (82%) children, median age 8 (4–26) years
    - 7 reported visiting friends and relatives (VFR) in Pakistan
    - None known to be vaccinated

[1]Chatham-Stephens, Kevin, et al. "Emergence of Extensively Drug-Resistant Salmonella Typhi Infections Among Travelers to or from Pakistan—United States, 2016–2018." *Morbidity and Mortality Weekly Report* 68.1 (2019): 11.

Epidemic Curve of Travelers to or from Pakistan with *Salmonella* Typhi—United States, 2016–2019



As of March 1, 2019

Study Rationale

- In light of the XDR Typhi outbreak and increasing availability of TCV
  - we characterized clinical, epidemiologic, and antimicrobial resistance data of pediatric typhoid fever cases reported to CDC

Study Design

Study Design

- **Objective**
  - Understand the epidemiology of typhoid fever in the US pediatric population from 1999-2015
- **Methods**
  - Analyzed[1] NTPFS demographic, clinical, and epidemiology characteristics and NARMS antimicrobial resistance (AMR) patterns for pediatric (< 18 years old) and adult cases, 1999-2015

[1]Statistical analysis performed using Fischer exact test, Cochrane Armitage test, false discovery rate used to correct for Type 1 errors due to multiple comparisons

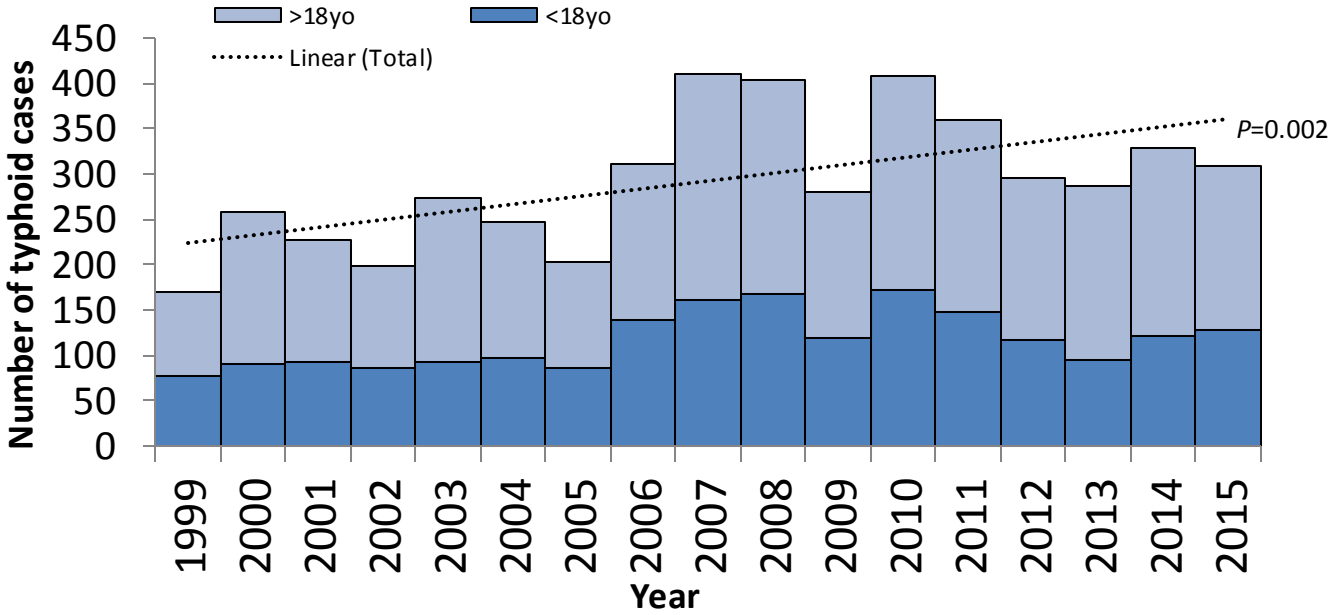
Definitions

- **Travel-associated**: travel outside U.S within 30 days before symptom onset
- **Vaccine eligible**: travel-associated case, age ≥ 2 years old, with travel to ≥ one country where CDC recommends typhoid vaccination
- **Fluoroquinolone nonsusceptible (FQ-NS):** MICs classified as intermediate (MIC =0.12–0.5 µg/mL) or resistant (MIC ≥1 µg/mL) to ciprofloxacin, or resistant to nalidixic acid
- **Multidrug resistance (MDR):** MICs classified as resistant to ampicillin, chloramphenicol, and trimethoprim-sulfamethoxazole (TMP-SMX)

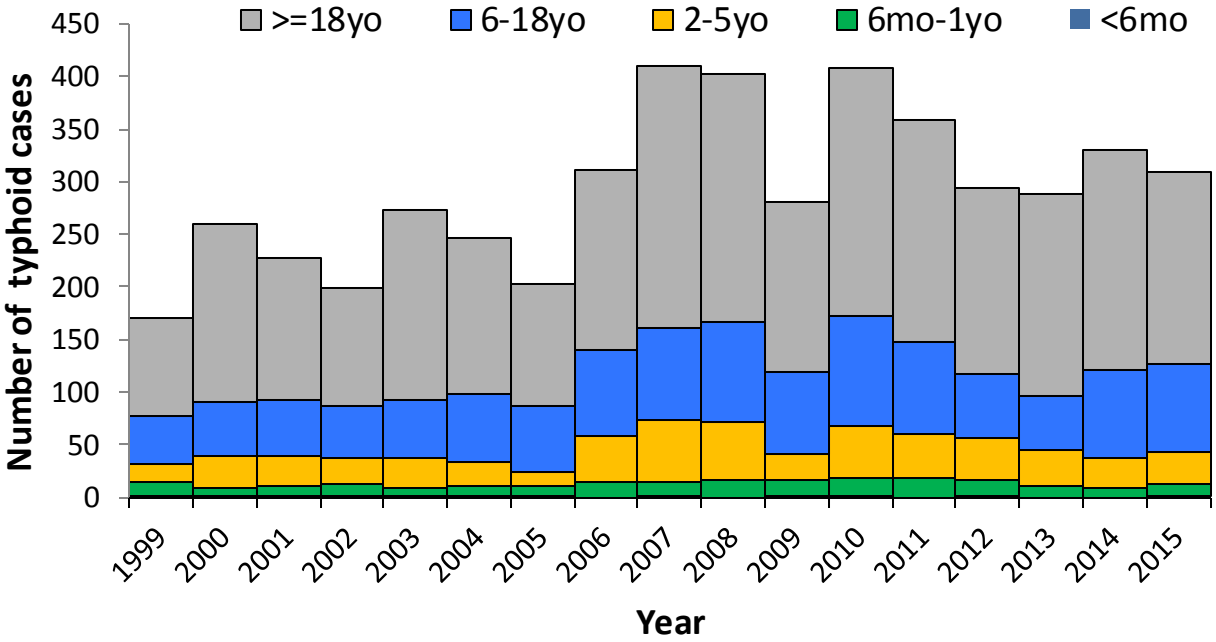
Preliminary Results

Slides courtesy of Dr. Jarred McAteer and CDC NARMS

Typhoid Fever Cases Reported to NTPFS by Year and Age Group – United States, 1999-2015 (n= 4,973)



Typhoid Fever Cases Reported to NTPFS by Year and Age Group – United States, 1999-2015 (n= 4,973)



Number of Pediatric Typhoid Fever Cases by Age Group – United States, 1999-2015 (n = 1,992)

Age Group	Total reported cases	Percent of pediatric cases
<6mo	14	<1%
6mo-1yo	210	11%
2-5yo	575	29%
6yo-17yo	1193	60%

Travel History among Typhoid Fever Cases Reported to NTPFS – United States, 1999-2015

Characteristics	AGE (years) <18	AGE (years) ≥18	P-value
Total reported cases	1992	2981	
Median age, y (range)	7 (0.02–17)	31 (18–103)	
Travel-associated*	1616 (83%)	2379 (83%)	0.69
Visiting friends/relatives (VFR)	1128 (71%)	1387 (63%)	<0.001

* Denominators for travel-associated cases: 1941 and 2873 respectively for children and adults, for VFR: 1590 and 2201 respectively

Vaccine Eligibility and Vaccination Status among Typhoid Fever Cases Reported to NTPFS – United States, 1999-2015

Characteristics	AGE (years) <18	AGE (years) ≥18	P-value
Travel-associated*	1616 (83%)	2379 (83%)	NS
Vaccine eligible	1435 (83%)	2303 (80%)	<0.01
Received vaccination	68 (5%)	92 (5%)	NS

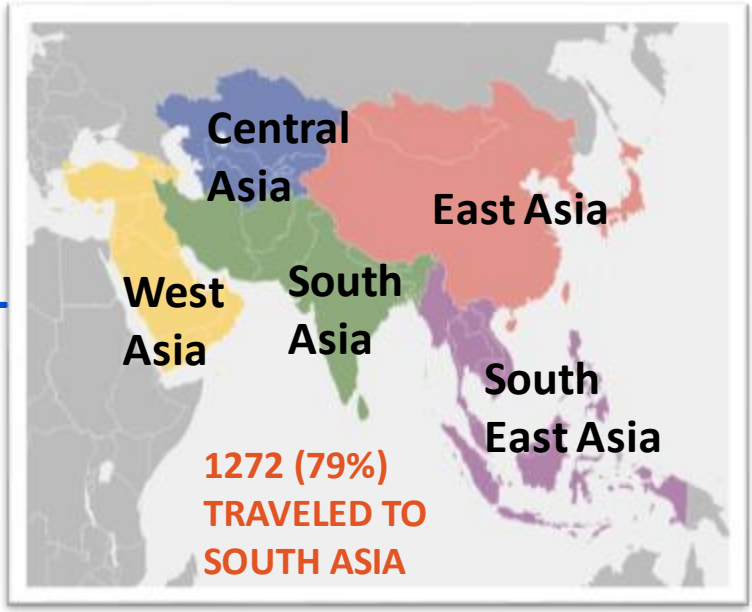
Among children with travel-associated typhoid: 134 (**8%**) were vaccine ineligible based on young age (6 months to under 2 years old)

*Denominators for travel-associated cases: 1941 and 2873 respectively for children and adults, for vaccine eligible: 1722 and 2873; for vaccinated: 1361 and 1921 respectively

Regions Visited by U.S. Pediatric Typhoid Fever Patients who Traveled in 30 Days before Illness (n=1,616)

Continent	Pediatric typhoid cases
Europe	3 (<1%)
Oceania	12 (<1%)
Africa	56 (3%)
Americas	135 (8%)
Asia	1,365 (84%)
Multiple	16 (1%)
*Missing	29 (2%)

*Missing country data



Single Countries Visited by U.S. Pediatric Typhoid Fever Patients in 30 Days before Illness (n=1,616)

Country	UN Region	Pediatric Typhoid cases (%)
India	South Asia	785 (49%)
Pakistan	South Asia	239 (15%)
Bangladesh	South Asia	227 (14%)

AMR patterns in isolates tested by NARMS — United States, 1999-2015 (n=5,004)

Characteristics	Typhoid fever isolates, n (%)		P-Value
	<18 (n=2003)	≥18 (n=3001)	
MDR*	320 (16%)	272 (9%)	<0.001
FQ-NS**	1216 (61%)	1619 (54%)	<0.001
Both MDR and FQ-NS	272 (14%)	236 (8%)	<0.001
Susceptible to 7 clinically relevant antibiotics***	723 (36%)	1312 (44%)	<0.001

*Resistant to ampicillin, chloramphenicol, TMP-SMX

**Fluoroquinolone nonsusceptible (defined as intermediate or resistant to ciprofloxacin and or resistant to nalidixic acid)

*** Nalidixic acid, ampicillin, chloramphenicol, TMP-SMX, ceftriaxone, ciprofloxacin, and azithromycin (tested since 2011)

AMR Patterns of Isolates from Pediatric Cases by Travel Destination — United States, 1999-2015

Region	Pediatric Cases	AMR patterns, n (%)		
		FQ-NS	MDR	MDR and FQ-NS
Asia	917	727 (79%)	158 (17%)	142 (15%)
South Asia	860	709 (82%)	149 (17%)	136 (16%)
India	521	465 (89%)	33 (6%)	30 (6%)
Bangladesh	168	139 (83%)	48 (29%)	47 (28%)
Pakistan	158	98 (62%)	67 (42%)	59 (37%)

Conclusions and Implications for Prevention

Summary: US Typhoid Cases, 1999-2015

- Increase in number of culture-confirmed pediatric typhoid fever cases reported annually from 1999-2015
- 83% of pediatric cases were travel-associated and 71% were VFR
  - Travel to South Asia, especially India and Pakistan, was common
- Typhi isolates from pediatric cases more likely to be fluoroquinolone non-susceptible and MDR than isolates from adult cases
  - Most isolates from cases who traveled to South Asia were fluoroquinolone non-susceptible
- Although most pediatric travelers were vaccine-eligible
  - 8% were not age eligible for current vaccines
  - Among vaccine-eligible, only 5% were vaccinated

Implications for Prevention

- Potential Benefits of TCVs
  - Increase pediatric vaccine eligibility for children ≥6 months
    - more opportunities for pre-travel consultation during routine pediatric visits (6, 9, 12 and 15 months)
    - Vaccinate young VFR travelers
- Strategies to promote more use of currently licensed typhoid vaccines
- In addition to vaccination, continue to promote safe food and water practices while traveling abroad

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