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Extensively Drug-resistant *Salmonella* Typhi Infections Emerge Among Travelers to or from Pakistan—United States, 2016–2018

Clinician Outreach and Communication Activity (COCA)

March 19, 2019

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  - **404-639-3286** or send an email to **media@cdc.gov**.
- **If you are a patient, please refer your questions to your healthcare provider.**

At the conclusion of the session, participants will be able to accomplish the following:

- Provide background on *Salmonella* Typhi and the ongoing XDR typhoid outbreak.
- List CDC's recommendations for diagnosing XDR typhoid.
- Describe the treatment options for typhoid fever infections diagnosed in the United States.
- Explain the prevention measures for XDR typhoid and who should be vaccinated.

Today's First Presenter

Grace D. Appiah, MD, MS
Medical Officer
Waterborne Disease Prevention Branch
Division of Foodborne, Waterborne, and Environmental Diseases
National Center for Emerging, Zoonotic, and Infectious Diseases
Centers for Disease Control and Prevention

Today's Second Presenter

Louise K. Francois Watkins, MD, MPH
Medical Officer
Enteric Diseases Epidemiology Branch
Division of Foodborne, Waterborne, and Environmental Diseases
National Center for Emerging, Zoonotic, and Infectious Diseases
Centers for Disease Control and Prevention

Extensively Drug-resistant Salmonella Typhi Infections Emerge Among Travelers to or from Pakistan—United States, 2016–2018

Grace D. Appiah, MD
Louise Francois Watkins, MD, MPH
Division of Foodborne, Waterborne and Environmental Diseases

COCA Call
March 19, 2019

Extensively Drug Resistant *Salmonella* Typhi: What Healthcare Providers Need to Know

- Clinical background and epidemiology of typhoid fever
- Management of XDR typhoid
- Prevention strategies for typhoid fever

Pediatric Case

- Rana, a 4 year old girl, presents to ED with fever (Tmax 39˚C) and abdominal pain for past 4 days and 3 week history of non-bloody diarrhea
  - nausea, vomiting, anorexia, and weight loss
  - previously healthy; Meds: None
  - lives with parents and 2 yo brother

Pediatric Case: Travel History

- Returned from 6 week trip to Pakistan
  - Traveled with family to visit relatives in Karachi, Lahore and Islamabad
    - Parents and brother had diarrheal illness in last 3 days of the trip, but all quickly recovered before return
    - Ate food prepared by relatives, in local restaurants; drank public water in homes and bottled water

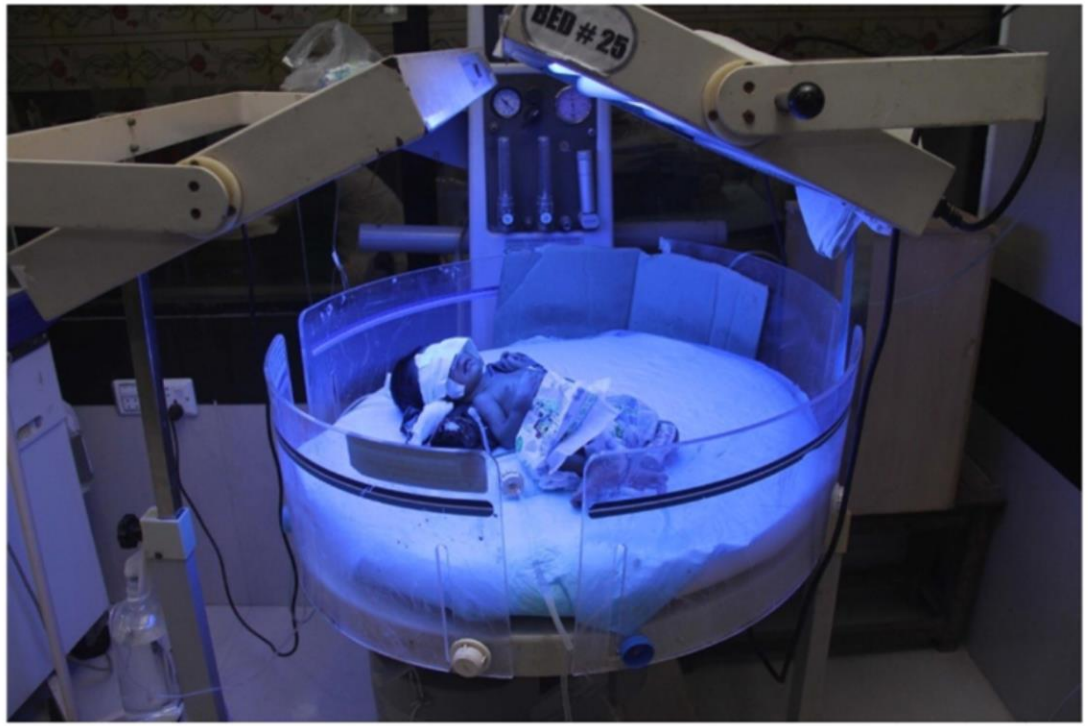
  - No typhoid vaccines were administered before travel
- Second trip to Pakistan, last trip was 2 years ago

Extensively Drug-Resistant (XDR) Typhoid Outbreak

Sewage seeping into drinking water in Karachi, Pakistan, likely helped spread bacteria that cause extensively drug-resistant typhoid. ASHRAF KHAN/IRIN

‘Frightening’ drug-resistant strain of typhoid spreads in Pakistan

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



A baby believed to have contracted a drug-resistant strain of typhoid, hospitalized in Hyderabad, Pakistan in February. Nadeem Khawer/European Pressphoto Agency

Question #1

- XDR typhoid strains are resistant to ampicillin, chloramphenicol, TMP-SMX AND which of the following antibiotics?

  A) azithromycin

  B) ciprofloxacin

  C) ceftriaxone

  D) meropenem

  E) B and C

Question #1

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  A) azithromycin

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  C) ceftriaxone

  D) meropenem

  E) B and C

Multi-drug resistant (MDR)

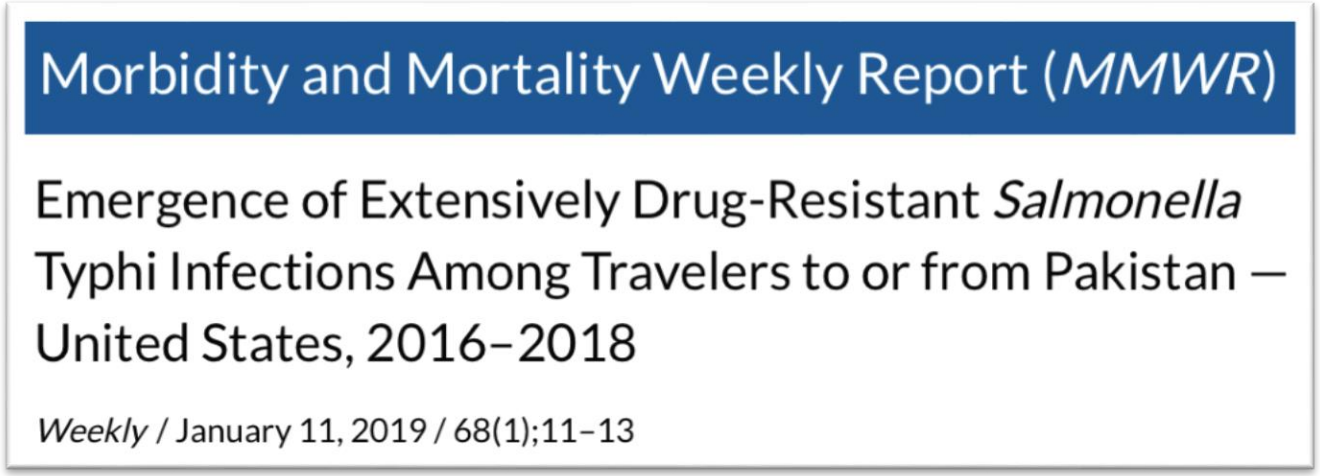
XDR resistance = MDR + fluoroquinolones + 3rd generation cephalosporins

XDR Typhoid Outbreak in Pakistan, 2016–2019

- Largest ceftriaxone-resistant outbreak
  - 6,204 cases reported
  - Fecal-contamination of drinking water
  - Risk factors included[1]
    - age (≤ 15 years), male sex, eating out, antimicrobials in 4 weeks before illness
  - Public health response ongoing

[1]Qamar, Farah Naz, et al. "Outbreak investigation of ceftriaxone-resistant Salmonella enterica serotype Typhi and its risk factors among the general population in Hyderabad, Pakistan: a matched case-control study." The Lancet Infectious Diseases 18.12 (2018): 1368-1376.

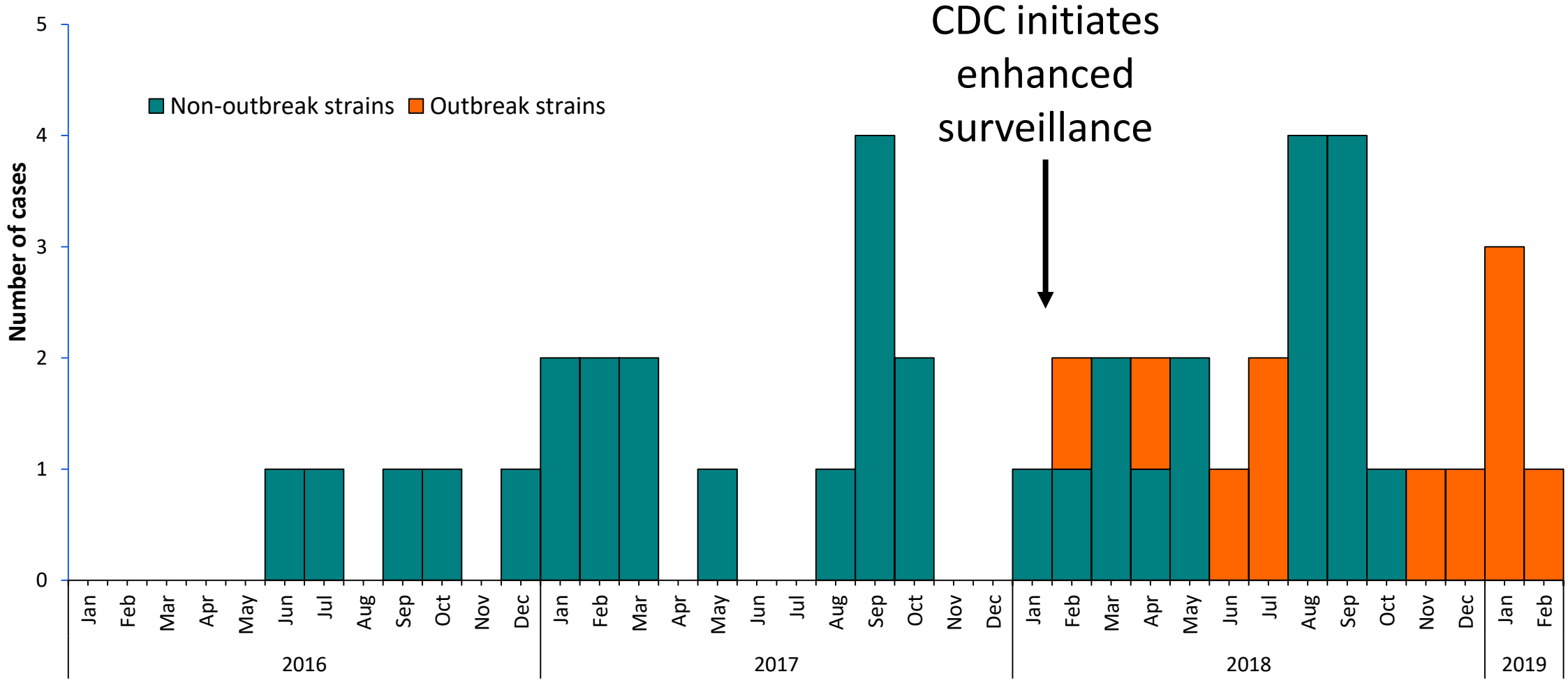
Extensively Drug-Resistant (XDR) Typhoid in U.S.



XDR Typhi in the United States, 2016–2019

- 46 patients with typhoid fever had travel to or from Pakistan
  - **11 travel-related cases with XDR Typhi**
    - 9 (82%) children, median age 8 (4–26) years
    - Visiting Friends and Relatives (VFR) in Pakistan (7); visiting US from Pakistan (1)
    - None known to be vaccinated
- All travelers to Pakistan are at high risk of getting XDR typhoid fever

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



As of March 1, 2019

Background

Typhoid Fever

- *Salmonella enterica* serotype Typhi
  - Gram-negative, motile bacillus
  - O (surface polysaccharide) and H (flagellar) antigens
  - Serogroup D
- Human-restricted

Question #2

- How is *Salmonella* Typhi transmitted?

  A) airborne

  B) vector-borne

  C) droplet

  D) food and waterborne

  E) none of the above

Question #2

- How is *Salmonella* Typhi transmitted?

  A) airborne

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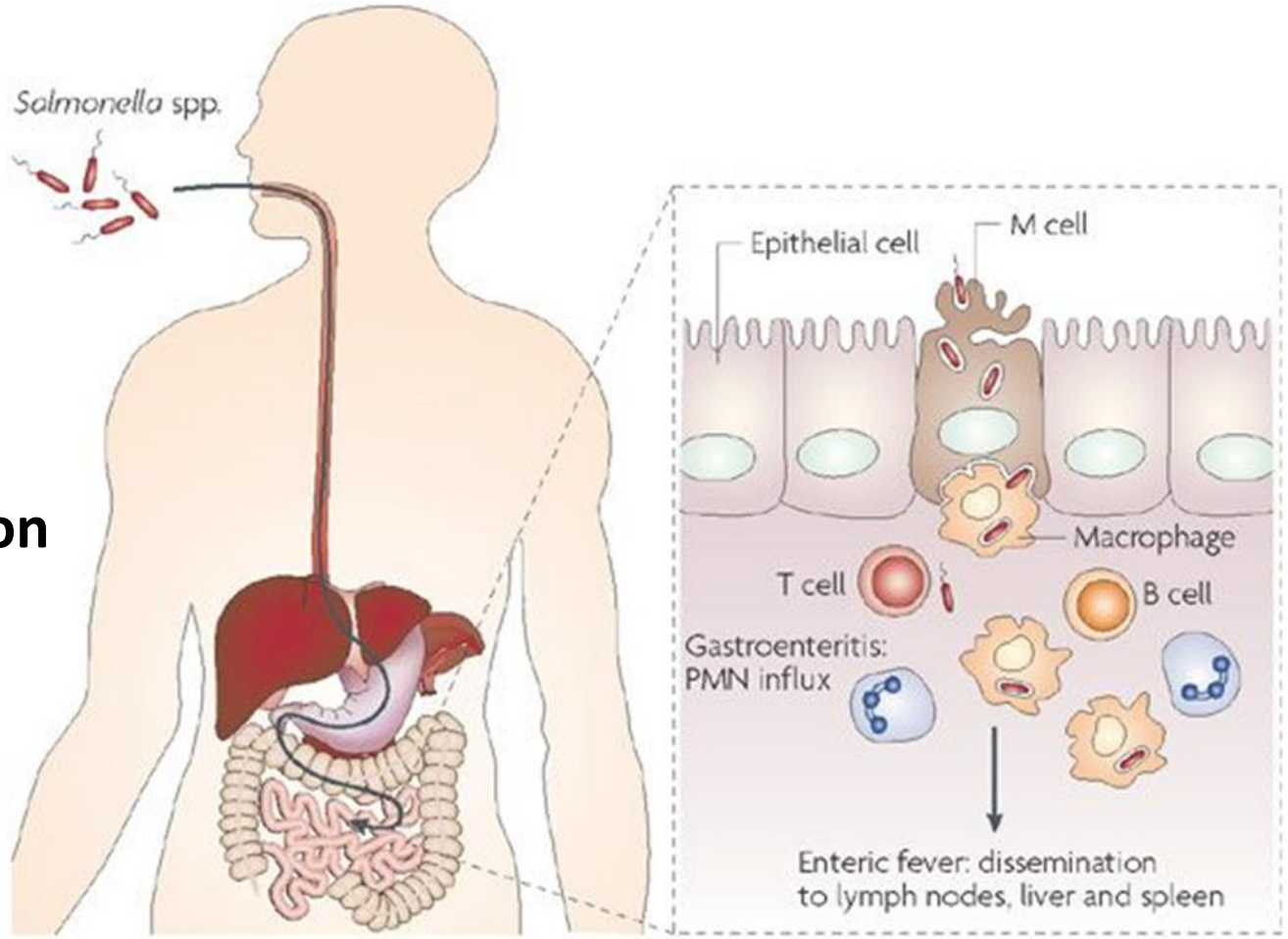
Fecal contamination of food or water

Pathophysiology

During incubation period (6-30d), adhere to small intestine



Multiply and enter blood stream

Haraga A, Ohlson MB, Miller SI. Salmonellae interplay with host cells. Nature Reviews Microbiology. 2008 Jan;6(1):53.

Question #3

- Which of the following is NOT a symptom or sign of typhoid?

  A) cough

  B) diarrhea

  C) constipation

  D) rash

  E) oral mucosal bleeding

Question #3

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Frequency of Symptoms and Signs in Patients with Typhoid Fever

Symptoms	Clinical Feature	Frequency
Flu-like symptoms	Fever	>95%
	Headache	80%
	Chills	40%
	Cough	30%
	Myalgia	20%
	Arthralgia	<5%
Abdominal symptoms	Anorexia	50%
	Abdominal pain	30%
	Diarrhea	20%
	Constipation	20%
Physical signs	Coated tongue	50%
	Hepatomegaly	10%
	Splenomegaly	10%
	Abdominal tenderness	5%
	Rash	<5%
	Generalized adenopathy	<5%

Modified from: Bennett JE, Dolin R, Blaser MJ. Principles and practice of infectious diseases; 2014 Aug 28. Pg 1275.

Clinical Presentation

- Non-specific, systemic febrile illness
- Physical findings include
  - abdominal tenderness
  - Hepatosplenomegaly
  - rose spots
- Severe complications include
  - intestinal hemorrhage
  - perforation
  - shock and death

Pediatric Case

- Compatible clinical illness and travel history
  - Fever ≥ 3 days and systemic symptoms, including gastrointestinal
  - Travel to an endemic region
- Physical exam findings
  - Febrile, ill-appearing but non-toxic child diffuse abdominal tenderness

you suspect typhoid fever, *now what*?

Question #4

- How should you diagnose typhoid fever in this patient?
  - A) Order blood and stool cultures
  - B) Order bone marrow culture
  - C) Order Widal test
  - D) Order urine cultures
  - E) All of the above

Question #4

- How should you diagnose typhoid fever in this patient?

  A) Order blood and stool cultures

  B) Order bone marrow culture

  C) Order Widal test

  D) Order urine culture

  E) All of the above

Making the Diagnosis

- Isolating *Salmonella* Typhi from culture specimen
  - Positive **blood culture** in **50-70%**
    - more frequently isolated from blood during 1st week of illness
  - Positive **stool culture** in **40%**
    - more frequently positive in 2nd or 3rd week of illness
  - Positive **bone marrow culture** in **90%** but rarely indicated
- Typhi can also be isolated from other clinical sites
  - Duodenal aspirates, rose spots and rarely, urine

Making the Diagnosis

- Serologic tests have limited diagnostic value
  - Widal test has poor specificity (50%-70%) and requires paired sera
    - False-negatives- early in illness
    - False-positives- past infection, vaccination or exposure to cross-reactive antigens
  - Unable to test for antimicrobial resistance

Antimicrobial Therapy

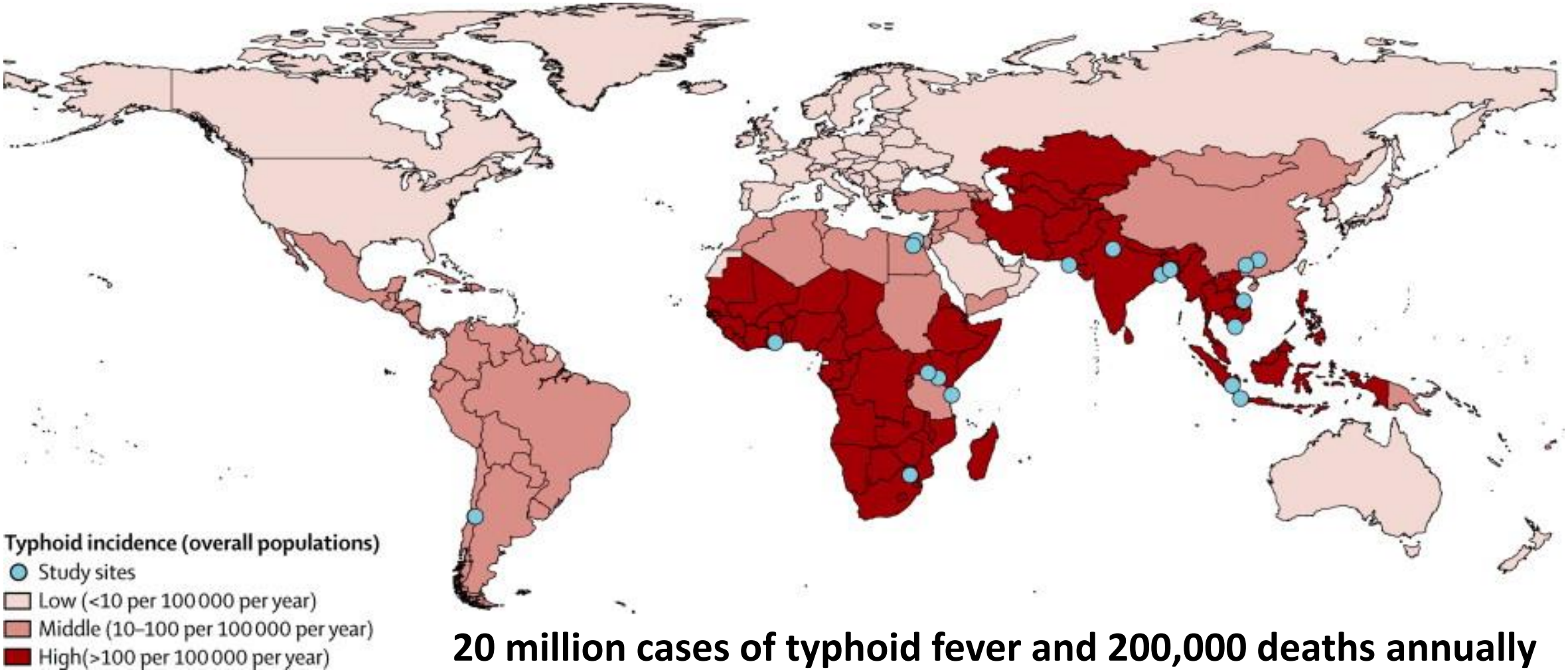
- Effective antimicrobial therapy reduces morbidity and mortality
  - *Without* antimicrobial therapy
    - acute illness may last for 3–4 weeks
    - death rates range between 12% and 30%
  - With effective antimicrobial therapy
    - symptoms subside within 2 days and fever recedes within 5 days
    - death rate approximately 1%

Chronic Carriage

- Chronic, asymptomatic infection persisting in gallbladder
  - Shedding in stool (or rarely urine) >12 months after acute infection
  - 2-5% chronic carriage rate
  - Increased risk with age, female sex
- Need antimicrobial therapy to eradicate carriage

Epidemiology

Epidemiology- Global



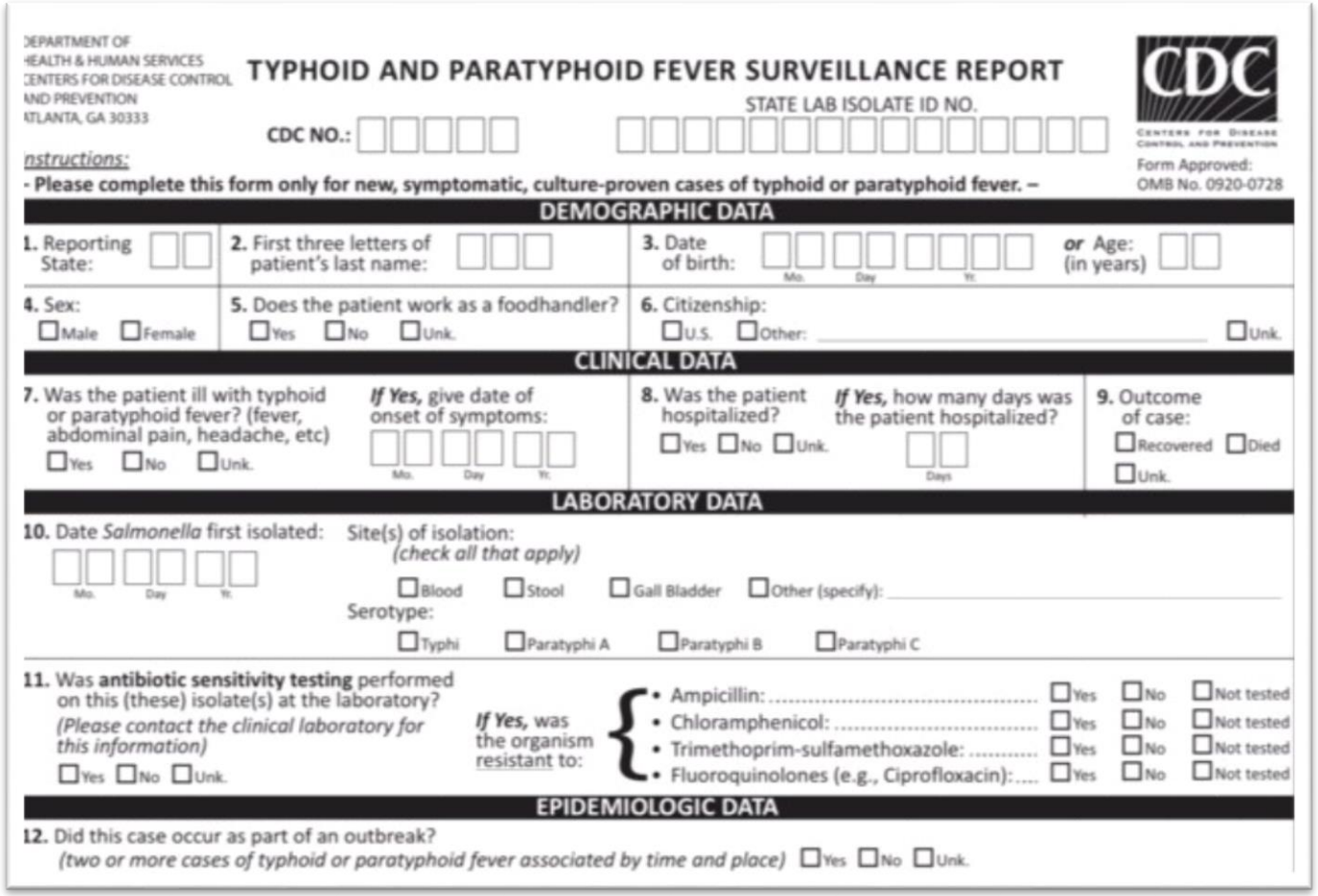
20 million cases of typhoid fever and 200,000 deaths annually

Mogasale, Vittal, et al. "Burden of typhoid fever in low-income and middle-income countries: a systematic, literature-based update with risk-factor adjustment." The Lancet Global health 2.10 (2014): e570-e580.

Epidemiology- United States

- Typhoid fever is uncommon
  - 300 laboratory-confirmed cases annually
  - Not all cases are diagnosed; 5,700 estimated cases per year
- Most infections acquired during international travel

National Typhoid Fever Surveillance



DEPARTMENT OF
HEALTH & HUMAN SERVICES
CENTERS FOR DISEASE CONTROL
AND PREVENTION
ATLANTA, GA 30333

TYPHOID AND PARATYPHOID FEVER SURVEILLANCE REPORT

CDC NO.: ☐☐☐☐☐ STATE LAB ISOLATE ID NO. ☐☐☐☐☐☐☐☐☐☐☐☐☐☐

CDC Centers for Disease Control and Prevention

Form Approved: OMB No. 0920-0728

Instructions:

- Please complete this form only for new, symptomatic, culture-proven cases of typhoid or paratyphoid fever. –

DEMOGRAPHIC DATA

1. Reporting State: ☐☐
2. First three letters of patient's last name: ☐☐☐
3. Date of birth: ☐☐ Mo. ☐☐ Day ☐☐☐☐ Yr. *or* Age: (in years) ☐☐
4. Sex: ☐Male ☐Female
5. Does the patient work as a foodhandler? ☐Yes ☐No ☐Unk.
6. Citizenship: ☐U.S. ☐Other: _____ ☐Unk.

CLINICAL DATA

7. Was the patient ill with typhoid or paratyphoid fever? (fever, abdominal pain, headache, etc) ☐Yes ☐No ☐Unk. *If Yes,* give date of onset of symptoms: ☐☐ Mo. ☐☐ Day ☐☐ Yr.
8. Was the patient hospitalized? ☐Yes ☐No ☐Unk. *If Yes,* how many days was the patient hospitalized? ☐☐ Days
9. Outcome of case: ☐Recovered ☐Died ☐Unk.

LABORATORY DATA

10. Date *Salmonella* first isolated: ☐☐ Mo. ☐☐ Day ☐☐ Yr.

Site(s) of isolation: *(check all that apply)*
☐Blood ☐Stool ☐Gall Bladder ☐Other (specify): _____

Serotype:
☐Typhi ☐Paratyphi A ☐Paratyphi B ☐Paratyphi C

11. Was **antibiotic sensitivity testing** performed on this (these) isolate(s) at the laboratory? *(Please contact the clinical laboratory for this information)* ☐Yes ☐No ☐Unk.

If Yes, was the organism resistant to:

• Ampicillin:	☐Yes	☐No	☐Not tested
• Chloramphenicol:	☐Yes	☐No	☐Not tested
• Trimethoprim-sulfamethoxazole:	☐Yes	☐No	☐Not tested
• Fluoroquinolones (e.g., Ciprofloxacin):	☐Yes	☐No	☐Not tested

EPIDEMIOLOGIC DATA

12. Did this case occur as part of an outbreak? *(two or more cases of typhoid or paratyphoid fever associated by time and place)* ☐Yes ☐No ☐Unk.

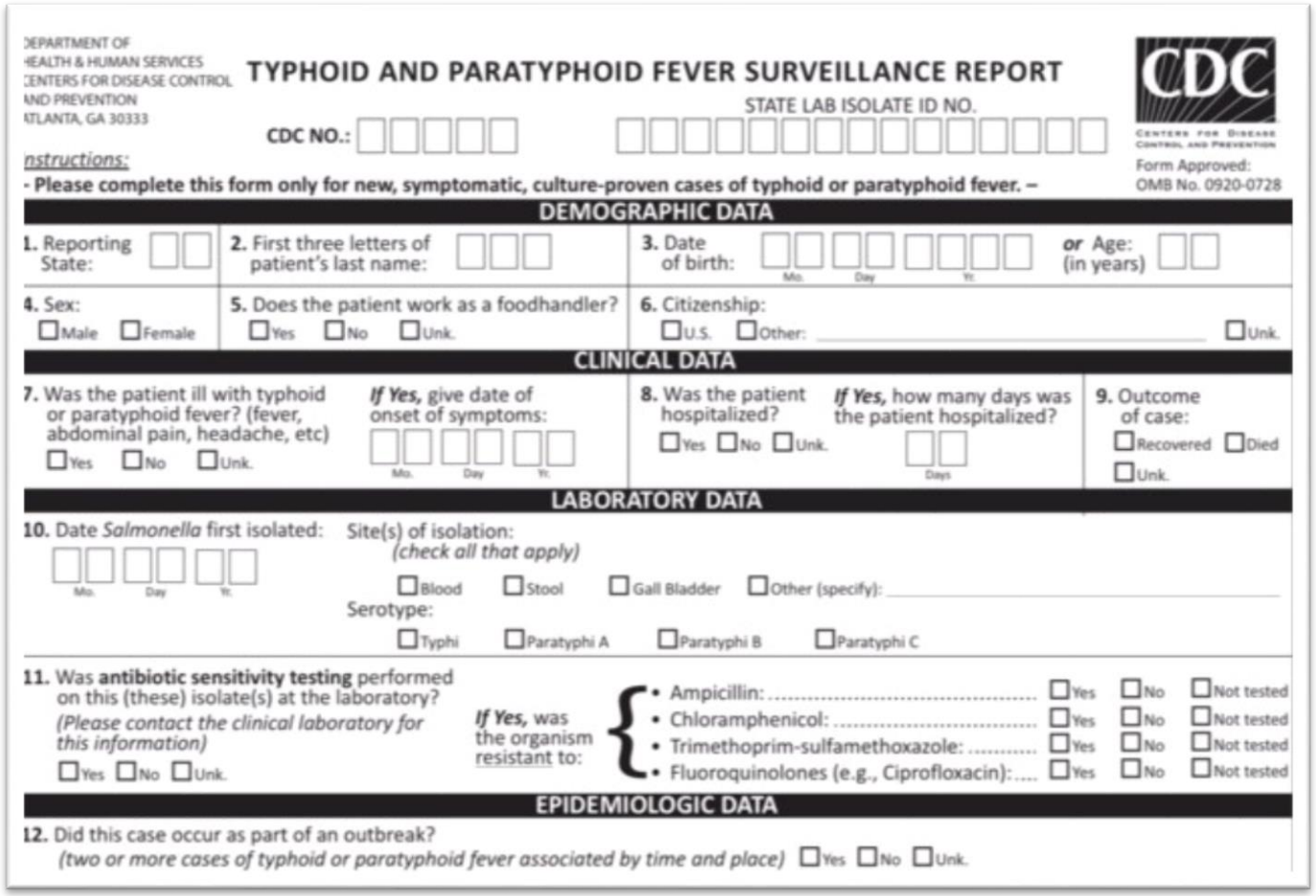
https://www.cdc.gov/nationalsurveillance/PDFs/typhi-surveillance-form.pdf

Typhoid surveillance (1975): state and local DOH send reports to CDC on lab-confirmed cases

NTPFS (2008): National Typhoid and Paratyphoid Surveillance System

Standard report form: *demographic, clinical, lab, and epidemiologic (vaccination status, and travel history) data*

NTPFS Case Definitions



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4. Sex: ☐Male ☐Female
5. Does the patient work as a foodhandler? ☐Yes ☐No ☐Unk.
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Site(s) of isolation: *(check all that apply)*
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If Yes, was the organism resistant to:
- Ampicillin: ☐Yes ☐No ☐Not tested
- Chloramphenicol: ☐Yes ☐No ☐Not tested
- Trimethoprim-sulfamethoxazole: ☐Yes ☐No ☐Not tested
- Fluoroquinolones (e.g., Ciprofloxacin): ☐Yes ☐No ☐Not tested

EPIDEMIOLOGIC DATA

12. Did this case occur as part of an outbreak? *(two or more cases of typhoid or paratyphoid fever associated by time and place)* ☐Yes ☐No ☐Unk.

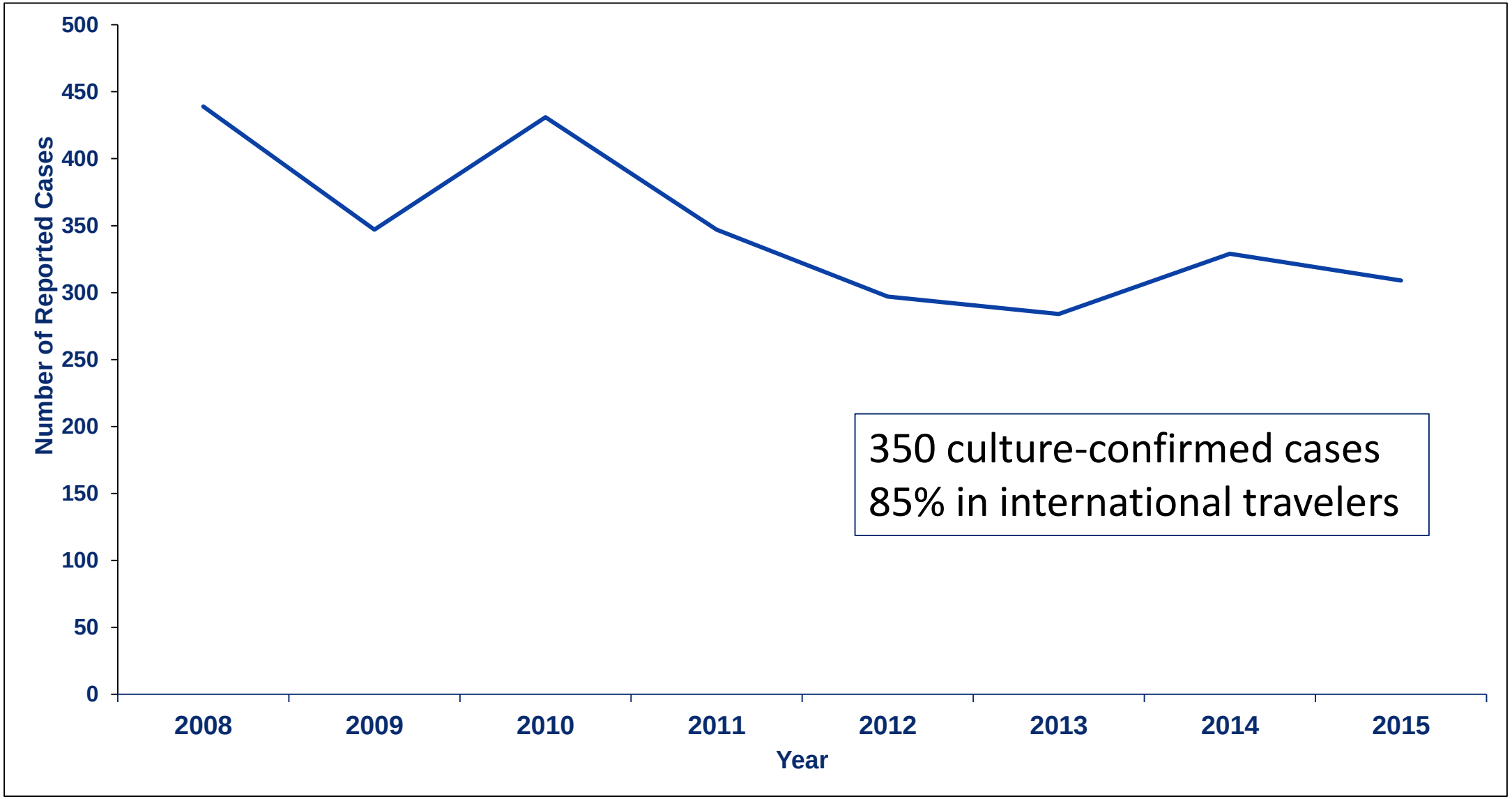
Typhoid case definition: compatible acute illness AND *Salmonella* serotype Typhi isolated from normally sterile site, or from stool or urine.

Travel-associated typhoid definition: travel outside U.S. in 30 days before illness onset

Domestically-acquired typhoid definition: no travel outside U.S. in 30 days before illness onset

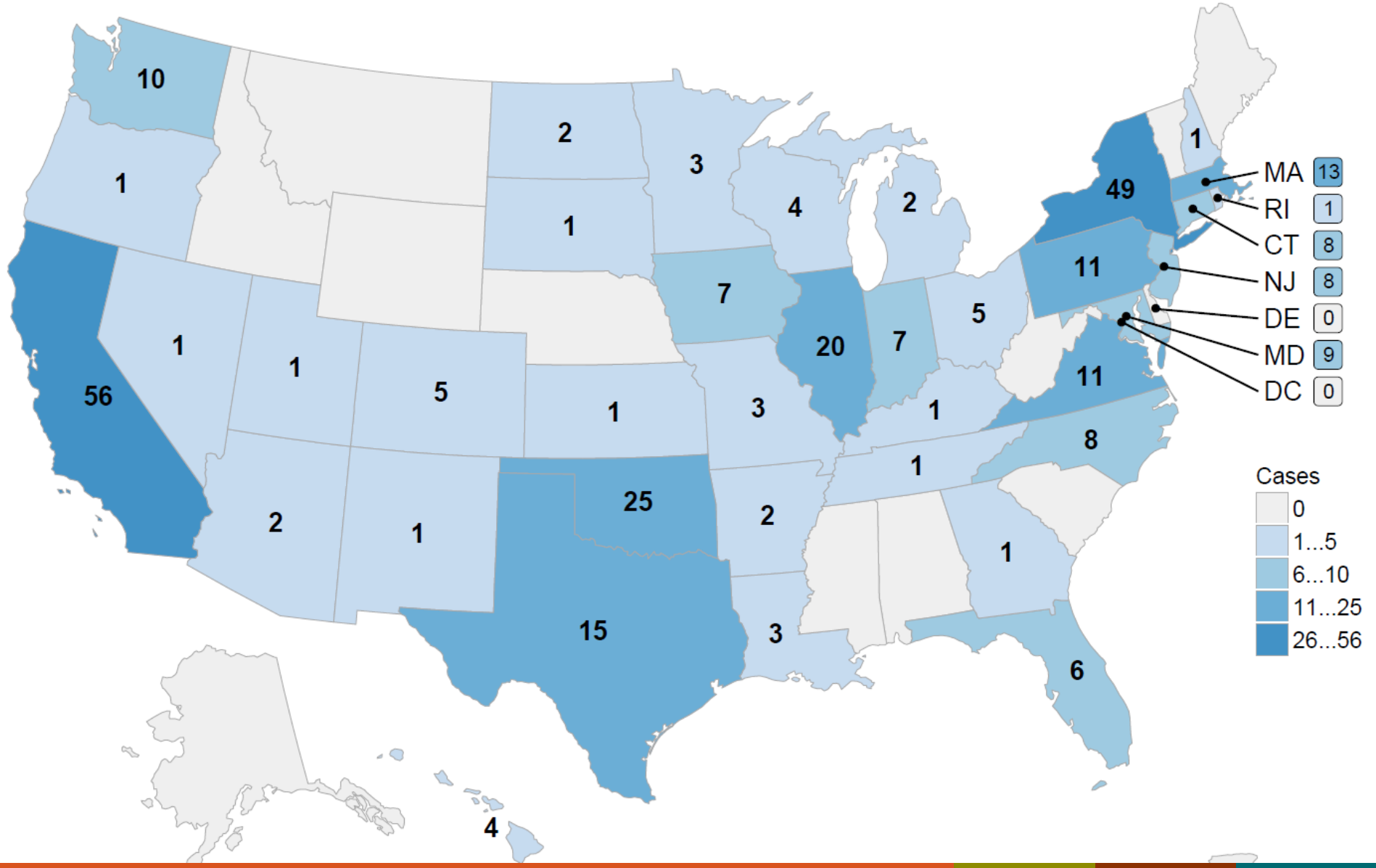
https://www.cdc.gov/nationalsurveillance/PDFs/typhi-surveillance-form.pdf

Number of reported typhoid cases, by year – United States, 2008-2015



Data from: https://www.cdc.gov/typhoid-fever/surveillance.html

Typhoid Cases by State, 2015 (n=309)



Characteristics of US Typhoid Cases, 2008-2012

Characteristic	Frequency
Total reported cases, no.	1872
Median age, y (range)	23 (0–93)
Female	883/1853 (48)
Vaccinated	61/1176 (5)
Travel-associated	1546/1799 (86)
Domestically acquired	253 (14)
Hospitalized	1420/1833 (77)
Died	6/1693 (<1)

Modified from: Date K, et al. CID. 2016; 63, 322–329

Single Country Visited by US Typhoid Fever Patients in 30 Days Before Illness, 2008-2012 (N= 1465)

Country	n (%)
India	894 (61)
Bangladesh	172 (12)
Pakistan	124 (8)
Mexico	46 (3)
Haiti	34 (2)
Philippines	19 (1)
Nigeria	19 (1)
Other	160 (11)

Modified from: Date K, et al. CID. 2016; 63, 322–329

Key Points about Typhoid Fever

- The first known outbreak of extensively drug-resistant (XDR) typhoid fever is occurring in Pakistan
- If you suspect that your patient has typhoid fever:
  - Obtain a complete travel history
  - Order blood and stool cultures, and request antimicrobial susceptibility testing
- Report all cases of confirmed typhoid fever to the appropriate local or state health departments

Management

Question #5

- Ceftriaxone is currently recommended for treatment of *Salmonella* Typhi infections in adults and children.
  - A) True
  - B) False

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  - **A) True**
  - B) False

Treatment Guidelines

- Infectious Diseases Society of America (2017)
  - Recommended: Ceftriaxone or ciprofloxacin
  - Alternative: Ampicillin, TMP-SMX, or azithromycin
- Red Book (2018)
  - Empiric: Azithromycin or ceftriaxone
  - Alternative: Ciprofloxacin, amoxicillin, or TMP-SMX
- World Health Organization (2018 fact sheet)
  - Resistance is making treatment more complicated
  - Newer antibiotics such as cephalosporins and azithromycin may be used in regions with fluoroquinolone resistance

TMP-SMX = trimethoprim-sulfamethoxazole

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TMP-SMX = trimethoprim-sulfamethoxazole

Antibiotic Considerations

- Efficacy
- Illness severity
- Cost and availability
- Side effects
- Antibiotic resistance

- Antibiotic options
  - Ampicillin
  - Azithromycin
  - Ceftriaxone
  - Chloramphenicol
  - Ciprofloxacin
  - Trimethoprim-sulfamethoxazole

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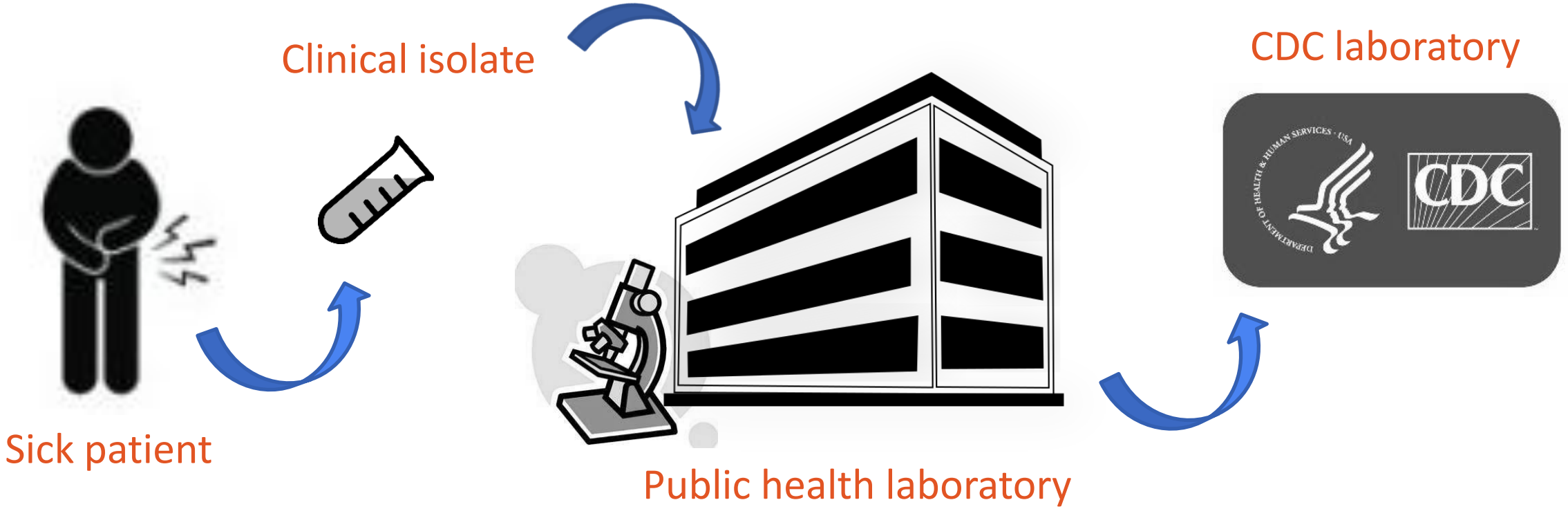
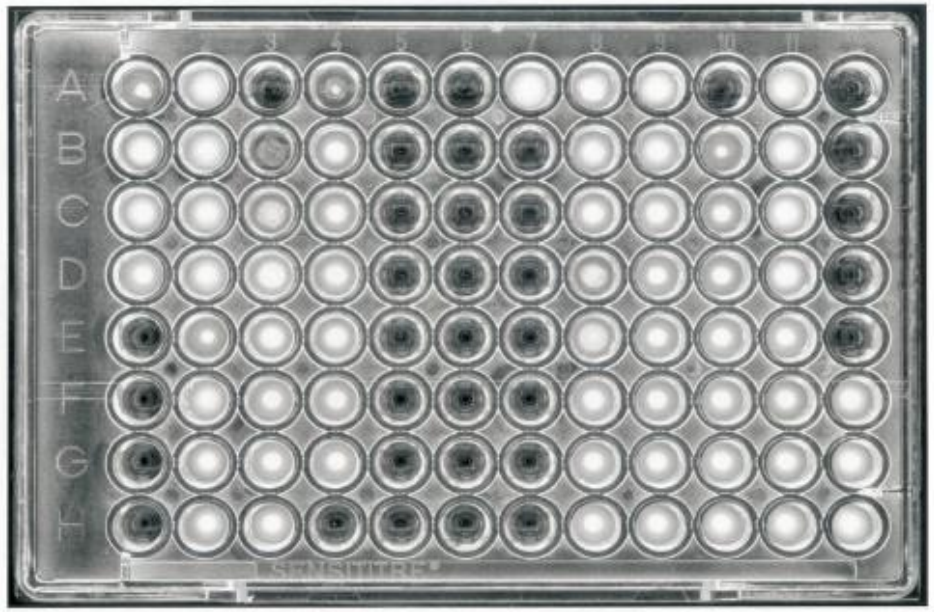
Surveillance for Antibiotic Resistance—United States



Surveillance for Antibiotic Resistance—United States

- National Antimicrobial Resistance Monitoring System (NARMS)
  - Conducts antimicrobial susceptibility testing (AST) by broth microdilution
  - Tests all *Salmonella* Typhi isolates submitted from U.S. public health laboratories
    - Typhi isolates tested since 1999



NARMS
National Antimicrobial Resistance Monitoring System

Antibiotic Resistance in *Salmonella* Typhi

- Based on NARMS surveillance data, 2015

Resistance <1%

- Azithromycin
- Ceftriaxone
- Meropenem

Resistance 10–12%

- Ampicillin
- Chloramphenicol
- Trimethoprim-sulfamethoxazole

Resistance >60%

- Ciprofloxacin*

* Resistance includes intermediate susceptibility

Fluoroquinolone Considerations

- Fluoroquinolones typically perform the best in susceptible strains
  - Shorter time to defervescence
  - Fewer side effects
  - Shorter duration of treatment without relapse
- Resistance to fluoroquinolones in returned travelers varies markedly by region[1]
  - India, Pakistan, Bangladesh: 81-93% Most U.S. travel-associated cases
  - Mexico and Central America: 12-15%
  - South America: < 10%
  - Africa: < 10%

[1]Date et al. Clin Infect Dis. 2016 August 01; 63(3): 322–329

Resistance Profile of XDR Typhi

- 9 U.S. isolates and 5 Pakistan isolates tested
  - All share XDR resistance profile
  - All have identical resistance mechanisms and carry the same IncY plasmid

Antibiotic	AST
Amoxicillin-clavulanic acid	I
Ampicillin	R
Azithromycin	S
Cefoxitin	S
Ceftriaxone	R
Chloramphenicol	R
Ciprofloxacin	R
Gentamicin	S
Meropenem	S
Nalidixic acid	R
Streptomycin	R
Sulfisoxazole	R
Tetracycline	S
Trimethoprim-sulfamethoxazole	R

AST = antimicrobial susceptibility testing
R = resistant; I = intermediate; S = susceptible

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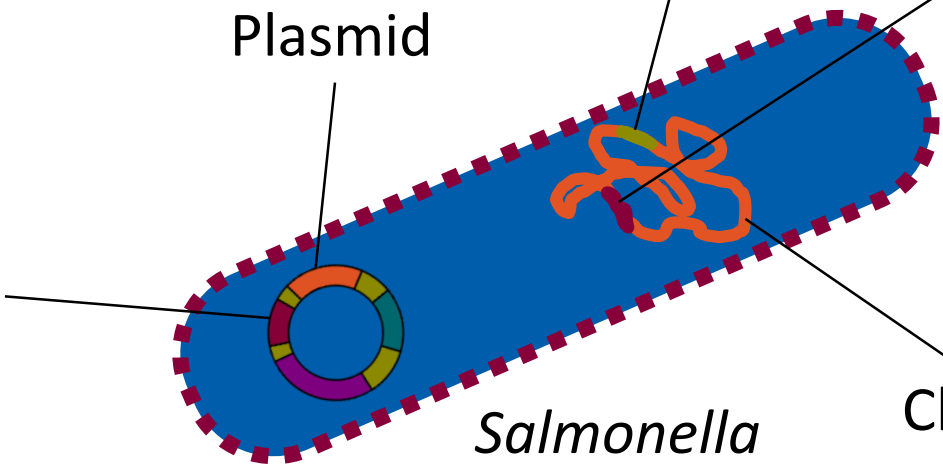
Mechanisms of Resistance in XDR *Salmonella* Typhi

- Chromosomal mutation
- Chromosomal resistance genes
- Plasmid-mediated resistance genes



Nalidixic acid
Ciprofloxacin

Resistance mutation

Resistance genes

Chloramphenicol
Streptomycin
Sulfisoxazole
Trimethoprim

IncY Plasmid

Ampicillin
Streptomycin
Sulfisoxazole
Ciprofloxacin
Ceftriaxone

Resistance genes

Salmonella Typhi

Chromosomal DNA

Based on data presented in Klemm et al. MBio. 2018 Feb 20;9(1).

Mechanisms of Resistance in XDR *Salmonella* Typhi

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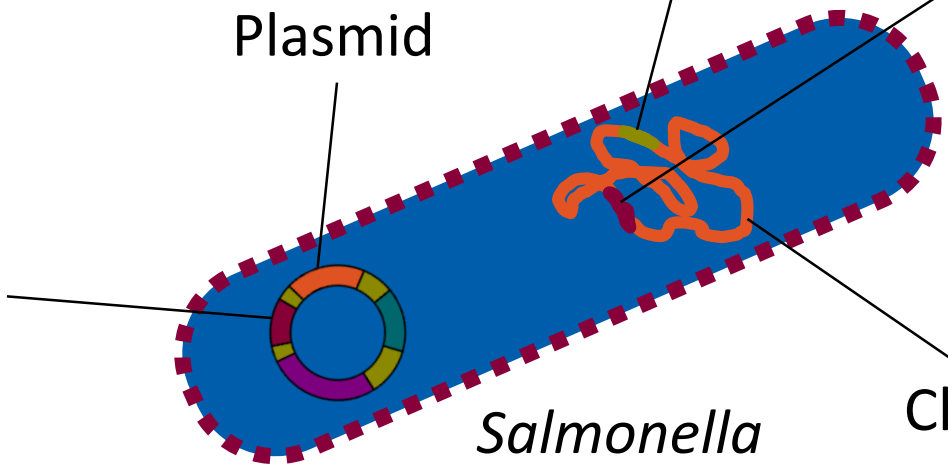


Nalidixic acid
Ciprofloxacin

Resistance mutation

Resistance genes

Chloramphenicol
Streptomycin
Sulfisoxazole
Trimethoprim

IncY Plasmid

Ampicillin
Streptomycin
Sulfisoxazole
Ciprofloxacin
Ceftriaxone

Resistance genes

Salmonella Typhi

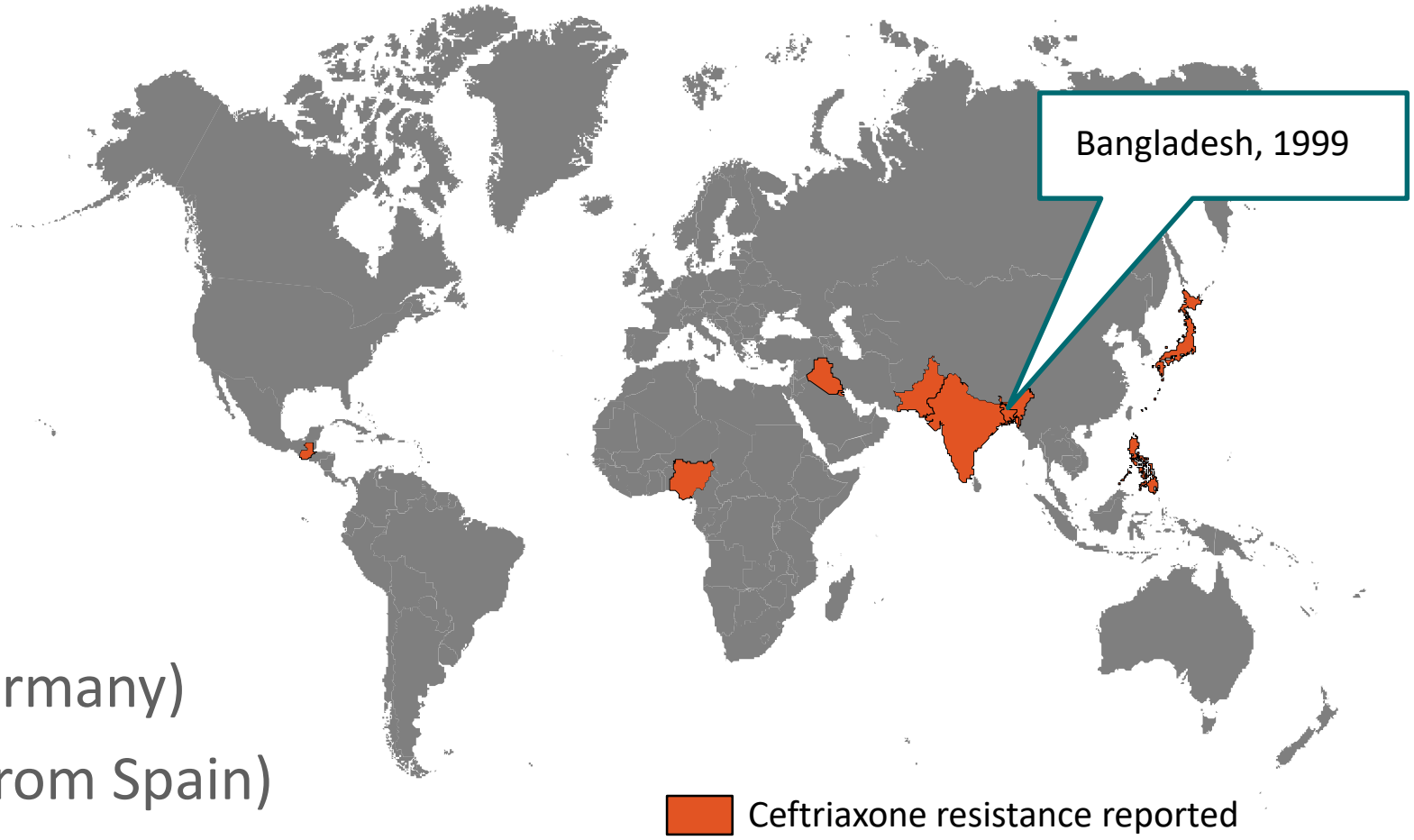
Chromosomal DNA

ESBL gene: *bla*CTX-M-15

Based on data presented in Klemm et al. MBio. 2018 Feb 20;9(1).

Global Ceftriaxone Resistance in *Salmonella* Typhi

- Sporadic cases reported from multiple countries before this outbreak
  - Bangladesh
  - India
  - Japan
  - Kuwait
  - Nigeria
  - Pakistan
  - Philippines
  - Iraq (traveler from Germany)
  - Guatemala (traveler from Spain)



CDC Traveler's Health Alert

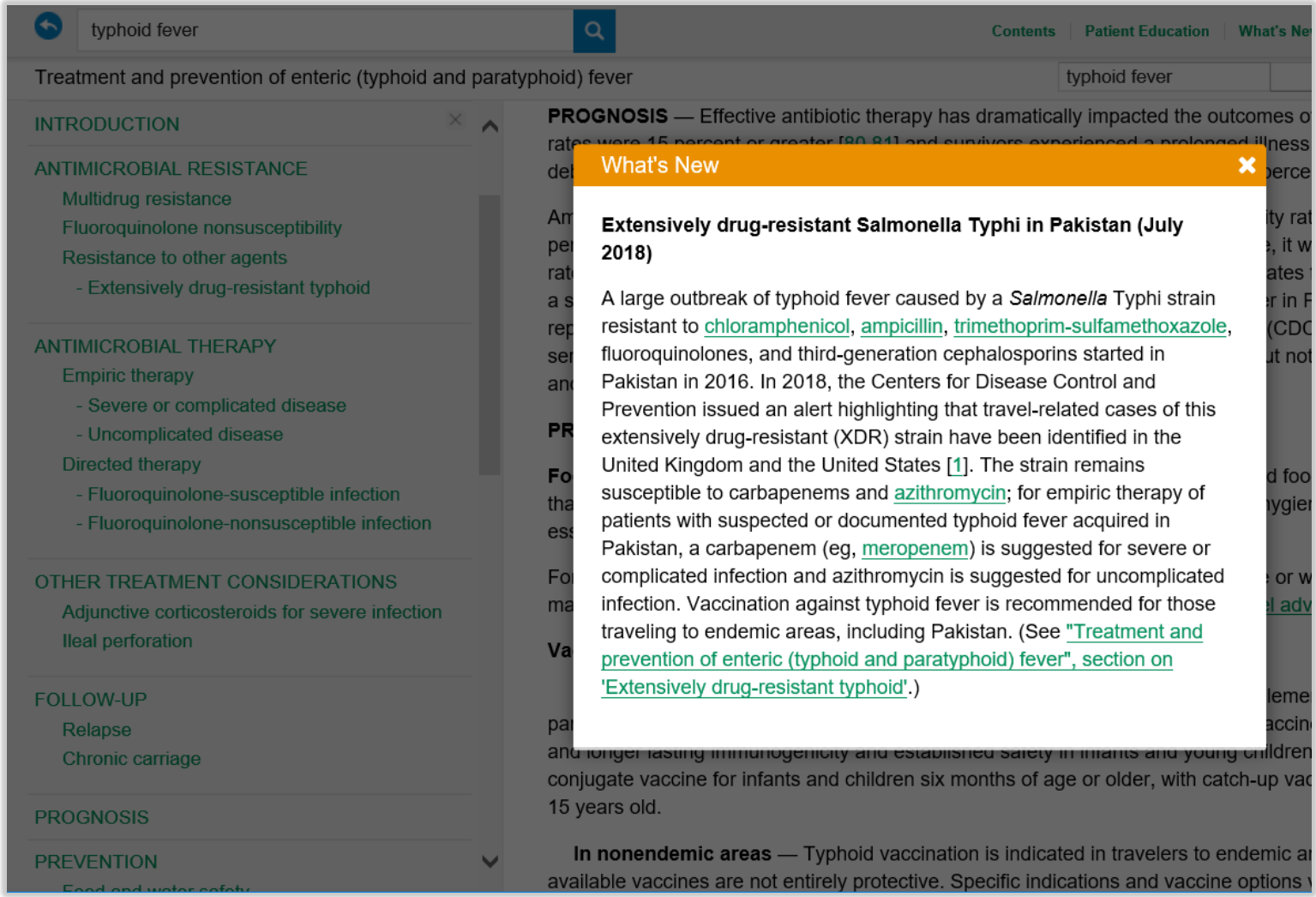
"Azithromycin is effective for uncomplicated typhoid fever (diarrhea or bacteremia without secondary complications)…"

"Carbapenems should be used for patients with suspected severe or complicated typhoid fever…"

- https://wwwnc.cdc.gov/travel/notices/alert/xdr-typhoid-fever-pakistan

Revised Clinical Guidance

- Up-to-Date has adopted recommendations from the CDC travel advisory



Evidence for Treatment with Azithromycin

- Multiple small clinical trials
  - Performs comparably to other antibiotics
    - **Ceftriaxone** (Frenck et al., 2000)
    - **Chloramphenicol** (Butler et al., 1999)
    - **Ciprofloxacin** (Girgis et al., 1999)
    - **Gatifloxacin** (Dolecek et al., 2008)
    - **Ofloxacin** (Chinh et al., 2000; Parry et al., 2007)
  - Short courses appear effective

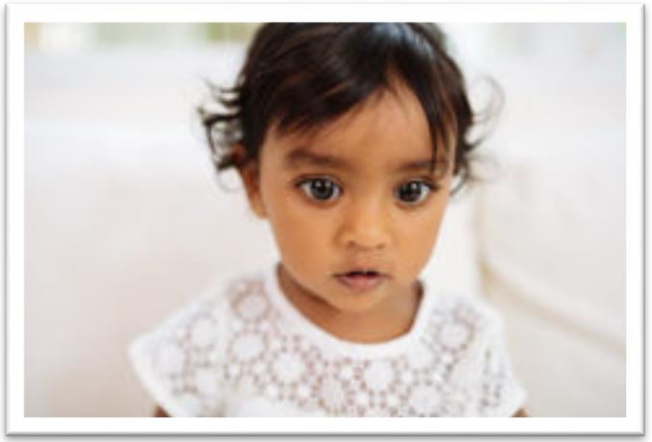
Evidence for Treatment with Meropenem

- No clinical trials
- Case reports of successful treatment
  - **Meropenem + aztreonam** (Yoon et al., 2009)
  - **Meropenem + fosfomycin** (Kleine et al., 2017)
  - **Meropenem alone** (Wong et al., 2019)

The first Canadian pediatric case of extensively drug-resistant *Salmonella* Typhi originating from an outbreak in Pakistan and its implication for empiric antimicrobial choices

Waison Wong[a], Hatem Al Rawahi[a], Samir Patel[b,c], Yvonne Yau[d], Alireza Eshaghi[b], Sandra Zittermann[b], Leah Tattum[e], Shaun K. Morris[a,f,g,*]

Pediatric Case: Blood Culture Results

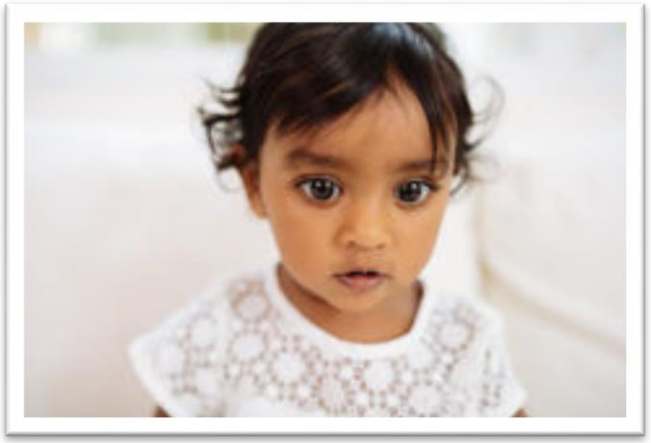


Antimicrobial Susceptibility Testing

Identification: *Salmonella* Typhi

Agent	Result	Interpretation
Ampicillin	≥32 µg/ml	Resistant
Ceftriaxone	>64 µg/ml	Resistant
Ertapenem	≤0.25 µg/ml	Susceptible
Azithromycin	≤16 µg/ml	Susceptible

Pediatric Case: Management



- Supportive care
- Azithromycin or meropenem as empiric treatment based on travel history
- Follow results of susceptibility testing
- Consider ID consult for XDR cases

Key Points about Management

- Most *Salmonella* Typhi infections in the U.S. are susceptible to azithromycin, ceftriaxone, and meropenem.
- Fluoroquinolones such as ciprofloxacin are effective in susceptible strains, but resistance is very high in travelers from South Asia
- Travel history is critical to the selection of optimal empiric treatment
  - Azithromycin or meropenem should be used in travelers coming from Pakistan

Prevention

Tips to Prevent Typhoid

Get yourself & your family vaccinated

Drink only boiled & filtered water

Avoid street food

Use sealed bottled mineral water while travelling

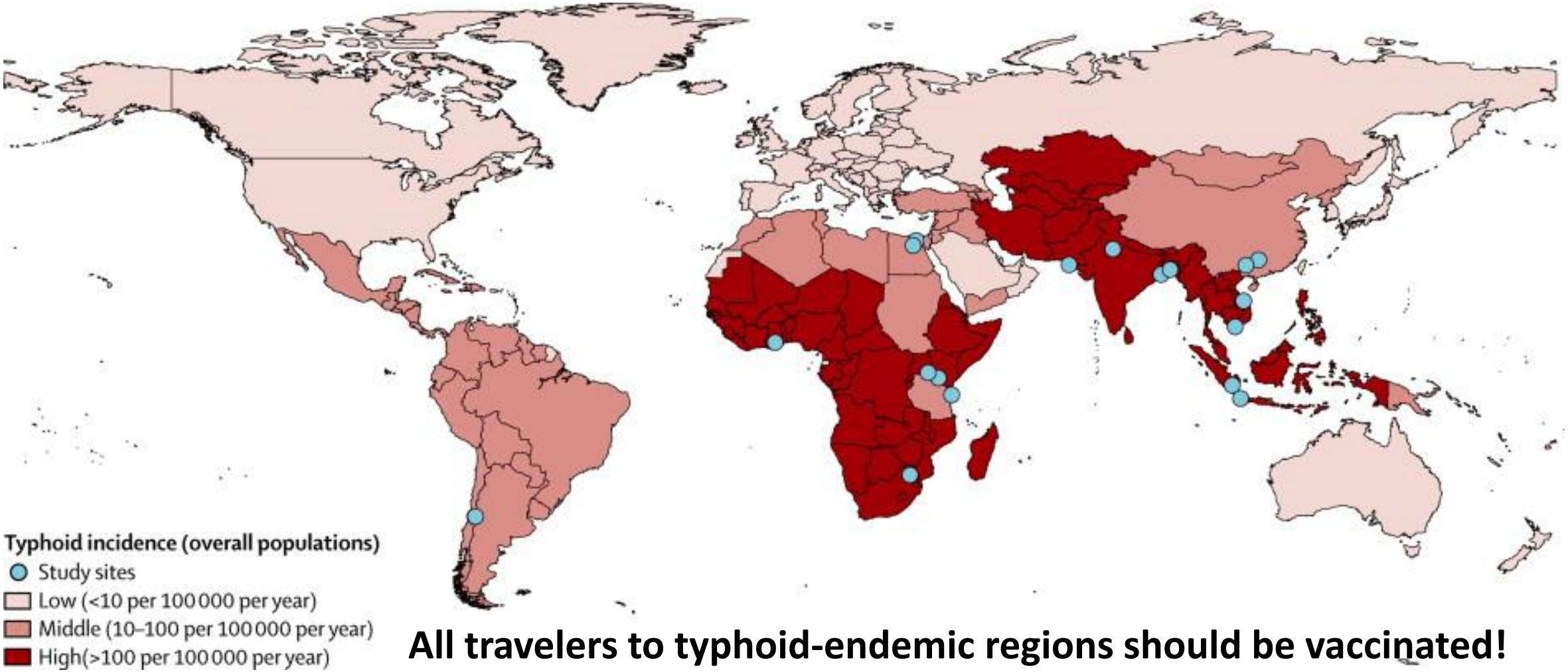
Peel & wash salads and fruits well

Practice good hand hygiene

Choose hot foods at restaurants

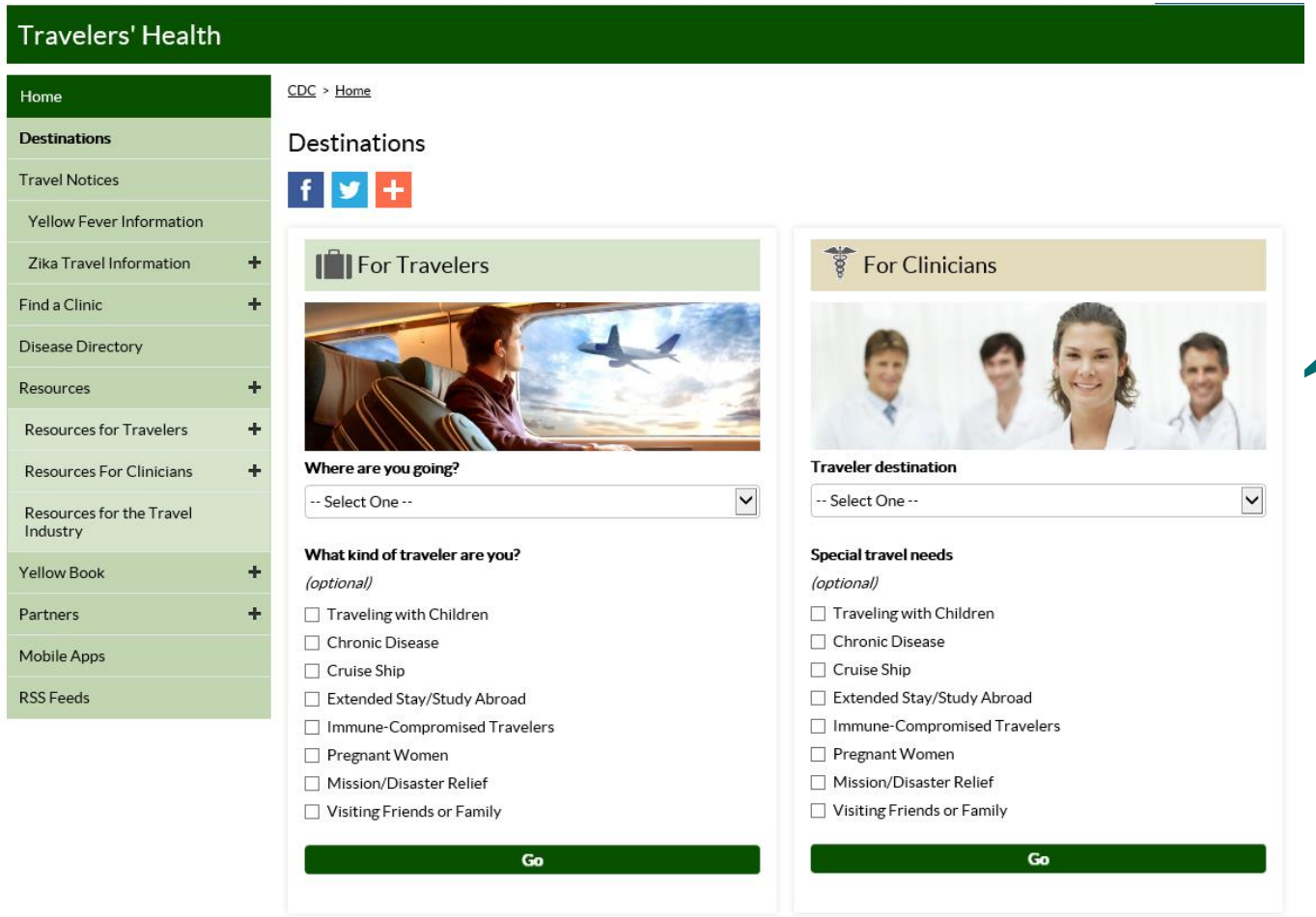
Avoid sharing spoons, forks with infected persons

Is your patient traveling?



All travelers to typhoid-endemic regions should be vaccinated!

CDC Traveler's Health page



Typhoid is common worldwide "**except** in industrialized regions such as the United States, Canada, western Europe, Australia, and Japan..."

- https://wwwnc.cdc.gov/travel/destinations/list

Question #6

- Which type of typhoid vaccines are licensed in the U.S.?
  - A) live-attenuated vaccine
  - B) conjugate vaccine
  - C) inactivated vaccine
  - D) toxoid vaccine
  - E) A and C

Question #6

- Which type of typhoid vaccines are licensed in the U.S.?

  A) **live-attenuated vaccine**

  B) conjugate vaccine

  C) **inactivated vaccine**

  D) toxoid vaccine

  E) A and C

Typhoid Vaccines in U.S.

Vaccine type	Vaccine name	How given	Number of doses	When taken	How long pre-travel	Minimum age	Booster needed
Live-attenuated	Ty21a (Vivotif)	Oral 	4	Every other day	1 week	6 years	Every 5 years
Inactivated	ViCPS (Typhim Vi)	Injection 	1	Once	2 weeks	2 years	Every 2 years

Typhoid Vaccines

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Inactivated	ViCPS (Typhim Vi)	Injection	1	Once	2 weeks	2 years	Every 2 years
Conjugate	**Typbar-TCV**	**Injection**	**1**	**Once**		**≥ 6 months**	

Key Points

- This outbreak is the first large-scale outbreak of typhoid fever with ceftriaxone resistance and has led to the first documented U.S. cases of ceftriaxone resistance
- Clinicians should be aware of this outbreak and should avoid ceftriaxone as a single-agent empiric treatment in patients returning from Pakistan
- The XDR *Salmonella* Typhi strain associated with this outbreak is susceptible to azithromycin and carbapenems
- US travelers to typhoid-endemic regions should receive pre-travel vaccination and follow safe food and water practices while abroad

Resources

- Alert: Extensively Drug-Resistant Typhoid Fever in Pakistan
- CDC's Typhoid Fever website
- CDC Yellow Book: Health Information for International Travel
- Food and Water Safety During Travel
- Medscape Commentary: Recognition and Management of Drug-Resistant Typhoid Fever
- Travelers' Health
- Typhoid Fever Vaccinations
- Typhoid Fever Vaccine Information Statements
- Typhoid Vaccine: Recommendations of the Advisory Committee on Immunization Practices (MMWR 2015)

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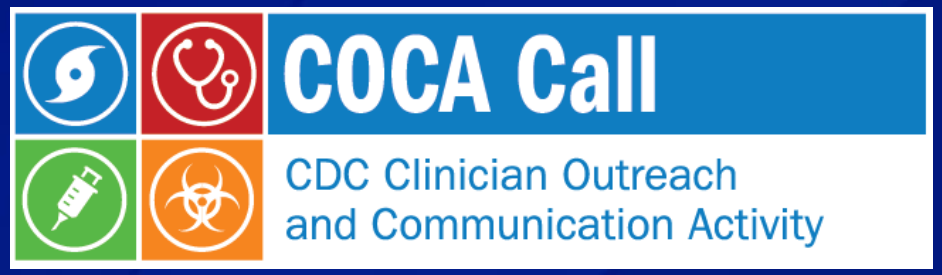

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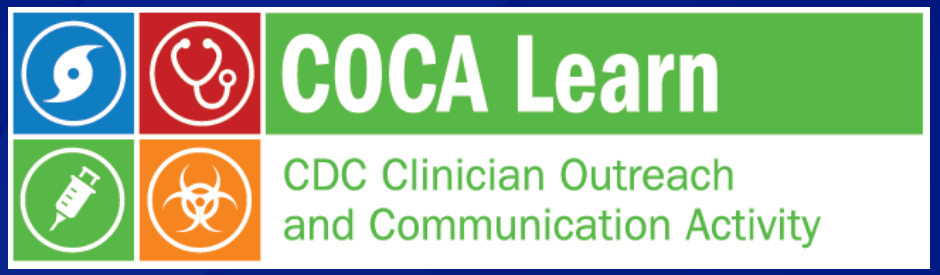

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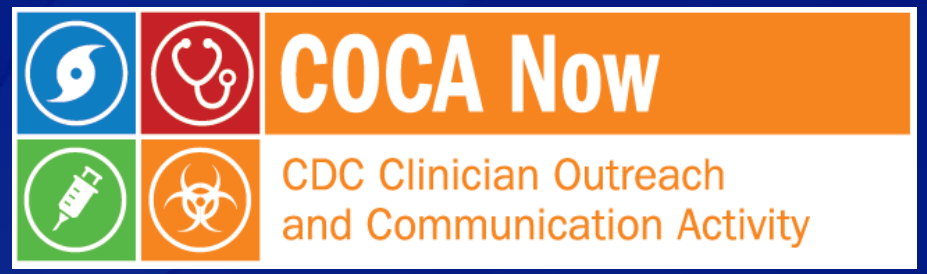

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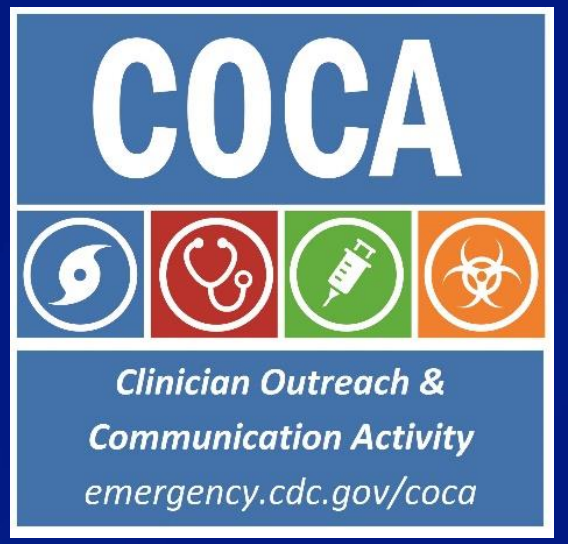

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