

FEBRUARY 16, 2021

HEALTH ADVISORY

This is an official
CDC HEALTH ADVISORY

Distributed via the CDC Health Alert Network
February 12, 2021, 1:00 PM ET
CDCHAN-00439

Extensively Drug-Resistant *Salmonella* Typhi Infections Among U.S. Residents Without International Travel

Summary

The Centers for Disease Control and Prevention (CDC) is providing—

- 1) Information on extensively drug-resistant (XDR) *Salmonella* Typhi (Typhi) infections among U.S. residents without international travel, and
- 2) Treatment recommendations for XDR Typhi infection.

Salmonella Typhi is a mandatory reportable condition to the North Dakota Department of Health (NDDoH) according to North Dakota Administrative Code 33-06-01, North Dakota Century Code 23-07-01. To report, call the NDDoH Division of Disease Control at 701-328-2378 or 800-472-2180. Questions about laboratory testing or specimen submission should be directed to the NDDoH Laboratory Services at 701-328-6272.

Background

Typhoid fever is a systemic illness caused by the bacterium *Salmonella enterica* serotype Typhi (Typhi). Most people in the United States diagnosed with typhoid fever acquired it during international travel, but some acquired it in the United States. The disease is treated with antibiotics; without appropriate antibiotic treatment, 12–30% of people with typhoid fever will die.

Typhi is transmitted through contaminated food and water and person-to-person contact. CDC recommends [vaccination](#) for people traveling to places where typhoid fever is common. Because typhoid fever vaccines are not 100% effective, travelers should always practice [safe eating and drinking habits](#) to help prevent infection.

In 2016, a large outbreak of extensively drug-resistant (XDR) Typhi infections began in Sindh province, Pakistan [1]. XDR Typhi strains are resistant to antibiotics generally recommended to treat typhoid fever, including ampicillin, ceftriaxone, chloramphenicol, ciprofloxacin, and trimethoprim-sulfamethoxazole.

Isolates from patients linked to the outbreak in Pakistan are susceptible to carbapenems and azithromycin. Infections among travelers to or from Pakistan have been reported globally, including in the United States.

As of January 14, 2021, CDC has received 71 reports of XDR Typhi infection in the United States, with specimens obtained from February 9, 2018, through November 16, 2020. Among 67 patients with known travel history, 58 (87%) had traveled to Pakistan in the 30 days before illness began ([Figure](#)).

Nine (13%) patients from six states (NY [3], CA [2], IL, MD, NJ, and TX) reported that they had not traveled to Pakistan or any other country. Specimens from these nine patients were obtained from November 7, 2019, through October 7, 2020, with eight obtained in 2020. Susceptibility testing of these specimens showed the same resistance pattern described in Pakistan. CDC has not identified linkages among these patients or a common source of infection.

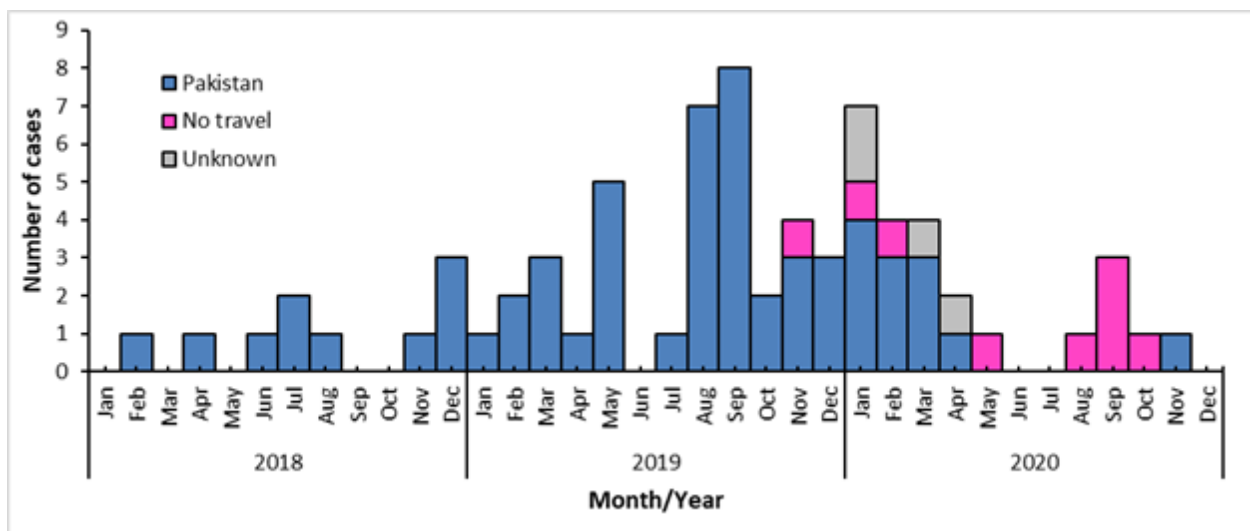
Case reporting of U.S. Typhi infections for 2020 is not yet complete. To date, 17 states have reported Typhi cases for 2020 compared with 39 states for 2019. Among 11 patients without international travel in 2020, eight patients were infected with XDR Typhi, one patient was infected with non-XDR Typhi, and susceptibility testing is pending for two others.

Before the outbreak in Pakistan, no case of ceftriaxone-resistant Typhi infection had been identified in the United States [2]. An unrelated cluster of ceftriaxone-resistant Typhi infections linked to Iraq has been reported in the United States and the United Kingdom [2].

Clinicians should consider empiric treatment with a carbapenem, azithromycin, or both agents for suspected typhoid fever in patients who did not travel out of the United States and for those who traveled to Pakistan or Iraq. Ceftriaxone remains an appropriate empiric treatment option for patients who traveled to countries other than Pakistan and Iraq. Clinicians should adjust treatment based on results of susceptibility testing.

This investigation is ongoing.

FIGURE. XDR TYPHI CASES BY MONTH OF FIRST POSITIVE CULTURE AND TRAVEL HISTORY — UNITED STATES, 2018–2020 (N = 71)



Recommendations for Clinicians

- Consider that typhoid fever symptoms and clinical presentation may resemble those of other febrile infectious diseases.
 - Symptoms of typhoid fever include fever, headache, constipation or diarrhea, malaise, chills, and myalgias.
 - Severe or complicated typhoid fever can include bacteremia with sepsis or shock, gastrointestinal complications (e.g., intestinal perforation, peritonitis, intestinal hemorrhage, hepatitis), and neurologic complications (e.g., encephalopathy).
- Obtain a 30-day international travel history from all patients with suspected or confirmed typhoid fever.
 - Although most Typhi infections are acquired during international travel, Typhi can be acquired in the United States.
- Order blood cultures if typhoid fever is suspected; multiple cultures are usually needed.
 - Bone marrow cultures have the highest sensitivity and may be considered for some patients, such as those who have already started or completed a course of antimicrobial treatment.
 - Stool, urine, and duodenal cultures may also be helpful.
- Order antimicrobial susceptibility testing for Typhi isolates and adjust treatment accordingly.
- Consider the following in the selection of **empiric treatment** for patients with typhoid fever while awaiting susceptibility testing results and when the patient is not linked to a culture-confirmed case of typhoid fever with a known antimicrobial resistance profile.
 - *U.S. patients who did not travel outside the United States in the 30 days before illness began:* Patients might be infected with XDR Typhi. Consider prescribing a carbapenem (particularly if patients have severe or complicated illness) or azithromycin for empiric treatment.
 - *U.S. patients who traveled to Pakistan in the 30 days before illness began:* Most patients are infected with XDR Typhi [2]. Prescribe a carbapenem (particularly if patients have severe or complicated illness) or azithromycin for empiric treatment.
 - *U.S. patients who traveled to Iraq in the 30 days before illness began:* Most patients have strains that are resistant or have reduced susceptibility to ciprofloxacin; some strains are also resistant to ampicillin and ceftriaxone [2]. Consider prescribing a carbapenem (particularly if patients have severe or complicated illness) or azithromycin for empiric treatment.
 - *U.S. patients who traveled to countries other than Pakistan and Iraq in the 30 days before illness began:* Most patients have strains that are susceptible to ceftriaxone [2], which remains an appropriate empiric treatment option.
- Consider that resistance to meropenem (a carbapenem) or azithromycin has not been documented in Typhi isolated in the United States during the past five years.
 - About 80% of Typhi strains isolated in the United States now are resistant or have decreased susceptibility to ciprofloxacin [3].
- Treat patients with XDR Typhi infection with a carbapenem, azithromycin, or both.
 - Treat patients with severe or complicated illness with a carbapenem, such as meropenem. Case reports have suggested that patients who do not improve on a carbapenem alone may benefit from the addition of a second antibiotic, such as azithromycin [4–7].
 - Patients with uncomplicated illness may be treated with oral azithromycin alone.
- Vaccinate patients who are at high risk for typhoid fever, including those traveling to parts of the world where typhoid fever is common, those in close contact with a typhoid carrier, and those who might work with Typhi in a laboratory.

- Counsel travelers about safe eating and drinking practices and advise them that vaccination is not 100% effective. People can become infected with Typhi through contaminated food and water and through person-to-person contact.
- Follow local health department requirements for reporting typhoid fever, which is a nationally notifiable illness. Because of the risk of asymptomatic carriage after recovery, many health departments recommend follow-up testing to ensure microbiological cure before people in high-risk occupations, such as food handlers, daycare workers, and healthcare workers, return to work.

For More Information

- [More typhoid fever information for healthcare professionals](#)
- [Travel notice about XDR typhoid fever in Pakistan](#)
- [Information about typhoid vaccination](#)
- [Food and water safety tips for international travelers](#)

References

1. Klemm EJ, Shakoor S, Page AJ, et al. [Emergence of an Extensively Drug-Resistant *Salmonella enterica* Serovar Typhi Clone Harboring a Promiscuous Plasmid Encoding Resistance to Fluoroquinolones and Third-Generation Cephalosporins](#). mBio. 2018 Feb 20; 9(1): e00105–18. doi: 10.1128/mBio.00105-18. PMID: 29463654.
2. François Watkins LK, Winstead A, Appiah GD, et al. [Update on Extensively Drug-Resistant *Salmonella* Serotype Typhi Infections Among Travelers to or from Pakistan and Report of Ceftriaxone-Resistant *Salmonella* Serotype Typhi Infections Among Travelers to Iraq - United States, 2018–2019](#). MMWR Morb Mortal Wkly Rep. 2020 May 22; 69(20): 618–622. doi: 10.15585/mmwr.mm6920a2. PMID: 32437343.
3. CDC. [National Antimicrobial Resistance Monitoring System \(NARMS\) Now: Human Data](#). Atlanta, Georgia: U.S. Department of Health and Human Services, CDC. 12/14/2020. <https://www.cdc.gov/narmsnow>. Accessed 12/15/2020.
4. Petrin CE, Steele RW, Margolis EA, et al. [Drug-Resistant *Salmonella typhi* in Pakistan](#). Clin Pediatr (Phila). 2020 Jan;59(1):31–33. doi: 10.1177/0009922819881203. Epub 2019 Oct 11. PMID: 31603009.
5. Liu PY, Wang KC, Hong YP, et al. [The first imported case of extensively drug-resistant *Salmonella enterica* serotype Typhi infection in Taiwan and the antimicrobial therapy](#). J Microbiol Immunol Infect. 2020 Mar 25; S1684-1182(20)30077-3. doi: 10.1016/j.jmii.2020.03.017. Epub ahead of print. PMID: 32253142.
6. Godbole GS, Day MR, Murthy S, et al. [First Report of CTX-M-15 *Salmonella Typhi* From England](#). Clin Infect Dis. 2018 Jun 1; 66(12): 1976–77. doi: 10.1093/cid/ciy032. PMID: 29471386.
7. López-Segura N, Corberó-Rivali C, Maldonado-Fernández MC, et al. [Imported extensively drug resistant typhoid fever in a child travelling to Spain from Pakistan](#). J Travel Med. 2019 Dec 23; 26(8): taz066. doi: 10.1093/jtm/taz066. PMID: 31504718.

The Centers for Disease Control and Prevention (CDC) protects people's health and safety by preventing and controlling diseases and injuries; enhances health decisions by providing credible information on critical health issues; and promotes healthy living through strong partnerships with local, national, and international organizations.

Categories of Health Alert Network messages:

- Health Alert** Requires immediate action or attention, highest level of importance
Health Advisory May not require immediate action; provides important information for a specific incident or situation

Health Update Unlikely to require immediate action; provides updated information regarding an incident or situation
HAN Info Service Does not require immediate action; provides general public health information

Categories of Health Alert Network messages:

Health Alert Requires immediate action or attention; highest level of importance

Health Advisory May not require immediate action; provides important information for a specific incident or situation

Health Update Unlikely to require immediate action; provides updated information regarding an incident or situation

HAN Info Service Does not require immediate action; provides general public health information