States include the SFG pathogens, *Rickettsia africae* (African tick-bite fever), *R. conorii* (Mediterranean spotted fever), *R. rickettsii* (Rocky Mountain spotted fever [RMSF], also known as Brazilian spotted fever); *R. typhi* (murine typhus); *Orientia tsutsugamushi* (scrub typhus); and *Anaplasma phagocytophilum* (anaplasmosis). Many other rickettsial agents cause human infections across the globe, but the true burden remains undetermined.

TRANSMISSION

Most rickettsial pathogens are transmitted directly to humans by infected arthropod vectors (i.e., fleas, lice, mites, or ticks) during feeding. Rickettsia also might be transmitted when a person inadvertently inoculates the arthropod bite wound (or other breaks in the skin) with rickettsial pathogens; this can happen by scratching skin contaminated with an arthropod's infectious fluids or feces, or by crushing the arthropod vector at the bite site. Inhaling bacteria or inoculating conjunctiva with infectious material also can initiate infection for some rickettsial pathogens.

Vectors that transmit each rickettsial species are listed in Table 5-04; some details are discussed here. Transmission of a few pathogens, particularly *Anaplasma* and *Ehrlichia* spp., through transfusion of infected blood products or by organ transplantation, is less common.

EPIDEMIOLOGY

Regardless of the length of travel (short- or long-term), all age groups are at risk for rickettsial infections during visits to endemic areas. Transmission risk increases with time spent participating in outdoor activities, particularly during seasons of peak feeding and lifecycle activity for the vector. In many parts of the world, however, rickettsial infections occur year-round. The most diagnosed rickettsial diseases in travelers are in the spotted fever or typhus groups; notably, rickettsial infections can also be caused by emerging and newly recognized species.

Spotted Fever Group

Tickborne spotted fever rickettsioses are the most frequently reported travel-associated rickettsial infections.

AFRICAN TICK-BITE FEVER

Travelers who go on safari—especially those traveling to national parks, game hunters, and ecotourists to sub-Saharan Africa—are at risk for African tick-bite fever caused by *R. africae*. *R. africae* is also endemic to several islands of the Caribbean West Indies, and imported cases have been described from this region.

R. africae remains the most frequently reported rickettsial infection acquired during travel. Commonly, cases of African tick-bite fever cluster among people traveling together, and diagnosis of the disease in 1 member of a family or tourist group can alert other similarly exposed people to seek care if they develop compatible signs and symptoms.

CAT FLEA RICKETTSIOSIS

R. felis, the cause of cat flea rickettsiosis, has been identified in various invertebrate hosts worldwide and has been reported as a major cause of febrile illness in some countries of Africa.

MEDITERRANEAN SPOTTED FEVER

Travel-associated cases of Mediterranean spotted fever (also known as Boutonneuse fever), caused by *R. conorii*, are less commonly reported but occur over a large geographic area, including but not limited to Africa, much of Europe, India, and the Middle East.

RICKETTSIALPOX

The causative agent of rickettsialpox, *R. akari*, is transmitted by house mouse mites, and circulates mainly in urban centers in the Balkan states, Korea, South Africa, Ukraine, and the United States. Outbreaks of rickettsialpox most often occur after contact with infected peridomestic rodents and their mites, especially during natural die-offs or exterminations of infected rodents that cause the mites to seek out new hosts, including humans. Urban rodents seem more often associated with human cases, but the agent has been identified in a few wild rodent populations.

ROCKY MOUNTAIN SPOTTED FEVER OR BRAZILIAN SPOTTED FEVER

RMSF (also known as Brazilian spotted fever and other local names) is caused by *R. rickettsii*. It occurs

Table 5-04 Rickettsial diseases in humans[1]

SPOTTED FEVER GROUP				
DISEASE	**RICKETTSIAL SPECIES**	**GEOGRAPHIC DISTRIBUTION**	**ANIMAL HOST(S)**	**VECTORS**
African tick-bite fever	*Rickettsia africae*	Sub-Saharan Africa; West Indies	Domestic and wild ruminants	Ticks
Aneruptive fever	*R. helvetica*	Asia; central and northern Europe	Rodents	Ticks
Astrakhan spotted fever	*R. conorii*, subsp. *caspiae* (proposed)	North Caspian region of Russia		Ticks
Cat flea rickettsiosis	*R. felis*	Africa; North and South America; Asia; Europe	Domestic cats, opossums, rodents	Fleas
Far Eastern spotted fever	*R. heilongjiangensis*	East Asia; northern China; far east Russia	Rodents	Ticks
Flinders Island spotted fever Thai tick typhus	*R. honei*, including strain "marmionii"	Australia; Thailand	Reptiles, rodents	Ticks
Indian tick typhus	*R. conorii*, subsp. *indica* (proposed)	South Asia		Ticks
Israeli tick typhus	*R. conorii*, subsp. *israelensis* (proposed)	Southern Europe; Middle East		Ticks
Japanese spotted fever	*R. japonica*	Japan	Rodents	Ticks
Lymphangitis-associated rickettsiosis	*R. sibirica mongolotimonae*	Africa; Asia (China); Europe (southern France, Portugal)	Rodents	Ticks
Maculatum infection	*R. parkeri*	North and South America	Rodents	Ticks
Mediterranean spotted fever (Boutonneuse fever)	*R. conorii*, subsp. *conorii* (proposed)	Africa; southern Europe; southern and western Asia (India)	Dogs, rodents	Ticks
Mediterranean spotted fever–like illness	*R. massiliae*	Central Africa (Mali); North America (USA); Europe (France, Greece, Portugal, Sicily, Spain, Switzerland)	Unknown (maybe dogs)	Ticks

(*continued*)

Table 5-04 Rickettsial diseases in humans (continued)

Mediterranean spotted fever–like illness	*R. monacensis*	North Africa; Europe	Lizards, possibly birds	Ticks
North Asian tick typhus Siberian tick typhus	*R. sibirica*	China; Mongolia; Russia	Rodents	Ticks
Queensland tick typhus	*R. australis*	Australia; Tasmania	Rodents	Ticks
Rickettsialpox	*R. akari*	Africa (South Africa); North and South America; Asia (Korea); southern and eastern Europe (Balkans, Turkey, Ukraine and former Soviet Union)	House mice, wild rodents	Mites
Rickettsiosis	*R. aeschlimannii*	South Africa; Morocco; Mediterranean littoral	Unknown	Ticks
Rocky Mountain spotted fever (RMSF; also known as Brazilian spotted fever; febre maculosa; São Paulo exanthematic typhus; Minas Gerais exanthematic typhus)	*R. rickettsii*	North, Central, and South America	Rodents	Ticks
Tickborne lymphadenopathy (TIBOLA) *Dermacentor*-borne necrosis and lymphadenopathy (DEBONEL)	*R. raoultii*	Asia; Europe	Unknown	Ticks
Tickborne lymphadenopathy (TIBOLA) *Dermacentor*-borne necrosis and lymphadenopathy (DEBONEL)	*R. slovaca*	Asia; southern and eastern Europe; recently found in a US tick colony (origin unknown)	European boar, lagomorphs, rodents	Ticks
TYPHUS GROUP				
DISEASE	**RICKETTSIAL SPECIES**	**GEOGRAPHIC DISTRIBUTION**	**ANIMAL HOST(S)**	**VECTORS**
Epidemic typhus Sylvatic typhus	*Rickettsia prowazekii*	Central Africa; North, Central and South America; Asia	Humans Flying squirrels	Human body louse Flying squirrel ectoparasites

Table 5-04 Rickettsial diseases in humans (continued)

Murine typhus	*R. typhi*	Temperate, tropical, and subtropical areas worldwide	Rodents	Fleas
SCRUB TYPHUS GROUP				
DISEASE	**RICKETTSIAL SPECIES**	**GEOGRAPHIC DISTRIBUTION**	**ANIMAL HOST(S)**	**VECTORS**
Scrub typhus	*Orientia tsutsugamushi*	Asia-Pacific region (north Australia, China, Indonesia, maritime Russia); Middle East (Afghanistan); possibly several countries in sub-Saharan Africa	Rodents	Trombiculid mites and chiggers
	O. chuto	United Arab Emirates (UAE)		
	O. chiloensis	Southern Chile		
ANAPLASMA GROUP				
DISEASE	**RICKETTSIAL SPECIES**	**GEOGRAPHIC DISTRIBUTION**	**ANIMAL HOST(S)**	**VECTORS**
Human anaplasmosis	*Anaplasma bovis*	USA	Unknown	Ticks
	A. capra	China	Goats, sheep	Ticks
	A. ovis	China; Cyprus; Greece	Sheep	Ticks
	A. phagocytophilum	Worldwide (primarily USA)	Deer, small mammals, rodents	Ticks
	A. platys	Argentina	Dogs	Ticks
EHRLICHIA GROUP				
DISEASE	**RICKETTSIAL SPECIES**	**GEOGRAPHIC DISTRIBUTION**	**ANIMAL HOST(S)**	**VECTORS**
Human ehrlichiosis	*Ehrlichia chaffeensis*	USA and possibly elsewhere worldwide	Deer; domestic and wild dogs; domestic ruminants; rodents	Ticks
	E. ewingii			

(*continued*)

Table 5-04 Rickettsial diseases in humans (continued)

	E. muris eauclairensis			
	E. muris muris			
	E. canis	Worldwide Human cases in Costa Rica, Venezuela	Dogs	Ticks
	E. ruminantium	South Africa	Domestic and wild ruminants	Ticks
NEOEHRLICHIA GROUP				
DISEASE	**RICKETTSIAL SPECIES**	**GEOGRAPHIC DISTRIBUTION**	**ANIMAL HOST(S)**	**VECTORS**
Human neoehrlichiosis	*Neoehrlichia mikurensis*	Asia; Europe	Rodents	Ticks
NEORICKETTSIA GROUP				
DISEASE	**RICKETTSIAL SPECIES**	**GEOGRAPHIC DISTRIBUTION**	**ANIMAL HOST(S)**	**VECTORS**
Sennetsu fever	*Neorickettsia sennetsu*	Japan; Malaysia; possibly other parts of Asia	Fish	Trematodes

[1]Highlighted rows indicate diseases described in more detail in the text.

throughout much of the Western Hemisphere, and cases are reported from Canada, Mexico, the United States, and many countries of Central and South America, including Argentina, Brazil, Colombia, Costa Rica, and Panama. Clusters of illness might be reported in families or in geographic areas. Contact with dogs in rural and urban settings, and outdoor activities (e.g., camping, fishing, hiking, hunting) increase the risk for infection.

Typhus Group

EPIDEMIC TYPHUS

Louseborne or epidemic typhus, caused by *R. prowazekii*, is rarely reported among tourists; more commonly, it occurs among people living in crowded conditions where body lice are prevalent (e.g., refugees housed in camps, incarcerated populations). Outbreaks often happen during the colder months. Travelers at greatest risk for epidemic typhus include people who provide medical or humanitarian aid to people living in refugee camps and those who visit impoverished areas affected by war, famine, or natural disasters. Active foci of epidemic typhus are in the Andes region of South America and some parts of Africa, including but not limited to Burundi, Ethiopia, and Rwanda.

Classical louseborne typhus has not occurred in the United States for approximately the past century; however, a zoonotic reservoir exists in the southern flying squirrel, and sporadic sylvatic

epidemic typhus cases are reported when these animals invade people's homes or cabins.

MURINE TYPHUS

Murine typhus, caused by *R. typhi*, is distributed worldwide, particularly in and around port cities and coastal regions with large rodent populations. People are at risk for fleaborne rickettsioses when traveling in endemic regions and when they are exposed to flea-infested cats, dogs, and peridomestic animals, or enter or sleep in areas infested with rodents. Murine typhus has been reported among travelers returning from Africa, Asia, and the Mediterranean Basin. Most cases acquired in the United States are reported from California, Hawaii, and Texas.

Scrub Typhus Group

Scrub typhus can be transmitted by many species of trombiculid mites that live in high grass and brush. Scrub typhus is endemic to regions of east Asia (China, northern Japan), Southeast Asia (India, Indonesia, Sri Lanka), the Pacific (eastern Australia), and several parts of south-central Russia. Cases of disease also have been described from several unexpected regions, including the United Arab Emirates and southern Chile, and appear to be caused by newly recognized species of *Orientia*.

More people worldwide are at risk for scrub typhus than for any other rickettsial disease; >1 million cases occur annually, mostly in farmers or people with occupational exposure. Travel-acquired cases of scrub typhus occasionally are reported among people who visit rural regions of countries where *O. tsutsugamushi* is endemic, and exposure is often associated with participating in recreational activities (e.g., camping, hiking, rafting). Rare urban cases have been described.

Anaplasmosmis & Ehrlichiosis

Although anaplasmosis (caused predominately by *A. phagocytophilum*) and ehrlichiosis (caused predominately by *E. chaffeensis*, *E. ewingii*, and *E. muris euclairensis*) are tickborne infections commonly reported in the United States, pathogenic species can be found in many regions of the world. Infections with these and other *Anaplasma* and *Ehrlichia* spp. have been reported in Africa, South America, Asia, and Europe, and occasionally among travelers.

Neoehrlichia & Neorickettsia

Neoehrlichia mikurensis is a tickborne pathogen that occurs in many parts of Asia and Europe. It generally infects people who are older or who are immunocompromised. Sennetsu fever, caused by *N. sennetsu*, occurs in Japan, Malaysia, and parts of Southeast Asia. This disease can be contracted from eating raw fish infested with neorickettsiae-infected flukes.

CLINICAL PRESENTATION

Rickettsial diseases are difficult to diagnose, even by health care providers experienced with these diseases. The incubation period for most rickettsial diseases ranges from 5–10 days. Travelers can experience signs and symptoms during their trip or not until 1–2 weeks after returning home.

Most symptomatic rickettsial diseases cause moderate illness, but others, including RMSF (also called Brazilian spotted fever), epidemic typhus, scrub typhus, and Mediterranean spotted fever, can be life-threatening in some cases, particularly when treatment is delayed. Clinical presentations vary with the causative agent and patient. Common symptoms that typically develop within 1 week of infection include fever, headache, malaise, nausea, or vomiting. Many rickettsioses also are accompanied by a maculopapular, petechial, or vesicular rash, or sometimes an eschar (a dark necrotic scab) at the site of the tick or mite bite (see Sec. 11, Ch. 8, Dermatologic Conditions).

Spotted Fever Group

AFRICAN TICK-BITE FEVER

African tick-bite fever is typically milder than most other rickettsioses, but recovery is facilitated with antimicrobial treatment. Suspect this disease in patients presenting with fever, headache, myalgia, and ≥1 eschars after recent travel to sub-Saharan Africa or the Caribbean.

MEDITERRANEAN SPOTTED FEVER

Mediterranean spotted fever can be life-threatening, and clinicians should suspect it in patients with fever, rash, and an eschar after recent travel to northern Africa or the Mediterranean Basin.

ROCKY MOUNTAIN SPOTTED FEVER OR BRAZILIAN SPOTTED FEVER

RMSF is characterized by fever, headache, abdominal pain, and nausea, and can progress rapidly into a serious systemic disease. A maculopapular or petechial rash is commonly reported, but eschars are not. RMSF is the most severe of the spotted fever rickettsioses, and case fatality ratios of 20%–40% are seen among patients for whom antimicrobial drug treatment was delayed.

Typhus Group

MURINE TYPHUS

Patients with murine typhus usually present with a moderately severe but nonspecific febrile illness. Only about half of patients develop a maculopapular rash, typically on the trunk. Although generally less severe than diseases like RMSF or scrub typhus, patients with murine typhus can develop organ failure or other severe sequelae requiring hospital-based management. Death can occur.

Scrub Typhus

Clinicians should include scrub typhus in the differential diagnosis of patients with a fever, headache, myalgias, and eschar after recent travel to destinations where the disease is endemic. Cough, encephalitis, lymphadenopathy, and rash might be present, and multisystem organ failure can develop.

Anaplasmosis & Ehrlichiosis

Clinicians should consider anaplasmosis or ehrlichiosis in febrile patients with leukopenia and an appropriate exposure history. Rash might occur in some children with ehrlichiosis, but is not a feature of anaplasmosis. Other clinical signs are similar to those of other rickettsioses.

DIAGNOSIS

As noted above, rickettsial diseases are difficult to diagnose, even by experienced clinicians. Timely presumptive diagnosis and initiation of antibiotic therapy is almost always based on clinical recognition and epidemiologic context. Serologic testing provides retrospective confirmation and is most accurate when acute and convalescent phase serum samples are compared; a ≥4-fold rise in antibody titer between paired specimens is diagnostic in indirect immunofluorescence antibody assays. Because of cross-reactivity of antigens, some antibodies might react in group-targeted serologic tests and provide evidence of exposure to the group level.

PCR assays and immunohistochemical analyses can be helpful, but results are highly dependent on the type and timing of submitted specimens. If an eschar is present, a swab or biopsy sample of the lesion can be evaluated by PCR to provide a species-specific diagnosis. Similarly, biopsy specimens of rash lesions or whole blood specimens can be evaluated by PCR but are generally less sensitive than samples derived from an eschar.

If anaplasmosis or ehrlichiosis is suspected, PCR of a whole blood specimen provides the best diagnostic test. A buffy coat might provide presumptive evidence of infection if examined to identify characteristic inclusion bodies within leukocytes (called intraleukocytic morulae).

Spotted fever rickettsiosis, anaplasmosis, and ehrlichiosis are nationally notifiable diseases in the United States. Commercial laboratories offer testing for rickettsioses, scrub typhus, anaplasmosis, and ehrlichiosis. Some species-targeted serologic tests are not routinely available at commercial laboratories, however, and are available only through CDC's Rickettsial Zoonoses Branch (rzbepidiag@cdc.gov).

TREATMENT

Because some rickettsioses can progress rapidly to severe illness, clinicians should initiate therapy as soon as infection is suspected and not wait to receive confirmatory test results. Immediate empiric treatment with a tetracycline (most commonly, doxycycline) is recommended for patients of all ages. Almost no other broad-spectrum antibiotic provides effective treatment.

Rigorous reevaluation of earlier reports of doxycycline-resistant scrub typhus has revealed those reports to be incorrect. *Orientia* spp. are doxycycline sensitive. Limited clinical experience

has shown that *A. phagocytophilum* and *R. africae* infections respond to treatment with rifampin, which can be an alternative for pregnant or doxycycline-intolerant patients. Chloramphenicol is the only recognized alternative treatment for diseases caused by *Orientia* and *Rickettsia* species, but oral formulations are not available in many areas; moreover, chloramphenicol use is associated with more deaths, particularly with *R. rickettsii* infection. Seek expert advice if considering treatment with an alternative antibiotic.

PREVENTION

No vaccine is available for preventing rickettsial infections. Antibiotic prophylaxis is not recommended for rickettsial diseases, and antimicrobial agents should not be given to asymptomatic people.

Instruct travelers going to rickettsia endemic areas to minimize their exposure to infectious arthropods (including fleas, lice, mites, ticks) and avoid animal reservoirs (particularly dogs and rats). Travelers can reduce risk for infection by properly using insect repellents on skin and clothing, conducting a self-examination after visits to vector-infested areas, and wearing protective clothing (see Sec. 4, Ch. 6, Mosquitoes, Ticks & Other Arthropods). These precautions are especially important for travelers with immune-compromising conditions, because they might be more susceptible to severe disease.

CDC websites: www.cdc.gov/rmsf/; www.cdc.gov/otherspottedfever/; www.cdc.gov/typhus/murine/; www.cdc.gov/anaplasmosis/; www.cdc.gov/ehrlichiosis/

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SALMONELLOSIS, NONTYPHOIDAL

Ian Plumb, Patricia (Patti) Fields, Beau Bruce

INFECTIOUS AGENT: Nontyphoidal *Salmonella* serotypes	
ENDEMICITY	Worldwide
TRAVELER CATEGORIES AT GREATEST RISK FOR EXPOSURE & INFECTION	Adventurous eaters Travelers who pet, touch, or handle animals
PREVENTION	Follow safe food and water precautions; avoid untreated water and undercooked or raw meat, eggs, dairy, and produce Practice good hand hygiene, especially after contact with animals or their environments
DIAGNOSTIC SUPPORT	A clinical laboratory certified in moderate complexity testing

INFECTIOUS AGENT

Salmonella are gram-negative, rod-shaped bacilli. More than 2,500 *Salmonella* serotypes have been described. *Salmonella* serotypes can be categorized as typhoidal, which cause typhoid and paratyphoid fever, and nontyphoidal serotypes, which cause other human illness, typically acute diarrhea. See the Sec. 5, Part 1, Ch. 24, Typhoid & Paratyphoid Fever, for illness caused by *Salmonella* serotypes Typhi, Paratyphi A, tartrate negative Paratyphi B, and Paratyphi C.

TRANSMISSION

Animal reservoirs include both domestic and wild animals, including food animals, amphibians, and reptiles. Human infection can result from direct contact with infected animals or their environments. Transmission usually occurs from eating contaminated foods (e.g., dairy, eggs, meat, raw produce); drinking contaminated water; or from contact with people who have a diarrheal illness. The risk for infection after exposure is increased by taking antibiotics or antacid medication.

EPIDEMIOLOGY

Nontyphoidal *Salmonella* is one of the leading bacterial causes of diarrhea, causing ≈150 million illnesses and ≈60,000 deaths globally each year. *Salmonella* infection is diagnosed in ≈5 per 1,000 travelers who return with diarrhea. Among travelers returning to the United States, the rate of confirmed infection per 100,000 air travelers is estimated to be 26 after travel to Africa; 6–9 after travel to the Caribbean, Central America, or Asia; and 2–3 after travel to South America, Europe, or Oceania.

CLINICAL PRESENTATION

Nontyphoidal *Salmonella* infection usually presents with an acute diarrheal illness. The incubation period of salmonellosis is typically 12–96 hours, but it can be ≥7 days. Illness manifests commonly with acute diarrhea, abdominal cramps, and fever, and usually resolves without treatment after 1–7 days.

Approximately 5% of people develop bacteremia or focal invasive infection (e.g., osteomyelitis, meningitis, endovascular infection, septic arthritis). Rates of invasive disease are generally higher among infants, older adults, and people who are immunocompromised, including those with HIV. People with atherosclerosis, hemoglobinopathies, or malignant neoplasms also have increased risk for extraintestinal infection. Infection with antibiotic-resistant organisms has been associated with a greater risk for bloodstream infection and hospitalization.

DIAGNOSIS

Culture provides confirmation of nontyphoidal *Salmonella* infection. Approximately 90% of isolates are obtained from routine stool culture; isolates also can be obtained from other sites of infection (e.g., abscesses, blood, cerebrospinal fluid, urine). Although clinical laboratories increasingly use culture-independent diagnostic tests to detect *Salmonella* infection, isolates are necessary for antimicrobial susceptibility testing and for characterization during public health investigations. Reflex bacterial culture is recommended, if possible, on the same specimen, for positive culture-independent specimens. Serologic testing is unreliable and not advised.

Salmonellosis is a nationally notifiable disease. Most states mandate that *Salmonella* isolates or clinical material be submitted to the local or state public health laboratory. Clinical laboratory staff should be aware of disease reporting and mandatory isolate submission regulations for their state; they can contact their local public health department with questions.

TREATMENT

Indications for Antibiotic Therapy

Most patients can be treated with supportive care alone, including oral rehydration therapy. Antibiotic therapy is not recommended for most patients with uncomplicated salmonellosis caused by nontyphoidal *Salmonella*; it does not shorten the duration of illness and can prolong bacterial shedding.

Consider antibiotic therapy for patients with suspected invasive disease (e.g., patients with severe diarrhea, high fever, manifestations of extraintestinal infection) and for patients at increased risk for invasive disease (e.g., infants, older adults, people who are immunocompromised, patients with known atherosclerosis). For these populations, treat infections empirically until susceptibility results are available.

Bacteremic patients generally require ≥7 days of antimicrobial drug therapy and an investigation for possible sites of infection. Longer therapy, specialist consultation, and surgical intervention might be required for extraintestinal infections. Immunocompromised patients are at risk for recurrent invasive disease and require therapy of longer duration.

Choice of Empiric Antimicrobial Drug Therapy

Salmonella resistance to older antimicrobial agents (ampicillin, chloramphenicol, and trimethoprim-sulfamethoxazole) has been recognized for many years; none of these should be considered first-line empiric agents in returning travelers (see Sec. 2, Ch. 6, Travelers' Diarrhea). Resistance to antimicrobial agents varies by *Salmonella* serotype and geographic region.

FLUOROQUINOLONES

Fluoroquinolones are considered first-line treatment in adult travelers. Resistance to fluoroquinolones among *Salmonella* strains has been rising globally, however; among travelers returning to the United States with a diagnosis of nontyphoidal salmonellosis during 2004–2014, decreased susceptibility to fluoroquinolones was present in 41% of isolates from travelers to Asia.

CEFTRIAXONE

Ceftriaxone can be used to treat children or adults with invasive disease. Although ceftriaxone resistance is rare, it has increasingly been detected among bloodstream isolates in sub-Saharan Africa. Azithromycin can be used for children and is an alternative agent for adults. Decreased susceptibility to azithromycin is rare, but has been documented in multiple settings globally. Clinical laboratories do not commonly test for resistance to azithromycin, however, because susceptibility breakpoints have not been established.

PREVENTION

No vaccine against nontyphoidal *Salmonella* infection is available. Travelers should follow preventive measures, such as eating food that is adequately cooked and drinking from safe sources (see Sec. 2, Ch. 8, Food & Water Precautions), and by frequently washing hands, especially after contact with animals or their environments. In general, travelers should avoid uncooked vegetables,

but travelers can gain some protection by washing raw produce properly.

People with diarrheal illness should avoid preparing food for others. After their symptoms have resolved, people who had diarrheal illness should continue to practice safe food preparation and carefully wash hands regularly because they can shed bacteria for weeks afterward.

CDC website: www.cdc.gov/salmonella

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SHIGELLOSIS

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INFECTIOUS AGENT: *Shigella* spp.	
ENDEMICITY	*Shigella flexneri* in low- and middle-income countries *S. sonnei* in high-income countries
TRAVELER CATEGORIES AT GREATEST RISK FOR EXPOSURE & INFECTION	Children Immigrants and refugees Mass gathering attendees Men who have sex with men Tourists Travelers visiting friends and relatives
PREVENTION METHODS	Practice good hand hygiene Follow safe food and water safety precautions Minimize fecal–oral exposures during sexual activity
DIAGNOSTIC SUPPORT	A clinical laboratory certified in moderate complexity testing; state health department

INFECTIOUS AGENT

Shigellosis is an acute infection of the intestine caused by bacteria in the genus *Shigella*. There are 4 species of *Shigella: S. dysenteriae*, *S. flexneri*, *S. boydii*, and *S. sonnei* (also referred to as group A, B, C, and D, respectively). Several distinct serotypes are recognized within the first 3 species.

TRANSMISSION

Shigella is transmitted via the fecal–oral route, through direct person-to-person contact, or indirectly through contaminated food, water, or fomites. Transmission directly from one person to another or via fomite is likely the most common mode of transmission in high resource settings; foodborne and waterborne transmission are additional important transmission routes in both high- and low-resource settings. Spread of *Shigella* through both direct and indirect sexual contact has been widely reported, primarily among men who have sex with men (MSM). Shigellosis is highly contagious; as few as 10 organisms can cause infection. Humans are the primary natural reservoir, although nonhuman primates also can be infected.

EPIDEMIOLOGY

Shigella spp. are endemic to temperate and tropical climates. Shigellosis is caused predominantly by *S. sonnei* in high-income countries, whereas *S. flexneri* is prevalent in low- and middle-income countries. Infections caused by *S. boydii* and *S. dysenteriae* are less common globally. *S. boydii* is mostly restricted to the Indian subcontinent, and *S. dysenteriae* accounts for most *Shigella* spp. isolated in sub-Saharan Africa and South Asia.

Worldwide, *Shigella* is estimated to cause 80–165 million cases of disease and 600,000 deaths annually, and most cases and deaths are among children. Among shigellosis cases worldwide, approximately 20–119 million illnesses and 6,900–30,000 deaths are attributed to foodborne transmission. Foodborne transmission has been reported among travelers in multiple outbreaks, and tourists became ill after eating contaminated foods in hotels and on airplanes and cruise ships. Common food vehicles include cold salads, vegetables, lettuce, and herbs; meat and dairy items and hot dishes also have been implicated.

Numerous outbreaks have also been attributed to waterborne transmission, in both treated and untreated recreational water, and through ingesting contaminated drinking water. Outbreaks of shigellosis tend to occur in settings where sanitation and hygiene practices are inadequate; common settings include schools and daycare centers, private residences, and restaurants. Other populations with reported outbreaks of shigellosis include MSM, people experiencing homelessness, and people in refugee camps.

Shigella spp. have been detected in stool samples of 5%–18% of patients with travelers' diarrhea, and studies in Australia and Canada found that 40%–50% of locally diagnosed shigellosis cases were associated with international travel. In the United States, ≈25% of sporadic cases of shigellosis are travel-associated, and *Shigella* spp. account for 13% of travel-associated enteric infections. In a study conducted among US travelers, most infections caused by *S. dysenteriae* (56%) and *S. boydii* (44%) were travel-associated, whereas infections caused by *S. flexneri* and *S. sonnei* were less often associated with travel (24% and 12%, respectively). In another study among US travelers, the risk for infection caused by *Shigella* spp. was greatest for people who had traveled to Africa, and then travelers to Central America, South America, and Asia. Infections caused by Shiga toxin–producing *S. flexneri* and *S. dysenteriae* have been reported repeatedly among travelers to Haiti and the Dominican Republic (Hispaniola).

Antimicrobial resistance is common in *Shigella*; resistant strains can be acquired during travel to areas of high endemicity. A systematic review of travel-associated *Shigella* infections from 139 countries showed that the percentage of antibiotic-resistant infections increased from 19% during 1990–1999, to 65% during 2000–2009. Moreover, most resistant *Shigella* spp. isolates originated from Asia (25%, excluding West Asia) and Central and South America (18%). The study also documented an increase in quinolone-resistant *Shigella* spp. from 30% during 1990–1999 to 53% during 2000–2009.

Likewise, in the United States, infection with quinolone-resistant *Shigella* spp. has been linked to international travel. Bowen et al. identified a large outbreak of ciprofloxacin-resistant

shigellosis in San Francisco after international travel, primarily to the Dominican Republic, Haiti, and India. Similarly, Grass et al. analyzed *Shigella* infections using linked data collected during 2004–2014 from the Foodborne Diseases Active Surveillance Network (FoodNet) and National Antimicrobial Resistance Monitoring System (NARMS). The authors found that international travel was associated with a 6-fold higher odds of infection with quinolone-resistant *Shigella*.

Resistance to third- and fourth-generation cephalosporins is less common but has also been documented in the United States and is more common in South and East Asia. Additionally, reduced susceptibility to azithromycin and ciprofloxacin has been documented among MSM in several countries, including the United States. Finally, widespread and extensive resistance to former first-line agents, including ampicillin, cotrimoxazole, and nalidixic acid, exists.

CLINICAL PRESENTATION

Illness typically begins 1–2 days after exposure with symptoms lasting 5–7 days. Disease severity varies according to species. *S. dysenteriae* serotype 1 (Sd1) is the agent of epidemic dysentery and often causes severe illness, whereas *S. sonnei* commonly causes milder, nondysenteric diarrheal illness. *Shigella* of any species can cause severe illness among people with compromised immune systems.

Shigellosis is characterized by watery, bloody, or mucoid diarrhea, fever, and stomach cramps. Tenesmus is also a common symptom. Illness in immunocompetent people is usually mild and self-limited. Occasionally, patients experience intestinal or extraintestinal complications, including intestinal perforation, seizures (in young children), and invasive focal infections. Postinfectious manifestations, including reactive arthritis, and hemolytic-uremic syndrome (HUS), can occur weeks after infection. HUS is associated with Shiga toxin–producing *Shigella* strains, particularly Sd1.

DIAGNOSIS

To confirm the diagnosis of shigellosis, perform a stool culture. Conduct antimicrobial susceptibility testing for patients who might require antimicrobial treatment. Rapid PCR-based diagnostic tests for *Shigella* are now increasingly available in the United States. This method cannot determine whether viable *Shigella* organisms are present in stool, however, and does not yield an isolate for susceptibility testing or for public health investigation and control. As such, if *Shigella* is detected using a PCR assay, consider performing reflex culture and susceptibility testing.

If additional diagnostic support is required, consult a clinical laboratory first. Testing performed at the Centers for Disease Control and Prevention, if appropriate, should be arranged through the state or county public health department. Shigellosis is a nationally notifiable disease in the United States.

TREATMENT

Shigellosis usually resolves within 5–7 days with supportive care alone; antimicrobial treatment given early in the course of illness can, however, shorten the duration of symptoms and of carriage (asymptomatic shedding of the organism in the stool). Consider antimicrobial treatment for patients with severe disease or those with compromised immune systems. Antimicrobial treatment can also be considered for patients working in occupations where their risk of transmitting *Shigella* to others is high (e.g., childcare workers, food handlers, health care workers) or to limit transmission in outbreak settings.

Whenever possible, use antimicrobial susceptibility results to direct antibiotic therapy. If empiric therapy is indicated, current clinical guidelines recommend azithromycin, ciprofloxacin, or ceftriaxone as first-line options. Given widespread resistance to commonly used first- and second-line agents, review local resistance trends and pertinent sexual and travel history before initiating empiric therapy. In the United States, populations at increased risk for multidrug-resistant *Shigella* infections include international travelers, people experiencing homelessness, MSM, and people infected with HIV. Information on antimicrobial resistance among shigellosis cases in the United States is available at https://wwwn.cdc.gov/narmsnow. Additional discussion of symptomatic management can be found in Sec. 2, Ch. 6, Travelers' Diarrhea.

PREVENTION

No vaccines are available for *Shigella*. The best defense against shigellosis is thorough, frequent handwashing; strict adherence to standard food and water safety precautions (see Sec. 2, Ch. 8, Food & Water Precautions); and minimizing fecal–oral exposures during sexual activity by using barriers during sex, washing the genitals and anal area before and after sex, and washing sex toys after use. When soap and water are not available, travelers can use alcohol-based hand sanitizers. Sec. 2, Ch. 6, Travelers' Diarrhea, contains general recommendations to prevent diarrhea while traveling.

CDC website: www.cdc.gov/shigella

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TETANUS

Anna Minta, Fiona Havers, Rania Tohme

INFECTIOUS AGENT: *Clostridium tetani*	
ENDEMICITY	Worldwide
TRAVELER CATEGORIES AT GREATEST RISK FOR EXPOSURE & INFECTION	Humanitarian aid workers Pregnant travelers Travelers not current with tetanus toxoid–containing vaccine
PREVENTION METHODS	Tetanus is a vaccine-preventable disease Properly manage wounds (vaccination + tetanus immune globulin)
DIAGNOSTIC SUPPORT	No confirmatory laboratory tests are available for tetanus; consult CDC's Tetanus website, www.cdc.gov/tetanus/clinicians.html

INFECTIOUS AGENT

The causative agent of tetanus is *Clostridium tetani*, a spore-forming, anaerobic, gram-positive bacterium. Ubiquitous in the environment, spores of *C. tetani* germinate into toxin-producing bacteria when they enter the body under specific conditions.

TRANSMISSION

Tetanus is transmitted via direct contamination of open wounds and non-intact skin. Non-neonatal tetanus typically is acquired when spores enter certain wounds, including wounds contaminated with dirt, animal or human excreta or saliva, or necrotic tissue. Burns, crush injuries, and deep punctures are also at increased risk for tetanus infection. Even wounds without visible contamination can become infected with tetanus spores; tetanus transmission has been associated with abortion, dental infection, injection drug use, otitis media, pregnancy, and surgery. Neonatal tetanus is typically acquired when spores contaminate the umbilical cord due to unhygienic delivery practices. Direct person-to-person transmission does not occur.

EPIDEMIOLOGY

Tetanus is distributed worldwide. It is more common in rural and agricultural regions; areas where contact with soil or animal excreta is likely; warm and moist environments; and areas where immunization against tetanus is inadequate. Because the spores exist in the environment, tetanus cannot be eradicated. In 2020, over 11,750 tetanus cases across the globe were reported to the World Health Organization / United Nations Children's Fund, of which 2,230 occurred in neonates. Most tetanus cases were reported from countries in Africa and Southeast Asia.

Maternal and neonatal tetanus elimination, defined as <1 neonatal tetanus case per 1,000 live births per year in every district in a country, has not been achieved in Afghanistan, Angola, Central African Republic, Guinea, Mali, Nigeria, Pakistan, Papua New Guinea, Somalia, Sudan, South Sudan, or Yemen. Any traveler not up to date with tetanus vaccination is at risk of acquiring tetanus infection. Because hygienic obstetric care might not be available, travelers (especially pregnant travelers) going to countries that have not eliminated maternal and neonatal tetanus might be at increased risk for morbidity and mortality from tetanus infection; in addition, proper wound management and tetanus immune globulin (TIG) are less likely to be available in these settings.

Tetanus can affect any age group. The risk for injuries after natural disasters is high; therefore, humanitarian aid workers should be up to date on tetanus vaccination before travel. The number of US travelers who acquire tetanus infection abroad is unknown; surveillance might be limited because travelers with injuries are unlikely to seek care at a travel clinic when they return from their trip. Injuries are common among travelers, however, and any tetanus-prone wound is a risk, so ensure that all travelers are properly vaccinated.

CLINICAL PRESENTATION

The incubation period is on average 10 days (range 3–21 days). The duration of the incubation period is inversely related to the severity of symptoms, and shorter incubation periods are associated with injuries closer to the central nervous system. Tetanus is classified as generalized, localized, and cephalic. Generalized tetanus, which occurs in >80% of cases, is characterized by lockjaw, generalized spasms, risus sardonicus, and opisthotonus. Symptoms of localized tetanus include muscle spasms confined to the injury site. Cephalic tetanus is characterized by a head or face wound and flaccid cranial nerve palsies. Progression from localized and cephalic tetanus to generalized tetanus can occur. Neonatal tetanus occurs in newborns who have contaminated umbilical stumps and whose mothers are unimmunized or inadequately immunized. Neonatal tetanus can lead to long-term sequelae, including behavioral, intellectual, and neurologic abnormalities. Severe tetanus can lead to respiratory failure and death. Case-fatality ratios for generalized tetanus vary between 25% and 100% and can only be reduced to 10%–20% where modern intensive care is available. The case-fatality ratio is <1% for localized tetanus.

DIAGNOSIS

Diagnosis is based on clinical findings with epidemiologic support; no confirmatory laboratory

tests are available. Tetanus is a nationally notifiable disease in the United States.

TREATMENT

The goals of treatment are to inactivate circulating toxin by immediately administering tetanus immune globulin (TIG); eliminate the bacteria with aggressive wound care and debridement to stop further toxin formation; provide supportive care; and provide antibiotic treatment for 7–10 days. Metronidazole is the most appropriate antibiotic; parenteral penicillin G is an alternative treatment. Patients with tetanus must be hospitalized in a quiet, dim room to minimize spasms. Additional supportive care measures include agents to control muscle spasm and autonomic dysfunction, and respiratory support. Patients should be vaccinated and receive TIG as described below. Additional information about diagnosis and treatment can be found at the Centers for Disease Control and Prevention (CDC) Tetanus website (www.cdc.gov/tetanus/clinicians.html).

PREVENTION

Vaccine

INDICATIONS FOR USE

Tetanus disease does not result in immunity. Vaccination is the only prevention against tetanus. Because immunity after vaccination wanes over time, lifelong vaccination with tetanus toxoid–containing vaccine (TTCV) is necessary to attain and sustain immunity against tetanus. All travelers should be up to date with vaccination before departure.

CHILDREN

DTaP (diphtheria-tetanus-acellular pertussis) and DT (diphtheria-tetanus) are indicated for children <7 years, while Tdap (tetanus-diphtheria-acellular pertussis) and Td (tetanus-diphtheria) are indicated for children ≥10 years. Infants and children should receive 5 doses of DTaP at 2, 4, 6, and 15–18 months, and at 4–6 years; adolescents should receive 1 dose of Tdap at 11–12 years of age. Children ≥7 years old can receive Tdap for catch-up vaccination.

ADULTS

Adults should receive TTCV booster doses every 10 years. Adults who have never received Tdap should receive Tdap; otherwise, clinicians can administer either Td or Tdap. Previously unvaccinated pregnant people should receive 2 doses of TTCV during their pregnancy. Pregnant people also should be properly vaccinated to prevent infant pertussis, irrespective of their vaccination history, by receiving Tdap during every pregnancy at 27–36 weeks' gestation, preferably earlier in this period. See the CDC Immunization Schedules website (www.cdc.gov/vaccines/schedules/index.html) for routine and catch-up vaccination schedules and minimum intervals between TTCV doses.

ADVERSE REACTIONS & SAFETY

TTCV are safe. The most common adverse reactions are fatigue, headache, and injection site pain.

CONTRAINDICATIONS & PRECAUTIONS

A severe allergic reaction (e.g., anaphylaxis) to a previous dose or a component of the vaccine is a contraindication for any TTCV (DTaP, DT, Tdap, or Td). For DTaP or Tdap, encephalopathy without an identifiable cause occurring within ≤7 days of a previous dose of DTP, DTaP, or Tdap is a contraindication to vaccine administration. Encephalopathy is a contraindication for the pertussis component of the vaccines; therefore, people with this contraindication should receive either DT in place of DTaP or Td in place of Tdap, to ensure protection against diphtheria and tetanus.

Precautions for all TTCV include Guillain-Barré syndrome ≤6 weeks after a previous dose of TTCV, history of Arthus-type hypersensitivity after a previous dose of tetanus or diphtheria toxoid–containing vaccine (in which case, vaccination should be deferred until ≥10 years after the last TTCV), and moderate or severe acute illness with or without fever.

Due to the pertussis component of these vaccines, an additional precaution for DTaP and Tdap is a progressive or neurologic disorder, in which case vaccination should be deferred. Please see Liang et al. (www.cdc.gov/mmwr/volumes/67/rr/rr6702a1.htm) for additional information about when TTCV can be given.

Table 5-05 Tetanus prophylaxis for wound management

HISTORY OF TTCV	CLEAN, MINOR WOUND		ALL OTHER WOUNDS[1]	
	TTCV[2]	TIG	TTCV[2]	TIG[3]
Unknown or <3 doses	Yes	No	Yes	Yes
≥3 doses	No[4]	No	No[5]	No

Abbreviations: TIG, tetanus immune globulin; TTCV, tetanus toxoid–containing vaccine.

Source: Table adapted from Liang et al. MMWR. 2018;67(2):1–44.

[1]*All other wounds* include, but are not limited to, wounds contaminated with dirt, feces, saliva, or soil; avulsions; puncture wounds; and wounds resulting from burns, crush injuries, frostbite, or missiles.
[2]Use age-appropriate TTCV: DTaP for children <7 years of age; Tdap or Td for children ≥7 years of age and adults; Tdap is preferred for people who have not already received Tdap. Do not use Tdap for people who are pregnant.
[3]People with severe immunodeficiency or HIV infection with contaminated wounds should receive TIG regardless of TTCV status.
[4]Yes, if ≥10 years have passed since last TTCV.
[5]Yes, if ≥5 years have passed since last TTCV.

Wound Management

Patients with wounds should be evaluated for risk for tetanus infection based on the type of wound and TTCV status, and clinicians should provide prophylaxis accordingly (see Table 5-05). Complete information on tetanus prophylaxis and the use of TIG when indicated for wound management is available from Liang et al. (www.cdc.gov/mmwr/volumes/67/rr/rr6702a1.htm).

CDC websites: www.cdc.gov/tetanus; www.cdc.gov/vaccines/pubs/pinkbook/tetanus.html

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TUBERCULOSIS

John Jereb

INFECTIOUS AGENT: *Mycobacterium tuberculosis* complex	
ENDEMICITY	Worldwide, but with wide variations by region and social context
TRAVELER CATEGORIES AT GREATEST RISK FOR EXPOSURE & INFECTION	Humanitarian aid workers and health care personnel working in high-prevalence settings (e.g., refugee camps; HIV clinics, and in-patient hospital wards) Immigrants and refugees
PREVENTION METHODS	Avoid high-risk social contexts Obtain pre- and posttravel testing and preventive treatment for new infections Get fit-tested and use respiratory protection (e.g., N95 respirators) in high-risk occupational settings Consider vaccination with bacillus Calmette-Guérin (no longer available in the United States)
DIAGNOSTIC SUPPORT	A clinical laboratory certified in moderate or high complexity testing; state or local health department; or consult with US TB Centers of Excellence for Training, Education, and Medical Consultation, www.cdc.gov/tb/education/tb_coe/default.htm

INFECTIOUS AGENT

Mycobacterium tuberculosis complex is a group of closely related rod-shaped, nonmotile, slow-growing, acid-fast bacteria, which includes *M. bovis* and *M. tuberculosis hominis*, the most common cause of human tuberculosis (TB), usually referred to as *M. tuberculosis*.

TRANSMISSION

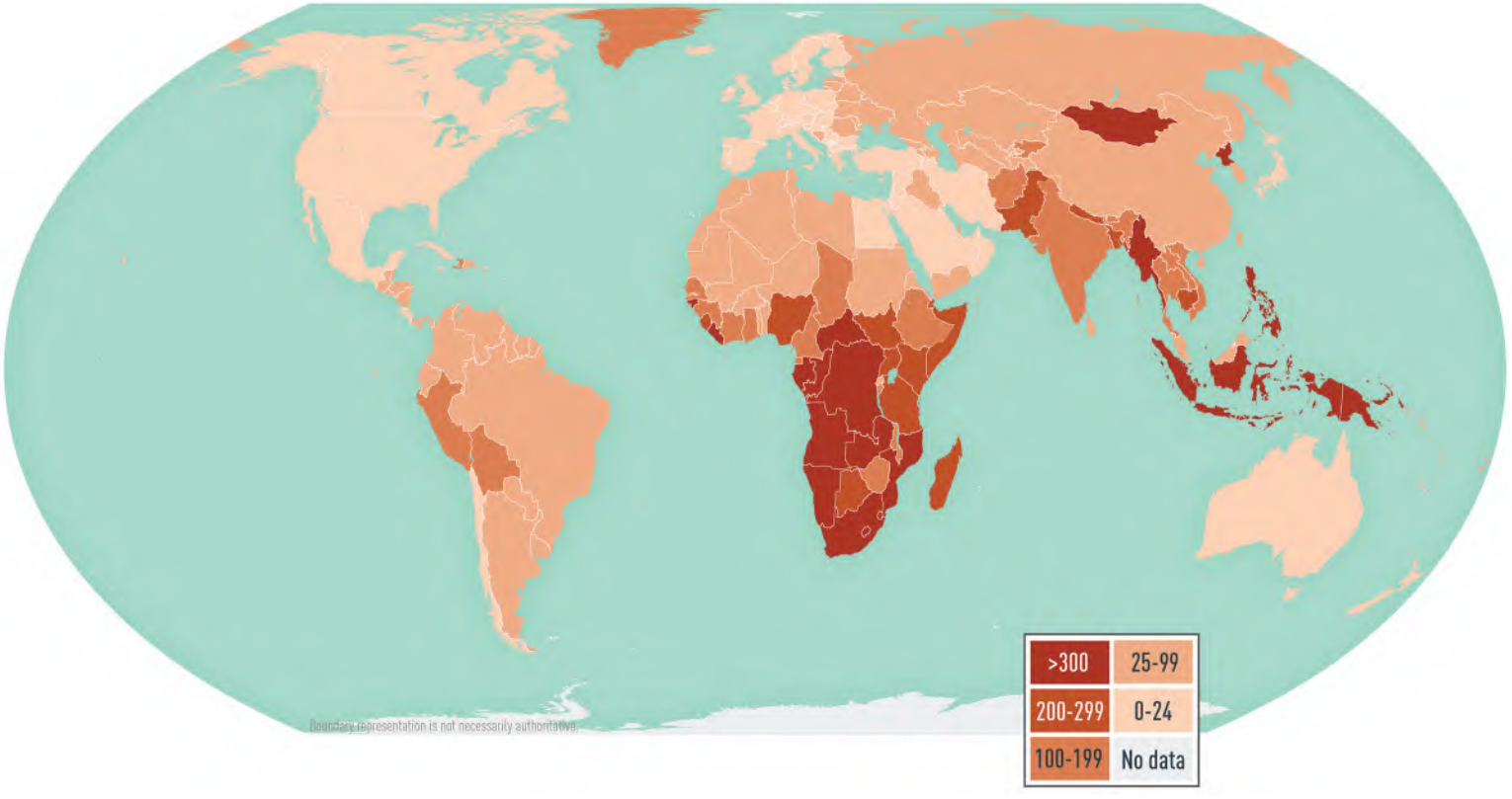
TB transmission occurs when a patient with a contagious form of the infection coughs, spreading bacilli through the air. People can acquire bovine TB (caused by *M. bovis*) by consuming unpasteurized dairy products from infected cattle.

The risk for *M. tuberculosis* transmission on an airplane is low, but instances of in-flight TB transmission have occurred. The risk of transmission is dependent on the contagiousness of the person with TB, seating proximity, flight duration, and host factors. To prevent transmission, people with contagious TB should not travel by commercial airplanes or other commercial conveyances. Typically, only TB of the lung or airway is contagious in community contexts, and health department authorities determine whether TB is contagious based on a person's chest radiograph, sputum tests, symptoms, and treatment received. The World Health Organization (WHO) issued guidelines for notifying passengers potentially exposed to TB on airplanes. Passengers concerned about possible TB exposure should see their primary health care provider or visit their local health department clinic for evaluation.

Bovine TB is a risk for travelers who consume unpasteurized dairy products in countries (e.g., Mexico) where *M. bovis* in cattle is common. *M. bovis* risk in some African countries has been postulated, but human *M. bovis* statistics are unavailable for those countries.

EPIDEMIOLOGY

According to the World Health Organization, ≈10 million new TB cases and ≈1.2 million TB-related deaths occurred in 2019. TB occurs throughout the world, but the incidence varies (see Map 5-02). In some countries in sub-Saharan Africa and Asia,



MAP 5-02 Estimated tuberculosis incidence rates per 100,000 population

Disease data sources: World Health Organization. Global tuberculosis report 2020 (https://apps.who.int/iris/bitstream/handle/10665/336069/9789240013131-eng.pdf); for French Guiana, *Tableau 5: Taux de déclaration de tuberculose maladie par Nouvelles régions (taux pour 100 000), France entière*, 2015–2020; Santé publique France; *La tuberculose: données* (Table 5: Tuberculosis disease reporting rate by New regions [rate per 100,000], Whole France, 2015–2020, Public Health France, Tuberculosis: data; www.santepubliquefrance.fr/maladies-et-traumatismes/maladies-et-infections-respiratoires/tuberculose/donnees/#tabs); for Taiwan, Statistics of Communicable Diseases and Surveillance Report 2019, Centers for Disease Control, Ministry of Health and Welfare, R.O.C. (Taiwan), November 2020 (www.cdc.gov.tw/En/File/Get/0nnMQjC37VAuhzVY3Vuq-A).

the annual incidence is several hundred per 100,000 population. In the United States, the annual incidence is <3 per 100,000 population, but immigrants from countries with a high TB burden and long-term residents of high-burden countries have a 10× greater incidence of TB than the US national average. Of note, US surveillance does not capture travel-related cases of TB.

Drug-resistant TB is an increasing concern. Multidrug-resistant (MDR) TB is resistant to at least the 2 most effective drugs, isoniazid and rifampin. MDR TB is less common than drug-susceptible TB, but globally ≈363,000 cases of MDR TB were diagnosed in 2019, and MDR TB accounts for >25% of TB cases in some countries (Table 5-06). MDR and higher-order resistance

Table 5-06 Estimated proportion of multidrug-resistant (MDR) tuberculosis (TB) cases in countries with high MDR TB burden, 2019

COUNTRY	% OF NEW TB CASES THAT ARE MDR	% OF RETREATMENT MDR TB CASES
Angola	2.5%	14%
Azerbaijan	11%	24%
Bangladesh	0.7%	11%
Belarus	38%	60%
China	7.1%	23%
DPR Korea	2.2%	16%
DR Congo	1.8%	11%
Ethiopia	0.7%	12%
India	2.8%	14%
Indonesia	2.4%	13%
Kazakhstan	27%	44%
Kenya	1.3%	4.6%
Kyrgyzstan	29%	60%
Mozambique	3.7%	13%
Myanmar	4.9%	18%
Nigeria	4.3%	14%
Pakistan	4.2%	7.3%
Papua New Guinea	3.4%	26%

(*continued*)

Table 5-06 Estimated proportion of multidrug-resistant (MDR) tuberculosis (TB) cases in countries with high MDR TB burden, 2019 (continued)

COUNTRY	% OF NEW TB CASES THAT ARE MDR	% OF RETREATMENT MDR TB CASES
Peru	6.3%	20%
Philippines	1.8%	28%
Republic of Moldova	33%	60%
Russian Federation	35%	71%
Somalia	8.7%	88%
South Africa	3.4%	7.1%
Tajikistan	29%	40%
Thailand	1.7%	10%
Ukraine	27%	43%
Uzbekistan	12%	22%
Vietnam	3.6%	17%
Zimbabwe	3.1%	14%

are of particular concern among HIV-infected or other immunocompromised people.

CLINICAL PRESENTATION

M. tuberculosis infection can be detected by a positive tuberculin skin test (TST) or interferon-γ release assay (IGRA) 8–10 weeks after exposure. Overall, only 5%–10% of otherwise healthy people who are infected progress to TB disease during their lifetimes. Progression to TB disease can take weeks to decades after initial infection. People with TB disease have symptoms or other manifestations of illness (e.g., an abnormal chest radiograph). For most people who become infected, *M. tuberculosis* remains in an inactive state (latent TB infection or LTBI) in which the infected person has no symptoms and cannot spread the infection to others.

TB disease can affect any organ, but affects the lungs in 70%–80% of cases. Typical TB symptoms include prolonged cough, fever, hemoptysis, night sweats, decreased appetite, and weight loss. The most common sites for TB outside the lungs (i.e., extrapulmonary TB) are the bladder, bones and joints, brain and meninges, genitalia, kidneys, lymph nodes, and pleura.

The risk for progression to disease is much higher in immunosuppressed people; for example, progression is 8%–10% per year in HIV-infected people not receiving antiretroviral therapy. People receiving tumor necrosis factor blockers to treat rheumatoid arthritis and other chronic inflammatory conditions also are at increased risk for disease progression.

DIAGNOSIS

Pretravel & Posttravel Testing

Before leaving the United States, travelers who anticipate possible prolonged exposure to TB

(e.g., people who will care for patients, or who will work in health care facilities, prisons or jails, refugee camps, or homeless shelters) and those planning prolonged stays in TB-endemic countries should have a pretravel IGRA (e.g., QuantiFERON-TB Gold Plus, T-SPOT.*TB*, 2-step tuberculin skin test [TST]). For details, see the following chapter in this section, . . . *perspectives*: Testing Travelers for *Mycobacterium tuberculosis* Infection.

If the predeparture test is negative, repeat IGRA or single TST 8–10 weeks after the traveler returns. The predeparture test and follow-up test should be the same test type to facilitate interpretation of results. People with HIV infection or other immunocompromising conditions are more likely to have an impaired response to either a skin or a blood test; be sure to ask travelers about such underlying conditions.

Travelers who suspect they have been exposed to TB should inform their health care provider of the possible exposure and receive a medical evaluation. Because drug resistance is relatively common in some parts of the world, consult with experts in infectious diseases or pulmonary medicine regarding proper management and coordinate consultations with input from the public health department.

Diagnostic Testing Recommendations

The Centers for Disease Control and Prevention (CDC), the American Thoracic Society (ATS), and the Infectious Diseases Society of America (IDSA) jointly published diagnostic recommendations for both TB disease and LTBI. Collect sputum or other respiratory specimens for culture and smears for acid-fast bacilli (AFB) from people being examined for pulmonary TB.

Although diagnosis of TB disease can be made using clinical criteria in the absence of microbiologic confirmation, perform laboratory testing to confirm the diagnosis, guide treatment decisions, and provide bacterial DNA for molecular epidemiology. Molecular tests for mutations that confer drug resistance can be performed directly on specimens and can guide initial treatment while culture results are pending. Culture-based susceptibility testing is recommended for all patients with a positive culture result, to help determine the appropriate drug regimen.

CULTURE METHODS

Culture methods, with referral to a public health reference laboratory in some instances, are necessary to identify the *M. tuberculosis* complex species responsible for infection. Culture and identification of *M. tuberculosis* takes ≈2 weeks, even with rapid culture techniques.

MICROSCOPY

A preliminary diagnosis of TB can be made when AFB are seen by microscopy on a sputum smear or in other body tissues or fluids. Microscopy cannot distinguish *M. tuberculosis* from nontuberculous mycobacteria, however, which is particularly problematic in countries like the United States, where the prevalence of infections with nontuberculous mycobacteria is greater than that of TB.

NUCLEIC ACID AMPLIFICATION TESTS

Less sensitive than culture but more sensitive than AFB smear, nucleic acid amplification tests (NAAT) are specific for the *M. tuberculosis* complex. NAAT methods detect all members of the *M. tuberculosis* complex. Thus, a positive NAAT result can rapidly confirm a diagnosis and help guide initial treatment until culture results return.

The availability of NAAT methods and the policies for ordering these tests are locally determined, and clinicians should consult their state health department. Diagnosis of extrapulmonary TB disease can be confirmed with a NAAT positive for *M. tuberculosis* complex or a culture positive for *M. tuberculosis* from affected body tissues or fluids.

Diagnostic Support

TB disease is a nationally notifiable condition in the United States. LTBI is also notifiable in many jurisdictions. LTBI is diagnosed by a positive result from an IGRA or TST after further examinations (e.g., chest radiograph, symptom review) have excluded TB disease.

Expertise in the diagnosis of TB and its specialty laboratory services, or local referral for such expertise, is available from the health departments of cities, counties, and states. In most settings, contact tracing is managed by public health officials. General information and expert medical consultation also are available from the CDC-sponsored US TB Centers of

Excellence for Training, Education, and Medical Consultation (www.cdc.gov/tb/education/tb_coe/default.htm).

TREATMENT

Latent Tuberculosis Infection

People with LTBI can be treated, and treatments are effective at preventing progression to TB disease. Clinicians must exclude TB disease before starting LTBI treatment. In the United States, several regimens exist for the treatment of drug-susceptible LTBI, including 3 months of once-weekly isoniazid and rifapentine; 4 months of daily rifampin; 3 months of daily isoniazid and rifampin; and 6–9 months of daily isoniazid. Given the low completion rates of the 6- to 9-month isoniazid regimen, shorter duration regimens are preferred.

Choose a regimen for patients based on coexisting medical conditions, potential for drug interactions, and drug-susceptibility results of the presumed source of exposure, if known. For example, rifampin has interactions with oral contraceptives and certain antiretroviral medications taken by people with HIV/AIDS. Individuals at especially high risk for TB disease who might have difficulty adhering to treatment, or who are given an intermittent dosing regimen, might be candidates for directly observed therapy for LTBI.

Tuberculosis Disease

CDC/ATS/IDSA published guidelines for treating drug-susceptible TB disease with a multiple-drug regimen administered by directly observed therapy for 6–9 months. Usually, the regimen is isoniazid, rifampin, ethambutol, and pyrazinamide for 2 months, then isoniazid and rifampin for an additional 4 months. Drug-resistant TB is more difficult to treat, historically requiring 4–6 drugs for 18–24 months and best managed by an expert. In a randomized controlled trial, a newer 6-month all-oral regimen of bedaquiline, pretomanid, and linezolid was effective in treating highly drug-resistant TB or patients who could not tolerate other regimens. This and other new regimens are being used in the United States.

PREVENTION

Travelers should avoid exposure to people with TB disease in crowded and enclosed environments (e.g., health care facilities, prisons or jails, or homeless shelters). Advise travelers who will be caring for patients, or who will be working in health care facilities where people with TB are likely to be patients, to consult infection control or occupational health experts about baseline LTBI screening, procedures for obtaining personal respiratory protective devices (e.g., N95 respirators), and recommendations for respirator selection and training.

Based on WHO recommendations, bacillus Calmette-Guérin (BCG) vaccine is used once, at birth, in countries with higher TB burdens to reduce the severe consequences of TB in infants and children. BCG vaccine has low and variable efficacy in preventing TB in adults, however. Some experts advocate vaccinating health care providers likely to be exposed to drug-resistant TB in settings where infection control measures like those recommended in the United States are not fully implemented; US Food and Drug Administration–approved vaccine formulations of BCG are no longer available in the United States. All people, including those who have received BCG vaccination, must follow recommended TB infection control precautions to the greatest extent possible. IGRA is preferred over the TST for pretravel and posttravel testing in those vaccinated with BCG, because BCG might induce false-positive TST results. No BCG effects on IGRA results have been detected in multiple studies.

To prevent infections from *M. bovis* and other foodborne pathogens, travelers should avoid consuming unpasteurized dairy products.

CDC website: www.cdc.gov/tb

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TESTING TRAVELERS FOR *MYCOBACTERIUM TUBERCULOSIS* INFECTION

John Jereb

Screening for asymptomatic *Mycobacterium tuberculosis* infections should only be carried out for travelers at risk of acquiring tuberculosis (TB) at their destinations (see Sec. 5, Part 1, Ch. 22, Tuberculosis). Screening with a tuberculin skin test (TST) or interferon-γ release assay (IGRA) in very-low-risk travelers might produce false-positive test results, leading to unnecessary additional screening or treatment. IGRAs, which require a single blood draw, are approximately as specific as TST in people who have not been vaccinated with bacillus Calmette-Guérin (BCG) and are more specific in BCG-vaccinated populations. Moreover, TST is prone to boosting sensitivity in serial testing, necessitating a 2-step initial test for establishing a baseline, which is unneeded with IGRAs. Using screening tests in very-low-prevalence populations will probably produce more false positives than true positives.

Travelers at risk for TB infection include those going to live in a TB-endemic country or anyone intending to spend any length of time in routine contact with patients in health care facilities or populations living in congregate settings (e.g., homeless shelters, prisons, refugee camps). People at low risk for exposure to TB, which includes most travelers, do not need to be screened before or after travel.

For travelers who anticipate a long stay or contact with a high-risk population, perform pretravel screening by using an IGRA or, when IGRA is not available, 2-step TST screening. CDC guidelines recommend testing with an IGRA (as opposed to TST) for people aged ≥5 years in low-risk populations. The American Academy of Pediatrics guidelines recommend an IGRA for children ≥2 years old; some pediatric TB experts use IGRAs for all children. If an IGRA is used for pretravel testing and there is concern for a false positive in an otherwise low-risk traveler, a second test can be used, which confirms TB infection only if both tests are positive. If the IGRA result is negative, repeat the traveler's test 8–10 weeks after they return from their trip; however, data supporting a recommendation for regular serial testing for a long-term traveler are limited.

If TST is used for pretravel testing, use the 2-step TST for any traveler undergoing TST testing for the first time. The 2-step method is not needed for travelers who have already been tested and found to have a negative result within the previous 2 years. For the 2-step method, anyone whose baseline TST yields a negative result should be retested 1–3 weeks after the initial test; if the second test result is negative, the patient can be considered not infected. If the second test result is positive, the patient is classified as having skin test boosting, possibly because of previous *M. tuberculosis* infection.

The 2-step TST is recommended over single TST in this population because some people infected with *M. tuberculosis* years earlier (or who were sensitized by BCG or nontuberculous mycobacteria) exhibit waning delayed-type hypersensitivity to tuberculin. When skin tested years after infection, these people might have a negative initial TST result even though they had been sensitized previously. The first TST

might stimulate the ability to react to subsequent tests, however, resulting in a "booster" reaction. When the test gets repeated at some future date, a positive result could be misinterpreted as a new *M. tuberculosis* infection (recent conversion) rather than a boosted reaction. For travelers who do not have enough time to complete a 2-step TST before departure, a single-step TST is an acceptable alternative, but an IGRA is preferred.

If the result of a pretravel test (either IGRA or 2-step TST) for *M. tuberculosis* infection is negative, a traveler should have a posttravel test with the same type of test used pretravel, 8–10 weeks after returning from their trip. People who have repeat TSTs should be tested with the same tuberculin purified protein derivative solution, because switching products can lead to different test results. The US Food and Drug Administration has approved 2 commercially available tuberculin solutions for skin testing: Aplisol (JHP Pharmaceuticals) and Tubersol (Sanofi Pasteur). During extended (>6 months) stays in, or repeated travel to, high-risk settings, travelers should have repeat testing every 6–12 months while traveling outside the United States and then 8–10 weeks after final return, all with the same type of test used pretravel.

In general, do not mix the types of tests used for a person. The discordance between TST and IGRA results is ≤15%; in most instances of discordance, the TST result is positive and the IGRA is negative. Multiple reasons for the discordance exist, and clinicians cannot be confident about the reason for discordance in any single person. If a clinician does decide to mix tests, going from TST to IGRA is better than the other way around, because the likelihood of a discordant result with the TST negative and the IGRA positive is much lower. Such discordant results might become unavoidable as more medical establishments switch from TSTs to IGRAs.

When testing travelers who were born or took up residence in TB-endemic areas, consider the greater background prevalence of infection in these places. In a study among 53,000 adults in Tennessee, the prevalence of a positive TST results among foreign-born participants was >11× that of US-born participants (34% vs. 3%). Confirming *M. tuberculosis* test status before travel would prevent the conclusion that a positive result after travel was due to recent infection.

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. . . *perspectives* chapters supplement the clinical guidance in this book with additional content, context, and expert opinion. The views expressed do not necessarily represent the official position of the Centers for Disease Control and Prevention (CDC).

TYPHOID & PARATYPHOID FEVER

Michael Hughes, Grace Appiah, Louise Francois Watkins

TYPHOID FEVER

INFECTIOUS AGENT: *Salmonella enterica* serotype Typhi	
ENDEMICITY	Africa Latin America Asia (greatest risk for infection is in South Asia)
TRAVELER CATEGORIES AT GREATEST RISK FOR EXPOSURE & INFECTION	Travelers to low- and middle-income countries where typhoid and paratyphoid fever are endemic Travelers to mass gatherings Travelers visiting friends and relatives
PREVENTION METHODS	Follow safe food and water precautions Typhoid fever is a vaccine-preventable disease
DIAGNOSTIC SUPPORT	A clinical laboratory certified in moderate complexity testing; state health department

PARATYPHOID FEVER

INFECTIOUS AGENTS: *Salmonella enterica* serotypes Paratyphi A, B, C	
ENDEMICITY	Africa Latin America Asia (greatest risk for infection is in South Asia)
TRAVELER CATEGORIES AT GREATEST RISK FOR EXPOSURE & INFECTION	Travelers to low- and middle-income countries where typhoid and paratyphoid fever are endemic Travelers to mass gatherings Travelers visiting friends and relatives
PREVENTION METHODS	Follow safe food and water precautions
DIAGNOSTIC SUPPORT	A clinical laboratory certified in moderate complexity testing; state health department

INFECTIOUS AGENT

Salmonella enterica serotypes Typhi, Paratyphi A, Paratyphi B, and Paratyphi C cause potentially severe and occasionally life-threatening bacteremic illnesses referred to as typhoid fever (for Typhi serotype) and paratyphoid fever (for Paratyphi serotypes), and collectively as enteric fever. Paratyphi B strains are differentiated into 2 distinct pathotypes on the basis of their ability to ferment tartrate: the first pathotype, Paratyphi B, is unable to ferment tartrate and is associated with paratyphoid fever; the second pathotype, Paratyphi B var. L(+) tartrate(+), ferments tartrate and is associated with gastroenteritis typical of nontyphoidal salmonellosis. For more details on nontyphoidal salmonellosis, see the Sec. 5, Part 1, Ch. 19, Nontyphoidal Salmonellosis.

TRANSMISSION

Humans are the only source of the bacteria that cause enteric fever; no animal or environmental reservoirs have been identified. Typhoid and paratyphoid fever are acquired through consumption of water or food contaminated by feces of an acutely infected or convalescent person, or a person with chronic, asymptomatic carriage. Risk for infection is high in low- and middle-income countries with endemic disease and poor access to safe food and water, and poor sanitation. Sexual contact, particularly among men who have sex with men, has been documented as a rare route of transmission.

EPIDEMIOLOGY

An estimated 11–21 million cases of typhoid fever and 5 million cases of paratyphoid fever occur worldwide each year, causing an estimated 135,000–230,000 deaths. In the United States during 2016–2018, ≈400 culture-confirmed cases of typhoid fever and 50–100 cases of paratyphoid fever caused by Paratyphi A were reported each year; paratyphoid fever caused by Paratyphi B and Paratyphi C is rarely reported. Approximately 85% of typhoid fever and 92% of paratyphoid fever cases in the United States occur among international travelers; most are in travelers returning from South Asia, primarily Bangladesh, India, and Pakistan. Other high-risk regions for infection include Africa, Latin America, and Southeast Asia; lower-risk regions include East Asia and the Caribbean.

Travelers visiting friends and relatives are at increased risk because they might be less careful with food and water while abroad than other travelers and might not seek pretravel health consultation or typhoid vaccination (see Sec. 9, Ch. 9, Visiting Friends & Relatives: VFR Travel). Although the risk of acquiring illness increases with the duration of stay, travelers have acquired typhoid fever even during visits of <1 week to countries where the disease is highly endemic (e.g., Bangladesh, India, Pakistan).

CLINICAL PRESENTATION

The incubation period of both typhoid and paratyphoid infections is 6–30 days. The onset of illness is insidious, with gradually increasing fatigue and a fever that increases daily from low-grade to 102°F–104°F (38°C–40°C) by the third or fourth day of illness. Fever is commonly lowest in the morning, peaking in the late afternoon or evening. Anorexia, headache, and malaise are nearly universal, and abdominal pain, constipation, or diarrhea are common. Diarrhea and vomiting are more common in children than in adults. People also can have dry cough, fatigue, myalgias, and sore throat. Hepatosplenomegaly often can be detected. A transient, maculopapular rash of rose-colored spots can occasionally be seen on the trunk.

The clinical presentation is often confused with malaria. Suspect enteric fever in a person with a history of travel to an endemic area who is not responding to antimalarial medication. Untreated, the disease can last for a month, and reported case-fatality ratios are 10%–30%. By comparison, the case-fatality ratio in patients treated early is usually <1%. Serious complications of typhoid fever occur in 10%–15% of hospitalized patients, generally after 2–3 weeks of illness, and include life-threatening gastrointestinal hemorrhage, intestinal perforation, and encephalopathy. Paratyphoid fever appears to have a lower case-fatality ratio than typhoid fever; however, severe cases do occur.

DIAGNOSIS

Typhoid and paratyphoid fever are nationally notifiable diseases in the United States. Clinicians should report cases to their state or local health department. Identification of a domestically acquired case should prompt a public health investigation to prevent other cases.

Blood Culture

Patients with typhoid or paratyphoid fever typically have bacteremia; blood culture is therefore the preferred method of diagnosis. A single culture is positive in only ≈50% of cases, however. Multiple blood cultures increase the sensitivity and might be required to make the diagnosis. Depending on the blood culture system used, cultures might need to be held and observed for up to 7 days before reporting a negative result. Although bone marrow culture is more invasive (and therefore less commonly performed), it increases the sensitivity to ≈80% of cases and is relatively

unaffected by previous or concurrent antibiotic use. Stool culture is not usually positive during the first week of illness and has less diagnostic sensitivity than blood culture. Urine culture has a lower diagnostic yield than stool culture.

Rapid Diagnostic Tests

Globally, several commercial rapid diagnostic tests for typhoid fever are available, but their sensitivity and specificity are not optimal. The Widal test measures elevated antibody titers; it is unreliable but widely used in developing countries because of its low cost. Serologic tests do not distinguish acute from past infection or vaccination and lack specificity; thus, blood culture remains the preferred method to diagnose acute infections.

Clinical Diagnosis

Poor sensitivity and specificity of rapid antibody tests and the time it takes to obtain a positive culture mean that the initial diagnosis must often be made clinically. Typhoid and paratyphoid fever are clinically indistinguishable. The combination of risk factors for infection and gradual onset of fever that increases in severity over several days should raise suspicion of enteric fever.

TREATMENT

Antibiotic therapy shortens the clinical course of enteric fever and reduces the risk for death. Treatment decisions are complicated by high rates of resistance to many antimicrobial agents, and antimicrobial treatment should be guided by susceptibility testing. A careful travel history can inform empiric treatment choices while awaiting culture results.

Multidrug-Resistant Infection

Established resistance to older antibiotics (e.g., ampicillin, chloramphenicol, trimethoprim-sulfamethoxazole) has led to these agents being recommended only as alternative antibiotics for infections with known susceptibility. Multidrug-resistant (MDR) Typhi with resistance to all 3 of these antibiotics has been present for decades. Regional estimates for MDR Typhi range from 9% in South Asia (2015–2018) to 35%–59% in parts of Africa (2010–2014).

Fluoroquinolones (e.g., ciprofloxacin) are still considered the treatment of choice for fluoroquinolone-susceptible infections in adults. Most Typhi and Paratyphi A infections in the United States are fluoroquinolone-nonsusceptible, however, and most (>90%) have occurred among travelers returning from South Asia. Fluoroquinolone-nonsusceptible infections have been associated with treatment failure or delayed clinical response. Therefore, azithromycin and ceftriaxone, antibiotics with historically low rates of resistance globally, are increasingly being used as empiric treatment for enteric fever.

Extensively Drug-Resistant Infection

In 2017, among all Typhi and Paratyphi A isolates tested by CDC's National Antimicrobial Resistance Monitoring System (NARMS), <1% were resistant to azithromycin or to ceftriaxone, based on resistance criteria for Typhi. Resistance to both agents is emerging, however. In 2016, an outbreak of extensively drug-resistant (XDR) typhoid fever began in Sindh Province, Pakistan. These XDR *Salmonella* Typhi isolates are typically resistant to ampicillin, ceftriaxone, chloramphenicol, ciprofloxacin, and trimethoprim-sulfamethoxazole, but susceptible to azithromycin and carbapenem antibiotics.

The first US cases of XDR typhoid fever associated with travel to Pakistan were diagnosed in 2018, and by early 2021 >70 XDR infections had been documented among residents of the United States, including 9 cases among patients who did not travel internationally in the 30 days before illness began (https://emergency.cdc.gov/han/2021/han00439.asp). Ceftriaxone resistance also has been identified in Typhi isolates from US travelers returning from Iraq. Additionally, resistance to azithromycin has been identified among Typhi and Paratyphi strains isolated from patients in Bangladesh, Cambodia, India, Nepal, Pakistan, Saudi Arabia, and the United States.

Empiric treatment should be guided by the patient's travel history. For patients with suspected typhoid fever who traveled to Iraq or Pakistan, or who did not travel internationally before their illness began, empirically treat uncomplicated illness with azithromycin, and treat complicated illness with a carbapenem. Ceftriaxone remains

an appropriate empiric treatment option for travelers returning from most other countries. Once culture results are available, use susceptibility information to guide treatment. Case reports have suggested that patients with XDR Typhi infection who do not improve on a carbapenem alone might benefit from the addition of a second antibiotic (e.g., azithromycin). Updated information about antimicrobial resistance among isolates from US patients with enteric fever in the United States can be found at the NARMS website (www.cdc.gov/narmsnow).

Cases Unresponsive to Treatment

Patients treated with antimicrobial agents can continue to have fever for 3–5 days, but the maximum temperature generally decreases each day. Patients sometimes feel worse during the first few days after commencing antibiotic treatment. If fever in a person with typhoid or paratyphoid infection does not subside within 5 days of initiating antibiotic therapy, however, consider treatment with alternative antibiotics or begin looking for a persistent focus of infection (e.g., an abscess, or an infection in a bone, joint, or other extraintestinal site).

Relapse, Reinfection & Chronic Carriage

Relapse, reinfection, and chronic carriage also can occur. Relapse occurs in ≤10% of patients 1–3 weeks after clinical recovery, requiring further antibiotic treatment. An estimated 1%–4% of treated patients become asymptomatic chronic carriers (defined as people who excrete the organism in stool for ≥12 months); a prolonged antibiotic course is usually required to eradicate the organism.

PREVENTION

Food & Water Precautions

Safe food and water precautions and frequent handwashing, especially before meals, are important in preventing both typhoid and paratyphoid fever (see Sec. 2, Ch. 8, Food & Water Precautions). Although recommended by the Advisory Committee on Immunization Practices (ACIP), typhoid vaccines are not 100% effective, and a large bacterial inoculum can overwhelm vaccine-induced immunity. Therefore, vaccinated travelers should follow recommended food and water precautions to prevent enteric fever and other infections. No vaccines are available for paratyphoid fever; thus, food and water precautions are the only prevention methods.

Vaccines

INDICATIONS

The ACIP recommends typhoid vaccine for travelers going to areas where risk for exposure to Typhi is recognized. Destination-specific vaccine recommendations are available at the CDC Travelers' Health website (https://wwwnc.cdc.gov/travel). Two typhoid vaccines are licensed for use in the United States: Vi capsular polysaccharide vaccine (ViCPS) (Typhim Vi, manufactured by Sanofi Pasteur) for intramuscular use; and live attenuated vaccine (Vivotif, manufactured from the Ty21a strain of serotype Typhi by PaxVax) for oral use. Both vaccines are unconjugated, which means the polysaccharide antigens are not paired with a protein to elicit a strong response from the immune system. Because these vaccines protect 50%–80% of recipients, remind travelers that typhoid immunization is not 100% effective, and take the opportunity to reinforce safe food and water precautions. Neither vaccine is licensed to prevent paratyphoid fever, although limited data from efficacy trials suggest that the Ty21a vaccine might provide some cross-protection against Paratyphi B.

Newer, protein conjugated Vi vaccines have greater efficacy in children <2 years old and protect people for longer than Vi unconjugated polysaccharide vaccines. Three typhoid Vi conjugate vaccines (TCV) have been licensed in India: Peda Typh (manufactured by Biomed); Typbar-TCV (manufactured by Bharat Biotech); and Zyvac TCV (manufactured by Zydus Cadila). Typbar-TCV also is licensed in Cambodia, Nepal, and Nigeria. Although none of these vaccines are licensed or available in the United States, Tybar-TCV received prequalification from the World Health Organization in 2018. The vaccine is approved for use in people ≥6 months old. In a human challenge study, Typbar-TCV had ≈87% protective efficacy. Interim analysis from a large

field study in Nepal has shown Typbar-TCV effectiveness of 81.6% in children after 15 months of follow-up.

ADMINISTRATION

For information on dosage, administration, and revaccination for the 2 typhoid vaccines licensed in the United States, see Table 5-07. The time required for primary vaccination differs, as do the lower age limits for each.

VI CAPSULAR POLYSACCHARIDE VACCINE

Primary vaccination with ViCPS consists of one 0.5-mL (25-μg) dose administered intramuscularly ≥2 weeks before travel. The vaccine is approved for use in people ≥2 years old. A dose is recommended every 2 years for those who remain at risk.

LIVE ATTENUATED TY21A VACCINE

Primary vaccination with Ty21a vaccine consists of 4 capsules, 1 taken every other day. The capsules should be kept refrigerated (not frozen), and all 4 doses must be taken to achieve maximum efficacy. Each capsule should be swallowed whole (not chewed) and taken with cool liquid no warmer than 98.6°F (37°C), approximately 1 hour before a meal and ≥2 hours after a previous meal. The manufacturer recommends avoiding alcohol consumption 1 hour before and 2 hours after administration, because alcohol can disintegrate the enteric coating.

Travelers should complete the Ty21a vaccine regimen ≥1 week before potential exposure. The approach for addressing a missed oral vaccine dose or taking a dose late is undefined. Some suggest that minor deviations in the dosing schedule (e.g., taking a dose 1 day late) might not alter vaccine efficacy; no studies have shown the effect of such deviations, however. If travelers do not complete 4 doses as directed, they might not achieve an optimal immune response. The vaccine is approved for use in people ≥6 years old. A booster dose is recommended every 5 years for those who remain at risk.

ADVERSE REACTIONS

Adverse reactions most often associated with ViCPS vaccine include headache, injection-site reactions, fever, and general discomfort. Adverse reactions to Ty21a vaccine are rare and mainly consist of abdominal discomfort, diarrhea, fever, headache, nausea, vomiting, and rash. Report adverse reactions to the Vaccine Adverse Event Reporting System at the website, https://vaers.hhs.gov/index.html, or by calling 800-822-7967.

Table 5-07 Typhoid fever vaccines

VACCINE	APPROVED AGES FOR USE	DOSE & ROUTE OF ADMINISTRATION	NUMBER OF DOSES	DOSING INTERVAL	REPEAT DOSES
Vi Capsular Polysaccharide Vaccine (ViCPS)—Typhim Vi					
Primary series	≥2 years	0.5 mL, IM injection	1	NA	NA
Booster	≥2 years	0.5 mL, IM injection	1	NA	Every 2 years
Live Attenuated Ty21a Vaccine—Vivotif[1]					
Primary series	≥6 years	1 capsule, orally every other day[2]	4	48 hours	NA
Booster	≥6 years	1 capsule, orally every other day[2]	4	48 hours	Every 5 years

Abbreviations: IM, intramuscular; NA, not applicable.

[1]Vaccine must be kept refrigerated at 35°F–46°F (2°C–8°C).
[2]Capsules should be taken with cool liquid, no warmer than 98.6°F (37°C)

PRECAUTIONS & CONTRAINDICATIONS

Neither the ViCPS nor the Ty21a vaccine should be given to people with an acute febrile illness; in addition, Ty21a is not recommended for use in people with acute gastroenteritis. Live vaccines, including Ty21a vaccine, should not be given to pregnant or immunocompromised people, including those with HIV. No information is available on the safety of the inactivated vaccine (ViCPS) in pregnancy; consider ViCPS for pregnant people when the benefits of vaccination outweigh potential risks (e.g., when the likelihood of exposure to Typhi is high).

The intramuscular vaccine (ViCPS) presents a theoretically safer alternative than the live, oral vaccine (Ty21a) for immunocompromised travelers. The Ty21a vaccine can be administered to household contacts of immunocompromised people; although vaccine organisms can be shed transiently in the stool of vaccine recipients, secondary transmission of vaccine organisms has not been documented. The only contraindication to vaccination with ViCPS vaccine is a history of severe local or systemic reactions after a previous dose.

Theoretical concerns have been raised about the immunogenicity of Ty21a vaccine in people concurrently receiving antimicrobial agents, live vaccines, or immune globulin. The growth of the live Ty21a strain is inhibited in vitro by various antimicrobial agents. The manufacturer advises that vaccination with the Ty21a vaccine should be delayed for >72 hours after the administration of any antimicrobial agent, and antibiotics should not be given to a patient ≤72 hours after the last dose of the Ty21a vaccine.

Ty21a vaccine can be administered simultaneously or at any interval before or after live virus vaccines (e.g., measles-mumps-rubella, oral polio, or yellow fever vaccines). Available data do not suggest that simultaneous administration of live virus vaccines decreases the immunogenicity of the Ty21a vaccine. If typhoid vaccination is warranted, it should not be delayed because of administration of viral vaccines. No data are available on coadministration of the Ty21a vaccine and the oral cholera vaccine (lyophilized CVD 103-HgR [Vaxchora]); taking the first Ty21a vaccine dose ≥8 hours after oral cholera vaccine might decrease potential interference between the vaccines. Simultaneous administration of the Ty21a vaccine and immune globulin does not appear to pose a problem.

CDC website: www.cdc.gov/typhoid-fever

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YERSINIOSIS

Louise Francois Watkins, Cindy Friedman

5

INFECTIOUS AGENTS: *Yersinia enterocolitica* and *Y. pseudotuberculosis*	
ENDEMICITY	Northern, temperate regions: northern Europe (particularly Scandinavia), Canada, Japan
TRAVELER CATEGORIES AT GREATEST RISK FOR EXPOSURE & INFECTION	Adventurous eaters Children
PREVENTION METHODS	Follow safe food and water precautions Avoid unpasteurized dairy products, raw or undercooked pork products, and untreated water
DIAGNOSTIC SUPPORT	A clinical laboratory certified in moderate complexity testing; state health department

INFECTIOUS AGENT

Yersinia species are facultative anaerobic gram-negative coccobacilli. The most common species that cause yersiniosis are *Yersinia enterocolitica* (serogroups O:3, O:5,27, O:8, and O:9), but disease is also caused by *Y. pseudotuberculosis.* The term "yersinosis" does not include illness caused by *Yersinia pestis*, the causative agent of plague, which is discussed separately (see Sec. 5, Part 1, Ch. 15, Plague); discussion of *Yersinia* spp. in this chapter excludes *Y. pestis*.

TRANSMISSION

Transmission of *Yersinia* spp. can occur from consuming or handling contaminated food, commonly raw or undercooked pork products (e.g., chitterlings); consuming milk that was not pasteurized, inadequately pasteurized, or contaminated after pasteurization; or drinking untreated water. *Yersinia* spp. also can be transmitted by direct or indirect contact with animals through the fecal–oral route. Pigs are a major reservoir of pathogenic *Y. enterocolitica*, but a variety of other domestic (e.g., dogs), farm (e.g., cattle), and wild (e.g., deer) animals can harbor *Yersinia* spp. Transmission through blood product transfusions has been reported.

EPIDEMIOLOGY

Most yersiniosis cases are reported from northern Europe, particularly Scandinavia, and from Canada and Japan. Yersiniosis is not, however, a reportable condition in most countries (including the United States), and infections in countries without surveillance programs might be underrepresented. In the United States, *Y. enterocolitica* causes ≈92% of infections with known species information, accounting for

approximately 117,000 illnesses, 640 hospitalizations, and 35 deaths every year.

In temperate climates, the risk for infection is increased during cooler months. Children are infected more often than adults. People with diseases that cause high iron levels (e.g., hemochromatosis, thalassemia), including those on iron chelation treatment, are at greater risk for infection and severe disease. The incidence among travelers to low- and middle-income countries is generally low, and most cases are believed to be due to foodborne transmission. A US study found that ≈6% of *Y. enterocolitica* infections were travel-associated.

CLINICAL PRESENTATION

The incubation period is 4–6 days (range 1–14 days), and symptom onset might be more gradual compared with infections caused by other enteric pathogens. Enterocolitis is the most common clinical presentation; symptoms typically include abdominal pain, diarrhea (which can be bloody and persist for several weeks), and fever. Sore throat also can occur, particularly in children. Mesenteric adenitis, which presents as pain mimicking appendicitis, has been well described. Necrotizing enterocolitis has been described in young infants. Reactive arthritis affecting the wrists, knees, and ankles can occur, usually 1 month after the initial diarrhea episode, resolving after 1–6 months. Erythema nodosum, manifesting as painful, raised red or purple lesions along the trunk and legs, can occur, and usually resolves spontaneously within 1 month.

DIAGNOSIS

Diagnosis is frequently made by isolating the organism from bile, blood, cerebrospinal fluid, mesenteric lymph nodes, peritoneal fluid, stool, a throat swab, or wounds. If yersiniosis is suspected, notify the clinical laboratory because cold enrichment, alkali treatment, or plating of a clinical specimen on CIN agar can be used to increase the likelihood of a positive culture. Several culture-independent diagnostic tests (CIDTs) are now available and have more than doubled the detection rate of *Yersinia* spp. in the United States. CIDT panels typically target only *Y. enterocolitica*, and the rarity of yersiniosis has precluded robust evaluation of the specificity and sensitivity of CIDT platforms through prospective studies. Culture is required to determine the species and for antimicrobial susceptibility testing. For questions about diagnostic testing beyond the capacity of the clinical laboratory, contact a local or state public health department. Public health officials can provide information and guidance on specimen submission, including submission to the Centers for Disease Control and Prevention (CDC) if appropriate.

TREATMENT

Most infections are self-limited. Antimicrobial drug therapy has not been shown to shorten the duration of uncomplicated enterocolitis or to alter the likelihood of postinfectious sequelae. Prescribe antibiotics for moderate to severe illness. *Y. enterocolitica* isolates are usually susceptible to aminoglycosides, third-generation cephalosporins, fluoroquinolones, tetracyclines, and trimethoprim-sulfamethoxazole and are typically resistant to first-generation cephalosporins and most penicillins.

PREVENTION

Travelers can reduce the risk for *Yersinia* spp. infection by avoiding consumption of unpasteurized milk products, raw or undercooked pork products, and untreated water (see Sec. 2, Ch. 8, Food & Water Precautions). Washing hands with soap and water before eating and preparing food, after contact with animals, and after handling raw meat helps reduce risk.

CDC website: www.cdc.gov/yersinia

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PART 2: VIRAL

Table 5-08 Vaccine-Preventable Diseases: Viral

VACCINE	TRADE NAME (MANUFACTURER)	DESCRIPTION[1] & ROUTE OF ADMINISTRATION	AGE LIMITS	DOSES	PRESCRIBING & BOOSTER INFORMATION, RECOMMENDATIONS & RESTRICTIONS
COVID-19	COMIRNATY (Pfizer-BioNTech)	mRNA, IM	www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/comirnaty-and-pfizer-biontech-covid-19-vaccine www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/covid-19.html		
	SPIKEVAX (Moderna)	mRNA, IM	www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/spikevax-and-moderna-covid-19-vaccine es/hcp/acip-recs/vacc-specific/covid-19.html		
	NOVAVAX (Novavax)	Recombinant	ency-preparedness-and-response/coronavirus-disease-2019-covid-19/nova ine-adjuvanted es/hcp/acip-recs/vacc-specific/covid-19.html		
Dengue	DENGVAXIA (Sanofi Pasteur)	Live-attenuat SC		3	*Restrictions apply* www.fda.gov/vaccines-blood-biologics/dengvaxia www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/dengue.html
Ebola Zaire	ERVEBO (Merck)	Live-attenuated, IM	≥18 y	1	*Restrictions apply* www.fda.gov/vaccines-blood-biologics/ervebo www.cdc.gov/vhf/ebola/clinicians/vaccine/index.html
Enterovirus-A71 (Hand, Foot & Mouth)	Available in China only				
Hepatitis A	HAVRIX (GlaxoSmithKline)	Inactivated, IM	**0.5 mL**		www.fda.gov/vaccines-blood-biologics/vaccines/havrix www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/hepa.html
			≥12 mo to <19 y	2	
			1.0 mL		
			≥19 y	2	

	VAQTA (Merck)	Inactivated, IM	**0.5 mL**	www.fda.gov/vaccines-blood-biologics/vaccines/vaqta www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/hepa.html
			≥12 mo to <19 y: 2	
			1.0 mL	
			≥19 y: 2	
Hepatitis A + Hepatitis B	TWINRIX (GlaxoSmithKline)	Inactivated HAV + Recombinant HBV, IM	**STANDARD DOSING**	www.fda.gov/vaccines-blood-biologics/vaccines/twinrix www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/hepa.html
			≥18 y: 3	
			ACCELERATED DOSING	
			≥18 y: 3 (+ booster)	
Hepatitis B	ENGERIX-B (GlaxoSmithKline)	Recombinant, IM	<20 y: 3	www.fda.gov/vaccines-blood-biologics/vaccines/engerix-b www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/hepb.html
			≥20 y: 3	
	HEPLISAV-B (Dynavax Technologies)	Recombinant, IM	≥18 y: 2	www.fda.gov/vaccines-blood-biologics/vaccines/heplisav-b www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/hepb.html
	PREHEVBRIO (VBI Vaccines)	Recombinant, IM	≥18 y: 3	www.fda.gov/vaccines-blood-biologics/prehevbrio www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/hepb.html
	RECOMBIVAX HB (Merck)	Recombinant, IM	**0.5 mL**	www.fda.gov/vaccines-blood-biologics/vaccines/recombivax-hb www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/hepb.html
			<20 y: 3	
			1.0 mL	
			11–15 y: 2	
			≥20 y: 3	

(*continued*)

Table 5-08 Vaccine-Preventable Diseases: Viral (continued)

VACCINE	TRADE NAME (MANUFACTURER)	DESCRIPTION[1] & ROUTE OF ADMINISTRATION	AGE LIMITS	DOSES	PRESCRIBING & BOOSTER INFORMATION, RECOMMENDATIONS & RESTRICTIONS
Influenza	For the list of influenza vaccines licensed for use in the United States, see: www.fda.gov/vaccines-blood-biologics/vaccines/vaccines-licensed-use-united-states; www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/flu.html				
Japanese encephalitis	IXIARO (Valneva)	Inactivated, IM	**0.25 mL**		www.fda.gov/vaccines-blood-biologics/vaccines/ixiaro www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/je.html
			≥2 mo to <3 y	2	
			0.5 mL		
			≥3 y	2	
Mumps	M-M-R II (Merck)	Live-attenuated, SC	<12 mo	3	www.fda.gov/vaccines-blood-biologics/vaccines/measles-mumps-and-rubella-virus-vaccine-live www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/mmr.html
			≥12 mo	2	
	ProQuad (Merck)	Live-attenuated, SC	≥12 mo to <13 y	2	www.fda.gov/vaccines-blood-biologics/vaccines/proquad www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/mmrv.html
Polio	IPOL (Sanofi Pasteur)	Inactivated, IM or SC	**CHILDREN**		www.fda.gov/vaccines-blood-biologics/vaccines/ipol-poliovirus-vaccine-inactivated-monkey-kidney-cell www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/polio.html www.cdc.gov/polio/what-is-polio/travelers.html
			≥6 wks	3	
			ADULTS TRAVELING TO AREAS WITH INCREASED RISK OF POLIO		
			UNVACCINATED, PARTLY VACCINATED, VACCINATION STATUS UNKNOWN		
			≥18 y	3	
			COMPLETELY VACCINATED		
			≥18 y	1-time booster	

Rabies	IMOVAX (Sanofi Pasteur)	Inactivated (human diploid cell), IM	all ages	2–3	www.fda.gov/vaccines-blood-biologics/vaccines/imovax www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/rabies.html
	RabAvert (Novartis)	Inactivated (purified chick embryo cell), IM	all ages	2–3	www.fda.gov/vaccines-blood-biologics/vaccines/rabavert-rabies-vaccine www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/rabies.html
Rubella	M-M-R II (Merck)	Live-attenuated, SC	<12 mo	3	www.fda.gov/vaccines-blood-biologics/vaccines/measles-mumps-and-rubella-virus-vaccine-live www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/mmr.html
			≥12 mo	2	
	ProQuad (Merck)	Live-attenuated, SC	≥12 mo to <13 y	2	www.fda.gov/vaccines-blood-biologics/vaccines/proquad www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/mmrv.html
Rubeola / Measles	M-M-R II (Merck)	Live-attenuated, SC	<12 mo	3	www.fda.gov/vaccines-blood-biologics/vaccines/measles-mumps-and-rubella-virus-vaccine-live www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/mmr.html
			≥12 mo	2	
	ProQuad (Merck)	Live-attenuated, SC	≥12 mo to <13 y	2	www.fda.gov/vaccines-blood-biologics/vaccines/proquad www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/mmrv.html
Tick-borne encephalitis	TICOVAC (Pfizer)	Inactivated, IM	**0.25 mL**		www.fda.gov/vaccines-blood-biologics/ticovac
			≥1–15 y	3	
			0.5 mL		
			≥16 y	3	

(*continued*)

Table 5-08 Vaccine-Preventable Diseases: Viral (continued)

VACCINE	TRADE NAME (MANUFACTURER)	DESCRIPTION[1] & ROUTE OF ADMINISTRATION	AGE LIMITS	DOSES	PRESCRIBING & BOOSTER INFORMATION, RECOMMENDATIONS & RESTRICTIONS
Varicella / Chickenpox	VARIVAX (Merck)	Live-attenuated, SC	1–12 y	2	www.fda.gov/vaccines-blood-biologics/vaccines/varivax www.cdc.gov/vaccines/vpd/varicella/hcp/
			≥13 y	2	
	ProQuad (Merck)	Live-attenuated, SC	≥12 mo to <13 y	2	www.fda.gov/vaccines-blood-biologics/vaccines/proquad www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/mmrv.html
Variola / Smallpox + Monkeypox	ACAM2000 (Emergent BioSolutions)	Live-attenuated vaccinia virus, percutaneous via bifurcated needle	all ages	1	*Restrictions apply* www.fda.gov/vaccines-blood-biologics/vaccines/acam2000 www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/smallpox.html
	JYNNEOS (Bavarian Nordic)	Live-attenuated non-replicating vaccinia virus, SC	≥18 y	2	Restrictions apply www.fda.gov/vaccines-blood-biologics/jynneos www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/smallpox.html
Yellow Fever	YF-VAX (Sanofi Pasteur)	Live-attenuated, SC	≥9 mo	1	www.fda.gov/vaccines-blood-biologics/vaccines/yf-vax www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/yf.html

Abbreviations: IM, intramuscular; SC, subcutaneously

[1]For an overview and description of vaccine types, see: www.hhs.gov/immunization/basics/types/index.html

B VIRUS

Ludmila Perelygina

INFECTIOUS AGENT: B Virus (*Macacine Herpesvirus* 1)	
ENDEMICITY	North Africa Asia
TRAVELER CATEGORIES AT GREATEST RISK FOR EXPOSURE & INFECTION	Children Tourists, particularly adventure tourists Veterinarians and laboratory workers
PREVENTION METHODS	Avoid feeding or petting macaque monkeys
DIAGNOSTIC SUPPORT	National B Virus Resource Center (404-413-6560; http://biotech.gsu.edu/virology/contactUs.html; http://bvirus.org)

INFECTIOUS AGENT

B virus (*Macacine herpesvirus* 1) is an enveloped, double-stranded DNA virus in the family *Herpesviridae*, genus *Simplexvirus*. B virus is also commonly referred to as herpes B, monkey B virus, herpesvirus B, and herpesvirus simiae. B virus is commonly found among macaques, a genus of Old World monkeys.

TRANSMISSION

B virus is typically transmitted to humans through bites or scratches from an infected macaque, but also can occur through contact with body fluids or tissues of an infected macaque. A single case of human-to-human transmission has been documented, in which a woman became infected through direct contact with lesions on her infected spouse.

EPIDEMIOLOGY

Macaques are the natural reservoir for B virus. No other primates are known to carry B virus unless they become infected through contact with infected macaques. Although B virus infections in macaques are usually asymptomatic or cause only mild disease, ≈70% of untreated infections in humans are fatal.

Infections in humans are rare. Since B virus was identified in 1932, <50 cases of human infection have been documented. People at greatest risk for B virus infection are laboratory workers, veterinarians, and others who have close contact with macaques or macaque cell cultures. International travelers visiting temples and parks with exotic animal life often come in direct contact with free-roaming macaques, which often carry B virus. Children are more likely to be bitten than adults. Although transmission of B virus from macaques to humans in public settings has not been documented, the potential risk for transmission exists.

CLINICAL PRESENTATION

Disease onset typically occurs within 1 month of exposure, although the actual incubation period can be as short as 3–7 days. The first signs of disease typically include influenza-like symptoms (fever, headache, myalgia) and sometimes vesicular lesions near the exposure site. Localized neurologic symptoms (e.g., pain, numbness, itching) might occur near the wound site. Lymphadenitis, lymphangitis, nausea, vomiting, and abdominal pain also can occur.

Spread of the infection to the central nervous system (CNS) causes acute ascending encephalomyelitis. Most patients with CNS involvement die despite antiviral therapy and supportive care. People who survive usually suffer serious neurologic sequelae. Respiratory failure associated with

ascending paralysis is the most common cause of death.

DIAGNOSIS

Before collecting clinical specimens for diagnostic testing, cleanse all wound sites thoroughly (see First Aid & Treatment, next). Obtaining specimens from wound sites before proper cleansing could force virus more deeply into exposed tissue.

In the United States, diagnostic testing of human specimens is performed only at the National B Virus Resource Center at Georgia State University (http://biotech.gsu.edu/virology). Detection of viral DNA by B virus PCR from clinical specimens is the standard for diagnosis.

Detection of B virus–specific antibodies in serum is also diagnostic. Collect and submit a baseline serum sample as close as possible to the time of injury, and again 14–21 days post-injury for serological testing to evaluate for B virus infection. Testing paired specimens is essential for a reliable diagnosis. Viral culture is generally unsuccessful because the virus is unlikely to remain viable during transit or after being frozen and thawed. For more information on specimen collection, storage, and shipment, see National B Virus Resource Center (http://biotech.gsu.edu/virology).

FIRST AID & TREATMENT

For suspected exposure, travelers should administer immediate first aid. Travelers should cleanse wounds by thoroughly washing and scrubbing the area with soap, concentrated detergent solution, povidone iodine, or chlorhexidine and water, then irrigate the area with running water for 15–20 minutes. For urine splashes to the eyes, travelers should perform repeated eye flushes for several minutes.

Antiviral therapy is recommended as postexposure prophylaxis in high-risk exposures (see www.cdc.gov/herpesbvirus/firstaid-treatment.html). When recommended, the drug of choice is valacyclovir, and an alternative is acyclovir. If B virus infection is diagnosed, initiate treatment with intravenous acyclovir or ganciclovir, depending on whether CNS symptoms are present.

PREVENTION

No vaccine is available for B virus. Laboratories should adhere to laboratory and animal facility protocols to reduce the risk for B virus transmission among workers. Visitors to parks and tourist destinations with free-roaming macaques should avoid feeding or petting the animals, and seek care for possible postexposure prophylaxis if a high-risk exposure occurs. Immediate cleaning of bite and scratch wounds is of utmost importance for disease prevention. Consider postexposure antiviral prophylaxis for high-risk exposures, including any deep bites, and scratches or other wounds to the head, neck, or torso. Contact a medical expert familiar with B virus infections at the earliest opportunity.

CDC website: www.cdc.gov/herpesbvirus/index.html

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CHIKUNGUNYA

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INFECTIOUS AGENT: Chikungunya virus	
ENDEMICITY	Tropical and subtropical regions worldwide
TRAVELER CATEGORIES AT GREATEST RISK FOR EXPOSURE & INFECTION	Adventure tourists Long-term travelers and expatriates Travelers visiting friends and relatives
PREVENTION METHODS	Avoid insect bites
DIAGNOSTIC SUPPORT	A clinical laboratory certified in high complexity testing; state health department; or contact CDC's Arboviral Diseases Branch (www.cdc.gov/ncezid/dvbd/specimensub/arboviral-shipping.html; 970-221-6400; dvbid@cdc.gov)

INFECTIOUS AGENT

Chikungunya virus is a single-stranded RNA virus that belongs to the family *Togaviridae*, genus *Alphavirus*.

TRANSMISSION

Chikungunya virus is transmitted to humans via the bite of an infected mosquito of the *Aedes* spp., predominantly *Aedes aegypti* and *Ae. albopictus*. Mosquitoes become infected when they feed on viremic nonhuman or human primates, both of which are likely the main amplifying reservoirs of the virus. Humans are typically viremic shortly before and in the first 2–6 days of illness.

Bloodborne transmission is possible; 1 case has been documented in a health care worker who sustained a needle stick after drawing blood from an infected patient. Furthermore, chikungunya virus has been identified in donated blood products undergoing screening, although no transfusion-associated cases have been identified to date. Cases also have been documented among laboratory personnel handling infected blood, through percutaneous punctures, and through aerosol exposure in the laboratory.

Maternal–fetal transmission has been documented during pregnancy; the greatest risk occurs in the perinatal period when the pregnant person is viremic at the time of delivery. Although chikungunya viral RNA was identified in the breast milk of 1 infected person, the breastfed infant had no symptoms or evidence of infection based on laboratory testing. Additionally, chikungunya viral RNA has been identified in semen, but no evidence of sexual transmission has been noted to date.

EPIDEMIOLOGY

Chikungunya virus occurs in tropical and subtropical regions. It often causes large outbreaks with high attack rates, affecting up to 75% of the population in areas where the virus is circulating. Outbreaks of chikungunya have occurred in Africa, the Americas, Asia, Europe, and islands in the Indian and Pacific Oceans. In late 2013, the first locally acquired cases of chikungunya were reported in the Americas on islands in the Caribbean. By the end of 2017, >2.6 million suspected cases of chikungunya had been reported in the Americas. Since then, the virus has continued to circulate and cause sporadic cases and periodic outbreaks in many areas of the world, including Africa, South America, and Asia.

Risk to travelers is greatest in areas experiencing ongoing chikungunya epidemics. Most

epidemics occur during the tropical rainy season and abate during the dry season. Outbreaks in Africa have occurred after periods of drought, however, where open water containers near human habitats served as vector-breeding sites. Risk for infection exists primarily during the day, because the primary vector, *Ae. aegypti*, aggressively bites during daytime. *Ae. aegypti* mosquitoes bite indoors or outdoors near dwellings and lay their eggs in domestic containers that hold water, including buckets and flowerpots.

Both adults and children can become infected and be symptomatic with chikungunya. After the outbreaks in the Americas during 2014–2017, >4,000 chikungunya cases were reported among US travelers, and 13 locally acquired cases were reported in the continental United States. In addition, the US territories of American Samoa, US Virgin Islands, and Puerto Rico reported locally acquired cases during 2014–2015; Puerto Rico also has been reporting sporadic cases since 2016. During 2018–2020, 340 US traveler cases were reported, with noticeably fewer cases in 2020 due to decreases in international travel during the coronavirus disease 2019 (COVID-19) pandemic.

CLINICAL PRESENTATION

Approximately 3%–28% of people infected with chikungunya virus will remain asymptomatic. For people who develop symptomatic illness, the incubation period is typically 3–7 days (range 1–12 days). Disease is most often characterized by sudden onset of high fever (temperature typically >102°F [39°C]) and joint pains. Fevers typically last for ≤1 week; the fever can be biphasic. Joint symptoms are typically severe, can be debilitating, and usually involve multiple joints, typically bilateral and symmetric. Joint pain occurs most commonly in hands and feet but can affect more proximal joints. Other symptoms include conjunctivitis, headache, myalgia, nausea, vomiting, or a rash. The rash, which is typically maculopapular, occurs after onset of fever and involves the trunk and extremities but also can include the palms, soles, and face.

Abnormal laboratory findings can include elevated creatinine and liver function tests, lymphopenia, and thrombocytopenia. Rare but serious complications of the disease include hepatitis, myocarditis, neurologic disease (cranial nerve palsies, Guillain-Barré syndrome, meningoencephalitis, myelitis), ocular disease (uveitis, retinitis), acute renal disease, and severe bullous skin lesions. Groups identified as having increased risk for more severe disease include neonates exposed intrapartum, adults >65 years of age, and people with underlying medical conditions (e.g., diabetes, heart disease, hypertension).

Acute symptoms of chikungunya typically resolve in 7–10 days. Some patients will have a relapse of rheumatologic symptoms (e.g., polyarthralgia, polyarthritis, tenosynovitis, Raynaud syndrome) in the months after acute illness. Studies have reported variable proportions, ranging from 5% to 80%, of patients with persistent joint pains, and prolonged fatigue, for months or years after their illness. Fatalities associated with infection occur but are rare and are reported most commonly in older adults and those with comorbidities.

People who are pregnant have symptoms and outcomes similar to those of other people, and most infections that occur during pregnancy will not result in the virus being transmitted to the fetus. Intrapartum transmission can, however, result in neonatal complications, including hemorrhagic symptoms, myocardial disease, and neurologic disease. Rare spontaneous abortions after first-trimester maternal infection have been reported.

DIAGNOSIS

The differential diagnosis of chikungunya virus infection depends on clinical features (signs and symptoms) and when and where the person was suspected of being infected. Consider other infections and diseases in the differential diagnosis, including adenovirus, other alphaviruses (Barmah Forest, Mayaro, O'nyong-nyong, Ross River, and Sindbis), dengue, enterovirus, leptospirosis, malaria, measles, parvovirus, rubella, group A *Streptococcus*, typhus, Zika, and postinfectious arthritis and rheumatologic conditions.

Laboratory diagnosis is generally accomplished by testing serum to detect virus, viral nucleic acid, or virus-specific IgM and neutralizing antibodies. Because the virus develops high levels of viremia during the first week after symptom onset, chikungunya can often be diagnosed by performing viral culture or nucleic acid amplification on

serum. Virus-specific IgM antibodies normally develop toward the end of the first week of illness but can remain detectable for months to years after infection. Rarely, serum IgM antibody testing can yield false-positive results due to cross-reacting antibodies against related alphaviruses (e.g., Mayaro virus, O'nyong-nyong virus). Plaque reduction neutralization tests (PRNT) can be used to confirm the infection and, if warranted, discriminate between cross-reacting antibodies.

Testing for chikungunya virus infection is performed at several state health department laboratories and commercial laboratories. Confirmatory testing for virus-specific neutralizing antibodies is available through the Centers for Disease Control and Prevention (CDC)'s Division of Vector-Borne Diseases (970-221-6400). Report suspected chikungunya cases to state or local health departments to facilitate diagnosis and mitigate the risk for local transmission. Because chikungunya is a nationally notifiable disease, state health departments should report laboratory-confirmed cases to CDC through ArboNET (https://wwwn.cdc.gov/arbonet), the national surveillance system for arboviral diseases.

TREATMENT

No specific antiviral treatment is available for chikungunya; a number of therapeutic options are being investigated, however. Treatment for symptoms include rest, fluids, and use of analgesics and antipyretics. Nonsteroidal anti-inflammatory drugs can be used to help with acute fever and pain. For patients who report travel to dengue-endemic areas, however, acetaminophen is the preferred first-line treatment for fever and joint pain to reduce the risk for hemorrhage until dengue can be ruled out. For patients with persistent joint pain, use of nonsteroidal anti-inflammatory drugs, corticosteroids, including topical preparations, and physical therapy might help lessen the symptoms.

PREVENTION

Currently, no vaccine or preventive drug is available; several candidate vaccines are in various stages of development. Travelers can best prevent infection by avoiding mosquito bites (see Sec. 4, Ch. 6, Mosquitoes, Ticks & Other Arthropods). Travelers at increased risk for more severe disease, including travelers with underlying medical conditions and people late in their pregnancy (because their fetuses are at increased risk), might consider avoiding travel to areas with ongoing chikungunya outbreaks. If travel is unavoidable, emphasize the importance of using protective measures against mosquito bites.

CDC website: www.cdc.gov/chikungunya

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