Injection Anthrax

Anthrax in injection drug users usually develops within 1–4 days of exposure; death occurs in more than a quarter of confirmed cases. Case-patients present with severe soft-tissue infection manifested by swelling, erythema, and excessive bruising at the injection site; pain might be less than anticipated for the degree of swelling. Most patients become septic.

Inhalation Anthrax

Inhalation anthrax usually develops within a week after exposure, but the incubation period could be prolonged, up to 2 months. Before 2001, fatality ratios for inhalation anthrax were 90%; since then, ratios have fallen to 45% with improved treatment. During the first few days of illness (the prodromal period), most patients exhibit fever, chills, and fatigue. These symptoms can be accompanied by cough, shortness of breath, chest pain, and nausea or vomiting, making inhalation anthrax difficult to distinguish from influenza, coronavirus disease 2019 (COVID-19), or community-acquired pneumonia.

Over the next day or so, shortness of breath, cough, and chest pain become more common, and nonthoracic complaints (e.g., nausea, vomiting, altered mental status, diaphoresis, headache) develop in a third or more of patients. Upper respiratory tract symptoms occur in only a quarter of patients, and myalgias are rare. Altered mental status or shortness of breath generally brings patients to the attention of the medical establishment and heralds the fulminant phase of illness.

Anthrax Meningitis

Anthrax meningitis can develop from hematogenous spread of any of the clinical forms of anthrax, or it can occur alone; half of all reported cases are sequelae of cutaneous anthrax. The condition should be suspected in patients with anthrax who have severe headache, altered mental status (including confusion), meningeal signs, or neurologic deficits of any kind. Intracranial bleeding occurs in about two-thirds of patients with anthrax meningitis. Most cases of anthrax meningitis are fatal.

DIAGNOSIS

Include anthrax in the differential diagnosis of travelers returning with unexplained fevers or new skin lesions. Ask about recent travel to anthrax-endemic areas (www.cdc.gov/anthrax/specificgroups/travelers.html) and inquire about activities, such as direct contact with animals and animal products, drumming, and souvenir purchases, including animal-hide drums, leather, and hides.

Any of several methods can be used to make a laboratory diagnosis of anthrax infection: bacterial culture with isolation of *B. anthracis*; detection of bacterial DNA, antigens, or toxins; or detection of a host immune response to *B. anthracis*. Although lethal toxin can be detected in a single acute-phase serum, detection of a host immune response requires paired acute- and convalescent-phase serum samples.

In the United States, anthrax is a nationally notifiable disease. Laboratory Response Network reference laboratories can perform confirmatory testing (e.g., isolate identification). Laboratories at the Centers for Disease Control and Prevention (CDC) can perform isolate identification and conduct other complex tests (e.g., mass spectrometry for toxin, quantitative serology, antigen detection in tissues). Internationally, relevant national reference laboratories should perform testing.

For diagnostic support and specimen submission guidance, contact the state, local, territorial, or tribal public health department. Public health departments should urgently notify CDC of any suspected anthrax cases through the CDC Emergency Operations Center (770-488-7100). CDC's Bacterial Special Pathogens Branch can coordinate testing needs in conjunction with the public health department and other CDC programs; specimen collection and submission guidelines and algorithms for laboratory diagnosis are available at www.cdc.gov/anthrax/lab-testing/index.html. Collect specimens for culture before initiating antimicrobial therapy.

Diagnostic procedures for inhalation anthrax include thoracic imaging studies to detect a widened mediastinum or pleural effusion. Drainage of pleural effusions can be useful for diagnosis and can increase survival because it removes a nidus for toxin. Regardless of route of infection, patients

with systemic anthrax should have a diagnostic evaluation to rule out meningitis.

TREATMENT

Treat naturally occurring localized or uncomplicated cutaneous anthrax with 7–10 days of a single oral antibiotic. First-line agents include ciprofloxacin (or levofloxacin or moxifloxacin) or doxycycline; clindamycin is an alternative, as is penicillin if the bacterial isolate is penicillin-susceptible. Pending results of confirmatory testing, treat systemic anthrax with combination broad-spectrum intravenous antimicrobial drugs and one of the anthrax antitoxins approved for use by the US Food and Drug Administration (www.phe.gov/about/barda/anthrax/Pages/antitoxins.aspx); delays in initiating therapy can be fatal. Online recommendations for the treatment and prevention of anthrax are available for the following groups:

- Adults: https://wwwnc.cdc.gov/eid/article/20/2/13-0687_article
- People who are pregnant, postpartum, and lactating: https://wwwnc.cdc.gov/eid/article/20/2/13-0611_article
- Children: http://pediatrics.aappublications.org/content/133/5/e1411

PREVENTION

In 2019, CDC published updated recommendations from the Advisory Committee on Immunization Practices (ACIP) for preexposure use of anthrax vaccine and for postexposure management of previously unvaccinated people (www.cdc.gov/mmwr/volumes/68/rr/rr6804a1.htm). Vaccination against anthrax is not recommended for most travelers, except for researchers working in anthrax-endemic areas who could be at high risk for direct contact with animals and animal products. Vaccine is also recommended to members of the military traveling to these areas.

To prevent anthrax exposures while visiting anthrax-endemic countries, travelers should avoid direct and indirect contact with animal carcasses and should not eat meat from animals butchered after having been found dead or ill. Cooking contaminated meats does not eliminate the risk of contracting anthrax. Thus, travelers should determine the provenance of the meat they are being served in rural areas, and ask for meat that has been inspected by health authorities.

No tests are available to determine if animal byproducts are free from *B. anthracis* spore contamination; travelers should be aware of regulations concerning and restrictions against the importation of prohibited animal products, trophies, and souvenirs. Additional information regarding import regulations can be found in Sec. 4, Ch. 9, Bringing Animals & Animal Products into the United States; at the US Department of Agriculture, Animal and Plant Health Inspection Service website, Import-Export Regulations (www.aphis.usda.gov/aphis/ourfocus/importexport); and the World Organization for Animal Health website, Terrestrial Animal Health Code, Anthrax (www.oie.int/en/disease/anthrax).

CDC website: www.cdc.gov/anthrax

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BARTONELLA INFECTIONS

Christina Nelson

BARTONELLA QUINTANA INFECTION

INFECTIOUS AGENT: *Bartonella quintana*	
ENDEMICITY	Worldwide, wherever human body lice are found
TRAVELER CATEGORIES AT GREATEST RISK FOR EXPOSURE & INFECTION	Humanitarian aid workers Immigrants and refugees in crowded conditions
PREVENTION METHODS	Bathe and launder clothes regularly Avoid overcrowding and sharing clothes or bedding
DIAGNOSTIC SUPPORT	A clinical laboratory certified in high complexity testing, or contact CDC's Division of Vector-Borne Diseases (970-221-6400)

CARRIÓN DISEASE

INFECTIOUS AGENT: *Bartonella bacilliformis*	
ENDEMICITY	South America, Andes Mountains at 1,000–3,000 m (≈3,300–9,800 ft) elevation
TRAVELER CATEGORIES AT GREATEST RISK FOR EXPOSURE & INFECTION	Adventure tourists
PREVENTION METHODS	Avoid insect bites
DIAGNOSTIC SUPPORT	A clinical laboratory certified in high complexity testing, or contact CDC's Division of Vector-Borne Diseases (970-221-6400)

CAT SCRATCH DISEASE

INFECTIOUS AGENT: *Bartonella henselae*	
ENDEMICITY	Worldwide, wherever cat fleas are found
TRAVELER CATEGORIES AT GREATEST RISK FOR EXPOSURE & INFECTION	Travelers who encounter cats
PREVENTION METHODS	Avoid kittens and stray cats Control fleas on felines
DIAGNOSTIC SUPPORT	A clinical laboratory certified in high complexity testing, or contact CDC's Division of Vector-Borne Diseases (970-221-6400)

INFECTIOUS AGENT

Several gram-negative bacteria in the genus *Bartonella* cause human disease through various transmission routes. Human illness primarily is caused by *B. quintana* (known historically as "trench fever"), *B. bacilliformis* (Carrión disease), and *B. henselae* (cat scratch disease [CSD]). A variety of *Bartonella* spp. can cause subacute, culture-negative endocarditis; other clinical syndromes (e.g., encephalitis, ocular disease, osteomyelitis) due to *Bartonella* spp. have been reported. Additional *Bartonella* spp. that cause human illness have been described recently.

TRANSMISSION

B. quintana is transmitted by the human body louse; *B. bacilliformis* is transmitted by infected phlebotomine sand flies of the genus *Lutzomyia*; and *B. henselae* is transmitted through scratches from domestic or feral cats, particularly kittens. Direct transmission of *B. henselae* to humans by the bite of infected cat fleas likely can occur but has not yet been proven.

EPIDEMIOLOGY

B. quintana and CSD infections occur worldwide. *B. quintana* infections typically occur in populations that lack access to proper hygiene, (e.g., refugees living in crowded conditions, people experiencing homelessness). Minimal data are reported on CSD among travelers, but in the United States, CSD is more common in children, in southern states, and during the months August–January.

Carrión disease has limited geographic distribution; transmission occurs in the Andes Mountains at 1,000–3,000 m (≈3,300–9,800 ft) elevation. Most cases are reported in Peru, but cases have also occurred in Bolivia, Chile, Colombia, and Ecuador. Short-term travelers to endemic areas are likely at low risk.

CLINICAL PRESENTATION

Bartonella quintana Infection

Symptoms of *B. quintana* infection include fever, headache, transient rash, and bone pain, mainly in the shins, neck, and back.

Carrión Disease

Carrión disease has 2 distinct phases: an acute phase (Oroya fever) characterized by fever, myalgia, headache, and anemia; and an eruptive phase (verruga peruana) characterized by red-to-purple nodular skin lesions.

Cat Scratch Disease

CSD typically manifests as a papule or pustule at the inoculation site and enlarged, tender lymph nodes that develop proximal to the inoculation site 1–3 weeks after exposure. *B. henselae* infections also can cause prolonged fever. Atypical manifestations include follicular conjunctivitis, encephalitis, neuroretinitis, osteomyelitis, or infection of the liver or spleen.

Bacillary Angiomatosis

Bacillary angiomatosis can present as skin, subcutaneous, or bone lesions, and is caused by *B. henselae* or *B. quintana*; peliosis hepatis manifests as liver lesions and is caused by *B. henselae*. Both occur primarily in people infected with HIV.

DIAGNOSIS

Bartonella quintana Infection

B. quintana infection can be diagnosed by serology, polymerase chain reaction (PCR) testing, or blood culture. Endocarditis caused by *Bartonella* spp. can be diagnosed by elevated serology and by PCR or culture of excised heart valve tissue.

Carrión Disease

Oroya fever is typically diagnosed via blood culture or direct observation of the bacilli in peripheral blood smears, but sensitivity of these methods is low. PCR and serologic testing also might aid diagnosis. Clinicians can contact CDC's Division of Vector-Borne Diseases for diagnostic consultation by calling 970-221-6400.

Cat Scratch Disease

CSD can be diagnosed presumptively in patients with typical presentation and a compatible exposure history. Serology can confirm the diagnosis, although cross-reactivity might limit

interpretation in some circumstances. Serology is available from large commercial laboratories. *B. henselae* also can be detected by PCR or culture of lymph node aspirates by using special techniques. Some specialized laboratories offer *Bartonella* testing with novel techniques, but lack adequate clinical validation data; clinicians should consider these options with caution.

TREATMENT

Each variation of Bartonella infection has distinct recommended treatments.

Bartonella quintana Infection

Doxycycline plus gentamicin is the recommended treatment for *B. quintana* bacteremia and associated symptoms (e.g., fever and rash).

Carrión Disease

Treat Oroya fever using chloramphenicol or ciprofloxacin.

Cat Scratch Disease

Antibiotics may not be necessary for the treatment of typical CSD, since it can resolve without treatment. Consider prescribing azithromycin for patients with extensive lymphadenopathy or to shorten the course of disease.

A small percentage of people will develop disseminated disease with severe complications. The effect of antibiotic treatment in reducing risk of progression to atypical disease is unknown. Doxycycline plus rifampin appears to promote disease resolution for *B. henselae* neuroretinitis; regimens and duration of treatment might vary by clinical presentation.

PREVENTION

Travelers should protect themselves from bites of body lice and sand flies (see Sec. 4, Ch. 6, Mosquitoes, Ticks & Other Arthropods). People, especially those who are immunocompromised, should avoid kittens and stray cats; rough play with associated scratches is a particular risk. People can reduce the risk for cats to carry *B. henselae* by controlling fleas and limiting cats' outdoor roaming. People also should wash their hands promptly after handling cats.

CDC website: www.cdc.gov/bartonella

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BRUCELLOSIS

María Negrón, Rebekah Tiller, Grishma Kharod

INFECTIOUS AGENT: *Brucella* spp.	
ENDEMICITY	Worldwide
TRAVELER CATEGORIES AT GREATEST RISK FOR EXPOSURE & INFECTION	People who consume unpasteurized dairy products or who have contact with infected animals
PREVENTION METHODS	Avoid contact with infected animals Practice safe food habits and avoid unpasteurized dairy products Use personal protective equipment, as appropriate
DIAGNOSTIC SUPPORT	A clinical laboratory certified in high complexity testing; state health department; CDC's Bacterial Special Pathogens Branch (bspb@cdc.gov); or the CDC Emergency Operations Center (770-488-7100)

INFECTIOUS AGENT

Brucella spp., the causative agents for brucellosis, are facultative, intracellular, gram-negative coccobacilli. The main *Brucella* spp. known to cause human disease are *Brucella abortus* (including the livestock vaccine strain *Brucella abortus* RB51), *B. melitensis*, *B. suis*, and *B. canis*.

EPIDEMIOLOGY & TRANSMISSION

Over 500,000 new human cases of brucellosis—a bacterial zoonosis—are reported worldwide each year. This number is likely an underestimate, however, because cases are underreported and often misdiagnosed because clinical symptoms are nonspecific, physicians might lack awareness, and laboratory capacity for diagnosis is limited. *B. melitensis* is the most frequently reported cause of brucellosis worldwide, but the most widespread potential source of infection is *B. abortus*.

Human infections occur most frequently among travelers to, or people living in, areas where the disease is endemic in animals—primarily cattle, goats, and sheep—in Africa, Central and South America, Asia, eastern Europe, along the Mediterranean Basin, and the Middle East. In North America, *Brucella* spp. are endemic to the feral swine population and wildlife around the Greater Yellowstone Area.

Humans most commonly acquire *Brucella* through consumption of unpasteurized dairy products (e.g., raw milk, and butter, soft cheese, or ice cream made from raw milk) from infected animals. The bacteria can also enter the body via skin wounds, mucous membranes, or inhalation, so direct contact with infected animal tissues or fluids can be an exposure risk. Activities such as carcass dressing and assisting birthing animals can increase the risk for contact with infective tissues and fluids.

Travelers' brucellosis can be caused by *B. suis* or *B. canis* infection because certain travelers might have contact with animal populations infected with these *Brucella* species (e.g., *B. suis* in feral swine and caribou or reindeer, and *B. canis* in dogs). Consumption of undercooked meat from infected animals can lead to infection, but this exposure risk is less likely because bacterial loads are lower in muscle. Person-to-person transmission has been reported but is rare. Exposure to *Brucella* during pregnancy can increase the risk for miscarriage, so travelers who are or might be pregnant should take extra precautions.

CLINICAL PRESENTATION

The incubation period of brucellosis is usually 2–4 weeks (range 5 days–6 months). Initial clinical presentation is nonspecific and includes

arthralgia, fatigue, fever, headache, malaise, myalgia, and night sweats. Focal infections are common and can affect most organs in the body. Osteoarticular involvement is the most common brucellosis complication, as is reproductive system involvement. Although rare, endocarditis can occur and is the principal cause of death among patients with brucellosis.

DIAGNOSIS

Blood culture is considered the diagnostic gold standard, but isolation rates can vary considerably (25%–80%) depending on stage of infection, previous use of antimicrobial drugs, type and volume of clinical specimen, and culture method used. Bacterial growth in culture can be observed within 3–5 days but might take longer; therefore, laboratories should hold cultures for ≥10 days before considering a sample negative.

To increase recovery of the organism, collect samples during a febrile episode and prior to starting antimicrobial drugs; when focal disease is suspected, collect samples for culture from the affected area (e.g., cerebrospinal fluid, joint aspirate). Inform the laboratory that brucellosis is suspected when submitting blood, bone marrow, or other clinical specimens for culture because the bacteria take longer to grow, and laboratory personnel require additional personal protective equipment when handling the clinical specimens and culture.

Serologic testing is the most common method for diagnosis. The serum agglutination test (SAT) is the standard method for serologic diagnosis and detects IgM, IgG, and IgA. The Bacterial Special Pathogens Branch at the Centers for Disease Control and Prevention (CDC) performs a modified version of the SAT, known as the *Brucella* microagglutination test (BMAT). In general, ELISA tests have good sensitivity and specificity and can detect IgM or IgG, and US commercial diagnostic laboratories have the capacity to perform these assays.

Because most *Brucella* serologic assays show variable levels of cross-reactivity with other gram-negative bacteria (e.g., *Escherichia coli* O:157, *Francisella tularensis*, *Yersinia enterocolitica*), consider the limitations of serologic testing for diagnosing brucellosis. In addition, *Brucella* antibodies can persist for >1 year despite successful antibiotic treatment. Finally, no validated serologic assays are available to detect antibodies produced against infections caused by *B. canis* and *B. abortus* RB51 strain in humans. If infection with either of these organisms is possible or suspected, perform a culture on a specimen taken prior to the start of antimicrobial drug therapy.

For diagnostic support and specimen submission guidance, contact the local, territorial, tribal, or state public health department. CDC's Bacterial Special Pathogens Branch (bspb@cdc.gov) can coordinate testing needs in conjunction with the public health department; CDC-specific guidance on specimen submission can be found at the CDC Test Directory (www.cdc.gov/laboratory/specimen-submission/list.html; enter *Brucella* in the search bar).

TREATMENT

A combined regimen of doxycycline (or oral tetracycline) and rifampin for ≥6 weeks is recommended for the treatment of uncomplicated infection. For complicated brucellosis (endocarditis, meningitis, osteomyelitis), consider adding an aminoglycoside in combination with doxycycline and extend the duration of therapy to 4–6 months. *B. abortus* RB51 is resistant to rifampin; modify treatment for brucellosis caused by this strain accordingly (e.g., doxycycline in combination with trimethoprim-sulfamethoxazole, unless contraindicated). Other antimicrobial agents have been used in various combinations; treatment should be guided by a clinician with expertise in infectious diseases. Incorrect or incomplete therapy, or late diagnosis, can result in relapse.

PREVENTION

Travelers should avoid unpasteurized dairy products, undercooked meat, and potentially contaminated meat products in countries where brucellosis is endemic. People who dress or butcher wild animals or who handle birthing products from animals potentially infected with *Brucella* spp. should wear appropriate protective equipment, including rubber gloves, goggles or

face shields, and gowns. Inform clinical microbiology laboratories when submitting specimens from patients with suspected brucellosis to ensure proper biosafety precautions in the laboratory handling of specimens and specimen derivatives.

For questions on laboratory diagnostics, post-exposure guidance, or treatment, contact the local, territorial, tribal, or state public health department, or CDC's Bacterial Special Pathogens Branch (bspb@cdc.gov).

CDC website: www.cdc.gov/brucellosis

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CAMPYLOBACTERIOSIS

Farrell Tobolowsky, Mark Laughlin, Rachael Aubert, Daniel Payne

INFECTIOUS AGENT: *Campylobacter* spp.	
ENDEMICITY	Worldwide
TRAVELER CATEGORIES AT GREATEST RISK FOR EXPOSURE & INFECTION	Children <5 years old Adults ≥65 years old Males People with immunodeficiencies
PREVENTION METHODS	Follow safe food and water precautions Practice good hand hygiene
DIAGNOSTIC SUPPORT	A clinical laboratory certified in moderate complexity testing

INFECTIOUS AGENT

Campylobacteriosis is caused by gram-negative, curved microaerophilic bacteria of the family *Campylobacteriacae*. Most infections are caused by *Campylobacter jejuni*; ≥18 other species, including *C. coli*, also cause human infections. *C. jejuni* and *C. coli* are carried normally in the intestinal tracts of many domestic and wild animals.

TRANSMISSION

The major modes of transmission include eating contaminated foods, especially undercooked chicken and foods contaminated by raw chicken, and consuming contaminated water or dairy products, most commonly unpasteurized milk. Transmission also occurs less commonly from contact with pets, particularly kittens and puppies, and farm animals (e.g., cows, poultry). Rarely, *Campylobacter* can be transmitted from person to person by the fecal–oral route. The infectious dose is small; <500 organisms can cause disease.

EPIDEMIOLOGY

Campylobacter is a leading cause of bacterial diarrheal disease worldwide and caused ≈96 million cases in 2010. In the United States, *Campylobacter* causes ≈1.5 million human illnesses every year. About 15% of illnesses are associated with international travel, and *Campylobacter* comprises a large proportion of travel-related enteric infections. All travelers are at risk for infection, but children <5 years of age, adults ≥65 years of age, males, and people with immunodeficiencies are at increased risk. Risk is greatest in US travelers to Africa, Asia, and South America, especially to areas where food handling practices and sanitation might not be adequate. The incidence of *Campylobacter* infection is greater in rural areas. Infection occurs year-round in low- and middle-income countries and exhibits late summer and fall seasonality in developed countries.

CLINICAL PRESENTATION

The incubation period is typically 2–4 days but can range from 1–10 days. Illness is characterized by diarrhea (frequently bloody), abdominal pain, fever, and occasionally nausea and vomiting. More severe illness can occur, characterized by dehydration, bloodstream infection, or symptoms mimicking acute appendicitis or ulcerative colitis. Postinfectious complications include irritable bowel syndrome (in 9%–13% of patients), reactive arthritis (2%–5%), and Guillain-Barré syndrome (GBS; 0.1%). *C. jejuni* is the most frequently observed bacterial infection preceding GBS, and ≈5%–41% of all GBS cases could be attributed to campylobacteriosis; symptoms usually begin 1–3 weeks after the onset of enteritis.

DIAGNOSIS

Campylobacteriosis diagnosis is traditionally based on isolation of the organism from stool specimens or rectal swabs by using selective media incubated under reduced oxygen tension at 42°C (107.6°F) for 72 hours. Direct detection in stool specimens using multi-analyte PCR panels has become common.

Collect stool specimens as early as possible after symptoms begin and before initiating antimicrobial drug treatment. Because the organism is fastidious, a delay in transporting the specimen to the laboratory will affect viability. If transport and processing are not possible within 2 hours of stool sample collection, place specimens in a transport medium, (e.g., Cary-Blair) according to standard guidelines. Laboratories might reject stool specimens without preservative that have been in transit for >2 hours. Campylobacter cannot be recovered from frozen specimens.

Culture and isolation of *Campylobacter* from the specimen are needed to subtype and test for antimicrobial susceptibility. Identification to the species level can be difficult using traditional biochemical methods; molecular methods, including PCR, 16S rRNA sequencing, or whole-genome sequencing often are required. Matrix-assisted laser desorption ionization time of flight (MALDI-TOF) mass spectroscopy provides a rapid, sensitive method for identifying *Campylobacter* species.

Culture-independent methods for direct detection of *Campylobacter* from stool specimens include both immunologic (antigen-based) and nucleic-acid amplification-based tests (NAATs). Several NAAT gastrointestinal panels are approved by the US Food and Drug Administration (FDA) to detect *Campylobacter* and a variety of other gastrointestinal pathogens. However, many of

these panels detect only *Campylobacter* species, and reflex culture is required for further identification, subtyping, and antimicrobial susceptibility testing (AST). The Clinical and Laboratory Standards Institute (CLSI) provides methods and interpretive criteria for AST.

Broth microdilution or disk diffusion can be performed under microaerophilic conditions, and clinical interpretive criteria (also known as susceptibility breakpoints) are available for both methods for ciprofloxacin, erythromycin, and tetracycline. Broth microdilution breakpoints are also available for doxycycline. Azithromycin susceptibility or resistance can be predicted by erythromycin testing.

Sensitivity and specificity of stool antigen tests are variable; in settings of low prevalence, the positive predictive value is likely to be low. Therefore, laboratories should confirm positive results of stool antigen tests by culture. Campylobacteriosis is a nationally notifiable disease in the United States.

TREATMENT

Campylobacteriosis is generally self-limited in healthy people, lasting ≤1 week and requiring only fluids and supportive care. Antimicrobial drug therapy decreases the duration of symptoms and bacterial shedding if administered early during illness. Because campylobacteriosis generally cannot be distinguished from other causes of travelers' diarrhea without a diagnostic test, use of empiric antibiotics in travelers should follow the guidelines for travelers' diarrhea (see Sec. 2, Ch. 6, Travelers' Diarrhea).

Rates of antibiotic resistance, especially fluoroquinolone resistance, have risen sharply in the past 20 years, and high rates of resistance are now seen in many regions, especially in South America and Southeast Asia. Travel abroad is a risk factor for infection with antimicrobial-resistant *Campylobacter*. Suspect resistant infections in returning travelers with campylobacteriosis in whom empiric fluoroquinolone treatment has failed. Macrolides like azithromycin are the current drugs of choice when antimicrobial drug treatment is indicated. Intravenous antibiotics might rarely be required for severe infections or for highly resistant strains.

PREVENTION

No vaccine is available. Travelers can best prevent infection by adhering to standard food and water safety precautions (see Sec. 2, Ch. 8, Food & Water Precautions) and by washing hands thoroughly with soap and water after contact with animals or environments that might be contaminated with animal feces. Antibiotic prophylaxis is not recommended.

CDC website: www.cdc.gov/foodsafety/diseases/campylobacter

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CHOLERA

Talia Pindyck, Bruce Gutelius, Eric Mintz

INFECTIOUS AGENT: Toxigenic *Vibrio cholerae* O1 or O139	
ENDEMICITY	Africa Americas (island of Hispaniola at very low levels) South and Southeast Asia
TRAVELER CATEGORIES AT GREATEST RISK FOR EXPOSURE & INFECTION	Humanitarian aid workers Refugees and internally displaced people Travelers going to endemic or outbreak areas
PREVENTION METHODS	Travelers who consistently observe safe food, water, sanitation, and hand hygiene precautions have virtually no risk of infection Cholera is a vaccine-preventable disease
DIAGNOSTIC SUPPORT	A clinical laboratory certified in moderate complexity testing; state health department

INFECTIOUS AGENT

Cholera is an acute bacterial intestinal infection caused by toxigenic *Vibrio cholerae* O-group 1 (O1) or O-group 139 (O139). Many other serogroups of *V. cholerae*, with or without the cholera toxin gene (including the nontoxigenic strains of the O1 and O139 serogroups), can cause a cholera-like illness. Only toxigenic strains of serogroups O1 and O139 have caused widespread epidemics and are reportable to the World Health Organization (WHO) as "cholera." Toxigenic strains of *V. cholerae* O1 are the source of an ongoing global pandemic that began in 1961, but the O139 serogroup is localized to a few areas in Asia.

V. cholerae O1 has 2 biotypes, classical and El Tor, and each biotype can be divided into distinct serotypes, Inaba Ogawa, and rarely, Hikojima. The symptoms of infection are indistinguishable, but more people infected with the El Tor biotype remain asymptomatic or have only a mild illness. Globally, most cholera cases are caused by O1 El Tor organisms. In recent years, an El Tor variant with characteristics of both classical and El Tor biotypes has emerged in Asia and spread to Africa and the Caribbean. This is the strain responsible for the epidemic on Hispaniola, the island shared by Haiti and the Dominican Republic; compared to older El Tor strains, this newer variant appears to be more virulent, causing a greater proportion of severe episodes of cholera with the potential for higher death rates.

TRANSMISSION

Toxigenic *V. cholerae* O1 and O139 are free-living bacterial organisms found in fresh and brackish water, often in association with copepods or other zooplankton, shellfish, and aquatic plants. Cholera infections are acquired most often from untreated drinking water in which toxigenic *V. cholerae* naturally occurs or has been introduced from the feces of an infected person. Other common vehicles include raw or undercooked food, especially fish and shellfish. Other foods, including produce, are less commonly implicated. Direct person-to-person transmission, including to health care workers during epidemics, has been reported.

When in countries affected by cholera, travelers who consistently observe recommendations regarding safe drinking water, food preparation and consumption, handwashing, and sanitation have virtually no risk of acquiring the disease.

EPIDEMIOLOGY

Cholera is endemic to ≈50 countries, primarily in South and Southeast Asia and Africa. During 2007–2017, the United States had 117 confirmed cholera cases among people who traveled internationally in the week before illness; ≈16% reported travel to India or Pakistan. Other reported destinations included other countries in Southeast Asia, East and West Africa, and the Caribbean. Sporadic cases in the United States associated with travel to or from cholera-affected countries in Asia and Africa continue to occur.

More than half (70/117, ≈60%) of US cases during 2007–2017 were linked to travel to Haiti, the Dominican Republic, or Cuba, the 3 Caribbean countries affected by a large cholera epidemic that began in Haiti in October 2010. Ninety-four percent (66/70) of case-patients reported travel to either Haiti or the Dominican Republic sometime during 2010–2017. The other case-patients had been to Cuba sometime during 2013–2015.

In 2018 and 2019, the most recent years for which data are available, no cholera cases in the United States were associated with travel to Haiti or the Dominican Republic, and those 2 countries reported far fewer cholera cases to WHO during these 2 years than in previous years. Although efforts were underway to eliminate cholera from Hispaniola, in October 2022, the Pan American Health Organization reported a resurgence of the disease in Haiti. Before 2022, the last confirmed case of cholera in Haiti was in 2019, and in the Dominican Republic in 2018.

Travelers to areas where cholera is endemic or where an active epidemic is occurring are at risk for cholera infection. Health care and response workers in cholera-affected areas (e.g., during an outbreak, after a disaster) also might be at increased risk for cholera. People who do not follow handwashing recommendations, and/or do not use latrines or other sanitation systems are at increased risk for infection. People who have low gastric acidity have a greater risk for infection, and they, along with those with blood type O, are at greater risk for developing severe disease if infected.

CLINICAL PRESENTATION

Cholera most commonly manifests as acute watery diarrhea in an afebrile person. The pathogen typically remains in the gastrointestinal tract and does not invade the bloodstream. Infection is often mild or asymptomatic, but it can be severe. Severe cholera (*cholera gravis*) occurs in ≈10% of cholera episodes and is characterized by profuse watery diarrhea, described as rice-water stools, often accompanied by nausea and vomiting that can rapidly lead to severe volume depletion.

Clinical findings include dry mucous membranes and loss of skin turgor, hypotension, tachycardia, and thirst. Additional symptoms, including muscle cramps, are secondary to the resulting electrolyte imbalances. Untreated cholera can cause rapid loss of body fluids, which can lead to severe dehydration, hypovolemic shock, and death within hours. The case-fatality ratio for untreated cholera can reach >50%, but with adequate and timely rehydration, the case-fatality ratio is <1%.

DIAGNOSIS

In the United States, cholera traditionally is confirmed by isolation and identification of toxigenic *V. cholerae* O1 recovered from a stool sample of a patient with acute, watery diarrhea. Before administering antimicrobial treatment, collect patient stool samples and preserve samples in Cary-Blair medium for transport at ambient temperature. Selective media (e.g., taurocholate-tellurite-gelatin agar, thiosulfate-citrate-bile salts agar) also can be used for pathogen isolation.

Reagents for serogrouping *V. cholerae* isolates are available in most state health department laboratories. Antigen-based rapid diagnostic tests (RDTs) do not yield an isolate for toxin detection, antimicrobial susceptibility testing, or subtyping. Reflex culture to recover an isolate should always be performed when a *V. cholerae* diagnosis is derived from an RDT, and clinicians should send the isolate to a public health laboratory for additional characterization.

Currently available commercial RDTs, which detect O1 and O139 antigens in human stool specimens using monoclonal antibodies, are useful for cholera outbreak detection and response, but should not be used to diagnose individual patients. Molecular methods (e.g., PCR, whole-genome sequencing) can detect *V. cholerae* and characterize its genetic profile and are increasingly used in public health laboratories. Cholera

is a nationally notifiable disease in the United States, and all isolates obtained in the United States should be sent to the Centers for Disease Control and Prevention (CDC) via state health department laboratories for identification and virulence testing.

TREATMENT

Rehydration is the cornerstone of cholera treatment. Administer oral rehydration solution and, when necessary, intravenous fluids and electrolytes; timely administration in adequate volumes will reduce case-fatality ratios to <1%. Antibiotics will reduce fluid requirements and duration of illness and are indicated in conjunction with aggressive hydration for severe cases and for patients with moderate dehydration and ongoing fluid losses.

Whenever possible, antimicrobial susceptibility testing should inform treatment choices. In most countries, doxycycline is recommended as the first-line antibiotic treatment for children, adults, and pregnant people. Previously, tetracycline antibiotics (including doxycycline) were not recommended for children due to concern for dental discoloration, or pregnant people due to concern for teratogenic effects. A recent systematic review among young children and pregnant people receiving doxycycline did not demonstrate a safety risk.

Multidrug-resistant isolates are emerging, particularly in South Asia, with resistance to quinolones, trimethoprim-sulfamethoxazole, and tetracycline. The strain from Hispaniola is also multidrug resistant; as of 2013, however, tested isolates were still sensitive to doxycycline and tetracycline. Macrolides, including erythromycin and azithromycin, are alternative agents for multidrug-resistant isolates. Zinc supplementation reduces the severity and duration of cholera and other diarrheal diseases in children living in resource-limited areas.

PREVENTION

Food & Water

Travelers should follow safe food and water precautions and frequently wash hands (see Sec. 2, Ch. 8, Food & Water Precautions). Antibiotic chemoprophylaxis is not recommended.

Vaccine

No country or territory requires vaccination against cholera as a condition for entry. CVD 103-HgR, a live, attenuated, single-dose oral cholera vaccine (Vaxchora, PaxVax), is licensed in the United States. The vaccine was previously marketed under the names Orochol and Mutacol in other countries.

INDICATIONS

The Advisory Committee on Immunization Practices (ACIP) recommends CVD 103-HgR vaccine for both pediatric and adult travelers (2–64 years old) visiting areas of active cholera transmission. An area of active cholera transmission is defined as a province, state, or other administrative subdivision within a country with endemic or epidemic cholera caused by toxigenic *V. cholerae* O1. It includes areas that are prone to recurrence of cholera epidemics that have had cholera activity within the past year. Locations where rare sporadic cholera cases have been reported are not considered active cholera areas.

CDC provides a list of countries for which cholera vaccine can be considered for travelers (see "Who is at risk?") at https://wwwnc.cdc.gov/travel/diseases/cholera. Cholera activity can occur in certain parts of a country or in certain settings, however, and information about places with cholera activity might be incomplete because of variations in surveillance and reporting. The vaccine is not routinely recommended for most travelers from the United States because they do not visit areas with active cholera transmission. Clinicians and travelers can find additional country-specific information on CDC's Travelers' Health website at https://wwwnc.cdc.gov/travel/destinations/list.

EFFICACY

In clinical efficacy trials, adults aged 18–45 years who received Vaxchora were protected against severe diarrhea after oral *V. cholerae* O1 challenge at 10 days (vaccine efficacy 90%) and at 3 months (vaccine efficacy 80%) after vaccination. In adults aged 46–64 years, vibriocidal antibody seroconversion rates, the best available marker for protection against cholera, were comparable to the response seen in adults aged 18–45 years. Multicenter randomized clinical efficacy trials

of CVD 103-HgR in children (published in 2020) demonstrated CVD 103-HgR induced serum vibriocidal antibody seroconversion on day 11 in >97% of recipients aged 2–17 years; efficacy was not assessed.

ADMINISTRATION

Prepare and administer Vaxchora in a health care setting equipped to dispose of medical waste. To prepare Vaxchora, reconstitute the buffer component in 100 milliliters (mL) of cold or room temperature, purified, non-carbonated, non-flavored bottled or spring bottled water. The package insert indicates that for children aged 2–5 years, half of the reconstituted buffer solution (50 mL) should be discarded before adding the active component (lyophilized *V. cholerae* CVD 103-HgR); after preparation, a single oral dose of Vaxchora for children aged 2–5 years is 50 mL. Patients should avoid eating or drinking for 60 minutes before and after taking Vaxchora vaccine. Administer Vaxchora as a single oral dose ≥10 days before potential cholera exposure.

BOOSTER DOSES

The safety and efficacy of revaccination with CVD 103-HgR have not been established.

SAFETY & ADVERSE REACTIONS

Serious adverse events were rare among recipients of Orochol and Mutacol, the previously marketed formulation of the CVD 103-HgR vaccine.

In clinical safety trials involving adults aged 18–45 years, headache, tiredness, and nausea, vomiting, and diarrhea were reported more commonly by CVD 103-HgR recipients than by placebo recipients within 7 days of vaccination. Among children and adolescents aged 2–17 years, adverse events more commonly reported by vaccine than by placebo recipients included abdominal pain, anorexia, headache, and tiredness. No vaccine-related serious adverse events were reported among participants aged 2–64 years.

Vaxchora is not currently licensed for use in children <2 years or adults >65 years of age. The safety and effectiveness of Vaxchora have not been established in pregnant or lactating people, or in immunocompromised people. No difference in adverse events were reported among HIV-positive recipients of an older formulation of the CVD 103-HgR vaccine and those who received placebo.

PRECAUTIONS & CONTRAINDICATIONS

Vaxchora is contraindicated in people with a history of severe allergic reaction to the ingredients of this or any other cholera vaccine. A study with the older formulation of CVD 103-HgR showed that concomitant use of chloroquine decreased the immune response to the vaccine; therefore, antimalarial prophylaxis with chloroquine should begin ≥10 days after administration of Vaxchora. Coadministration of mefloquine and proguanil with CVD 103-HgR did not diminish the vaccine's immunogenicity. Antimicrobial drugs might decrease the immune response to CVD 103-HgR, so clinicians should not administer the vaccine to patients who have received antibiotics in the previous 14 days.

Vaxchora might be shed in the stool for ≥7 days, and the vaccine strain could be transmitted to nonvaccinated close contacts. Clinicians and travelers should use caution when considering whether to use the vaccine in people with close contacts who are immunocompromised.

CDC website: www.cdc.gov/cholera

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DIPHTHERIA

Anna Acosta, Sarah Bennett

5

INFECTIOUS AGENT: Toxigenic strains of *Corynebacterium diphtheriae* biotypes *mitis*, *gravis*, *intermedius*, or *belfanti*	
ENDEMICITY	The Americas (Haiti and the Dominican Republic) Asia and the South Pacific Eastern Europe Middle East
TRAVELER CATEGORIES AT GREATEST RISK FOR EXPOSURE & INFECTION	Travelers not current with diphtheria toxoid vaccine
PREVENTION METHODS	Diphtheria is a vaccine-preventable disease
DIAGNOSTIC SUPPORT	A clinical laboratory certified in high complexity testing; state health department; request Elek testing for toxin production by contacting CDC Emergency Operations Center (770-488-7100)

INFECTIOUS AGENT

Diphtheria is caused by toxigenic strains of *Corynebacterium diphtheriae* biotype *mitis*, *gravis*, *intermedius*, or *belfanti*. Toxigenic strains of *C. ulcerans* also cause rare cases of a diphtheria-like illness.

TRANSMISSION

Transmission occurs person-to-person through respiratory droplets or direct contact with secretions from cutaneous diphtheria lesions, and rarely, by fomites.

EPIDEMIOLOGY

Diphtheria is endemic to many regions around the world: Haiti and the Dominican Republic in the Americas; Asia and the South Pacific; Eastern Europe; and the Middle East. Since 2016, respiratory diphtheria outbreaks have occurred in Bangladesh, Burma (Myanmar), Haiti, Indonesia, South Africa, Ukraine, Venezuela, Vietnam, and Yemen. Cutaneous diphtheria is common in tropical countries. Respiratory and cutaneous diphtheria have been reported in travelers to countries with endemic disease. The last case of respiratory diphtheria in a US traveler was reported in 2003, but toxin-producing cutaneous *C. diphtheriae* was identified from 4 US residents who returned from travel between September 2015 and March 2018. Diphtheria can affect any age group, especially people who are not fully vaccinated with diphtheria toxoid vaccine.

CLINICAL PRESENTATION

The incubation period is 2–5 days (range 1–10 days). Affected anatomic sites include the mucous membranes of the upper respiratory tract (nose, pharynx, tonsils, larynx, and trachea [respiratory diphtheria]), skin (cutaneous diphtheria), or rarely, mucous membranes at other sites (eye, ear, vulva). Nasal diphtheria can be asymptomatic or mild, with a blood-tinged discharge.

Respiratory diphtheria has a gradual onset and is characterized by a mild fever (rarely >101°F [38.3°C]), sore throat and difficulty swallowing, malaise, loss of appetite, and if the larynx is involved, hoarseness. The hallmark of respiratory diphtheria is a pseudomembrane that appears within 2–3 days of illness onset, covers the mucous lining of the tonsils, pharynx, larynx, or nares, and that can extend into the trachea. The pseudomembrane is firm, fleshy, grey, and adherent; it typically will bleed after attempts to remove or dislodge it. Fatal airway obstruction can result if the pseudomembrane extends into the larynx or trachea or if a piece of it becomes dislodged. The case-fatality ratio is 5%–10%.

DIAGNOSIS

A presumptive diagnosis is usually based on clinical features. Diagnosis is confirmed by isolating *C. diphtheriae* from culture of nasal or throat swabs or pseudomembrane tissue and testing for toxin production by the Elek test. Laboratory capacity for diphtheria culture and Elek testing varies by country, and testing might be available through national reference or commercial laboratories. In the United States, the Centers for Disease Control and Prevention (CDC) has the only laboratory able to perform Elek testing. Diphtheria is a nationally notifiable disease in the United States, and clinicians can contact their state health department or the CDC Emergency Operations Center for more information.

TREATMENT

Patients with respiratory diphtheria require hospitalization to monitor response to treatment and manage complications. Equine diphtheria antitoxin (DAT) is the mainstay of treatment and can be administered without waiting for laboratory confirmation. In the United States, DAT is available to physicians under an investigational new drug protocol by contacting their state health department, followed by the CDC Emergency Operations Center at 770-488-7100.

In addition to DAT, treating physicians should prescribe an antibiotic (erythromycin or penicillin) to eliminate the causative organisms, stop toxin production, and reduce communicability. Patients will require supportive care, including airway and cardiac monitoring. In addition, close contacts of patients should receive antimicrobial prophylaxis with erythromycin or penicillin.

PREVENTION

All travelers should be up to date with diphtheria toxoid vaccine before departure. After a primary series and childhood and adolescent boosters, all adults should receive booster doses with a diphtheria toxoid–containing vaccine at 10-year intervals, given either as Td (tetanus-diphtheria) or Tdap (tetanus-diphtheria-acellular pertussis). This booster is particularly important for travelers who will live or work in countries where diphtheria is endemic.

CDC website: www.cdc.gov/diphtheria

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ESCHERICHIA COLI, DIARRHEAGENIC

Jennifer Collins, Danielle Tack, Talia Pindyck, Patricia Griffin

5

INFECTIOUS AGENT: *Escherichia coli* (diarrheagenic)	
ENDEMICITY	Worldwide
TRAVELER CATEGORIES AT GREATEST RISK FOR EXPOSURE & INFECTION	All travelers, especially those going to low- and middle-income countries
PREVENTION MEASURES	Follow safe food and water precautions
DIAGNOSTIC SUPPORT	A clinical laboratory certified in moderate complexity testing

INFECTIOUS AGENT

Escherichia coli are gram-negative bacteria that inhabit the gastrointestinal tract. Most types do not cause illness, but 5 pathotypes are associated with diarrhea: enterotoxigenic *E. coli* (ETEC), Shiga toxin–producing *E. coli* (STEC), enteropathogenic *E. coli* (EPEC), enteroaggregative *E. coli* (EAEC), and enteroinvasive *E. coli* (EIEC). In addition, diffusely adherent *E. coli* (DAEC) might also be associated with diarrhea. Pathotypes that are common causes of urinary tract infections, bloodstream infections, and meningitis are not covered here.

E. coli serotypes are determined by surface antigens (O and H), and specific serotypes tend to cluster within specific pathotypes. Pathotype determination typically is based on testing for virulence genes. Some *E. coli* have virulence genes of >1 pathotype; for example, the O104:H4 strain that caused a 2011 outbreak in Germany produced Shiga toxin and had adherence properties typical of EAEC.

STEC also are called verotoxigenic *E. coli* (VTEC), and the term enterohemorrhagic *E. coli* (EHEC) commonly is used to specify STEC strains capable of causing human illness, especially bloody diarrhea and hemolytic uremic syndrome (HUS).

TRANSMISSION

Diarrheagenic *E. coli* pathotypes can be passed in the feces of humans and other animals. Transmission occurs through the fecal–oral route, via consumption of contaminated food or water, and through person-to-person contact, contact with animals or their environment, and swimming in untreated water. Humans constitute the main reservoir for non-STEC pathotypes that cause diarrhea in humans. The intestinal tracts of animals, especially cattle and other ruminants, are the primary reservoirs of STEC.

EPIDEMIOLOGY

The 2010 World Health Organization (WHO) Global Burden of Foodborne Diseases report estimated ≈111 million illnesses and ≈63,000 deaths caused by diarrheagenic *E. coli* globally each year. Rates of infection vary by region, and certain types of diarrheagenic *E. coli* infections, mainly ETEC, are associated with travel to low- and middle-income countries. The incidence of travel-associated diarrhea caused by *E. coli* is likely underestimated because many travelers do not seek medical care or have stool testing performed, particularly if diarrhea is non-bloody, as commonly occurs with ETEC infection. Moreover, many clinical laboratories do not use methods that can detect diarrheagenic *E. coli* other than STEC in stool samples.

Risk for travelers' diarrhea can be divided into 3 levels, according to the destination country. Low-risk countries include Australia, Canada, Greenland, Japan, New Zealand, the United States, and countries in northern and western Europe. Intermediate-risk countries include Argentina, Brazil, Chile, Morocco, Portugal, South Africa, Thailand (in Bangkok, Chiang Mai, and Phuket; risk to travelers going to rural areas is likely greater), Uruguay, and most countries in the Caribbean, eastern Europe, and the Middle East. High-risk countries include Afghanistan, Burma (Myanmar), the Indian subcontinent, Indonesia, Iran, Malaysia, Mexico, Papua New Guinea, most countries in Africa, and countries in Central America and northern South America, including Bolivia and Paraguay.

STEC infections are most commonly reported in industrialized countries, and ≈85% of STEC infections among international travelers are caused by non-O157 serotypes. Additional information about travelers' diarrhea is available in Sec. 2, Ch. 6, Travelers' Diarrhea.

CLINICAL PRESENTATION

Diarrheagenic *E. coli* infections, other than STEC, have incubation periods ranging from 8 hours to 3 days. The median incubation period of STEC infection is 3–4 days, with a range of 1–10 days. Clinical manifestations of diarrheagenic *E. coli* vary by pathotype (see Table 5-02).

DIAGNOSIS

Diagnostic testing is not usually recommended for uncomplicated travelers' diarrhea unless treatment is indicated. Until recently, diarrheagenic *E. coli* other than STEC could not be distinguished from non-pathogenic *E. coli* in stool using routine tests in clinical laboratories. Commercial molecular tests have increasingly become available and can identify ETEC, EPEC, EAEC, and EIEC through detection of virulence genes.

Consider several caveats when interpreting results of such tests. The combination of virulence genes that confer pathogenicity has not been determined for all pathotypes, and *E. coli* sometimes have virulence genes from >1 pathotype due to transfer of mobile genetic elements. Some studies have identified some genes, including the *eae* gene used to diagnose EPEC, at a similar frequency in stools from healthy people as from those with acute diarrhea. Identification of 2 virulence genes in a specimen does not mean they are carried by the same organism. Finally, molecular tests detect genetic material, which does not always correspond to the presence of viable organisms.

Using PCR or whole-genome sequence analysis to facilitate recognition of specific *E. coli* pathotypes, state public health and Centers for Disease Control and Prevention laboratories can assist in outbreak investigations. When STEC infection is suspected, stool samples should be cultured for *E. coli* O157 and simultaneously tested for Shiga toxins or the genes that encode them. For more information, see www.cdc.gov/mmwr/preview/mmwrhtml/rr5812a1.htm. Send all presumptive *E. coli* O157 isolates and Shiga toxin–positive specimens to a public health laboratory for further characterization and for outbreak detection. Rapid, accurate diagnosis of STEC infection is important because early clinical management decisions can affect patient outcomes, and early detection can help prevent further transmission.

TREATMENT

Maintenance of hydration and electrolyte balance with oral rehydration is important, especially in patients with vomiting or profuse diarrhea. Travelers with mild non-bloody diarrhea can use

Table 5-02 Mechanism of pathogenesis & typical clinical syndrome of *Escherichia coli* pathotypes

PATHOTYPE	MECHANISM OF PATHOGENESIS	INCUBATION PERIOD	ILLNESS DURATION	TYPICAL CLINICAL SYNDROME
DAEC	Diffuse adherence to epithelial cells	Unknown	Unknown	Watery diarrhea but pathogenicity not conclusively demonstrated
EAEC	Small and large bowel adherence mediated via various adhesins and accessory proteins; enterotoxin and cytotoxin production	8–48 hours	3–14 days; persistent diarrhea (>14 days) has been reported	Watery diarrhea with mucous, occasionally bloody; can cause prolonged or persistent diarrhea in children
EIEC	Mucosal invasion and inflammation of large bowel	10–18 hours	4–7 days	Watery diarrhea that might progress to bloody diarrhea (dysentery-like syndrome); fever
EPEC	Small bowel adherence and epithelial cell effacement mediated by intimin	9–12 hours	12 days	Severe acute watery diarrhea that can be persistent; common cause of infant diarrhea in developing countries
ETEC	Small bowel adherence via various adhesins that confer host specificity; heat-stable or heat-labile enterotoxin production	10–72 hours	1–5 days	Acute watery diarrhea, occasionally severe; afebrile
STEC	Large bowel adherence mediated via intimin (or less commonly by other adhesins); Shiga toxin 1, Shiga toxin 2 production; Shiga toxin production is linked to induction of the bacteriophages carrying the Shiga toxin genes; some antibiotics induce these bacteriophages	1–10 days (usu. 3–4 days)	Typically, 5–7 days; persistent diarrhea (>14 days) has been reported	Watery diarrhea that progresses (often for STEC O157, less often for non-O157) to bloody diarrhea in 1–3 days; abdominal cramps and tenderness; fever is low-grade, if present; hemolytic uremic syndrome complicates ≈6% of diagnosed STEC O157 infections (15% among children aged <5 years) and 1% of non-O157 STEC infections

Abbreviations: DAEC, diffusely adherent *Escherichia coli*; EAEC, enteroaggregative *E. coli*; EIEC, enteroinvasive *E. coli*; EPEC, enteropathogenic *E. coli*; ETEC, enterotoxigenic *E. coli*; STEC, Shiga toxin–producing *E. coli*.

loperamide to decrease the frequency of loose stools. Travelers with moderate illness can consider self-treatment with an antibiotic, and those with bloody diarrhea or severe illness (that keeps them confined to their room) should generally receive antibiotic therapy. Travelers can use loperamide as an adjunctive therapy to antibiotics taken for moderate or severe travelers' diarrhea.

Azithromycin is preferred for bloody diarrhea or severe illness and is an option for moderate non-bloody diarrhea. Fluoroquinolones (e.g., ciprofloxacin) can be effective, but resistant strains are increasing in frequency, particularly in Asia; other agents are also preferred because fluoroquinolones have been associated with adverse effects, including tendinopathies, QT interval prolongation (a cardiac conduction abnormality), and *Clostridioides difficile* enterocolitis.

If treatment with azithromycin or a fluoroquinolone does not improve the condition within 24 hours, travelers should continue the antibiotic for no longer than 3 days. A 3-day course of rifaximin is effective for some non-bloody diarrheal illnesses. Administering certain antimicrobial agents to patients whose clinical syndrome suggests STEC infection could increase their risk of developing HUS (Table 5-02). Studies of children with STEC O157 infection have shown that early use of intravenous fluids (within the first 4 days of diarrhea onset) might decrease the risk of oligoanuric renal failure.

Antimicrobial-resistant *E. coli* are increasing worldwide. Carefully weigh the decision to use an antibiotic against the severity of illness; the possibility that the pathogen is resistant; and the risk for adverse reactions (e.g., HUS, rash, other manifestations of allergy), antibiotic-associated colitis, and vaginal yeast infection. Some studies suggest that loperamide combined with antibiotics can be used safely in many patients. Due to a potential risk for complications, including toxic megacolon and HUS, avoid treating bloody diarrhea or STEC infection solely with antimotility drugs.

PREVENTION

No vaccine is available for *E. coli* infection. Although bismuth subsalicylate and certain antimicrobial agents (e.g., fluoroquinolones, rifaximin) can prevent *E. coli* diarrhea, chemoprophylaxis is not recommended for most travelers. Furthermore, antimicrobial drug use can adversely affect the intestinal microbiota and increase susceptibility to gut infections.

Remind travelers of the importance of adhering to food and water precautions (see Sec. 2, Ch. 8, Food & Water Precautions), and instruct travelers about the importance of handwashing. Because soap and water might not be readily available, travelers should consider taking hand sanitizer with ≥60% alcohol with them when they travel.

CDC website: www.cdc.gov/ecoli

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HELICOBACTER PYLORI

Bradley Connor

INFECTIOUS AGENT: *Helicobacter pylori*	
ENDEMICITY	Worldwide
TRAVELER CATEGORIES AT GREATEST RISK FOR EXPOSURE & INFECTION	All travelers
PREVENTION METHODS	None
DIAGNOSTIC SUPPORT	A clinical laboratory certified in moderate complexity testing

INFECTIOUS AGENT

Helicobacter pylori is a small, curved, microaerophilic, gram-negative, rod-shaped bacterium.

TRANSMISSION

H. pylori is believed to be transmitted mainly by fecal–oral route, but also possibly by oral–oral.

EPIDEMIOLOGY

H. pylori is recognized as one of the most common chronic bacterial infections worldwide, and about two-thirds of the world's population is infected; it is more common in developing countries. Short-term travelers appear to be at low risk of acquiring *H. pylori* through travel, but expatriates and long-stay travelers could be at greater risk.

CLINICAL PRESENTATION

Although usually asymptomatic, *H. pylori* infection is the major cause of peptic ulcer disease and gastritis worldwide, which often present as gnawing or burning epigastric pain. Less commonly, symptoms include loss of appetite, nausea, or vomiting. Designated as a carcinogen by the World Health Organization, *H. pylori* infection is the strongest known risk factor for non-cardia gastric adenocarcinoma. Infected people have a 2–6-fold increased risk of developing gastric cancer and mucosal associated-lymphoid-type (MALT) lymphoma compared with their uninfected counterparts.

DIAGNOSIS

H. pylori diagnosis can be made through fecal antigen assay, urea breath test, rapid urease test, or histology of a biopsy specimen. A positive serology indicates present or past infection.

TREATMENT

Asymptomatic infections generally do not need to be treated. Determine treatment on an individual basis, and treat patients with active duodenal or gastric ulcers if they are infected. Standard treatment is bismuth quadruple therapy: proton pump inhibitor (PPI) or H2-blocker + bismuth + metronidazole + tetracycline. Clarithromycin triple therapy (PPI + clarithromycin + amoxicillin or metronidazole) is an option in regions where *H. pylori* clarithromycin resistance is known to be <15% and in patients with no previous history of macrolide exposure.

Recently, combination therapies using rifabutin have become available, especially for refractory cases. Longer treatment durations (14 days vs. 7 days) provide higher eradication success rates (see http://gi.org/guideline/treatment-of-helicobacter-pylori-infection).

PREVENTION

No specific recommendations.

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LEGIONNAIRES' DISEASE & PONTIAC FEVER

William (Chris) Edens

INFECTIOUS AGENT: *Legionella* spp.	
ENDEMICITY	Worldwide
TRAVELER CATEGORIES AT GREATEST RISK FOR EXPOSURE & INFECTION	Travelers >50 years of age, current or former smokers, have chronic lung conditions, or are immunocompromised
PREVENTION METHODS	Travelers at increased risk for infection should avoid recognized high-risk exposures (e.g., hot tubs)
DIAGNOSTIC SUPPORT	A clinical laboratory certified in moderate or high complexity testing; state health department

INFECTIOUS AGENT

Gram-negative bacteria of the genus *Legionella* cause Legionnaires' disease and Pontiac fever. Most cases of Legionnaires' disease are caused by *Legionella pneumophila*, but all species of *Legionella* can cause disease.

TRANSMISSION

The most common route of transmission is by inhalation of aerosolized water containing the bacteria, although transmission can sometimes occur through aspiration of water containing the bacteria. A single episode of possible person-to-person transmission of Legionnaires' disease has been reported.

Legionella is ubiquitous in freshwater sources worldwide, but quantities of *Legionella* in these environments are insufficient to cause disease. In the built environment, *Legionella* can amplify in water systems, depending on the conditions. Factors associated with amplification include warm water temperatures of 77°F–108°F [25°C–42°C]); water stagnation; presence of scale, sediment, and biofilm in the pipes and fixtures; and absence of disinfectant.

To cause disease, *Legionella* spp. must be aerosolized and inhaled by a susceptible host. The most common sources of transmission include potable water (via showerheads and faucets), cooling towers, hot tubs, and decorative fountains.

EPIDEMIOLOGY

Legionella growth and transmission can occur anywhere in the world when the right conditions exist. The capacity to diagnose and report cases of Legionnaires' disease is better established, however, in industrialized settings. In the United States, the incidence of Legionnaires' disease is

increasing; the number of reported Legionnaires' disease cases increased nearly 900% between 2000 and 2018.

Legionnaires' disease cases and outbreaks have been reported worldwide. Large outbreaks associated with cooling towers were reported in Spain in 2001 (449 confirmed cases) and Portugal in 2014 (377 cases). In 2015, a cooling tower in Bronx, New York, was associated with 138 cases of Legionnaires' disease. Travel-associated outbreaks have also been reported. In 2015, 114 cases (11 confirmed Legionnaires' disease, 29 suspected Legionnaires' disease, and 74 Pontiac fever cases) were identified among visitors to a hotel in Chicago, Illinois; and during 2016–2017, 51 confirmed cases of Legionnaires' disease were associated with travel to Dubai.

Despite the presence of *Legionella* spp. in many aquatic environments, the risk of developing Legionnaires' disease is low for most people. Travelers who are >50 years old, are current or former smokers, have chronic lung conditions, or are immunocompromised are at increased risk for infection when exposed to aerosolized water containing *Legionella* spp. Travel-associated Legionnaires' disease outbreaks can occur on cruise ships, in hotels, and at resorts. A common feature among these settings is the presence of a large, often complex, water system that can be challenging to maintain properly.

Approximately 10% of all reported cases of Legionnaires' disease in the United States occur in people who have traveled during the 10 days before symptom onset. Exposures among travelers can occur when a person is in or near a hot tub, showering in a hotel, standing near a decorative fountain, or touring in cities with buildings that have cooling towers. Patients with Legionnaires' disease often do not recall specific water exposures because exposure frequently occurs during normal activities.

CLINICAL PRESENTATION

Legionellosis is primarily composed of 2 clinically and epidemiologically distinct syndromes: Legionnaires' disease and Pontiac fever. Though rare, *Legionella* spp. have also been associated with disease outside of the lungs (extrapulmonary). Legionnaires' disease typically presents with severe pneumonia, which usually requires hospitalization and can be fatal in ≈10% of cases. Symptom onset occurs 2–10 days (rarely, ≤19 days) after exposure. In outbreak settings, <5% of people exposed to the source of the outbreak develop Legionnaires' disease. Nearly all cases of legionellosis in the United States are reported as Legionnaires' disease.

Pontiac fever is milder than Legionnaires' disease and presents with fever, headache, or muscle aches, but no signs of pneumonia. Pontiac fever can affect healthy people as well as those with underlying illnesses, and symptoms occur within 72 hours of exposure. Nearly all patients fully recover without antimicrobial drug therapy or hospitalization. Up to 95% of people exposed during outbreaks of Pontiac fever can develop symptoms of disease.

DIAGNOSIS

The preferred diagnostic tests for Legionnaires' disease are the *Legionella* urinary antigen test and culture of lower respiratory secretions (sputum, bronchoalveolar lavage) on media that supports growth of *Legionella* spp. The most common diagnostic test, the urinary antigen test, only detects *L. pneumophila* serogroup 1; this serogroup accounts for 80%–90% of cases.

Isolation of *Legionella* by culture is important to detect non–*L. pneumophila* serogroup 1 infections and is necessary to compare clinical to environmental isolates during an outbreak investigation. Diagnosis by PCR of lower respiratory secretions also is possible, but the number of commercially available tests is limited. Because of differences in the mechanisms of disease, *Legionella* spp. cannot be isolated in people who have Pontiac fever. Legionnaires' disease, Pontiac fever, and extrapulmonary legionellosis are nationally notifiable diseases in the United States.

TREATMENT

For travelers with suspected Legionnaires' disease, administer specific antimicrobial drug treatment promptly while diagnostic tests are being processed. Preferred antimicrobial agents include fluoroquinolones and macrolides. Patients with severe cases might have prolonged intensive care unit stays. Treating physicians should consult with an infectious disease specialist. Because Pontiac fever is a self-limited illness, antimicrobial

drugs have no benefit, and treatment is focused on supportive care.

PREVENTION

No vaccine for Legionnaires' disease is available, and antibiotic prophylaxis is not effective. Water management programs for building water systems and devices at risk for *Legionella* growth and transmission can lower the potential for illnesses and outbreaks. Travelers at increased risk for infection, such as older people or people with immunocompromising conditions (e.g., cancer, diabetes), might choose to avoid high-risk exposures (e.g., hot tubs). If exposure cannot be avoided, travelers should seek medical attention promptly if they develop symptoms of Legionnaires' disease or Pontiac fever.

CDC website: www.cdc.gov/legionella

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LEPTOSPIROSIS

Ilana Schafer, Renee Galloway, Robyn Stoddard

INFECTIOUS AGENT: *Leptospira* spp.	
ENDEMICITY	Worldwide, higher incidence in tropical areas
TRAVELER CATEGORIES AT GREATEST RISK FOR EXPOSURE & INFECTION	Adventure tourists, outdoor athletes, and others exposed to fresh water or mud Humanitarian aid workers, particularly at sites of hurricanes or floods Military personnel
PREVENTION METHODS	Avoid contact with animal urine and water or soil contaminated with animal urine Use personal protective equipment Use chemoprophylaxis
DIAGNOSTIC SUPPORT	A clinical laboratory certified in high complexity testing; state health department; or contact CDC's Bacterial Special Pathogens Branch (bspb@cdc.gov) for additional identification and genotyping, molecular detection, or serology.

INFECTIOUS AGENT

Leptospira spp., the causative agent of leptospirosis, are obligate aerobic, gram-negative spirochete bacteria.

TRANSMISSION

Leptospira are transmitted through abrasions or cuts in the skin, or through the conjunctiva and mucous membranes. Macerated skin resulting from prolonged water exposure is another suspected route of infection. Humans can be infected by direct contact with urine or reproductive fluids from infected animals, through contact with urine-contaminated freshwater sources or wet soil, or by consuming contaminated food or water. Infection rarely occurs through animal bites or human-to-human contact. Rodents are an important reservoir for *Leptospira*, but most mammals, including dogs, horses, cattle, and swine, and many wildlife species, can be infected and shed the bacteria in their urine.

EPIDEMIOLOGY

Leptospirosis has a worldwide distribution; incidence is greater in tropical climates, however. Regions with the highest estimated morbidity and mortality include parts of sub-Saharan Africa, parts of Latin America, and in the Caribbean, South and Southeast Asia, and Oceania. Travelers to endemic areas are at increased risk when participating in recreational freshwater activities (e.g., boating, swimming), particularly after heavy rainfall or flooding. Prolonged exposure to contaminated water and activities that involve head immersion or swallowing water increase the risk for infection.

Participating in activities involving mud (e.g., adventure races) also increases a traveler's risk for infection, as does working directly with animals in endemic areas, especially when exposed to their body fluids, and visiting or residing in areas with rodent infestation. Leptospirosis occurs most commonly in adult males. The estimated worldwide annual incidence is >1 million cases, including ≈59,000 deaths.

Outbreaks can occur after heavy rainfall or flooding in endemic areas, especially in urban areas of low- and middle-income countries, where housing conditions and sanitation are poor and rodent infestation is common. Outbreaks of leptospirosis have occurred after flooding in popular US travel destinations, including Florida, Hawaii, Puerto Rico, and the US Virgin Islands. Nearly half of the leptospirosis cases reported in the continental United States during 2014–2018 that had an identified geographic source of infection were associated with international travel. Most US cases are reported outside the continental United States in the domestic travel destinations of Hawaii and Puerto Rico.

CLINICAL PRESENTATION

The incubation period for leptospirosis is 2–30 days, but illness usually occurs 5–14 days after exposure. Most infections are thought to be asymptomatic, but clinical illness can present as a self-limiting acute febrile illness, estimated to occur in ≈90% of clinical infections, or as a severe, potentially fatal illness with multiorgan dysfunction in 5%–10% of patients. In patients who progress to severe disease, the illness can be biphasic, with a temporary decrease in fever between phases.

The acute, septicemic phase lasts ≈7 days and presents as an acute febrile illness with symptoms including headache, which can be severe and include photophobia and retro-orbital pain; chills; myalgias, characteristically involving the calves and lower back; conjunctival suffusion, characteristic of leptospirosis but not occurring in all cases; nausea; vomiting; diarrhea; abdominal pain; cough; and rarely, a skin rash.

The second or immune phase is characterized by antibody production and the presence of leptospires in the urine. In patients who progress to severe disease, clinical findings can include cardiac arrhythmias, hemodynamic collapse, hemorrhage, jaundice, liver failure, aseptic meningitis, pulmonary insufficiency, and renal failure. The classically described syndrome, Weil's disease, consists of renal and liver failure.

Among patients with severe disease, the case-fatality ratio is 5%–15%. Severe pulmonary hemorrhagic syndrome is a rare but severe form of leptospirosis that can have a case-fatality ratio >50%. Poor prognostic indicators include older age, development of altered mental status, respiratory insufficiency, or oliguria.

DIAGNOSIS

Submit a combination of samples for leptospirosis testing, including serum samples; whenever possible, obtain acute and convalescent sample pairs. During early disease, PCR analysis of whole blood (collected in the first week of illness) and urine (collected after the first week of illness) can be helpful. PCR analysis of cerebrospinal fluid (CSF) also can be helpful in diagnosing patients with signs of meningitis.

Diagnosis of leptospirosis is often based on serology; microscopic agglutination test (MAT) is the reference standard and can only be performed at certain reference laboratories. Various serologic screening tests are available at commercial laboratories, including ELISA and ImmunoDOT/DotBlot rapid diagnostic tests. The use of IgM-specific serologic screening tests is recommended, and positive screening tests should be confirmed with MAT.

Detection of the organism in acute whole blood using real-time PCR can provide a more timely diagnosis during the early, septicemic phase, and PCR also can be performed on CSF or convalescent urine. A positive PCR result is confirmatory for infection. Culture is insensitive, slow, and requires special media; it is therefore not recommended as the sole diagnostic method.

The Zoonoses and Select Agent Laboratory at the Centers for Disease Control and Prevention (CDC) performs MAT and PCR for diagnosis of leptospirosis as well as culture identification and genotyping of isolates. Clinicians can find information on diagnostic testing at CDC and sample submission instructions at www.cdc.gov/nczid/dhcpp/bacterial_special/zoonoses_lab.html. Clinicians can consult on a suspected leptospirosis case by contacting CDC's Bacterial Special Pathogens Branch, by calling the CDC Emergency Operations Center (770-488-7100). Leptospirosis is a nationally notifiable disease, and the Council for State and Territorial Epidemiologists' case definition can be found at https://ndc.services.cdc.gov/case-definitions/leptospirosis-2013.

TREATMENT

If leptospirosis is suspected, initiate antimicrobial therapy as soon as possible, without waiting for diagnostic test results. Early treatment can be effective in decreasing the severity and duration of infection. For patients with mild symptoms, doxycycline is a drug of choice, unless contraindicated; alternative options include ampicillin, amoxicillin, or azithromycin. Intravenous penicillin is the drug of choice for patients with severe leptospirosis; ceftriaxone and cefotaxime are alternative antimicrobial agents. As with other spirochetal diseases, antibiotic treatment of patients with leptospirosis might cause a Jarisch-Herxheimer reaction; the reaction is rarely fatal. Patients with severe leptospirosis might require hospitalization and supportive therapy, including intravenous hydration and electrolyte supplementation, dialysis in cases of oliguric renal failure, and mechanical ventilation in cases of respiratory failure.

PREVENTION

The best way to prevent infection is to avoid exposure. Advise travelers to avoid exposure to potentially contaminated bodies of freshwater, flood waters, potentially infected animals or their body fluids, and areas with rodent infestation. Educate travelers who might be at increased risk for infection to consider taking additional preventive measures (e.g., wearing protective clothing, especially footwear), instructing them to cover cuts and abrasions with occlusive dressings, counseling them on boiling or chemically treating potentially contaminated drinking water, and providing chemoprophylaxis. Limited studies have shown that chemoprophylaxis with doxycycline (200 mg orally, weekly) begun 1–2 days before and continuing through the period of exposure, might be effective in preventing clinical disease in adults and could be considered for people at high risk and with short-term exposures. No human vaccine is available in the United States.

CDC website: www.cdc.gov/leptospirosis

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5

LYME DISEASE

Paul Mead, David McCormick

INFECTIOUS AGENT: *Borrelia burgdorferi* sensu lato complex	
ENDEMICITY	North America, in the Northeast, mid-Atlantic, and upper Midwest of the United States Northern Asia (temperate forest regions) Europe
TRAVELER CATEGORIES AT GREATEST RISK FOR EXPOSURE & INFECTION	Adventure tourists Long-term travelers and expatriates
PREVENTION METHODS	Avoid tick bites
DIAGNOSTIC SUPPORT	A clinical laboratory certified in moderate complexity testing; Contact CDC's Division of Vector-Borne Diseases (970-221-6400; dvbid@cdc.gov)

INFECTIOUS AGENT

Lyme disease is caused by spirochetes belonging to the *Borrelia burgdorferi* sensu lato complex, including *B. afzelii*, *B. burgdorferi* sensu stricto, and *B. garinii*.

TRANSMISSION

Borrelia spirochetes are transmitted through the bite of infected *Ixodes* (blacklegged) ticks, typically immature (nymphal) ticks. Nymphal ticks are small, about the size of a poppy seed, and elude easy detection. Patients with Lyme disease might be unaware that they were ever bitten.

EPIDEMIOLOGY

Borrelia transmission has not been documented in the tropics. In Europe, Lyme disease is endemic from southern Scandinavia into the northern Mediterranean countries of Greece, Italy, and

Spain, and east from the British Isles into central Russia. Incidence is greatest in central and eastern European countries. In Asia, infected ticks range from western Russia through Mongolia, northeastern China, and into Japan; human infection appears to be uncommon in most of these areas, however. In North America, highly endemic areas include the northeastern and north-central United States.

Lyme disease is occasionally reported in travelers to the United States returning to their home countries. Consider Lyme disease in the differential diagnosis of patients with consistent symptoms and a history of camping, hiking, or outdoor activities. Some case reports describe Lyme disease in Australian and US travelers returning from Europe and endemic regions of the United States, but no data are available regarding the incidence of travel-acquired infection.

CLINICAL PRESENTATION

The incubation period of Lyme disease is typically 3–30 days. Approximately 80% of people infected with *B. burgdorferi* develop a characteristic rash, erythema migrans (EM), within 30 days of exposure. EM is a red, expanding rash, with or without central clearing, often accompanied by symptoms of fatigue, fever, headache, mild stiff neck, arthralgia, or myalgia.

Within days or weeks, infection can spread to other parts of the body, causing more serious neurologic conditions (meningitis, radiculopathy, and facial palsy) or cardiac abnormalities (myocarditis with atrioventricular heart block). Left untreated, infection can progress over several months to cause monoarticular or oligoarticular arthritis, peripheral neuropathy, or rarely, encephalopathy. These long-term sequelae can occur over variable periods of time, ranging from months to years.

Infection with European strains of *Borrelia* can result in manifestations rarely seen in the United States, specifically lymphocytoma, an acute blister-like lesion, and acrodermatitis chronica atrophicans, characterized by atrophic patches of bluish-red skin that develop over a period of years and typically involve the extremities.

DIAGNOSIS

In people with a history of recent travel to an endemic area (with or without a recollection of a tick bite) a diagnosis of Lyme disease can be made by identifying an EM rash. For patients with evidence of disseminated infection (cardiac, musculoskeletal, neurologic manifestations), serologic testing using commercial assays can aid in diagnosis. Lyme disease is nationally notifiable.

Serological tests used to diagnose domestically acquired Lyme disease might not reliably identify infections acquired internationally. Some laboratories offer testing for additional *Borrelia* species that cause Lyme disease in Europe but are not found in the United States. These tests are only appropriate for people with a history of travel outside the United States. For diagnostic support, contact the Centers for Disease Control and Prevention (CDC)'s Division of Vector-Borne Diseases (970-221-6400; dvbid@cdc.gov).

TREATMENT

Most patients can be treated with oral doxycycline, amoxicillin, or cefuroxime axetil; or with intravenous ceftriaxone (for details, see www.cdc.gov/lyme). Diagnosis and management of disseminated infection can be complicated and may require referral to an infectious disease specialist or rheumatologist.

PREVENTION

Advise patients to avoid tick habitats (e.g., wooded, brushy, or grassy areas); use an Environmental Protection Agency–registered insect repellent on exposed skin and clothing; and carefully check every day for attached ticks. Instruct patients to minimize areas of exposed skin by wearing long-sleeved shirts, long pants, and closed shoes, and to tuck in shirts and tuck pants into socks to help reduce risk for tick bites (see Sec. 4, Ch. 6, Mosquitoes, Ticks & Other Arthropods).

CDC website: www.cdc.gov/lyme

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MELIOIDOSIS

Lindy Liu, Jay Gee, David Blaney

5

INFECTIOUS AGENT: *Burkholderia pseudomallei*	
ENDEMICITY	Tropical and subtropical regions worldwide Primarily Southeast Asia, South Asia, and Australia Some parts of Africa, the Americas, and Middle East
TRAVELER CATEGORIES AT GREATEST RISK FOR EXPOSURE & INFECTION	Adventure travelers and ecotourists Construction and resource extraction workers Military personnel Travelers who contact contaminated soil or water
PREVENTION METHODS	Avoid contaminated soil and water
DIAGNOSTIC SUPPORT	A clinical laboratory certified in high complexity testing; state health department; or contact CDC's Bacterial Special Pathogens Branch (bspb@cdc.gov) for additional support

INFECTIOUS AGENT

Burkholderia pseudomallei, a saprophytic gram-negative bacillus, is the causative agent of melioidosis. The bacteria are found in soil and water and are widely distributed in tropical and subtropical countries.

TRANSMISSION

B. pseudomallei can infect both animals and humans through damaged skin (e.g., open wounds, cuts, burns) or mucous membranes. Damaged skin coming in direct contact with contaminated soil or water is the most frequent route for natural infection. Ingestion and inhalation are two other routes of infection. The risk of spread from person-to-person is considered extremely low as there are few documented cases of transmission via this route.

EPIDEMIOLOGY

Melioidosis goes underreported or unrecognized in many tropical and subtropical areas; >165,000 cases are estimated to occur annually, mainly in Southeast Asia and in northern Australia. *B. pseudomallei* is endemic to Southeast Asia, Papua New Guinea, much of the Indian subcontinent, southern China, Hong Kong, and Taiwan. It is considered highly endemic to northeast Thailand, Malaysia, Singapore, and northern Australia.

B. pseudomallei has also been found in the Americas, including the Caribbean and the Gulf Coast of the United States (Mississippi).

Sporadic cases of disease have been reported among residents of or travelers to Aruba, British Virgin Islands, Colombia, Costa Rica, Ecuador, El Salvador, Guatemala, Guadeloupe, Guyana, Honduras, Martinique, Mexico, Panama, Peru, Puerto Rico, US Virgin Islands, and Venezuela. Clusters of melioidosis have been reported in northeastern Brazil. The true extent of distribution the bacteria remains unknown.

Among the average of 12 melioidosis cases reported annually to the Centers for Disease Control and Prevention (CDC), most occur in people with a history of recent travel to a region where *B. pseudomallei* is known to be endemic. Risk for infection is greatest for adventure travelers, construction and resource extraction workers, ecotourists, military personnel, and other people whose contact with contaminated soil or water might expose them to the bacteria. The bacteria can also be present in untreated water and raw or undercooked food. Infections have been reported in people who spent <1 week in an endemic area. Cases, especially those presenting as pneumonia, are often associated with periods of high rainfall (e.g., during typhoons or the monsoon season).

Even in regions where melioidosis is highly endemic (e.g., northern Australia, Thailand), most healthy people exposed to *B. pseudomallei* never develop melioidosis. People with certain conditions, however, are at greater risk for disease. Risk factors for developing melioidosis include diabetes, excessive alcohol use, chronic lung disease (e.g., chronic obstructive pulmonary disease or cystic fibrosis), chronic renal disease, thalassemia, and malignancy or other non-HIV–related immune suppression.

CLINICAL PRESENTATION

Incubation period is generally 1–21 days, with a median of 4 days; people who receive a high inoculum can become symptomatic within a few hours. Melioidosis also can remain latent for months or years before symptoms develop. It can present as a localized infection, pneumonia, bacteremia, or disseminated infection involving any organ, including the brain.

Symptoms are nonspecific and will vary depending on the route of infection. Symptoms can include abdominal discomfort; abscesses or ulcerations; chest pain, cough, and respiratory distress; disorientation, headache, and seizures; fever; localized pain and swelling; muscle or joint pain; and weight loss. Patients generally present with acute illness, but ≈9% present with ≥2 months of symptoms. Chronic melioidosis often mimics *Mycobacterium tuberculosis* infection clinically. Subclinical infection is also possible.

DIAGNOSIS

Prompt diagnosis and treatment are critical. Guided by clinical syndrome, collect specimens from all relevant infection sites for culture. Depending on the site(s) of suspected infection, recommended specimens for collection include blood, cerebrospinal fluid, pericardial fluid, peritoneal fluid, purulent exudate (from skin or internal abscesses), sputum, synovial fluid, and urine; throat and rectal swabs can also be collected. Culturing *B. pseudomallei* from any clinical specimen is diagnostic for melioidosis because the bacterium is not considered part of the natural microbiota. Alert clinical laboratory personnel in advance that specimen cultures may grow *B. pseudomallei* and to follow proper safety precautions.

Although an indirect hemagglutination assay (IHA) is widely used, no serologic test can confirm melioidosis. In the United States, the Laboratory Response Network (https://emergency.cdc.gov/lrn) can perform confirmatory testing on isolates. CDC laboratories can conduct confirmatory testing in addition to other complex tests (e.g., antimicrobial susceptibility testing, IHA, and genetic analysis by whole-genome sequencing). Submissions to CDC are handled through coordination with local or state public health labs; clinicians should consult local or state public health departments to arrange testing. Information and procedures for submitting specimens to CDC's Bacterial Special Pathogens Branch in the Division of High-Consequence Pathogens and Pathology are available at www.cdc.gov/ncezid/dhcpp/bacterial_special/zoonoses_lab.html.

TREATMENT

Treatment of melioidosis requires long-term antibiotic therapy (acute phase followed by eradication phase), and consultation with an infectious disease or tropical medicine specialist is strongly advised. Intravenous ceftazidime, or meropenem for severe cases with sepsis, is typically used for initial treatment, for a minimum of 14 days.

BOX 5-01 Melioidosis infection precautions: a checklist for travelers visiting areas where *Burkholderia pseudomallei* is endemic

- ☐ Avoid contact with soil or muddy water, particularly after heavy rains
- ☐ Protect open wounds, cuts, or burns. Use waterproof bandages to help keep damaged skin from contacting soil or water. Thoroughly wash any open wounds, cut, or burns that contact soil.
- ☐ For people with diabetes, foot care and preventing contamination of foot or other open wounds is important.
- ☐ Wear protective footwear and gloves when doing yard work, agricultural work.
- ☐ Wear waterproof boots during and after flooding or storms to prevent infection through the feet and lower legs.
- ☐ Avoid drinking untreated water and eating undercooked or raw foods.

Depending on response to therapy, clinicians can extend intravenous treatment for up to 8 weeks in severe cases. After initial treatment, provide 3–6 months of eradication treatment with oral trimethoprim-sulfamethoxazole (TMP-SMX) or amoxicillin-clavulanic acid (for patients unable to tolerate TMP-SMX). Relapses can occur, especially in patients who receive a shorter-than-recommended course of therapy.

PREVENTION

People who live in or who visit areas where *B. pseudomallei* is endemic—especially those individuals with underlying health conditions that place them at increased risk for developing melioidosis—should follow the precautions listed in Box 5-01.

CDC website: www.cdc.gov/melioidosis

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MENINGOCOCCAL DISEASE

Lucy McNamara, Amy Blain

INFECTIOUS AGENT: *Neisseria meningitidis*	
ENDEMICITY	Worldwide, but greatest incidence occurs in the meningitis belt of Africa (see Map 5-01)
TRAVELER CATEGORIES AT GREATEST RISK FOR EXPOSURE & INFECTION	Unvaccinated travelers to countries in the meningitis belt, particularly travelers having prolonged contact with local populations during an epidemic
PREVENTION METHODS	Meningococcal disease is vaccine-preventable
DIAGNOSTIC SUPPORT	A clinical laboratory certified in moderate complexity testing; state health department

INFECTIOUS AGENT

Neisseria meningitidis is a gram-negative diplococcus bacterium. Meningococci are classified into serogroups based on the composition of their capsular polysaccharide. The 6 major meningococcal serogroups associated with disease are A, B, C, W, X, and Y.

TRANSMISSION

Meningococci spread through respiratory secretions and require close contact for transmission. Both asymptomatic carriers and people with overt meningococcal disease can be sources of infection. Asymptomatic carriage is transient and typically affects ≈5%–10% of the population at any given time.

EPIDEMIOLOGY

N. meningitidis is found worldwide, but incidence is greatest in the "meningitis belt" of sub-Saharan Africa (Map 5-01). Meningococcal disease is hyperendemic in this region, and periodic epidemics during the dry season (December–June) reach an incidence of up to 1,000 cases per 100,000 population. By contrast, rates of disease in Australia, Europe, South America, and the United States range from 0.10–2.4 cases per 100,000 population per year.

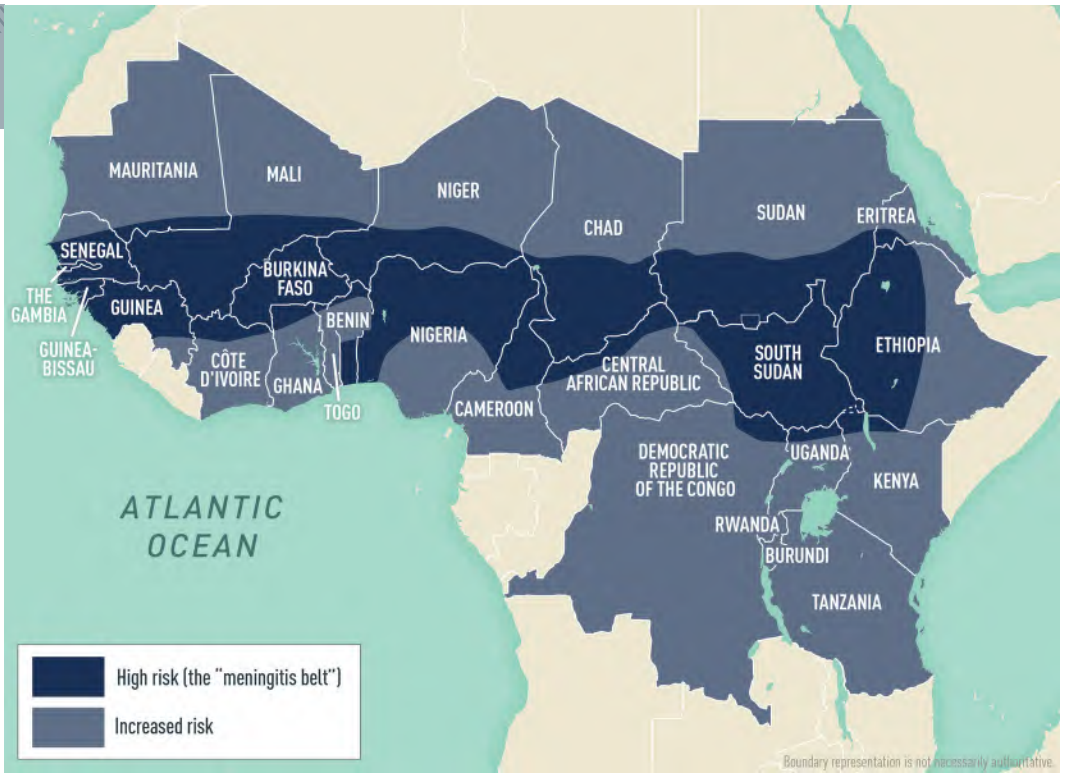
Although meningococcal disease outbreaks can occur anywhere in the world, they are most common in the African meningitis belt, where large-scale epidemics occur every 5–12 years. Historically, outbreaks in the meningitis belt were primarily due to serogroup A. With the introduction of a monovalent serogroup A meningococcal conjugate vaccine (MenAfriVac) in the region starting in 2010, however, recent meningococcal outbreaks in the meningitis belt have primarily been caused by serogroups C and W; serogroup X outbreaks also have been reported.

Outside the meningitis belt, infants, adolescents, and adults >80 years of age have the highest rates of disease. In meningitis belt countries, high rates of disease are seen in people ≤30 years old; the highest rates are in children and adolescents aged 5–14 years.

Unvaccinated travelers visiting meningitis belt countries and having prolonged contact with local populations during an epidemic are at greatest risk for meningococcal disease. The Hajj pilgrimage to Saudi Arabia also has been associated with outbreaks of meningococcal disease among returning pilgrims and their contacts, including 4 cases in travelers from the United States during a large Hajj-associated outbreak in 2000.

CLINICAL PRESENTATION

Meningococcal disease generally occurs 1–10 days after exposure and presents as meningitis in ≈50% of cases in the United States. Meningococcal



MAP 5-01 The meningitis belt & other areas at risk for meningococcal meningitis epidemics

Disease data source: World Health Organization. International Travel and Health. Geneva, Switzerland: 2015.

meningitis is characterized by sudden onset of headache, fever, and neck stiffness, sometimes accompanied by nausea, vomiting, photophobia, or altered mental status. Meningococcal disease progresses rapidly and has a case-fatality rate of 10%–15%, even with antimicrobial drug treatment. Without rapid treatment, fatality rates can be much higher.

Approximately 30% of people with meningococcal disease present with meningococcal sepsis, known as meningococcemia. Symptoms of meningococcemia can include abrupt onset of fever, chills, vomiting, diarrhea, and a petechial or purpuric rash, which can progress to purpura fulminans. Meningococcemia often involves hypotension, acute adrenal hemorrhage, and multiorgan failure. An additional 15% of meningococcal disease cases in the United States, primarily among adults >65 years of age, present as bacteremic pneumonia.

Other presentations (e.g., septic arthritis) also occur. Among infants and children aged <2 years, meningococcal disease can have nonspecific symptoms. Neck stiffness, usually seen in people with meningitis, might be absent in this age group.

DIAGNOSIS

Early diagnosis and treatment are critical. If bacterial meningitis is suspected, collect blood for culture right away and perform a lumbar puncture (LP) to collect cerebrospinal fluid (CSF) for microscopic examination and Gram stain. In general, diagnosis is made by isolating *N. meningitidis* from a normally sterile body site (e.g., blood, CSF) either by culture or by PCR detection of *N. meningitidis*–specific nucleic acid. State health departments can provide diagnostic and testing support if needed.

Signs and symptoms of meningococcal meningitis are like those of other causes of bacterial meningitis (e.g., *Haemophilus influenzae*, *Streptococcus pneumoniae*). Proper treatment and prophylaxis depend on correctly identifying

the causative organism. Meningococcal disease is nationally notifiable in the United States; report cases to the state or local health department without delay.

TREATMENT

Meningococcal disease can be rapidly fatal and should always be viewed as a medical emergency. As soon as disease is suspected and blood cultures and CSF have been collected, deliver appropriate treatment; if the LP is to be delayed for any reason (e.g., imaging studies of the head prior to LP), administer antimicrobial drugs immediately after collecting blood cultures. Begin empiric antimicrobial drug treatment early and prior to receiving diagnostic test results.

Third-generation cephalosporins are recommended for empiric treatment. Although ampicillin or penicillin also can be used for treatment, determine meningococcal isolate susceptibility before switching to one of these antibiotics; recent reports indicate emerging penicillin resistance among meningococcal isolates in the United States. If a patient presents with suspected bacterial meningitis of uncertain etiology, some treatment algorithms recommend empiric use of dexamethasone in addition to an antimicrobial drug until a bacterial etiology is established; if meningococcal meningitis is confirmed or suspected, steroids can be discontinued.

PREVENTION

Vaccine

Five meningococcal vaccines (3 quadrivalent, 2 monovalent) are licensed and available in the United States. Travelers should receive vaccines 7–10 days before travel to enable time for protective antibody levels to develop. See Table 5-03 for more information about available meningococcal vaccines.

ROUTINE IMMUNIZATION

The Advisory Committee on Immunization Practices (ACIP) recommends routine administration of a quadrivalent meningococcal conjugate vaccine (MenACWY) for all people aged 11–18 years. Administer a single dose of vaccine to patients at age 11 or 12 years and a booster dose at age 16 years. Routine immunization with MenACWY is not recommended for other age groups in the United States, except for people at increased risk for meningococcal disease, including those with a persistent complement component deficiency (C3, C5-9, properdin, factor D, factor H); people taking a complement component inhibitor (e.g., eculizumab [Soliris] or ravulizumab [Ultomiris]); people who have functional or anatomic asplenia; or people with HIV. ACIP describes vaccine, product, number of doses, and booster dose recommendations, based on age and risk factors for each risk group, in Meningococcal Vaccination: Recommendations of the Advisory Committee on Immunization Practices, United States, 2020 (www.cdc.gov/mmwr/volumes/69/rr/rr6909a1.htm).

ACIP also recommends adolescents and young adults aged 16–23 years be vaccinated with a serogroup B meningococcal (MenB) vaccine series, based on shared clinical decision-making. A MenB vaccine series provides short-term protection against most strains of serogroup B meningococcus; 16–18 years is the optimal age for MenB vaccination. ACIP also recommends routine use of MenB vaccine for people aged ≥10 years who are at increased risk for meningococcal disease, including people who have persistent complement component deficiency and those with functional or anatomic asplenia. ACIP recommendations for use of MenB vaccines can be found in Meningococcal Vaccination: Recommendations of the Advisory Committee on Immunization Practices, United States, 2020 (www.cdc.gov/mmwr/volumes/69/rr/rr6909a1.htm).

IMMUNIZATION FOR TRAVELERS

QUADRIVALENT MENINGOCOCCAL CONJUGATE (MENACWY) VACCINES

ACIP recommends that travelers aged ≥2 months who visit or reside in parts of the meningitis belt of sub-Saharan Africa (see Map 5-01) during the dry season (December–June) receive vaccination with a MenACWY vaccine before travel. The Centers for Disease Control and Prevention (CDC) issues advisories for travelers to other countries when outbreaks of meningococcal disease are recognized; travelers should check the CDC Travelers' Health website (https://wwwnc.cdc.gov/travel/notices) before travel. There are 3 meningococcal vaccines licensed and available in

Table 5-03 Meningococcal vaccines licensed & available in the United States: recommendations for travelers to or residents of countries where meningococcal disease is hyperendemic or epidemic[1]

VACCINE	TRADE NAME (MANUFACTURER)	AGE AT VACCINE INITIATION	DOSE	SERIES
Meningococcal (serogroups A, C, W, and Y) oligosaccharide diphtheria CRM_{197} conjugate vaccine (MenACWY-CRM)	Menveo (GlaxoSmithKline)	2 months old	0.5 mL IM	4-dose series[2] DOSE 1: Infant is 2 months old DOSE 2: 2 months after DOSE 1 (infant is 4 months old) DOSE 3: 2 months after DOSE 2 (infant is 6 months old) DOSE 4: 6 months after DOSE 3 (infant is 12 months old)
		3–6 months old	0.5 mL IM	Multi-dose series[2] (number of doses depends on age at vaccine initiation) DOSE 1: Infant is between 3–6 months old SUBSEQUENT DOSES: After DOSE 1, give 1 dose every 8 weeks until the infant is ≥7 months old, then give 1 additional dose after the infant is ≥12 months old
		7–23 months old	0.5 mL IM	2-dose series[2] DOSE 1: Child is 7–23 months old DOSE 2: ≥12 weeks after DOSE 1 *and* the child is ≥12 months old
		≥2 years old	0.5 mL IM	1 dose[2,3]
Meningococcal (serogroups A, C, W, and Y) polysaccharide diphtheria toxoid conjugate vaccine (MenACWY-D)	Menactra (Sanofi Pasteur)	9–23 months old	0.5 mL IM	2-dose series[2] DOSE 1: Child is 9–23 months old DOSE 2: ≥12 weeks after DOSE 1[4]
		≥2 years old	0.5 mL IM	1 dose[2,3]

Meningococcal (serogroups A, C, W, and Y) polysaccharide tetanus toxoid conjugate vaccine (MenACWY-TT)	MenQuadfi (Sanofi Pasteur)	≥2 years old	0.5 mL IM	1 dose[2,3]
Meningococcal serogroup B vaccine (MenB-FHbp)[5]	Trumenba (Pfizer)	10–25 years old	0.5 mL IM	2-dose series[6,7,8] DOSE 1: Between 10–25 years old DOSE 2: 6 months after DOSE 1
Meningococcal serogroup B vaccine (MenB-4C)[5]	Bexsero (GlaxoSmithKline)	10–25 years old	0.5 mL IM	2-dose series[7,8] DOSE 1: Between 10–25 years old DOSE 2: ≥1 month after DOSE 1

Abbreviations: IM, intramuscular

[1]Source: TABLE 9. Recommended vaccination schedule and intervals for people who travel to or are residents of countries where meningococcal disease is hyperendemic or epidemic—Advisory Committee on Immunization Practices, United States, 2020 (www.cdc.gov/mmwr/volumes/69/rr/rr6909a1.htm#T9_down).
[2]For people at continued risk, revaccination (booster) with meningococcal conjugate vaccine (MenACWY-CRM, -D, or -TT) is recommended for the following age groups: <7 years old, a single dose 3 years after primary vaccination and every 5 years thereafter; ≥7 years old, a single dose 5 years after primary vaccination and every 5 years thereafter.
[3]A 2-dose primary series (DOSE 2 given 8–12 weeks after DOSE 1) is recommended for the following groups: people with HIV; people with anatomic or functional asplenia; people with persistent complement component deficiency (C3, C5-9, properdin, factor D, factor H); and people taking a complement component inhibitor (e.g., eculizumab [Soliris] or ravulizumab [Ultomiris]).
[4]Can be administered ≥8 weeks apart in travelers.
[5]MenB-FHbp and MenB-4C are not interchangeable; the same vaccine should be used for all doses, including booster doses.
[6]A 3-dose primary series (DOSE 2 given 1–2 months after DOSE 1; DOSE 3 given 6 months after DOSE 2) is recommended for the following groups: people with anatomic or functional asplenia; people with persistent complement component deficiency (C3, C5-9, properdin, factor D, factor H); people taking a complement component inhibitor (e.g., eculizumab [Soliris] or ravulizumab [Ultomiris]); microbiologists routinely exposed to *Neisseria meningitidis* isolates; and people at risk during a serogroup B meningococcal disease outbreak.
[7]A single booster dose of MenB vaccine is recommended for people at increased risk due to a serogroup B meningococcus outbreak if they completed the MenB primary series ≥1 year prior (≥6 months might also be considered by public health professionals). See: www.cdc.gov/meningococcal/downloads/meningococcal-outbreak-guidance.pdf.
[8]A booster dose of MenB vaccine is recommended 1 year after completion of the primary vaccination series and every 2–3 years thereafter for people who remain at increased risk of serogroup B meningococcal disease for any other reason.

the United States for children; the age at vaccine initiation and schedule differs for each. See Table 5-03 for more information about meningococcal vaccines for young children.

The Kingdom of Saudi Arabia (KSA) requires travelers >2 years of age making the Umrah or Hajj pilgrimage to provide documentation of quadrivalent vaccine ≥10 days and ≤3 years before arrival for polysaccharide vaccine (MPSV4, no longer available in the United States) and ≤5 years before arrival for conjugate vaccine (see www.moh.gov.sa/en/Hajj/HealthGuidelines/HealthGuidelinesDuringHajj/Pages/HealthRequirements.aspx). Travelers should confirm visa requirements with the KSA embassy. Although the KSA Ministry of Health advises against travel to Hajj for pregnant people or children, these groups should receive meningococcal vaccination according to licensed indications for their age if they travel.

International travelers at risk for meningococcal disease who were previously vaccinated with a quadrivalent vaccine should receive a booster dose. For children who completed the primary dose or series at <7 years of age, administer a booster dose of MenACWY after 3 years and repeat every 5 years thereafter for those who live in or travel to hyperendemic areas. For people who received the primary dose or series at ≥7 years of age, administer a booster dose after 5 years and every 5 years thereafter for people who live in or travel to a hyperendemic area.

MONOVALENT VACCINES (SEROGROUPS A, B & C)

In 2010, the Meningitis Vaccine Project introduced MenAfriVac, a monovalent serogroup A meningococcal conjugate vaccine, into meningitis belt countries through mass vaccination campaigns and the routine childhood immunization schedule. This vaccine is not licensed for use in the United States. US travelers going to live or work in the meningitis belt should receive a quadrivalent meningococcal conjugate vaccine (MenACWY) before leaving, to protect against 4 serogroups.

MenB vaccine is not recommended for people who live in or travel to meningitis belt countries, because serogroup B disease is extremely rare in this region. MenB vaccine is not routinely recommended for travelers to other regions of the world unless an outbreak of serogroup B disease has been reported.

In some countries outside the meningitis belt, meningococcal vaccination (e.g., monovalent conjugate C vaccine or MenB vaccine) might be recommended as part of the routine immunization program for infants. Clinicians can consider meningococcal vaccination for infants residing in these countries, according to the routine immunization recommendations of that country.

SAFETY & ADVERSE REACTIONS

Side effects after MenACWY vaccination include low-grade fevers and local reactions (e.g., injection-site pain, arm swelling, pain that limits movement of the injected arm). Symptoms are generally mild to moderate and resolve within 48–72 hours. Severe adverse events (e.g., high fever, chills, joint pain, rash, seizures) are rare (<5% of vaccinees).

Although no clinical trials of meningococcal vaccines have been conducted in people who are pregnant or lactating, post-licensure safety data have not identified any serious safety concerns to the mother or fetus. Pregnancy or lactation should not preclude vaccination with MenACWY if indicated.

PRECAUTIONS & CONTRAINDICATIONS

People with moderate or severe acute illness should defer vaccination until their condition improves. Vaccination is contraindicated for people who have had a severe allergic reaction to any component of the vaccines or to a prior dose of the vaccine. A severe allergic reaction to any diphtheria toxoid- or CRM_{197}-containing vaccine also is a contraindication for MenACWY-D and MenACWY-CRM; severe allergic reaction to any tetanus toxoid–containing vaccine is a contraindication for MenACWY-TT.

To avoid interference with the immune response to meningococcal vaccine, MenACWY-D should be given either before or at the same time as DTaP in children. MenACWY-D may be given at any time in relation to Tdap or Td.

All meningococcal vaccines are inactivated and can be given to people who are immunosuppressed.

POSTEXPOSURE PROPHYLAXIS

In the United States and most industrialized countries, antibiotic chemoprophylaxis is recommended for close contacts of a patient with

invasive meningococcal disease to prevent secondary cases. Chemoprophylaxis ideally should be initiated within 24 hours after the index patient is identified; prophylaxis given >2 weeks after exposure has little value.

Antibiotics used for prophylaxis include ceftriaxone, ciprofloxacin, and rifampin. Ceftriaxone is recommended for pregnant people. CDC provides detailed information on meningococcal prophylaxis in the Manual for the Surveillance of Vaccine-Preventable Diseases (www.cdc.gov/vaccines/pubs/surv-manual/chpt08-mening.html).

CDC website: www.cdc.gov/meningococcal

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PERTUSSIS / WHOOPING COUGH

Tami Skoff, Anna Acosta

INFECTIOUS AGENT: *Bordetella pertussis*	
ENDEMICITY	Worldwide
TRAVELER CATEGORIES AT GREATEST RISK FOR EXPOSURE & INFECTION	Infants <1 year of age People who are pregnant People who have not been vaccinated against pertussis
PREVENTION METHODS	Pertussis is a vaccine-preventable disease
DIAGNOSTIC SUPPORT	A clinical laboratory certified in moderate complexity testing; state health department

INFECTIOUS AGENT

Pertussis is caused by *Bordetella pertussis*, a fastidious gram-negative coccobacillus.

TRANSMISSION

B. pertussis transmission occurs person-to-person via aerosolized respiratory droplets or by direct contact with respiratory secretions.

EPIDEMIOLOGY

Pertussis is endemic worldwide, even in areas with high vaccination rates. International travel, therefore, does not generally place US travelers at increased risk for infection, as compared to home. Travelers are, however, at increased risk if they come into close contact with infected people. Pertussis has resurged in many countries with successful vaccination programs, especially countries that have transitioned from whole-cell pertussis vaccine formulations to acellular pertussis preparations, including the United States. Although limited data are available on the global burden of pertussis, disease rates are presumed to be highest among young children in countries where vaccination coverage is low, primarily developing countries. In industrialized countries, reported pertussis incidence is highest among infants too young to be vaccinated.

Immunity conferred by childhood vaccination and natural disease wanes with time; therefore, adolescents and adults who have not received a tetanus-diphtheria-pertussis (Tdap) booster vaccination can become infected or reinfected with pertussis. Infants, especially those too young to be protected by a complete vaccination series, are at highest risk for severe illness and death from pertussis.

CLINICAL PRESENTATION

In classic pertussis disease, mild upper respiratory tract symptoms typically begin 7–10 days (range 5–21 days) after exposure (catarrhal stage), after which a cough develops and becomes paroxysmal (paroxysmal stage). Coughing paroxysms can vary in frequency and often are followed by vomiting. Fever is absent or minimal. The coughing paroxysms gradually resolve into milder and less frequent coughing, but paroxysms can recur with subsequent respiratory infections (convalescent stage). The clinical case definition for pertussis includes cough for ≥2 weeks with paroxysms, whoop, post-tussive vomiting, or apnea with or without cyanosis.

Infants aged <6 months can have atypical disease, with a short catarrhal stage, gagging, gasping, or apnea as early manifestations. Among infants aged <2 months, the case-fatality ratio is ≈1%. The illness can be milder, and the characteristic paroxysmal cough and whoop might be absent, in children, adolescents, and adults who were previously vaccinated.

DIAGNOSIS

Factors such as prior vaccination status, disease stage, antibiotic use, specimen collection and transport conditions, and use of nonstandardized tests can affect the sensitivity, specificity, and interpretation of available diagnostic tests for *B. pertussis*. Centers for Disease Control and Prevention (CDC) guidelines for laboratory confirmation of pertussis include culture and PCR when the above clinical case definition is met. Serology is not included as a confirmatory test in the current case definition for reporting purposes. Direct fluorescent antibody (DFA) testing is no longer recommended for diagnosing pertussis because of poor sensitivity and specificity. Testing for *B. pertussis* is widely available in commercial laboratories. Clinicians can consult Vaccine-Preventable Diseases Reference Centers for additional testing support if needed (www.aphl.org/programs/infectious_disease/Pages/VPD.aspx). Pertussis is a nationally notifiable disease

TREATMENT

Clinicians can treat pertussis in people aged ≥1 month with a macrolide antibiotic (azithromycin, clarithromycin, or erythromycin); for infants aged <1 month, azithromycin is preferred. Antimicrobial drug therapy with a macrolide antibiotic administered <3 weeks after cough onset can limit transmission to others.

PREVENTION

Vaccine

Travelers should be up to date on pertussis vaccinations before departure. Multiple pertussis vaccines are available in the United States for infants

and children; 2 vaccines are available for adolescents and adults. A complete listing of licensed vaccines is available at www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm093833.htm.

INFANTS & CHILDREN

In the United States, all infants and children should receive 5 doses of acellular pertussis vaccine in combination with diphtheria and tetanus toxoids (DTaP) at ages 2, 4, 6, and 15–18 months, and at 4–6 years. Providers can use an accelerated schedule of doses to complete the DTaP series before travel, if needed.

Children aged 7–10 years who are not fully vaccinated against pertussis and for whom no contraindication to pertussis vaccine exists should receive a single dose of tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine (Tdap) to provide protection against pertussis. If children need additional doses of tetanus and diphtheria toxoid–containing vaccines, administer them according to catch-up guidance, with Tdap preferred as the first dose (see www.cdc.gov/vaccines/schedules/hcp/imz/catchup.html).

ADOLESCENTS & ADULTS

Adolescents aged 11–18 years who have completed the recommended childhood DTaP vaccination series should receive a single dose of Tdap, preferably at age 11–12 years. Adults aged ≥19 years who have not previously received Tdap should receive a single dose of Tdap instead of tetanus and diphtheria toxoids (Td) vaccine for booster immunization against tetanus, diphtheria, and pertussis, regardless of the interval since their last tetanus or diphtheria toxoid–containing vaccine.

To ensure continued protection against tetanus and diphtheria, administer booster doses of either Td or Tdap every 10 years throughout a patient's life. Follow the catch-up schedule for Td/Tdap for adolescents and adults who have never been immunized against pertussis, tetanus, or diphtheria; who have not completed an immunization series; or whose immunity is uncertain.

PREGNANT PEOPLE

Even if vaccinated previously, a person should receive a dose of Tdap with each pregnancy. Although Tdap can be given at any time during pregnancy, to maximize the maternal antibody response and passive antibody transfer to the infant, optimal timing for Tdap administration is at 27–36 weeks' gestation, preferably during the earlier part of the period.

POSTEXPOSURE PROPHYLAXIS

Postexposure prophylaxis is recommended for all household contacts of cases and for people at high risk of developing severe disease (e.g., infants, people in the third trimester of their pregnancy, anyone who will have contact with a person at high risk of severe illness). The recommended agents and dosing regimens for prophylaxis are the same as for the treatment of pertussis.

CDC website: www.cdc.gov/pertussis

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PLAGUE

David McCormick, Paul Mead

INFECTIOUS AGENT: *Yersinia pestis*	
ENDEMICITY	Sub-Saharan Africa and Madagascar North America (Western United States) South America Central and Southeast Asia, and India
TRAVELER CATEGORIES AT GREATEST RISK FOR EXPOSURE & INFECTION	Adventure tourists Long-term travelers and expatriates
PREVENTION METHODS	Avoid insect bites Use postexposure prophylaxis
DIAGNOSTIC SUPPORT	A clinical laboratory certified in high complexity testing; state health department; or contact CDC's Division of Vector-Borne Diseases (970-221-6400; dvbid@cdc.gov)

INFECTIOUS AGENT

Yersinia pestis, the causative organism for plague, is a gram-negative coccobacillus.

TRANSMISSION

Y. pestis transmission usually occurs through the bite of infected rodent fleas. Less common exposures include handling infected animal tissues (e.g., among hunters and wildlife personnel); inhaling infectious droplets from cats or dogs with plague; and, rarely, contact with a patient who has pneumonic plague.

EPIDEMIOLOGY

Plague is endemic to rural areas in central and southern Africa, especially eastern Democratic Republic of the Congo, northwestern Uganda, and Madagascar; parts of the southwestern United States; the northeastern part of South America; central Asia; and the Indian subcontinent. The overall risk for travelers is low, and encountering *Y. pestis* while traveling is unlikely.

Although travelers' risk is negligible (no plague cases have been reported among travelers returning to the United States in >40 years), cases of plague can lead to societal disruptions that complicate travel. For example, during a plague outbreak in India in the 1980s, planes from India were temporarily prevented from landing in Europe, although none of the passengers had symptoms of plague. In 2017, schools in the Republic of Seychelles were closed and large public gatherings banned in response to a plague outbreak in neighboring Madagascar.

CLINICAL PRESENTATION

The incubation period is typically 1–6 days. Plague illness has 3 possible clinical presentations: bubonic (the most common), pneumonic, or septicemic. Clinical symptoms and signs of bubonic plague include rapid onset of fever and painful, swollen, and tender lymph nodes, usually axillary, cervical, or inguinal. Pharyngeal plague is rare and presents with fever, sore throat, and cervical lymphadenitis; in its early stages, it may be clinically indistinguishable from more common causes of pharyngitis. For pneumonic plague, signs and symptoms include high fever, overwhelming pneumonia, cough, bloody sputum, and chills. For septicemic plague, signs and symptoms include fever, prostration, and hemorrhagic or thrombotic phenomena, progressing to acral gangrene. Meningitis can also develop in up to 10% of patients with plague.

DIAGNOSIS

Y. pestis can be isolated from bubo aspirates, blood cultures, or sputum culture if pneumonic. State

public health laboratories or Centers for Disease Control and Prevention (CDC) laboratories can confirm diagnosis by culture or serologic tests for the *Y. pestis* F1 antigen. Plague is a nationally notifiable disease. For diagnostic support, clinicians can contact CDC's Division of Vector-Borne Diseases (970-221-6400; dvbid@cdc.gov).

TREATMENT

Treatment for plague differs by clinical presentation and illness severity. Several different classes of antimicrobials effectively treat plague, but aminoglycosides and fluoroquinolones are considered first-line. Treating physicians can use doxycycline for bubonic or pharyngeal plague, but these should not be used for pneumonic or septicemic plague, or plague meningitis. If plague meningitis is suspected, use dual antibiotic therapy with chloramphenicol and a fluoroquinolone or aminoglycoside. For full treatment recommendations, see Antimicrobial Treatment and Prophylaxis of Plague: Recommendations for Naturally Acquired Infections and Bioterrorism Response (www.cdc.gov/mmwr/volumes/70/rr/rr7003a1.htm).

PREVENTION

Travelers can prevent plague by reducing contact with fleas and potentially infected rodents and other wildlife. Although a live attenuated vaccine has been in use in Russia since the 1930s, no plague vaccine is currently available for commercial use in the United States or western Europe. A killed whole-cell vaccine was available in the United States for people with occupational risk, but this vaccine was discontinued in 1999. Australia continued to use this vaccine until 2005. Newer vaccines using a recombinant F1 antigen are in development, but none are commercially available or currently approved for use by the US Food and Drug Administration. Oral antibiotics, including doxycycline, ciprofloxacin, and levofloxacin can be prescribed for postexposure prophylaxis.

CDC website: www.cdc.gov/plague

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PNEUMOCOCCAL DISEASE

Jennifer Loo Farrar

INFECTIOUS AGENT: *Streptococcus pneumoniae*	
ENDEMICITY	Worldwide
TRAVELER CATEGORIES AT GREATEST RISK FOR EXPOSURE & INFECTION	Very young children and older adults Travelers with chronic illnesses or immunosuppressed
PREVENTION METHODS	Pneumococcal disease is vaccine-preventable
DIAGNOSTIC SUPPORT	A clinical laboratory certified in moderate complexity testing; or call the CDC Emergency Operations Center (770-488-7100) and ask for the Respiratory Diseases Branch, *Streptococcus* Laboratory, or email pneumococcus@cdc.gov

INFECTIOUS AGENT

A gram-positive diplococcus *Streptococcus pneumoniae*, also called pneumococcus, causes pneumococcal disease.

TRANSMISSION

S. pneumoniae is transmitted person-to-person through close contact via respiratory droplets.

EPIDEMIOLOGY

S. pneumoniae is a major cause of bacterial meningitis and the most common bacterial cause of community-acquired pneumonia worldwide. Disease incidence is higher in low- and middle-income countries than in high-income countries. Pneumococcal meningitis outbreaks have occurred recently in countries in the meningitis belt of Africa (see Sec. 5, Part 1, Ch. 13, Meningococcal Disease). Infections from pneumococcus also have been reported in travelers attending mass gatherings (e.g., the Hajj pilgrimage, Olympic Games) due to crowded conditions and limited space. Risk for infection is greatest in very young children, older adults, and people with chronic illnesses or immune suppression.

CLINICAL PRESENTATION

The major clinical syndromes of pneumococcal disease are pneumonia, bacteremia, and meningitis. Pneumococcal pneumonia classically presents with sudden onset of fever and malaise, pleuritic chest pain, cough with purulent or blood-tinged sputum, or dyspnea. In older people, fever, shortness of breath, or altered mental status are possible initial symptoms.

Symptoms of pneumococcal meningitis include headache, lethargy, vomiting, irritability, fever, neck stiffness, and seizures. People with cochlear implants are at increased risk for pneumococcal meningitis. *S. pneumoniae* infection causes meningitis less frequently than it causes pneumonia.

DIAGNOSIS

S. pneumoniae infection is diagnosed by isolation of the organism from blood or other normally sterile body sites (e.g., pleural fluid, cerebrospinal fluid [CSF]). Tests are also available to detect pneumococcal antigen in body fluids (e.g., urine). The urinary antigen test is commercially available, simple to use, and has reasonable specificity to detect pneumococcal infection in adults, making it a useful addition for diagnostic evaluation.

Suspect pneumococcal pneumonia when a sputum specimen contains gram-positive diplococci, polymorphonuclear leukocytes, and few epithelial cells. Gram-positive diplococci on staining of CSF might indicate pneumococcal meningitis. High white blood cell counts should raise suspicion for bacterial infection.

TREATMENT

Therapy depends on the syndrome, and clinicians should treat patients presenting with community-acquired pneumonia empirically for pneumococcal infection. In 30% of severe cases, pneumococcal bacteria are resistant to ≥1 antimicrobial drug, although the level and type of resistance varies geographically. Studies show that pneumococcal macrolide resistance is widely variable, between 20%–90%. Pneumococcal resistance to fluoroquinolones is relatively low in the United States and Europe. Global prevalence of drug-resistant *S. pneumoniae* causing community-acquired pneumonia is currently unknown.

In outpatient settings, current clinical practice guidelines for pneumonia management recommend amoxicillin for children, and macrolides (e.g., azithromycin) or doxycycline for previously healthy adults. For adults with chronic or immunosuppressing conditions, a respiratory fluoroquinolone (e.g., moxifloxacin, levofloxacin) or a β-lactam plus a macrolide are recommended.

In inpatient settings, the initial treatment includes a broad-spectrum cephalosporin plus a macrolide or a respiratory fluoroquinolone alone. For some pneumococcal infections, consider adding vancomycin until antimicrobial susceptibility results are available. Use a broad-spectrum cephalosporin plus vancomycin to treat patients with presumptive pneumococcal meningitis by CSF staining until susceptibility results are available.

PREVENTION

The 13-valent pneumococcal conjugate vaccine (PCV13) provides protection against the 13 serotypes responsible for most severe illness. PCV13 has been part of the US infant immunization schedule since 2010, and Advisory Committee on Immunization Practices (ACIP) recommends

PCV13 for some adults aged ≥65 years and adults aged 19–64 with immunocompromising conditions.

ACIP recommends 23-valent pneumococcal polysaccharide vaccine (PPSV23) for all adults aged ≥65 years and people aged 2–64 years with underlying medical conditions. PCV13 and PPSV23 should not be coadministered. Intervals between administering PCV13 and PPSV23 differ by age and risk group (see www.cdc.gov/vaccines/vpd/pneumo/hcp/recommendations.html).

A 20-valent pneumococcal conjugate vaccine (PCV20) was licensed for use in adults in June 2021, and the 15-valent pneumococcal conjugate vaccine (PCV15) was licensed for use in adults in July 2021. On October 20, 2021, the ACIP approved recommendations to use PCV20 alone, or PCV15 in series with PPSV23, for all adults aged ≥65 years and for adults aged 19–64 years with underlying medical conditions who have not previously received a pneumococcal conjugate vaccine or whose vaccination history is unknown. Official guidance on use of these vaccines is being developed.

CDC website: www.cdc.gov/pneumococcal

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Q FEVER

Gilbert Kersh

INFECTIOUS AGENT: *Coxiella burnetii*	
ENDEMICITY	Worldwide, except New Zealand
TRAVELER CATEGORIES AT GREATEST RISK FOR EXPOSURE & INFECTION	Animal handlers, e.g., veterinarians, butchers, farmers, and farm workers People visiting rural areas and farms with livestock
PREVENTION METHODS	Avoid exposure to infected animals Follow safe food precautions and avoid unpasteurized dairy products Vaccine available in Australia, but not in the United States
DIAGNOSTIC SUPPORT	A clinical laboratory certified in high complexity testing; state health department; call the CDC Emergency Operations Center (770-488-7100) and ask for the Rickettsial Zoonoses Branch; or consult www.cdc.gov/qfever/public-health/index.html

INFECTIOUS AGENT

The causative agent of Q fever is the gram-negative intracellular bacterium *Coxiella burnetii*.

TRANSMISSION

C. burnetii is most commonly transmitted through inhalation of aerosols or dust contaminated with dried birth fluids or excreta from infected animals, usually cattle, goats, or sheep. *C. burnetii* is highly infectious and persists in the environment. Infections via ingestion of contaminated unpasteurized dairy products and human-to-human transmission via sexual contact have been reported, but rarely.

EPIDEMIOLOGY

C. burnetti has a worldwide distribution but is absent from New Zealand. *C. burnetti* prevalence is greatest in Africa and countries in the Middle East. Reported rates of human infection are higher in France and Australia than in the United States. The largest known Q fever outbreak reported to date involved ≈4,000 human cases during 2007–2010 in the Netherlands. Cases of Q fever in travelers are most often reported in people who visited rural areas or farms with cattle, goats, sheep, or other livestock. During 1990–2013, ≥250 travel-related cases of Q fever were reported in the literature.

Occupational exposure to infected animals, particularly during parturition, poses a high risk for infection among butchers, farmers, meat packers, veterinarians, and seasonal or migrant farm workers. Examples of travel-acquired Q fever include cases in soldiers deployed to rural areas, travelers with livestock contact and consumption of unpasteurized milk, and travelers obtaining treatments that involved the injection of fetal sheep cells. In a 2008 review of 708 returned travelers evaluated for fever, Q fever was diagnosed in 5 people (0.7%).

CLINICAL PRESENTATION

The incubation period is typically 2–3 weeks but can be shorter after exposure to large numbers of organisms. Estimates suggest that over half of acute infections are mild or asymptomatic. The most common clinical presentation of acute infection is a self-limiting febrile illness, with hepatitis or pneumonia associated with more severe acute infections. Chronic infections occur primarily in patients with preexisting cardiac valvulopathies, vascular abnormalities, or immunosuppression. Without proper treatment, infection during pregnancy poses a risk for adverse pregnancy outcomes. The most common manifestations of chronic disease are endocarditis and endovascular infections. Chronic infections might become apparent months or years after the initial exposure.

DIAGNOSIS

Serologic evidence of a 4-fold rise in phase II IgG by indirect fluorescent antibody test between paired acute and convalescent serum samples collected 3–4 weeks apart is the gold standard for diagnosis. Consider a single high serum phase II IgG titer (>1:64) in conjunction with clinical evidence of infection as indicative of probable acute Q fever. PCR testing of serum or whole blood is useful for confirmation of acute Q fever if samples are taken ≤14 days after symptom onset.

Chronic Q fever diagnosis requires a phase I IgG titer >1:512 and clinical evidence of persistent infection (e.g., endocarditis, infected vascular aneurysm, osteomyelitis). Identifying *C. burnetii* in whole blood, serum, or tissue samples by PCR, immunohistochemical staining, or isolation can be used to confirm chronic disease. Tests for direct detection of *C. burnetii* might not be widely available, but the Rickettsial Zoonoses Branch at the Centers for Disease Control and Prevention (CDC) can assist. Information about diagnostic testing is available at www.cdc.gov/qfever/public-health/index.html, or call the CDC Emergency Operations Center (770-488-7100) and ask to be directed to the Rickettsial Zoonoses Branch. Q fever is a nationally notifiable disease.

TREATMENT

Doxycycline is the most frequently used and most effective treatment for acute Q fever. For pregnant people, children aged <8 years with mild illness, and patients allergic to doxycycline, trimethoprim-sulfamethoxazole is an alternative treatment option. Treatment for acute Q fever is not recommended for asymptomatic people or for those whose symptoms

have resolved. Chronic *C. burnetii* infections require long-term combination therapy, and the combination of doxycycline and hydroxychloroquine for ≥18 months provides the best treatment outcomes. Alternative treatments include trimethoprim-sulfamethoxazole and fluoroquinolones, but these are less effective. Treatment of Q fever also might involve surgery to remove infected tissue.

PREVENTION

To prevent Q fever, travelers should avoid areas where potentially infected animals are kept and avoid consumption of unpasteurized dairy products. A human vaccine for Q fever has been developed and used in Australia but is not available in the United States.

CDC website: www.cdc.gov/qfever

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RICKETTSIAL DISEASES

William Nicholson, Christopher Paddock

INFECTIOUS AGENTS: *Rickettsia*, *Orientia*, *Anaplasma*, *Ehrlichia*, *Neoehrlichia*, *Neorickettsia* spp.	
ENDEMICITY	Worldwide
TRAVELER CATEGORIES AT GREATEST RISK FOR EXPOSURE & INFECTION	People exposed to vector fleas, lice, mites, or ticks
PREVENTION METHODS	Avoid insect and arthropod bites
DIAGNOSTIC SUPPORT	A clinical laboratory certified in high complexity testing; state health department; or contact CDC's Rickettsial Zoonoses Branch (rzbepidiag@cdc.gov)

INFECTIOUS AGENTS

Rickettsial infections are caused by various bacteria within 6 genera of the order Rickettsiales: *Rickettsia*, *Orientia*, *Anaplasma*, *Ehrlichia*, *Neoehrlichia*, and *Neorickettsia* (Table 5-04). *Rickettsia* spp. are classically divided into the spotted fever group (SFG) and the typhus group, although more recently these have been classified into as many as 4 groups. *Orientia* spp. comprise the scrub typhus group, which has only recently expanded from the single species *O. tsutsugamushi*.

Rickettsial species (and diseases) that travelers are more likely to encounter outside the United