each affected body site. Clinically, varicella is the most common rash illness likely to be confused with smallpox (see Sec. 5, Part 2, Ch. 24, Varicella / Chickenpox). Lesions on the palms or soles and a centrifugal distribution of lesions on the body, which are characteristic of smallpox, can sometimes help distinguish orthopoxvirus infection from varicella.

Cowpox & Vaccinia

Human infections with cowpox, cowpox-like viruses, vaccinia, and wild vaccinia-like viruses are most often self-limited, characterized by localized vesicular-pustular lesions, which in cowpox occasionally are ulcerative. Fever and other constitutional symptoms might occur briefly after lesions first appear. Lesions can be painful and persist for weeks.

Monkeypox

As with smallpox, a person infected with monkeypox virus classically experiences a febrile prodrome (characterized by high fever, malaise, headache, or back pain) followed by a widespread, characteristic, vesiculopustular rash that sometimes involves the palms and soles. Marked lymphadenopathy is common in classic presentations of monkeypox, distinguishing it from smallpox.

Cases associated with the worldwide outbreak that began in 2022 have exhibited a different clinical presentation than classic monkeypox. During the outbreak, rash lesions have been reported as being smaller and less diffusely spread; multiple lesions locally scattered over specific parts of the body or only a single lesion have been observed. In many cases, lesions have involved the anogenital area and caused pain and proctitis. The illness has been self-limited and most patients have not required hospitalization; some deaths have been reported, however.

DIAGNOSIS

PCR testing or virus isolation can confirm an orthopoxvirus infection. Do not send laboratory specimens to CDC without a prior consultation. Guidance on preparation and collection of specimens and other clinically relevant issues can be found at www.cdc.gov/poxvirus/monkeypox/clinicians/index.html and www.cdc.gov/smallpox/clinicians/index.html.

Monkeypox

During the 2022 monkeypox outbreak, public health laboratories and multiple commercial laboratories in the United States tested specimens prior to sending samples to CDC for additional characterization or specialized tests. CDC provides laboratory testing and consultation with monkeypox subject matter experts when requested.

Particularly during the 2022 outbreak, clinicians have confused monkeypox (in part due to its atypical presentation) with infections that can present similarly. Evaluate patients for these other infections as well as monkeypox. Moreover, co-infections with a sexually transmitted infection (e.g., syphilis) or with varicella have been known to occur. CDC is frequently updating its clinical guidance and management recommendations during the global monkeypox outbreak; see www.cdc.gov/poxvirus/monkeypox/clinicians/clinical-guidance.html for current information.

TREATMENT

Treatment of orthopoxvirus infections is mainly supportive care through hydration, nutritional supplementation, and prevention of secondary infections. To diminish the chances of spreading virus to other parts of the body or to other people, keep all pox lesions covered until the scab detaches; advise patients to avoid touching their eyes before proper hand washing. Managing orthopoxvirus infections in patients at high risk for severe outcomes (e.g., immunocompromised people, those with underlying skin conditions, those with eye involvement) can be challenging. Topical antivirals (e.g., trifluridine drops) have been used to treat ocular involvement. Tecovirimat (TPOXX), brincidofovir (Tembexa), and vaccinia immune globulin have been licensed by the US Food and Drug Administration to treat smallpox or vaccinia complications and are stocked in the US government's Strategic National Stockpile (SNS).

Monkeypox

During the 2022 global outbreak, health care providers have used Tecovirimat to treat patients with monkeypox. Anecdotally, use of this drug has been associated with shorter illness courses, although more evaluations are needed to better understand its role in treatment. Tecovirimat is available through a CDC–sponsored Investigational New Drug protocol for the treatment of monkeypox.

PREVENTION

To reduce the chances of contracting monkeypox and other orthopoxvirus infections, travelers should avoid contact with sick or dead animals, including wild animals, pets, and domestic ruminants (e.g., buffalo, cattle). They should also avoid direct contact with ill humans.

Two vaccines are licensed for the prevention of smallpox in the United States. People at occupational risk for orthopoxvirus infection (e.g., laboratorians who work with variola, monkeypox, or vaccinia viruses; military personnel who travel to regions in the world where variola virus could be encountered) are vaccinated for preexposure prophylaxis. The Advisory Committee on Immunization Practices only recommends preexposure prophylaxis for people at occupational risk for orthopoxvirus infection (e.g., because of health care delivery to a patient or laboratory work involving orthopoxviruses). Members of the US military might be required to receive the vaccine.

Monkeypox

Monkeypox is not considered a sexually transmitted infection, but it can be transmitted through close, sustained, physical contact, including sexual contact. Vaccinations might be recommended for people having direct or indirect exposure to a person with monkeypox; because of the evolving nature of the 2022 global outbreak, refer to the CDC website (www.cdc.gov/poxvirus/monkeypox/clinicians/vaccines/index.html) for the latest updates. Additional prevention strategies associated with safer sex, social gatherings, and monkeypox, can be found at www.cdc.gov/poxvirus/monkeypox/prevention/sexual-health.html.

CDC websites: www.cdc.gov/poxvirus/index.html; www.cdc.gov/smallpox/index.html

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TICK-BORNE ENCEPHALITIS

Susan Hills, Carolyn Gould, Caitlin Cossaboom

INFECTIOUS AGENT: Tick-borne encephalitis (TBE) virus	
ENDEMICITY	Western and northern Europe, extending to northern and eastern Asia
TRAVELER CATEGORIES AT GREATEST RISK FOR EXPOSURE & INFECTION	Adventurous eaters Expatriates living in endemic areas Travelers participating in outdoor activities in forested areas
PREVENTION METHODS	Avoid tick bites Practice safe food precautions and avoid unpasteurized dairy products Tick-borne encephalitis is a vaccine-preventable disease
DIAGNOSTIC SUPPORT	State health department; or contact CDC Arboviral Diseases Branch (www.cdc.gov/ncezid/dvbd/specimensub/arboviral-shipping.html; 970-221-6400; dvbid@cdc.gov)

INFECTIOUS AGENT

Tick-borne encephalitis (TBE) virus is a single-stranded RNA virus that belongs to the genus *Flavivirus*. TBE virus has 3 main subtypes: European, Far Eastern, and Siberian.

TRANSMISSION

TBE virus is transmitted to humans through the bite of an infected tick of the *Ixodes* species, primarily *I. ricinus* (European subtype) or *I. persulcatus* (Far Eastern and Siberian subtypes). Preferred habitats for these tick species include the edges of forests, areas with deciduous or coniferous trees, and low-growing dense brush and other vegetation. Ticks act as both the vector and virus reservoir, and small rodents are the primary amplifying host. People also can acquire TBE by ingesting unpasteurized dairy products (e.g., milk, cheese) from infected cows, goats, or sheep. Infrequently, TBE virus transmission has been reported through laboratory exposure and slaughtering viremic animals. Direct person-to-person spread of TBE virus occurs only rarely, through blood transfusion, solid organ transplantation, or breastfeeding.

EPIDEMIOLOGY

TBE is focally endemic in a geographic region spreading from western and northern Europe through to northern and eastern Asia. Approximately 5,000–10,000 TBE cases are reported from endemic countries each year, with large annual fluctuations. The number of human TBE cases reported from an area might not be a reliable predictor of a traveler's risk for infection because reporting of local cases depends on various factors, including the intensity of diagnosis and surveillance and the vaccine coverage in the population.

Russia, including Siberia, has the most reported cases. The highest disease incidence in recent years has been reported from the Baltic states (Estonia, Latvia, Lithuania), Czech Republic, and Slovenia. Other European countries with reported cases or known endemic areas include Austria, Belarus, Belgium, Bosnia, Bulgaria, Croatia, Denmark, Finland, France, Germany, Hungary, Italy, Liechtenstein, Moldova, Netherlands, Norway, Poland, Romania, Serbia, Slovakia, Sweden, Switzerland, Ukraine, and the United Kingdom. Asian countries with reported

TBE cases or virus activity include China, Japan, Kazakhstan, Kyrgyzstan, Mongolia, and South Korea.

Attack Rate Among Travelers

TBE virus transmission is highly variable by place and over time, and tick population density and infection rates in TBE virus–endemic areas are not consistent. The risk for TBE virus infection for an individual traveler is greatly affected by their planned itinerary and activities. Most infections result from tick bites acquired in forested areas while bicycling, birdwatching, camping, fishing, hiking, or collecting berries, flowers, or mushrooms. People with outdoor occupations, (e.g., farmers, forestry workers, military personnel training in forested areas) are also at increased risk. The risk is negligible for people who remain in urban or unforested areas and who do not consume unpasteurized dairy products.

During 2000–2020, 11 cases of TBE were reported among US civilian travelers. Of these, 10 (91%) cases occurred among males, and most (73%) were in people >19 years old. Destinations where infections likely were acquired included China, Russia, and several countries in Europe. During 2012–2020, an additional 9 TBE cases were reported among US military personnel or their dependents residing in Germany.

Travelers at risk for TBE virus infection might also be at risk for other tickborne diseases because the same ticks that transmit TBE virus also can transmit other pathogens, including *Borrelia burgdorferi* (the agent for Lyme disease), *Anaplasma phagocytophilum* (anaplasmosis), and *Babesia* spp. (babesiosis); simultaneous infection with multiple organisms has been described.

Seasonality & Geographic Range

Most TBE cases occur during April–November, with peaks in early and late summer when ticks are most active. Most cases occur in areas <2,500 ft (≈750 m) in elevation. During the past 30 years, the range of TBE virus transmission appears to have expanded to new geographic areas and to higher elevations; the virus has been found at ≥5,000 ft (≈1,500 m). These trends are likely due to a complex combination of changes in diagnostics and surveillance, changes in human activities, and other socioeconomic, ecologic, and climatic factors.

CLINICAL PRESENTATION

Most (≈2/3) infections are asymptomatic. The median incubation period for TBE is 8 days (range 2–28 days). Acute neuroinvasive disease is the most recognized clinical manifestation of TBE virus infection. Often, however, TBE presents with milder disease forms or a biphasic course.

Phases

The first phase of TBE is characterized by a nonspecific febrile illness sometimes accompanied by anorexia, headache, malaise, myalgia, and nausea, vomiting, or both. This phase usually lasts for several days and might be followed by an afebrile and relatively asymptomatic period. For patients who progress to more severe clinical illness, the second phase reflects central nervous system involvement, specifically aseptic meningitis, encephalitis, or meningoencephalomyelitis. Clinical findings can include altered mental status, ataxia, cognitive dysfunction, cranial nerve palsies, limb paresis, meningeal signs, rigidity, seizures, and tremors.

Sequelae

TBE disease severity increases with age; incidence and disease severity are greatest in people aged ≥50 years. Although TBE tends to be less severe in children, residual symptoms and neurologic deficits have been described. Clinical course and long-term outcome vary by TBE virus subtype, although some of the reported differences could be due to access to medical care, or testing or methodologic biases in published reports.

The European subtype is associated with milder disease, a case-fatality ratio of <2%, and neurologic sequelae in ≤30% of patients. The Far Eastern subtype is often associated with a more severe disease course, including a case-fatality ratio of 20%–40% among neurologic disease cases and higher rates of severe sequelae. The Siberian subtype has a case-fatality ratio of 6%–8%, with rare reports of cases with slow or chronic progression over months.

DIAGNOSIS

Suspect TBE in travelers who develop a nonspecific febrile illness that progresses to neuroinvasive disease ≤4 weeks after arriving from an endemic area. A history of tick bite might suggest TBE diagnosis; ≈30% of TBE patients do not recall a tick bite, however.

Serology

Serology is typically used for laboratory diagnosis. IgM-capture ELISA performed on serum or cerebrospinal fluid is almost always positive during the neuroinvasive phase of the illness. When interpreting results, consider the patient's vaccination history, date of symptom onset, and information about other flaviviruses known to circulate in the same geographic area that might cross-react with serologic assays.

Nucleic Acid Amplification Testing

During the first phase of the illness, TBE virus or viral RNA sometimes can be detected. By the time neurologic symptoms are recognized, however, the virus or viral RNA is usually undetectable. Therefore, virus isolation and reverse transcription PCR (RT-PCR) testing should not be used to rule out TBE diagnosis. No commercially available tests can diagnose TBE. Contact the state or local health department or the Centers for Disease Control and Prevention (CDC) Arboviral Diseases Branch, Division of Vector-Borne Diseases (970-221-6400), for assistance with diagnostic testing.

TREATMENT

No specific antiviral treatment is available for TBE. Therapy consists of supportive care and management of complications.

PREVENTION

Personal Protective Measures

Travelers should avoid consuming unpasteurized dairy products and use all measures to avoid tick bites (see Sec. 4, Ch. 6, Mosquitoes, Ticks & Other Arthropods).

Vaccine

In August 2021, the US Food and Drug Administration approved Pfizer's TICOVAC as the first TBE vaccine for use in the United States. Also marketed as FSME-IMMUN in Europe, TICOVAC is an inactivated, whole-virus vaccine with formulations for children (1–15 years) and adults (≥16 years). Five other TBE vaccines, not licensed for use in the United States, are available internationally.

INDICATIONS FOR USE

The risk for most US travelers visiting TBE-endemic areas is very low. Based on activities, destination, duration of travel, and season, some people who travel abroad are at increased risk for infection (Box 5-06). In February 2022, the Advisory Committee on Immunization Practices approved recommendations for vaccine use among people traveling or moving to a TBE-endemic area who will have extensive tick

BOX 5-06 Factors that increase the risk for tick-borne encephalitis (TBE) virus infection among travelers

- Travel during the warmer spring and summer months when ticks are more active
- Participating in recreational outdoor activities (e.g., camping, fishing, hiking, hunting) in or near tick habitats
- Working in outdoor settings (e.g., farming, forestry work, field research) where there is an increased risk of contact with infected ticks
- Longer stays in, or repeated travel to, endemic areas might increase a traveler's likelihood for exposure to TBE virus. The specific activities undertaken while in those areas, however, represent a more important risk for infection than time spent abroad.

BOX 5-07 Risk–benefit considerations for vaccination against tick-borne encephalitis (TBE)

RISK FOR TBE VIRUS EXPOSURE & INFECTION

Travelers most likely to be at greater risk for exposure and infection include both shorter-term (e.g., <1 month) travelers with daily or frequent exposure, and longer-term travelers with regular (e.g., a few times a month) exposure

Likelihood of exposure to TBE virus-infected ticks depends on activities and itinerary, including specific destination, rural vs. urban, season, duration

Future (additional) travel to TBE-endemic areas can also increase risk for exposure and infection

SEVERITY OF TBE DISEASE

Rare occurrence of TBE vs. potentially high morbidity and mortality

Increased risk for severe disease among certain populations (e.g., travelers ≥50 years old)

Individual perception and tolerance of risk for a potentially severe disease

VACCINE-ASSOCIATED RISKS

Availability of a vaccine with good long-term immunogenicity and safety profile

Possibility (but low probability) for serious adverse events from the vaccine

exposure based on planned outdoor activities and itinerary. In addition, consider TBE vaccine for people traveling or moving to a TBE-endemic area who might engage in outdoor activities in areas where ticks are likely to be found. Base a recommendation to vaccinate on an assessment of planned activities and itinerary, risk factors for a poorer medical outcome, and personal perception and tolerance of risk (Box 5-07).

ADMINISTRATION

Dose and primary vaccination schedule vary by age (Table 5-21). Each dose is administered intramuscularly.

SAFETY & ADVERSE REACTIONS

Although TICOVAC has only recently been licensed in the United States, the current vaccine formulation has been available internationally for >20 years, and >75 million doses have been administered with no serious safety concerns identified. Adverse events reported most commonly include tenderness and pain at the injection site in ≥10% of vaccine recipients. In children and adolescents, the most common systemic symptoms include fever, headache, and restlessness; in adults, headache, fatigue, and myalgia. Serious adverse events are reported only rarely.

Table 5-21 TICOVAC tick-borne encephalitis (TBE) vaccine administration schedule

AGE	DOSE	PRIMARY VACCINATION SCHEDULE	BOOSTER
1–15 years	0.25 mL	DOSE 1: Day 0 DOSE 2: 1–3 months after DOSE 1 DOSE 3: 5–12 months after DOSE 2	≥3 years after completion of primary immunization series if ongoing exposure or reexposure to TBE virus is expected
≥16 years	0.5 mL	DOSE 1: Day 0 DOSE 2: 14 days–3 months after DOSE 1 DOSE 3: 5–12 months after DOSE 2	≥3 years after completion of primary immunization series if ongoing exposure or reexposure to TBE virus is expected

CONTRAINDICTIONS & PRECAUTIONS

A severe allergic reaction to any component of TICOVAC is a contraindication to administration. Some individuals with altered immunocompetence might have reduced immune responses to TICOVAC, and immunocompromise and immunosuppression are precautions to vaccination. No studies have assessed the safety of TICOVAC in people who are pregnant or lactating.

CDC website: www.cdc.gov/tick-borne-encephalitis/index.html

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VARICELLA / CHICKENPOX

Mona Marin, Jessica Leung

INFECTIOUS AGENT: Varicella-zoster virus	
ENDEMICITY	Worldwide
TRAVELER CATEGORIES AT GREATEST RISK FOR EXPOSURE & INFECTION	Travelers without evidence of immunity
PREVENTION METHODS	Varicella is a vaccine-preventable disease
DIAGNOSTIC SUPPORT	A clinical laboratory certified in moderate complexity testing; state public health department; or CDC National VZV Laboratory, www.cdc.gov/chickenpox/lab-testing/collecting-specimens.html

INFECTIOUS AGENT

Varicella-zoster virus (VZV) is a member of the *Herpesviridae* family. Humans are the only VZV reservoir, and disease occurs only in humans. After primary infection as varicella (chickenpox), VZV remains latent in the sensory-nerve ganglia and can reactivate later, causing herpes zoster (shingles).

TRANSMISSION

VZV transmission occurs person to person, primarily via the respiratory route, by inhalation of aerosols from vesicular fluid of skin lesions of varicella or herpes zoster; VZV also can spread by direct contact with the vesicular fluid of skin lesions and possibly infected respiratory tract secretions. VZV enters the host through the upper respiratory tract or the conjunctiva. Varicella is a highly contagious viral disease with secondary attack ratios of ≈85% (range 61%–100%) in susceptible household contacts; contagiousness after community exposure is lower. Herpes zoster is ≈20% as infectious as varicella; in susceptible people, contact with herpes zoster rash causes varicella, not herpes zoster.

Virus communicability from patients with varicella begins ≈1–2 days before the onset of rash and ends when all lesions are crusted, typically 4–7 days after onset of rash in immunocompetent people; communicability might be longer in immunocompromised people. Vaccinated people who get chickenpox might develop lesions that do not crust. These people are considered contagious until no new lesions have appeared for 24 hours. Patients with herpes zoster are contagious while they have active, vesicular lesions (usually 7–10 days). In utero infection also can occur due to transplacental passage of the virus during maternal varicella infection.

EPIDEMIOLOGY

Varicella occurs worldwide. In temperate climates, varicella tends to be a childhood disease, with peak incidence among preschool and school-aged children; <5% of adults are susceptible to varicella. Disease typically occurs during late winter and early spring. In tropical climates, by contrast, infection tends to be more common later in childhood, with greater susceptibility among adults than in temperate climates, especially in less densely populated areas. The highest incidence of disease in tropical climates occurs during the driest, coolest months.

With the implementation of the childhood varicella vaccination program in the United States in 1996, substantial declines in disease incidence have occurred. Although still endemic, the risk for VZV exposure is now lower in the United States than in most other parts of the world. As of 2019, 18% of countries have introduced a routine varicella vaccination program, and an additional 6% have varicella vaccination programs for risk groups only.

Because varicella is endemic worldwide, all susceptible travelers are at risk for infection during travel. Additionally, exposure to herpes zoster poses a risk for varicella in susceptible travelers, although localized herpes zoster is much less contagious than varicella. Infants, adults, and immunocompromised people without evidence of immunity are at highest risk for severe varicella (see Box 5-08 for acceptable evidence of immunity).

CLINICAL PRESENTATION

Varicella is generally a mild disease in children, and most people recover without serious complications. The average incubation period is 14–16 days (range 10–21 days). Infection often is characterized by a short (1- or 2-day) prodromal period (fever, malaise), which might be absent in

BOX 5-08 Acceptable evidence of immunity to varicella

Birth in the United States before 1980 (not acceptable criterion for health care personnel, immunocompromised people, or pregnant people)

Documentation of age-appropriate vaccination

- Preschool-aged children (≥12 months through 3 years of age): 1 dose
- School-aged children (≥4 years of age), adolescents, and adults: 2 doses

Health care provider's diagnosis of varicella or verification of a history of varicella

Health care provider's diagnosis of herpes zoster or verification of a history of herpes zoster

Laboratory evidence of immunity or laboratory confirmation of disease

children, and a generalized pruritic rash. The rash consists of crops of macules, papules, and vesicles (typically 250–500 lesions), which first appear on the chest, back, and face, then spread over the entire body in ≥3 successive waves and resolve by crusting. A characteristic of varicella is the presence of lesions in different stages of development at the same time.

Serious complications can occur, most commonly in infants, adults, and immunocompromised people. Complications include cerebellar ataxia, encephalitis, hemorrhagic conditions, pneumonia, and secondary bacterial infections of skin lesions, sometimes resulting in bacteremia or sepsis; rarely (≈1 in 40,000 varicella cases), these complications can cause death.

Modified varicella, also known as breakthrough varicella, can occur in vaccinated people. Breakthrough varicella is usually mild, with <50 lesions, low or no fever, and shorter duration for rash. The rash could be atypical in appearance, with fewer vesicles and predominance of maculopapular lesions. Breakthrough varicella is contagious, although less so than varicella in unvaccinated people.

DIAGNOSIS

Varicella is a nationally notifiable disease in the United States. Often based on an appropriate exposure history and the presence of a generalized maculopapulovesicular rash, the clinical diagnosis of varicella in the United States has become increasingly challenging because a growing number of cases now occur in vaccinated people in whom disease is mild and rash is atypical. Although not routinely performed, laboratory diagnosis is becoming increasingly useful. State public health and commercial laboratories can perform diagnostic tests for laboratory confirmation of varicella. See Collecting Specimens for Varicella-Zoster Virus (VZV) Testing (www.cdc.gov/chickenpox/lab-testing/collecting-specimens.html) for additional information on specimen collection and testing for varicella.

Nucleic Acid Amplification Testing

For laboratory confirmation, skin lesions are the preferred specimen source. Vesicular swabs or scrapings and scabs from crusted lesions can be used to identify varicella-zoster virus DNA by PCR testing (the preferred method because it is the most sensitive and specific) or direct fluorescent antibody. In the absence of vesicles or scabs, collect scrapings of maculopapular lesions for testing.

Serologic Testing

Serologic tests also can be used to confirm disease but are less reliable than PCR or direct fluorescent antibody methods for virus identification. A substantial rise in serum varicella IgG titers from acute- and convalescent-phase samples by any standard serologic assay can confirm a diagnosis retrospectively; these antibody tests might not be reliable in immunocompromised people. Additionally, in vaccinated people, baseline IgG levels might be high; thus, a 4-fold increase in convalescent serum samples might not be achieved. Of note, testing for varicella-zoster IgM by using commercial kits is not recommended, because available methods lack sensitivity and specificity; false-positive IgM results are common in the presence of high IgG levels. A positive IgM also does not distinguish between primary infection and reactivation.

TREATMENT

Treatment with antiviral medications is not recommended routinely for otherwise healthy children with varicella. Consider oral acyclovir treatment for people at increased risk for moderate to severe disease (e.g., people >12 years old); people with chronic cutaneous or pulmonary disorders; people who are receiving long-term salicylate therapy; people who are receiving short, intermittent, or aerosolized courses of corticosteroids; and possibly secondary cases among household contacts. Intravenous acyclovir is recommended for immunocompromised people, including patients being treated with high-dose corticosteroids for ≥2 weeks and people with virally mediated complications (e.g., pneumonia). Therapy initiated within 24 hours of illness onset maximizes efficacy. Do not use aspirin or aspirin-containing products to relieve fever from varicella; also avoid ibuprofen, if possible.

PREVENTION

Vaccine

INDICATIONS FOR USE

In the United States, all people, including those traveling or living abroad, should be assessed for varicella immunity; people who do not have evidence of immunity should receive age-appropriate vaccination if they do not have contraindications to vaccination. Vaccination against varicella is not a requirement for entry into any country, including the United States, but people who do not have evidence of immunity (Box 5-08) should be considered at risk for varicella during international travel.

ADMINISTRATION

Varicella vaccine contains live, attenuated VZV. Single-antigen varicella vaccine is licensed for people aged ≥12 months, and the combination measles-mumps-rubella-varicella (MMRV) vaccine is licensed only for children 1–12 years. CDC recommends varicella vaccine for all people aged ≥12 months without evidence of immunity to varicella who do not have contraindications to the vaccine. For children ≥12 months and <13 years, the recommendation is for 2 doses of vaccine administered ≥3 months apart. Typically, the first dose is given at 12–15 months of age and the second at 4–6 years of age. The second dose can be given before age 4, however, provided ≥3 months have passed since the first dose. For people aged ≥13 years, the recommendation is for 2 doses of vaccine administered ≥4 weeks apart. There is no recommendation for varicella vaccination for infants aged <12 months before international travel.

CONTRAINDICATIONS

Contraindications to vaccination include allergy to vaccine components, immunocompromising conditions or treatments, and pregnancy. When evidence of immunity is uncertain, a possible history of varicella is not a contraindication to varicella vaccination. Vaccine effectiveness is ≈80% after 1 dose and 92%–95% after 2 doses.

SAFETY & ADVERSE REACTIONS

The varicella vaccine is generally well tolerated. The most common adverse events after vaccination are self-limited injection-site reactions (e.g., pain, redness, swelling, soreness). Fever or a varicella-like rash, usually consisting of a few lesions at the injection site or generalized rash with a few lesions, are reported less frequently.

Compared with use of separate MMR and varicella vaccines at the same visit, use of the combination MMRV vaccine is associated with a higher risk for fever and febrile seizures, ≈1 additional febrile seizure for every 2,300–2,600 MMRV vaccine doses administered. Fever and febrile seizures typically occur 5–12 days after the first dose of MMRV; the greatest incidence occurs among children aged 12–23 months. Use of separate MMR and varicella vaccines helps avoid this risk. For detailed information regarding the varicella vaccine, visit CDC's website, Chickenpox (Varicella) Vaccination, www.cdc.gov/chickenpox/vaccination.html.

POSTEXPOSURE PROPHYLAXIS

Vaccine

CDC recommends administering postexposure varicella vaccine to unvaccinated healthy people aged ≥12 months without other evidence of immunity, to prevent or modify the disease. Administer the vaccine as soon as possible ≤5 days after exposure to rash, if the exposed person has no contraindications. Among children, protective efficacy was reported as ≥90% when vaccination occurred ≤3 days of exposure. Administration of a second postexposure dose is recommended for exposed people who previously received 1 dose, so their vaccinations are current and to best protect against future exposures.

Varicella-Zoster Immune Globulin

CDC recommends that people without evidence of immunity who have contraindications to vaccination and who are at risk for severe varicella and complications receive postexposure prophylaxis with varicella-zoster immune globulin. The varicella-zoster immune globulin product licensed in the United States is VariZIG.

People who should receive VariZIG after exposure include immunocompromised people, pregnant people without evidence of immunity, and some neonates and infants. VariZIG provides maximum benefit when administered as soon as possible after exposure, but might be effective if

administered as late as 10 days after exposure. In the United States, VariZIG can be obtained from specialty distributors (see https://varizig.com).

If VariZIG is not available, consider administering a single dose (400 mg/kg) of intravenous immune globulin (IVIG) ≤10 days of exposure. In the absence of both VariZIG and IVIG, some experts recommend prophylaxis with acyclovir for people without evidence of immunity who have contraindications to varicella vaccination; the recommended dose is 80 mg/kg/day in 4 divided doses for 7 days, up to a maximum dose of 800 mg 4 times per day, beginning 7–10 days after exposure. Published data on the benefit of acyclovir as postexposure prophylaxis among immunocompromised people are limited.

CDC website: www.cdc.gov/chickenpox/

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VIRAL HEMORRHAGIC FEVERS

Trevor Shoemaker, Mary Joung Choi

ARENAVIRUSES

INFECTIOUS AGENT: Family *Arenaviridae*	
ENDEMICITY	Sub-Saharan Africa (Lassa, Lujo) South America (Chapare, Guanarito, Junin, Machupo, Sabia) United States (Lymphocytic choriomeningitis virus)
TRAVELER CATEGORIES AT GREATEST RISK FOR EXPOSURE & INFECTION	Travelers to rural areas or farmlands where rodent reservoir species are prevalent Health care workers treating infected patients
PREVENTION METHODS	Avoid areas where rodent reservoirs are present Use standard barrier precautions and personal protective equipment in medical settings
DIAGNOSTIC SUPPORT	Contact state or local health department

BUNYAVIRUSES

INFECTIOUS AGENT: Order *Bunyavirales*	
ENDEMICITY	Sub-Saharan Africa: Crimean-Congo hemorrhagic fever (CCHF, family *Nairoviridae*); Rift Valley fever (RVF, family *Phenuiviridae*) Eastern Europe through Central Asia: CCHF United States: Hantavirus (family *Hantaviridae*)
TRAVELER CATEGORIES AT GREATEST RISK FOR EXPOSURE & INFECTION	Travelers to areas with infected livestock, tick or mosquito vectors, or rodent reservoirs People handling infected raw meat or animal products Health care workers treating patients with CCHF People camping in rural areas or staying in homes infested with rodents or their excrement (hantavirus)
PREVENTION METHODS	Practice safe food precautions; avoid handling, cooking, or eating raw or undercooked meat or animal products Avoid unprotected contact with blood, fluids, or tissues of potentially infected animals; avoid touching sick or dead livestock Avoid mosquito and tick bites Use standard barrier precautions and personal protective equipment in medical settings (CCHF)
DIAGNOSTIC SUPPORT	Contact state or local health department

FILOVIRUSES

INFECTIOUS AGENT: Family *Filoviridae*	
ENDEMICITY	Sub-Saharan Africa Southeast Asia (Reston)
TRAVELER CATEGORIES AT GREATEST RISK FOR EXPOSURE & INFECTION	Travelers to areas where suspected bat reservoir species are prevalent Health care workers treating infected patients People in contact with sick or dead wildlife, or nonhuman primates
PREVENTION METHODS	Practice safe food precautions; avoid handling, cooking, or eating raw or undercooked meat or animal products Avoid touching sick or dead wildlife and nonhuman primates Avoid eating fruit found on the ground Use standard barrier precautions and personal protective equipment in medical settings Ebola is a vaccine-preventable disease (restrictions apply, see text below for details)
DIAGNOSTIC SUPPORT	Contact state or local health department

FLAVIVIRUSES

INFECTIOUS AGENT: Family *Flaviviridae*	
ENDEMICITY	Asia, Europe, former Soviet Union (Tick-borne encephalitis) Egypt, Saudi Arabia (Alkhurma) Southern India (Kyasanur Forest disease) Omsk and neighboring oblasts (Omsk)
TRAVELER CATEGORIES AT GREATEST RISK FOR EXPOSURE & INFECTION	People touching infected livestock or ticks (Alkhurma) Travelers to areas where rodent reservoirs and tick species are prevalent (Omsk) People with recreational or occupational exposure to rural or outdoor settings, or contact with infected ticks or animals (Tick-borne encephalitis, Kyasanur Forest disease, Omsk)
PREVENTION METHODS	Avoid unprotected contact with blood, fluids, or tissues of potentially infected animals (Alkhurma) Avoid tick bites
DIAGNOSTIC SUPPORT	Contact state or local health department

INFECTIOUS AGENTS

Viral hemorrhagic fever (VHF) diseases are caused by 3 families (*Arenaviridae*, *Filoviridae*, *Flaviviridae*) and 1 order (*Bunyavirales*) of enveloped RNA viruses. *Arenaviridae* (arenaviruses) include Chapare, Guanarito, Junin, Lassa, and Lujo viruses; lymphocytic choriomeningitis virus (LCMV); and Machupo and Sabia viruses. Viruses in the order *Bunyavirales* include the *Arenaviridae* family viruses, Crimean-Congo hemorrhagic fever (CCHF) virus (family *Nairoviridae*), hantaviruses (family *Hantaviridae*), and Rift Valley fever (RVF) virus (family *Phenuiviridae*). *Filoviridae* (filoviruses) include Ebola, Marburg, and Reston viruses. *Flaviviridae* (flaviviruses) include Alkhurma, Kyasanur Forest disease, Omsk hemorrhagic fever, dengue, and yellow fever viruses. For details on dengue and yellow fever, see the respective chapters in this section.

TRANSMISSION

Human-to-Human

Some VHF viruses (arenaviruses, CCHF virus, filoviruses) spread from person to person by direct contact with symptomatic patients, body fluids, or cadavers, or through inadequate infection control in a hospital setting. In the community, VHF viruses are generally transmitted through direct physical contact of unprotected skin or mucous membranes and the blood or other infectious body fluids of patients in the acute phase of disease or from patients who have died.

After recovery from acute Ebola virus disease (EVD) or Marburg virus disease (MVD), the virus or its RNA persists in some specific body fluids of convalescent patients. Ebola virus RNA has been detected in breast milk up to 21 days after the onset of the disease, and in vaginal secretions up to 33 days after onset. Ebola virus and Marburg virus have been cultured from ocular aqueous humor at 2 and 3 months after disease onset, respectively. Evidence suggests that Ebola and Marburg viruses can be sexually transmitted from a male survivor to his partner months after recovery. In pregnant people with EVD, in utero transmission of Ebola virus to the fetus can occur.

Zoonotic

ARTHROPOD VECTORS

Some bunyaviruses (RVF virus) and flaviviruses (dengue and yellow fever) can be transmitted by the bites of infected mosquitoes. Other bunyaviruses (CCHF virus) and flaviviruses (Alkhurma, Kyasanur Forest disease, and Omsk viruses) can be transmitted by the bites of infected ticks or by crushing infected ticks.

BATS

Bats are suspected reservoir species for filoviruses (Ebola and Marburg viruses) in the genus *Ebolavirus*; the natural reservoir for Marburg virus is the Egyptian fruit bat (*Rousettus aegyptiacus*).

LIVESTOCK

Some bunyaviruses (CCHF and RVF viruses) and flaviviruses (Alkhurma virus) can be transmitted during the slaughter of infected animals or from the consumption of raw meat or unpasteurized milk of an infected animal.

RODENTS & INSECTIVORES

Arenaviruses and some bunyaviruses (hantaviruses) can be transmitted by direct contact with infected animals or from inhalation of, or contact with, materials contaminated with rodent excreta.

EPIDEMIOLOGY

The viruses that cause VHF are distributed over much of the globe. Each virus is associated with ≥1 nonhuman host or vector species, restricting the virus and the initial contamination to the areas inhabited by these species. The diseases caused by these viruses are seen in people who live in or visit these areas. Humans are incidental hosts for these enzootic diseases; person-to-person transmission of some viruses can occur, however.

Arenaviral Diseases

Except Tacaribe virus—which was found in bats but has not been reported to cause disease in humans—arenaviruses are maintained in rodents and transmitted to humans. Most infections are mild, but some result in hemorrhagic fever with high death rates. Arenaviruses are categorized as Old World (Eastern Hemisphere) and New World (Western Hemisphere).

OLD WORLD ARENAVIRUSES

Old World arenaviruses (and the diseases they cause) include Lassa virus (Lassa fever), Lujo virus, and LCMV. In otherwise healthy people, LCMV infection can cause meningitis, encephalitis, and congenital fetal infection; in organ transplant recipients, it is reported to cause severe disease with multiple organ failure. Lassa fever occurs across rural West Africa, with hyperendemic areas in parts of Guinea, Liberia, Nigeria, and Sierra Leone. Lujo virus infection has been described in the Republic of South Africa during a health care–associated outbreak, and in Zambia.

NEW WORLD ARENAVIRUSES

New World arenaviruses (and the diseases they cause) include Chapare virus, Guanarito (Venezuelan hemorrhagic fever), Junin (Argentine hemorrhagic fever), Machupo (Bolivian hemorrhagic fever), and Sabia (Brazilian hemorrhagic fever).

RESERVOIR HOST SPECIES

Reservoir host species of arenaviruses include Old World rats and mice (family *Muridae*, subfamily *Murinae*) and New World rats and mice (family *Muridae*, subfamily *Sigmodontinae*). These rodent types are found worldwide, including Africa, the Americas, Asia, and Europe. Virus is transmitted through inhalation of rodent urine aerosols, ingestion of rodent-contaminated food, or by direct contact of broken skin or mucosa with rodent excreta.

Risk for Lassa virus infection is associated with peridomestic rodent exposure, where inappropriate food storage increases the risk for exposure. Several cases of Lassa fever have been confirmed in international travelers staying in traditional countryside dwellings. Health care–associated transmission and close family member infection with Lassa, Lujo, and Machupo viruses occurs through droplet spread and direct contact.

Bunyaviral Diseases

CRIMEAN-CONGO HEMORRHAGIC FEVER

CCHF is endemic to areas where ticks of the genus *Hyalomma* are found in Africa (including South Africa) and Eurasia (including the Balkans, the Middle East, Russia, and western China). CCHF is highly endemic to Afghanistan, Iran, Pakistan, and Turkey. In 2016, Spain reported its first identified human cases. *Hyalomma* ticks are primarily associated with livestock but will also bite humans.

Livestock and other tick hosts might develop CCHF viremia from tick bites but do not develop clinical disease. CCHF virus is transmitted to humans by infected ticks or by direct handling

and preparation of fresh carcasses of infected animals, usually domestic livestock. Human-to-human transmission can occur through droplets or direct contact.

HANTAVIRUS PULMONARY SYNDROME & HEMORRHAGIC FEVER WITH RENAL SYNDROME

Hantaviruses can cause hantavirus pulmonary syndrome (HPS) or hemorrhagic fever with renal syndrome (HFRS). Viruses that cause HPS are found in the Western Hemisphere (North, Central, and South America); those that cause HFRS occur worldwide. The viruses that cause both HPS and HFRS are transmitted to humans through contact with urine, feces, or saliva of infected rodents. Travelers staying in rodent-infested dwellings are at risk for HPS and HFRS. Human-to-human transmission of hantavirus has been reported only with Andes virus in Chile and Argentina. A reported case of imported Andes virus in the United States occurred in 2018 in a traveler returning from Chile and Argentina.

RIFT VALLEY FEVER

RVF primarily affects livestock, causing stillbirths and high mortality in neonatal cattle, goats, and sheep. In humans, RVF virus infection causes fever, hemorrhage, encephalitis, and retinitis. RVF virus is endemic to sub-Saharan Africa. Sporadic outbreaks have occurred in humans in Comoros, Egypt, Madagascar, Mali, Mauritania, Mayotte, Senegal, South Sudan, Sudan, and Uganda. Large epidemics occurred in Madagascar in 1990, and again in 2008; in Kenya, Somalia, and Tanzania during 1997–1998 and 2006–2007; in Saudi Arabia and Yemen in 2000; in Botswana, Mauritania, Namibia, and South Africa in 2010; and in Niger during 2016–2017. RVF virus is transmitted to livestock by mosquitoes; people more frequently become infected through direct contact with clinically affected animals or their body fluids, including through slaughter or consumption of infected animals.

Filoviral Diseases

People at greatest risk of EVD or MVD include family members, health care workers, or others who, without personal protective equipment (PPE), come into direct contact with infected patients or corpses. People who come into close contact or proximity to bats (e.g., those who visit caves or mines with bats) and people who handle infected primates or carcasses are also at risk. A postulated route of infection to humans (as well as to ground-dwelling animals) involves consumption of fallen or dropped fruit contaminated by the saliva or urine of infected, fruit-foraging bats. Additionally, the sexual partners of males who recently survived EVD or MVD might be at risk if they have had contact with virus-infected semen.

EBOLA VIRUS DISEASE

Countries where domestically acquired EVD cases have been reported and that should be considered areas where future epidemics could occur include Côte d'Ivoire, Democratic Republic of the Congo, Gabon, Guinea, Liberia, Republic of the Congo, Sierra Leone, South Sudan, and Uganda.

Prior to 2014, Ebola outbreaks typically had been limited in scope and geographic extent. In March of 2014, however, an outbreak of Ebola virus was detected in a rural area of Guinea near the borders with Liberia and Sierra Leone. By June 2014, cases were reported in all 3 countries and across many districts. Additional cases occurred in Italy, Mali, Nigeria, Senegal, Spain, the United Kingdom, and the United States, after infected people traveled from West Africa. The outbreak was the largest and most complex Ebola epidemic ever reported.

Since the 2014, Ebola outbreaks have been reported in the Democratic Republic of the Congo in 2017, 2018, 2020, and 2021, and in Guinea in 2021. Cases were also reported in Uganda in 2018–2019, and in 2022. Reston virus (in the genus *Ebolavirus*) is believed to be endemic to the Philippines but has not been shown to cause human disease.

MARBURG VIRUS DISEASE

Countries with confirmed human cases of MVD include Angola, Democratic Republic of the Congo, Guinea, Kenya, Uganda, and possibly Zimbabwe. Four cases occurred in travelers visiting caves harboring bats, including Kitum Cave in Kenya and Python Cave in Maramagambo Forest, Uganda. Miners in the Democratic Republic of the

Congo and Uganda have also acquired Marburg virus infection from working in underground mines harboring bats.

CLINICAL PRESENTATION

Signs and symptoms vary by disease, but in general, patients with VHF present with abrupt onset of fever, headache, myalgias, and prostration, followed by coagulopathy with a petechial rash or ecchymoses and sometimes overt bleeding in severe forms. Gastrointestinal symptoms (abdominal pain, diarrhea, vomiting) are commonly observed. Vascular endothelial damage leads to shock and pulmonary edema; liver injury is common.

Syndromic findings associated with specific *Arenaviridae* infections include pharyngitis, retrosternal pain, hearing loss in adults, and anasarca in newborns (Lassa); and spontaneous abortion and birth defects (Lassa fever, LCMV). Syndromic findings associated with specific *Bunyavirales* infections include ecchymoses and bruising (CCHF virus); renal failure (hantavirus, HFRS); and retinitis and partial blindness (RVF). Laboratory abnormalities include elevated liver enzymes, initial drop in leukocyte count, and thrombocytopenia. Because the incubation period can extend up to 21 days, patients might not develop illness until they return from travel; a thorough travel and exposure history is critical.

DIAGNOSIS

Immediately notify local health authorities of any suspected cases of VHF occurring in patients residing in the United States. For laboratory testing requests, notify your local or state health department. To notify the Centers for Disease Control and Prevention (CDC) directly about any patients requiring evacuation to the United States, contact the CDC Emergency Operations Center at 770-488-7100.

Appropriate PPE, including implementation of droplet and contact precautions, is indicated for any patients in whom a VHF is suspected. Airborne transmission of VHF viruses has not been documented in hospitals or households during any of the human outbreaks investigated to date. Certain procedures (e.g., bronchoscopy, endotracheal intubation) might, however, create mechanically generated aerosols that could be infectious. As such, airborne precautions are recommended for aerosol-generating procedures.

Postmortem samples of blood (collected by cardiac puncture) or skin collected within a few hours after death can be used for diagnosis. Whole blood or serum can be used for virologic testing by reverse transcription PCR (RT-PCR), antigen detection, or virus isolation, and to test for immunologic (IgM, IgG) evidence of infection. Skin biopsies fixed in formalin can be tested by immunohistochemistry, RT-PCR, and virus isolation. Consider collecting an oral swab from deceased patients when an alternative sample cannot be collected.

Special handling procedures are required when submitting blood and other body fluid specimens for diagnostic testing. Please contact the CDC Emergency Operations Center at 770-488-7100 for more information.

TREATMENT

The mainstay treatment for VHFs is early and aggressive supportive care directed at maintaining effective intravascular volume and correcting electrolyte imbalances. Convalescent-phase plasma is effective in treating Argentine hemorrhagic fever but is available only in Argentina. Ribavirin is effective if given early in the course of disease for treating Lassa fever and other Old World arenaviruses, New World arenaviruses, and potentially CCHF, but it is not approved for use by the US Food and Drug Administration (FDA) for these indications. Compassionate use intravenous ribavirin can be obtained from Bausch Health; initiate requests by contacting CDC's Viral Special Pathogens Branch (770-488-7100).

Two FDA-approved treatments are available for Ebola virus (species *Zaire ebolavirus*). Ebanga (single monoclonal antibody) and Inmazeb (triple monoclonal antibody cocktail) are both approved to treat acute EVD in adult and pediatric patients. In a randomized clinical control trial, Ebanga reduced mortality rates to 35%, and Inmazeb reduced rates to 33%. Both drugs particularly reduced deaths in patients with low viral loads; mortality rates in patients treated with Ebanga were 9.9% and were 11.2% in patients treated with Inmazeb.

Patients with EVD also might have concomitant malaria infection; consider empiric use of antimalarial therapy when rapid diagnostic testing is not immediately available. In general, avoid administering NSAIDs (e.g., diclofenac, ibuprofen) because of their antiplatelet activity.

PREVENTION

The risk of acquiring a VHF is very low for most international travelers. Travelers at increased risk for exposure include people who engage in animal research, and health care workers and others who do not have adequate PPE when caring for patients in communities where outbreaks are occurring. Prevention should focus on avoiding unprotected contact with sources of infection, including anyone suspected of having VHF, and host or vector species in endemic countries. Travelers should not visit locations where outbreaks are occurring. In addition, travelers should avoid contact with bats and rodents, and avoid blood or body fluids of livestock in RVF- or CCHF-endemic areas. To prevent vectorborne diseases, travelers should use insecticide-treated mosquito nets and use insect repellent (see Sec. 4, Ch. 6, Mosquitoes, Ticks & Other Arthropods).

For VHFs that can be transmitted person to person (EVD, MVD, Lassa Fever, CCHF), early identification and isolation of ill travelers, consistent implementation of basic infection-control measures and prompt notification of public health authorities are the keys to preventing secondary transmission. Early identification strategies include eliciting a travel history from all patients who present for care, and posting signs and placards asking patients with recent international travel to self-identify. Promptly isolate any patients with recent international travel who have symptoms consistent with a VHF by placing them in a private room or a separate enclosed area with a private bathroom or covered bedside commode. To minimize disease transmission risk, only essential health care providers wearing appropriate PPE should evaluate a patient and provide care. Prompt notification of the facility's infection-control program and state and local health departments is also key.

Vaccines

In February 2020, the Advisory Committee on Immunization Practices (ACIP) recommended ERVEBO for preexposure vaccination of adults aged ≥18 years in the United States at risk for Ebola exposure; groups meeting this definition include those responding to outbreaks of EVD due to Ebola virus (species *Zaire ebolavirus*). In November 2021, ACIP expanded its preexposure vaccination recommendations to include health care personnel at federally designated Ebola treatment centers in the United States, and laboratory workers or other staff at Biosafety Level 4 facilities in the United States that handle replication-competent Ebola virus (species *Zaire ebolavirus*).

Investigational vaccines exist for Argentine hemorrhagic fever and RVF, but neither is approved by FDA or commercially available in the United States.

CDC website: www.cdc.gov/vhf

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YELLOW FEVER

Mark Gershman, J. Erin Staples

INFECTIOUS AGENT: Yellow fever virus	
ENDEMICITY	Sub-Saharan Africa Tropical South America
TRAVELER CATEGORIES AT GREATEST RISK FOR EXPOSURE & INFECTION	Unimmunized people visiting forested or savannah regions of endemic areas, or visiting destinations with ongoing yellow fever outbreaks
PREVENTION METHODS	Avoid insect bites Yellow fever is a vaccine-preventable disease
DIAGNOSTIC SUPPPORT	State health department; or contact CDC's Arboviral Diseases Branch (www.cdc.gov/ncezid/dvbd/specimensub/arboviral-shipping.html; 970-221-6400; dvbid@cdc.gov)

INFECTIOUS AGENT

Yellow fever (YF) virus is a single-stranded RNA virus that belongs to the genus *Flavivirus*.

TRANSMISSION

Vectorborne transmission of YF virus occurs via the bite of an infected mosquito, primarily *Aedes* or *Haemagogus* spp. Nonhuman primates and humans are the main reservoirs of the virus, and anthroponotic (human-to-vector-to-human) transmission occurs. YF virus has 3 transmission cycles: sylvatic (jungle), intermediate (savannah), and urban.

The sylvatic (jungle) cycle involves transmission of virus between nonhuman primates and mosquito species found in forest canopies. Virus is transmitted from monkeys to humans via mosquitoes when occupational or recreational activities encroach into the jungle. In Africa, an intermediate (savannah) cycle involves transmission of YF virus from tree hole–breeding *Aedes* spp. to humans in jungle border areas. YF virus can be transmitted from monkeys to humans or from human to human via these mosquitoes. The urban cycle involves transmission of virus between humans and peridomestic mosquitoes, primarily *Ae. aegypti*.

Humans infected with YF virus experience the highest levels of viremia shortly before onset of fever and for the first 3–5 days of illness, during which time they can transmit the virus to mosquitoes. Because of the high level of viremia,

bloodborne transmission theoretically can occur via transfusion or needlesticks. One case of perinatal transmission of wild-type YF virus from a woman who developed symptoms of YF 3 days prior to delivery has been documented; the infant subsequently tested positive for YF viral RNA and died of fulminant YF on the 12th day of life.

EPIDEMIOLOGY

YF occurs in sub-Saharan Africa and tropical South America, where it is endemic and intermittently epidemic (see Table 5-22 and Table 5-23 for lists of countries with risk of YF virus transmission). Most YF disease in humans is due to sylvatic or intermediate transmission cycles. Urban YF occurs periodically in Africa and sporadically in the Americas. In areas of Africa with persistent circulation of YF virus, natural immunity accumulates with age; consequently, infants and children are at greatest risk for disease. In South America, YF occurs most frequently in unimmunized young people exposed to mosquito vectors through their work in forested areas.

RISK FOR TRAVELERS

A traveler's risk for acquiring YF is determined by their immunization status as well as destination-specific (e.g., local rate of virus transmission) and travel-associated (e.g., exposure duration, occupational and recreational activities, season) factors. Reported cases of human disease are the principal but crude indicator of disease risk. Case reports from a destination might be absent because of a low level of transmission, a high level of immunity in the population (e.g., due to vaccination), or failure of local surveillance systems to detect cases. Because "epidemiologic silence" does not mean absence of risk, travelers should not go into endemic areas without taking protective measures.

YF virus transmission in rural West Africa is seasonal; a period of elevated risk occurs at the end of the rainy season and the beginning of the dry season, usually July–October. In East Africa, YF virus transmission is generally less predictable because long periods (years) often pass between virus activity in this region; when YF

Table 5-22 Countries with risk for yellow fever (YF) virus transmission[1]

AFRICA		
Angola	Democratic Republic of the Congo	Mali[2]
Benin	Equatorial Guinea	Mauritania[2]
Burkina Faso	Ethiopia[2]	Niger[2]
Burundi	Gabon	Nigeria
Cameroon	The Gambia	Senegal
Central African Republic	Ghana	Sierra Leone
Chad[2]	Guinea	South Sudan
Congo, Republic of the	Guinea-Bissau	Sudan[2]
Côte d'Ivoire	Kenya[2]	Togo
	Liberia	Uganda
THE AMERICAS		
Argentina[2]	French Guiana	Peru[2]
Bolivia[2]	Guyana	Suriname
Brazil[2]	Panama[2]	Trinidad and Tobago[2]
Colombia[2]	Paraguay	Venezuela[2]
Ecuador[2]		

[1]Current as of November 2022. Defined by the World Health Organization (WHO) as countries or areas where YF "has been reported currently or in the past and vectors and animal reservoirs currently exist." See www.who.int/publications/m/item/countries-with-risk-of-yellow-fever-transmission-and-countries-requiring-yellow-fever-vaccination-(november-2022).
[2]These countries are not holoendemic (only a portion of the country has risk of YF virus + transmission). For details, see Map 5-10, Map 5-11, and YF vaccine recommendations (Sec. 2, Ch. 5, Yellow Fever Vaccine & Malaria Prevention Information, by Country).

Table 5-23 Countries with low potential for exposure to yellow fever (YF) virus[1]

AFRICA		
Eritrea[2] Rwanda	São Tomé and Príncipe Somalia[2]	Tanzania Zambia[2]

[1]The countries on this list have low potential for exposure to YF virus and are not included on the World Health Organization list of countries with risk for YF virus transmission (Table 5-22). Unless a country requires proof of YF vaccination from all arriving travelers (Table 5-25), or specifies otherwise, proof of YF vaccination should not be required for travelers arriving from the countries on this list.

[2]Classified as "low potential for exposure to YF virus" only in some areas; remaining areas are classified as having no risk of exposure to YF virus.

virus transmission occurs in East Africa, seasonality is similar to that in West Africa.

The risk for infection by sylvatic vectors in South America is greatest during the rainy season (January–May, with a peak incidence during February and March). *Ae. aegypti* can transmit YF virus episodically, however—even during the dry season—in both rural and densely settled urban areas.

During 1970–2015, 11 cases of YF were reported in people from the United States and Europe who traveled to West Africa (6 cases) or South America (5 cases); 8 (73%) died. Only 1 traveler had a documented history of YF vaccination; that traveler survived. Starting in 2016, the number of travel-associated YF cases increased substantially, primarily because of outbreaks in Angola and Brazil. During 2016–mid-2021, >37 travel-associated cases were reported in unvaccinated travelers who were residents of nonendemic areas or countries, including ≥15 European travelers and 1 American traveler to Peru.

The risk of acquiring YF during travel is difficult to predict because of variations in ecologic determinants of virus transmission. For a 2-week stay, the estimated risk for illness and for death due to YF for an unvaccinated traveler visiting an endemic area are as follows: for West Africa, risk for illness is 50 per 100,000 and risk for death is 10 per 100,000; for South America, risk for illness is 5 per 100,000 and risk for death is 1 per 100,000. These estimates are based on the risk to resident populations, often during peak transmission season, and might not accurately reflect the risk to travelers who have a different immunity profile, follow mosquito bite precautions, have less outdoor exposure, or who travel during off-peak periods. A traveler's risk for becoming infected is likely greater when outbreaks are occurring at their destination.

CLINICAL PRESENTATION

Most people infected with YF virus have minimal or no symptoms and are unlikely to seek medical attention. For those who develop symptomatic illness, the incubation period is typically 3–6 days. The initial illness is nonspecific: backache, chills, fever, headache, myalgia, nausea and vomiting, and prostration. Most improve after the initial presentation. After a brief remission of ≤48 hours, ≈12% of infected patients progress to a more serious form of the disease, characterized by hemorrhagic symptoms, jaundice, and eventually shock and multisystem organ failure. The case-fatality rate for severe cases is 30%–60%.

DIAGNOSIS

YF is a nationally notifiable disease. A preliminary diagnosis is based on clinical presentation and exposure details. Laboratory diagnosis is best performed by virus isolation or nucleic acid amplification tests (e.g., reverse transcription PCR [RT-PCR]) or by serologic assays. Perform virus isolation or nucleic acid amplification tests for YF virus or YF viral RNA early in the course of the illness. By the time more overt symptoms are recognized, the virus or viral RNA might no longer be detectable; thus, virus isolation and nucleic acid amplification testing should not be used to rule out a diagnosis of YF.

Serologic assays can be used to detect virus-specific IgM and IgG antibodies. Because of the possibility of cross-reactivity between antibodies against other flaviviruses, however, more specific antibody testing (e.g., a plaque reduction neutralization test) should be performed to confirm the infection. Contact your state or local health department or call the Centers for Disease Control and Prevention (CDC) Arboviral Diseases Branch at 970-221-6400 for assistance with diagnostic testing for YF virus infections.

TREATMENT

No specific medications are available to treat YF virus infections; treatment is directed at symptomatic relief or life-saving interventions. Fluids, rest, and use of analgesics and antipyretics might relieve symptoms of aching and fever. Avoid prescribing medications than can increase the risk for bleeding (e.g., aspirin or other nonsteroidal anti-inflammatory drugs). During the first few days of illness, protect infected people from further mosquito exposure by keeping them indoors or under a mosquito net, so they do not contribute to the transmission cycle.

PREVENTION

Personal Protective Measures

The best way to prevent mosquito-borne diseases, including YF, is to avoid mosquito bites (see Sec. 4, Ch. 6, Mosquitoes, Ticks & Other Arthropods).

Vaccine

YF is preventable by a relatively safe, effective vaccine. All YF vaccines currently manufactured are live attenuated viral vaccines. Only one YF vaccine (YF-VAX, Sanofi Pasteur) is licensed for use in the United States (Table 5-24). Periodically in the United States, shortages of YF-VAX have occurred due to production issues, including one that lasted from late 2015 until early 2021. To address this most recent shortage, Sanofi Pasteur collaborated with the CDC and the US Food and Drug Administration (FDA) to import and distribute Stamaril (a YF vaccine comparable to YF-VAX, manufactured at the company's facility in France) under an expanded-access investigational new drug protocol.

The different YF vaccine products, including those manufactured outside the United States, have no substantial differences in reactogenicity or immunogenicity. Consider people who receive YF vaccines licensed in other countries but not approved by the FDA to be protected against YF. For the most current information on YF vaccine availability, check the CDC Travelers' Health website at https://wwwnc.cdc.gov/travel.

INDICATIONS FOR USE

YF vaccine is recommended for people aged ≥9 months who are living in or traveling to areas with risk for YF virus transmission in Africa or South America. In addition, some countries require proof of YF vaccination for entry. For country-specific YF vaccination recommendations and requirements, see Sec. 2, Ch. 5, Yellow Fever Vaccine & Malaria Prevention Information, by Country.

Because of the risk for serious adverse events after YF vaccination, clinicians should only vaccinate people at risk for YF virus exposure or who require proof of vaccination to enter a country. To further minimize the risk for serious adverse events, carefully observe the contraindications and consider vaccination precautions before administering YF vaccine (Box 5-09). For

Table 5-24 Vaccine to prevent yellow fever (YF)

VACCINE	TRADE NAME (MANUFACTURER)	AGE	DOSE	ROUTE	SCHEDULE	BOOSTER
17D	YF-VAX (Sanofi Pasteur)	≥9 months[1]	0.5 mL[2]	Sub-cutaneous	1 dose	Not recommended for most people[3]

[1]Ages 6–8 months and ≥60 years are precautions, and age <6 months is a contraindication to receiving YF vaccine.

[2]YF-VAX is available in single-dose and multiple-dose (5-dose) vials.

[3]For further details regarding revaccination, see Prevention: Vaccine: Booster Doses, in this chapter.

BOX 5-09 Yellow fever vaccine contraindications & precautions

CONTRAINDICATIONS

Age <6 months
Allergy to vaccine component[1]
HIV infection (symptomatic) or CD4 T lymphocyte counts <200/mL (or <15% of total lymphocytes in children aged <6 years)[2,3]
Primary immunodeficiencies
Immunosuppressive and immunomodulatory therapies
Malignant neoplasms
Thymus disorder associated with abnormal immune cell function
Transplantation

PRECAUTIONS

Age 6–8 months
Age ≥60 years
Breastfeeding
HIV infection (asymptomatic) and CD4 T lymphocyte counts 200–499/mL (or 15%–24% of total lymphocytes in children aged <6 years)[2,3]
Pregnancy

[1]If considering vaccination, desensitization can be performed under direct supervision of a physician experienced in the management of anaphylaxis.

[2]Symptoms of HIV are classified in Centers for Disease Control and Prevention. 1993 Revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. MMWR Recomm Rep 1992;41(RR-17). Available from: www.cdc.gov/mmwr/preview/mmwrhtml/00018871.htm (see Table 1 Adults and Adolescents); and Panel on Antiretroviral Therapy and Medical Management of HIV-Infected Children. Guidelines for the use of antiretroviral agents in pediatric HIV infection 2010. pp. 20–2. Available from: www.hopkinsmedicine.org/som/faculty/appointments/_documents/_ppc_documents/portfolios/Hutton/Hutton-Portfolio-Samples/guidelines-for-the-use-of-antiretroviral-agents-in-pediatric-hiv-infection.pdf.

[3]In 2010, the Advisory Committee on Immunization Practices (ACIP) used this clinical classification of levels of immunosuppression among HIV-infected people to inform yellow fever vaccine recommendations (see Staples et al., Yellow fever vaccine: recommendations of the Advisory Committee on Immunization Practices). A revised surveillance case definition for HIV infection was published in 2014. To date, ACIP has not updated YF vaccine recommendations for people infected with HIV.

additional information, refer to the YF vaccine recommendations of the Advisory Committee on Immunization Practices (ACIP) at www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/yf.html.

ADMINISTRATION

For all eligible people, subcutaneously administer a single 0.5 mL injection of reconstituted vaccine, which is the standard dose.

COADMINISTRATION WITH OTHER VACCINES

INACTIVATED VACCINES

No evidence exists that inactivated vaccines interfere with the immune response to YF vaccine. Therefore, inactivated vaccines can be administered either simultaneously or at any time before or after YF vaccination.

LIVE ATTENUATED VIRAL VACCINES

ACIP recommends that YF vaccine be given at the same time as other live viral vaccines. If simultaneous administration is not possible, wait 30 days between vaccinations, because the immune response to a live viral vaccine could be impaired if it is administered within 30 days of another live viral vaccine. One study demonstrated that coadministration of YF vaccine and measles-mumps-rubella (MMR) vaccine decreased the seroconversion ratios to all antigens, except measles. Two more recent studies also showed a less robust antibody concentration in people who seroconverted after vaccine coadministration. These studies suggest that whenever possible, it is best to give YF and MMR vaccines 30 days apart. Of greater importance, however, is ensuring that travelers are vaccinated appropriately before travel; coadministration of YF and MMR vaccines is therefore acceptable.

No data are available on the immune response to nasally administered live attenuated influenza vaccine given simultaneously with YF vaccine.

LIVE BACTERIAL VACCINES

Data suggest that oral Ty21a typhoid vaccine (Vivotif), a live bacterial vaccine, can be administered simultaneously or at any interval before or after YF vaccine. No data are available on the immune response to live attenuated oral cholera vaccine (Vaxchora) administered simultaneously with YF vaccine.

FRACTIONAL DOSING

In recent years, several countries have extended vaccine supplies during large YF outbreaks by administering partial vaccine doses, usually 0.1 mL, a practice known as fractional dosing. Limited study data have demonstrated immunogenicity of fractional dosing is comparable to that of full-dose YF vaccination at 1 month and ≤1 year after subcutaneous administration; knowledge gaps regarding fractional dosing remain, however.

In the United States, FDA has not approved fractional dosing of YF vaccine. Furthermore, WHO notes that fractional dosing does not meet YF vaccination requirements under the International Health Regulations (IHR); proof of vaccination for international travel cannot be issued to a person who has received only a fractional dose.

BOOSTER DOSES

In 2014, the WHO Strategic Advisory Group of Experts on Immunization concluded that a single primary dose of YF vaccine provides sustained immunity and lifelong protection against YF disease and that revaccination (a booster dose) is not needed. In 2016, the IHR were officially amended to specify that a completed International Certificate of Vaccination or Prophylaxis (ICVP or "yellow card") is valid for the lifetime of the vaccinee, and countries cannot require proof of revaccination against YF as a condition of entry, even if the last vaccination was >10 years prior.

ACIP also has stated that a single dose of YF vaccine provides long-lasting protection and is adequate for most travelers. ACIP guidelines do differ slightly from those of WHO, however, by specifying that additional doses of YF vaccine are recommended for the following groups of travelers: people who were pregnant when they received their initial dose of vaccine (administer 1 additional dose before they are next at risk for YF); people who received a hematopoietic stem cell transplant after receiving a dose of YF vaccine (revaccinate before they are next at risk for YF as long as they are sufficiently immunocompetent); people infected with HIV when they received their last dose of YF vaccine (administer a dose every 10 years if they continue to be at risk for YF).

Consider administering a booster dose to travelers who received their last dose of YF vaccine ≥10 years previously if they will be going to higher-risk settings based on activities, duration of travel, location, and season. This consideration applies to travelers planning prolonged stays in endemic areas, those traveling to endemic areas (e.g., rural West Africa) during peak transmission season, or travelers visiting areas with ongoing outbreaks.

Although booster doses of YF vaccine are not recommended for most travelers, and despite the 2016 changes to the IHR, clinicians and travelers should nonetheless review the entry requirements for destination countries. For more information on country-specific recommendations and requirements, see Sec. 2, Ch. 5, Yellow Fever Vaccine & Malaria Prevention Information, by Country.

ADVERSE EVENTS

COMMON ADVERSE REACTIONS

Reactions to YF vaccine are generally mild; 10%–30% of vaccinees report mild systemic symptoms, including headache, low-grade fever, and myalgia, that begin within days after vaccination and last 5–10 days.

SERIOUS ADVERSE REACTIONS

HYPERSENSITIVITY REACTIONS

Immediate hypersensitivity reactions, characterized by bronchospasm, rash, or urticaria, are uncommon. Anaphylaxis after YF vaccine is reported to occur at a rate of 1.3 cases per 100,000 doses administered.

YELLOW FEVER VACCINE–ASSOCIATED NEUROLOGIC DISEASE

Yellow fever vaccine–associated neurologic disease (YEL-AND) represents a collection of clinical syndromes, including acute disseminated encephalomyelitis, Guillain-Barré syndrome,

meningoencephalitis, and, rarely, cranial nerve palsies. Historically, YEL-AND was diagnosed primarily among infants as encephalitis, although more recent case reports have described various neurological syndromes among people of most age groups. YEL-AND is rarely fatal.

Almost all cases of YEL-AND reported globally occur in first-time vaccine recipients. The onset of illness for documented cases in the United States is 2–56 days after vaccination. The incidence of YEL-AND in the United States is 0.8 per 100,000 doses administered, but is greater (2.2 per 100,000 doses) in people aged ≥60 years.

YELLOW FEVER VACCINE–ASSOCIATED VISCEROTROPIC DISEASE

Yellow fever vaccine–associated viscerotropic disease (YEL-AVD) is a severe illness similar to wild-type YF disease, in which vaccine virus proliferates in multiple organs, often leading to multiorgan dysfunction or failure and occasionally death. Since 2001, >100 confirmed and suspected cases of YEL-AVD have been reported throughout the world.

YEL-AVD has been reported to occur only after the first dose of YF vaccine; no laboratory-confirmed YEL-AVD has been reported after booster doses. For YEL-AVD cases reported in the United States, the median time from YF vaccination until symptom onset is 4 days (range 1–18 days). The case-fatality ratio is ≈48% and the incidence is 0.3 cases per 100,000 doses of vaccine administered. The incidence of YEL-AVD is greater for people aged ≥60 years (1.2 per 100,000 doses) and greater still for people aged ≥70 years.

CONTRAINDICATIONS

Contraindications to receiving YF vaccine include age <6 months; various forms of altered immunity, including symptomatic HIV infection or HIV infection with severe immunosuppression; and hypersensitivity to vaccine components.

A person who has an absolute YF vaccine contraindication should not be vaccinated, because they have a condition that increases their risk for having a serious adverse event following vaccination. Encourage these people to consider alternative travel plans. If they cannot avoid travel to a YF-endemic area, provide them with a medical waiver (see below for details), emphasize the importance of strict adherence to protective measures against mosquito bites, and discuss risks associated with being unvaccinated.

AGE YOUNGER THAN 6 MONTHS

YF vaccine is contraindicated in infants aged <6 months because the rate of YEL-AND is high, 50–400 cases per 100,000 infants vaccinated. The mechanism of increased neurovirulence in infants is unknown, but could be due to the immaturity of the blood–brain barrier, an increased or more prolonged viremia, or immune system immaturity. Travel to YF-endemic countries for children aged <6 months should be postponed or avoided.

ALTERED IMMUNE STATUS

HIV INFECTION

YF vaccine is contraindicated in people with AIDS or other clinical manifestations of HIV infection, including those with CD4 T lymphocyte counts <200/mL, or <15% of total lymphocytes for children <6 years old. This contraindication is based on the potential increased risk for encephalitis in this population. See the section on Precautions (later in this chapter) for guidance regarding HIV-infected people who do not meet the above criteria.

THYMUS DISORDER

YF vaccine is contraindicated in people with a thymus disorder associated with abnormal immune cell function (e.g., myasthenia gravis, thymoma). There is no evidence of immune dysfunction or increased risk for YF vaccine–associated serious adverse events in people who have undergone incidental thymectomy or who have had indirect radiation therapy in the distant past; these people can be vaccinated.

OTHER IMMUNODEFICIENCIES

YF vaccine is contraindicated in people who are immunodeficient or immunosuppressed, whether due to an underlying (primary) disorder or medical treatment. Organ transplant recipients and patients with malignant neoplasms are among those for whom YF vaccine is contraindicated (see Sec. 3, Ch. 1, Immunocompromised Travelers).

IMMUNOSUPPRESSIVE & IMMUNOMODULATORY THERAPIES

YF vaccine is contraindicated in people whose immunologic response is either suppressed or modulated by current or recent radiation therapy or drugs. Drugs with known immunosuppressive or immunomodulatory properties (Table 3-04) include, but are not limited to, alkylating agents, antimetabolites, high-dose systemic corticosteroids, interleukin blocking agents (e.g., anakinra, tocilizumab), monoclonal antibodies targeting immune cells (e.g., alemtuzumab, rituximab), or tumor necrosis factor-α inhibitors (e.g., etanercept).

People receiving therapies such as those listed above are presumed to be at increased risk for YF vaccine–associated serious adverse events; administration of live attenuated vaccines is contraindicated in the package insert for most of these drugs (see Sec. 3, Ch. 1, Immunocompromised Travelers). Even among people who have discontinued immunosuppressive or immunomodulatory therapies, defer administration of live viral vaccines until their immune function has improved. Family members of people with altered immune status who themselves have no contraindications can receive YF vaccine.

HYPERSENSITIVITY

YF vaccine is contraindicated in people with a history of acute hypersensitivity reaction to a previous dose of the vaccine or to any of the vaccine components, including chicken proteins, eggs, egg products, or gelatin. If vaccination of a person with a questionable history of hypersensitivity to a vaccine component is considered essential, skin testing and, if indicated, desensitization should be performed by an experienced clinician according to instructions provided in the manufacturer's vaccine prescribing information (see www.fda.gov/media/76015/download).

PRECAUTIONS

A person with a precaution (relative contraindication) to YF vaccine has a condition that might increase their risk for having a serious adverse event following vaccination, or that could interfere with the ability of the vaccine to produce immunity. YF vaccination precautions include age 6–8 months, age ≥60 years, asymptomatic HIV infection with moderate immunosuppression, pregnancy, and breastfeeding.

Discussing the benefits and risks of YF vaccination with all patients—but particularly those with underlying precautions—is an essential part of the pretravel consultation. If travel to a YF risk area is unavoidable for a person with a vaccine precaution, the discussion about vaccination should balance the risk for YF virus exposure against the risk for having a serious post-vaccination adverse event.

Solicit information from the traveler about their risk tolerance level, and include this in the shared decision making about whether to administer YF vaccine. If the decision is made not to vaccinate the traveler, provide a medical waiver, emphasize the critical importance of adhering to insect bite precautions, and discuss risks associated with being unvaccinated. When no risk for YF exists in the itinerary, but international travel requirements are in effect in the traveler's destination(s), the vaccine risk outweighs the disease; avoiding vaccination and issuing a medical waiver to fulfill health regulations is reasonable, but this decision should be made in deliberation with the patient.

AGE 6–8 MONTHS

Two cases of YEL-AND have been reported in infants aged 6–8 months. By 9 months of age, risk for YEL-AND is believed to be substantially lower. ACIP recommends that, whenever possible, travel to YF-endemic countries for children aged 6–8 months should be postponed or avoided.

AGE ≥60 YEARS

The rate of reported serious adverse events after YF vaccination in people aged ≥60 years is 7.7 per 100,000 doses distributed, compared with 3.8 per 100,000 for all YF vaccine recipients. The risks for YEL-AND and YEL-AVD are increased in this age group. Because YEL-AVD has been reported exclusively, and YEL-AND almost exclusively, in primary vaccine recipients, carefully consider the risks and benefits of vaccinating older travelers against YF vaccine for the first time.

HIV INFECTION

Combined studies of >500 asymptomatic HIV-infected people classified as having moderate immune suppression, defined as CD4 T lymphocyte counts of 200–499/mL for people ≥6 years old (or 15%–24% of total lymphocytes for children aged <6 years) identified no serious adverse events after receipt of YF vaccine. HIV infection has, however, been associated with a reduced immunologic response to YF vaccine, and this diminished immune response has been correlated with HIV RNA levels and CD4 T cell counts.

If an asymptomatic HIV-infected person has no evidence of immune suppression based on CD4 counts (CD4 T lymphocyte counts ≥500/mL for people ≥6 years old or ≥25% of total lymphocytes for children aged <6 years), YF vaccine can be administered. Because YF vaccination might be less effective in eliciting an immune response in asymptomatic HIV-infected people, consider measuring their neutralizing antibody response to vaccination before travel. Contact your state health department or the CDC Arboviral Diseases Branch (970-221-6400) to discuss serologic testing.

PREGNANCY

Safety of YF vaccination during pregnancy has not been studied in any large prospective trials. In 2 observational studies of people vaccinated against YF during pregnancy, a slightly increased risk for minor congenital abnormalities (mainly pigmented nevi) was detected in one study, and a higher rate of spontaneous abortions was reported in the other. Neither finding was substantiated by subsequent studies.

If possible, pregnant people should avoid travel to YF risk areas. If travel is unavoidable and the risk for YF virus exposure is felt to outweigh the vaccination risk, recommending vaccination is appropriate. By contrast, if the vaccine risk is believed to outweigh the risk for YF virus exposure, suggest or offer a medical waiver to the traveler to fulfill health regulations.

The proportion of people vaccinated during pregnancy who develop a YF virus–specific IgG antibody response is variable depending on the study (39% or 98%) and might be correlated with the trimester when they received the vaccine. Because pregnancy can reduce immunologic responsiveness, consider serologic testing to document a protective immune response to the vaccine. Although no specific data are available, ACIP recommends that a person wait 4 weeks after receiving the YF vaccine before conceiving.

BREASTFEEDING

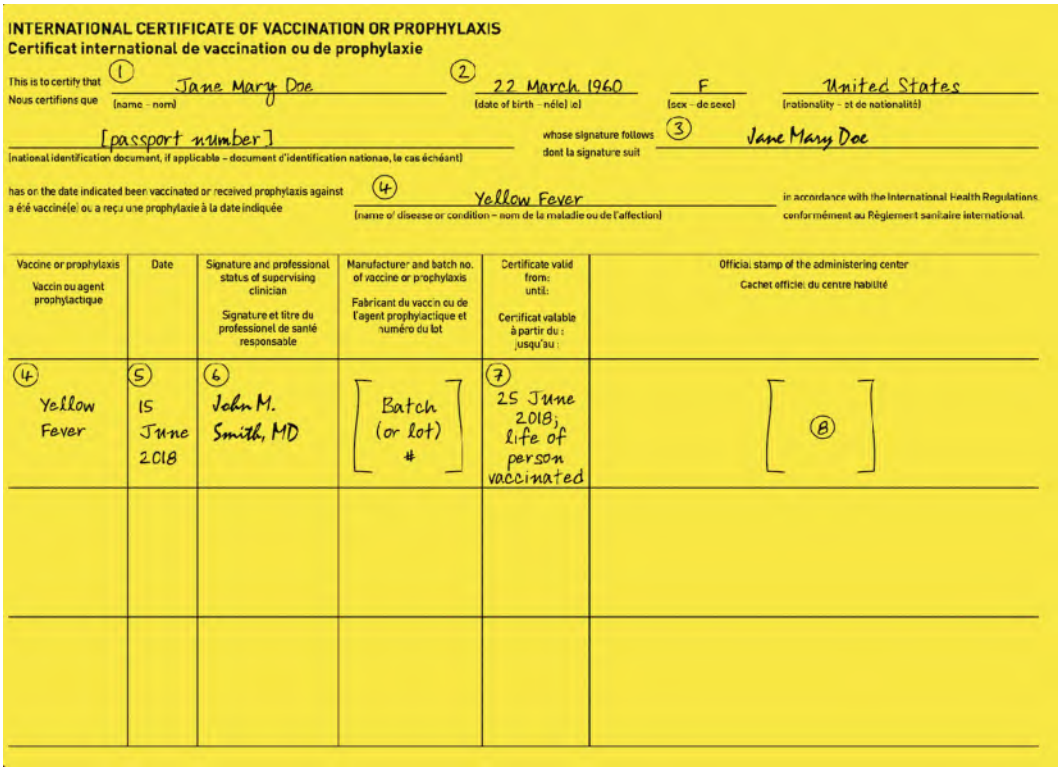
At least 3 YEL-AND cases have been reported in exclusively breastfed infants whose mothers were vaccinated with YF vaccine. All 3 infants were <1 month old at the time of exposure, and encephalitis was diagnosed in all 3 infants. Until specific research data are available, avoid vaccinating breastfeeding people against YF. When a person who is nursing cannot avoid or postpone travel to YF-endemic areas, however, recommend vaccination. Although no data are available to support the practice, some experts recommend that breastfeeding people should pump and discard their breast milk for ≥2 weeks after YF vaccination before resuming breastfeeding.

OTHER CONSIDERATIONS

No data are available regarding possible increased occurrence of adverse events or decreased vaccine efficacy after YF vaccine administration in people with other chronic medical conditions that can affect immune response (e.g., diabetes mellitus, liver disease [including hepatitis C virus infection], or renal disease). Limited data suggest that autoimmune disease, either by itself or in conjunction with other risk factors, including immunosuppressive medication, could increase the risk for YEL-AVD. Therefore, use caution if considering vaccination of such patients. Factors to consider when assessing a patient's general level of immune competence include clinical stability, comorbidities, complications, disease severity and duration, and which medications they are taking.

INTERNATIONAL CERTIFICATE OF VACCINATION OR PROPHYLAXIS

The IHR permit countries to require proof of YF vaccination documented on an ICVP (Figure 5-02) as a condition of entry for travelers arriving from certain countries, even if only in transit, to prevent YF virus importation and transmission in the destination country. Some countries require evidence



INTERNATIONAL CERTIFICATE OF VACCINATION OR PROPHYLAXIS
Certificat international de vaccination ou de prophylaxie

This is to certify that (1) Jane Mary Doe (name - nom) (2) 22 March 1960 (date of birth - née) (e) F (sex - de sexe) United States (nationality - et de nationalité)

[passport number] (national identification document, if applicable - document d'identification nationae, le cas échéant) whose signature follows dont la signature suit (3) Jane Mary Doe

has or the date indicated been vaccinated or received prophylaxis against a été vaccinée(e) ou a reçu une prophylaxie à la date indiquée (4) Yellow Fever (name of disease or condition - nom de la maladie ou de l'affection) in accordance with the International Health Regulations conformément au Règlement sanitaire international

Vaccine or prophylaxis Vaccin ou agent prophylactique	Date	Signature and professional status of supervising clinician Signature et titre du professionel de santé responsable	Manufacturer and batch no. of vaccine or prophylaxis Fabricant du vaccin ou de l'agent prophylactique et numéro du lot	Certificate valid from: until: Certificat valable à partir du : jusqu'au :	Official stamp of the administering center Cachet officiel du centre habilité
(4) Yellow Fever	(5) 15 June 2018	(6) John M. Smith, MD	[Batch (or lot) #]	(7) 25 June 2018; life of person vaccinated	[(8)]

FIGURE 5-02 International Certificate of Vaccination or Prophylaxis (ICVP): instructions for completion[1,2]

[1]Clinics offering yellow fever vaccine can purchase ICVP (Form CDC 731; formerly PHS 731), from the US Government Publishing Office website
(http://bookstore.gpo.gov) or by phone (866-512-1800).
[2]Instructions for ICVP completion
(1) Print the traveler's name exactly as it appears in their passport.
(2, 5, 7) Enter all dates in the format shown: day (in numerals), month (spelled in letters), year. In the example above, the patient's date of birth is correctly entered as 22 March 1960.
(3) Space reserved for the patient's signature.
(4) For yellow fever (YF) vaccination, print "Yellow Fever" in both spaces. If the ICVP is used to document proof of another required vaccination or prophylaxis (following an amendment to the International Health Regulations or by recommendation of the World Health Organization), write the disease or condition name in this space. Other vaccinations may be listed on the other side of the ICVP booklet.
(5) Enter the date of vaccine administration, as shown.
(6) The health care provider should enter their handwritten signature, as shown. A signature stamp is not acceptable. For yellow fever vaccine, the health care provider signing the ICVP may be the stamp owner, or another health care provider authorized by the stamp holder to administer or supervise the administration of the vaccine.
(7) The ICVP is valid beginning 10 days after the date of primary YF vaccination. Add that date to this box along with the suggested wording "life of person vaccinated," as shown.
(8) Imprint the Uniform Stamp of the vaccinating center in this box.

of vaccination from all entering travelers, including those arriving directly from the United States (Table 5-25).

People with YF vaccine contraindications who must travel to destinations that require proof of vaccination should receive a medical waiver from a YF vaccine provider before their departure; see Medical Waivers (Exemptions) below. Travelers without proof of vaccination or a medical waiver arriving to destinations that require

Table 5-25 Countries that require proof of yellow fever (YF) vaccination from all arriving travelers[1]

AFRICA		
Angola Benin Burkina Faso Burundi Cameroon Central African Republic Congo, Republic of the	Côte d'Ivoire Democratic Republic of the Congo Gabon Ghana Guinea-Bissau Mali	Niger Sierra Leone South Sudan Togo Uganda
THE AMERICAS		
French Guiana		

[1]Current as of November 2022. Country requirements for YF vaccination are subject to change at any time; check with the destination country's embassy or consulate before departure.

this documentation for entry could be denied entry or face mandatory quarantine (up to 6 days) or vaccination on site.

ICVP Validation

Anyone who received YF vaccination after December 15, 2007, must provide proof of vaccination on the new ICVP. If the person received the vaccine before December 15, 2007, their original International Certificate of Vaccination against Yellow Fever (ICV) card is still valid as proof of vaccination. Vaccinees should receive a completed ICVP, signed by the vaccine provider and validated with the stamp of the center where the vaccine was given. Failure to secure validations can cause a traveler to be denied entry, quarantined, or possibly revaccinated at the point of entry to a country.

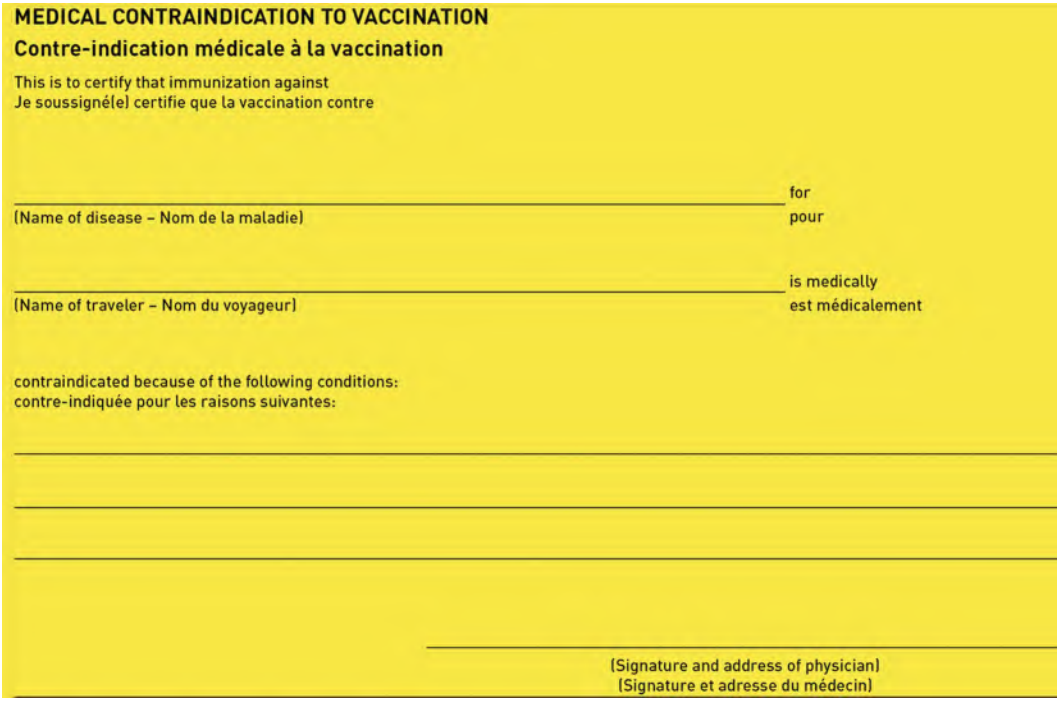
A properly completed ICVP is valid beginning 10 days after the date of primary vaccination. As of July 2016, the YF vaccine booster requirement was eliminated in the IHR, and a completed ICVP is considered valid for the lifetime of the vaccinee. Clinics offering YF vaccine can purchase ICVPs (Form CDC 731; formerly PHS 731) from the US Government Publishing Office website (http://bookstore.gpo.gov) or by phone (866-512-1800).

Designated Yellow Fever Vaccination Centers & Providers

The ICVP must bear the original signature of a YF vaccine provider, who can be a physician or other authorized licensed health care professional who supervises the administration of the vaccine. A signature stamp is not acceptable. YF vaccination must be given at a designated center that possesses an official "uniform stamp," which must be used to validate the ICVP. In the United States, state and territorial health departments are responsible for designating nonfederal YF vaccination centers and issuing uniform stamps to YF vaccine providers. Information about the location and hours of YF vaccination centers is available from the CDC Travelers' Health website (https://wwwnc.cdc.gov/travel/yellow-fever-vaccination-clinics/search).

Medical Waivers (Exemptions)

A YF vaccine provider issuing a medical waiver for YF vaccine should complete and sign the Medical Contraindications to Vaccination section of the ICVP (Figure 5-03). Reasons other than medical contraindications are not acceptable for exemption from vaccination. The YF vaccine provider should also provide the traveler with a signed and dated exemption letter on letterhead stationery,



MEDICAL CONTRAINDICATION TO VACCINATION

Contre-indication médicale à la vaccination

This is to certify that immunization against
Je soussigné(e) certifie que la vaccination contre

_____ for
(Name of disease – Nom de la maladie) pour

_____ is medically
(Name of traveler – Nom du voyageur) est médicalement

contraindicated because of the following conditions:
contre-indiquée pour les raisons suivantes:

_____

_____

_____

_____
(Signature and address of physician)
(Signature et adresse du médecin)

FIGURE 5-03 International Certificate of Vaccination or Prophylaxis (ICVP): Medical Contraindication to Vaccination section

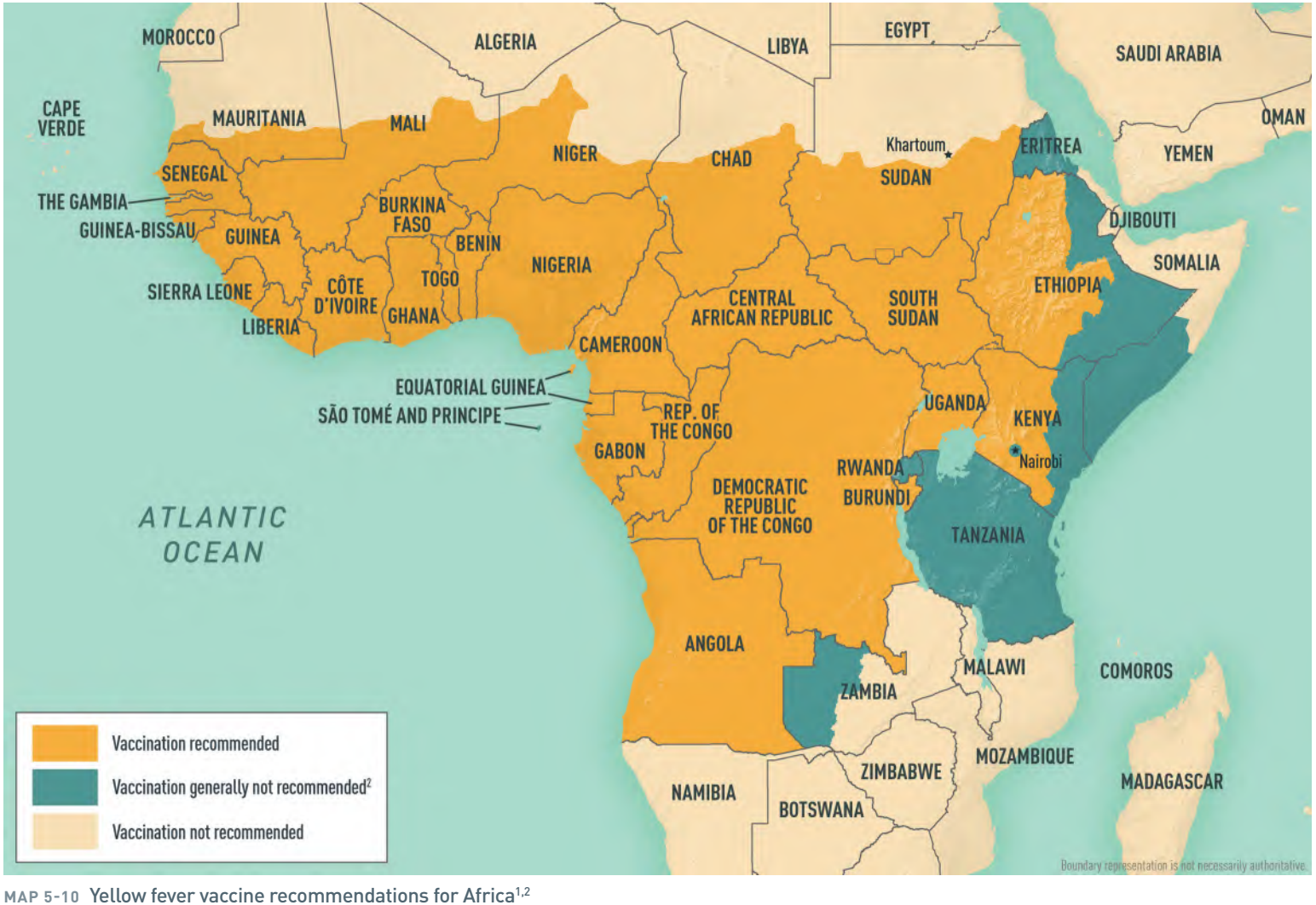
clearly stating the contraindications to vaccination and bearing the imprint of the uniform stamp used by the YF vaccination center to validate the ICVP. Risks associated with not being vaccinated should be discussed, and the importance of strict adherence to mosquito bite prevention measures emphasized.

Medical waivers might not be accepted by the destination country. To improve the likelihood that a border official will grant a waiver holder entry to their intended destination, recommend that travelers contact the local embassy or consulate of the country or countries well in advance of travel to obtain specific and authoritative advice regarding waiver documentation requirements. All information provided should be kept with the completed Medical Contraindications to Vaccination and waiver letter.

VACCINE REQUIREMENTS VERSUS RECOMMENDATIONS

Country entry requirements for proof of YF vaccination under the IHR differ from CDC's recommendations. Countries are permitted to establish YF vaccine entry requirements to prevent the YF virus importation and transmission within their borders. Unless issued a medical waiver by a YF vaccine provider, travelers must comply with these requirements to enter the country.

Certain countries require vaccination from travelers arriving from all countries (Table 5-25); others require vaccination only for travelers above a certain age coming from countries with risk for YF virus transmission (see Sec. 2, Ch. 5, Yellow Fever Vaccine & Malaria Prevention Information, by Country). The WHO defines areas with risk for YF virus transmission as places where YF virus activity has been reported currently or in the past, and where vectors and animal reservoirs exist. Countries that contain areas with only low potential for YF virus exposure (Table 5-23) are not included on the official WHO list of countries with risk for YF virus transmission (Table 5-22). Unless a country requires proof of YF vaccination from all arriving travelers, proof



MAP 5-10 Yellow fever vaccine recommendations for Africa[1,2]

[1]Current as of November 2022. This map is an updated version of the 2010 map created by the Informal WHO Working Group on the Geographic Risk of Yellow Fever.
[2]Yellow fever (YF) vaccination is generally not recommended for travel to areas where the potential for YF virus exposure is low. Vaccination might be considered, however, for a small subset of travelers going to these areas who are at increased risk for exposure to YF virus due to prolonged travel, heavy exposure to mosquitoes, or inability to avoid mosquito bites. Factors to consider when deciding whether to vaccinate a traveler include destination-specific and travel-associated risks for YF virus infection; individual, underlying risk factors for having a serious YF vaccine-associated adverse event; and country entry requirements.

MAP 5-11 Yellow fever vaccine recommendations for the Americas[1,2,3]

[1]Current as of November 2022. This map is an updated version of the 2010 map created by the Informal WHO Working Group on the Geographic Risk of Yellow Fever.

[2]In 2017, the Centers for Disease Control and Prevention (CDC) expanded its yellow fever vaccine recommendations for travelers going to Brazil because of a large outbreak in multiple states in that country. For more information and updated recommendations, refer to the CDC Travelers' Health website (https://wwwnc.cdc.gov/travel).

[3]Yellow fever (YF) vaccination is generally not recommended for travel to areas where the potential for YF virus exposure is low. Vaccination might be considered, however, for a small subset of travelers going to these areas who are at increased risk for exposure to YF virus due to prolonged travel, heavy exposure to mosquitoes, or inability to avoid mosquito bites. Factors to consider when deciding whether to vaccinate a traveler include destination-specific and travel-associated risks for YF virus infection; individual, underlying risk factors for having a serious YF vaccine-associated adverse event; and country entry requirements.

of YF vaccination should not be required of travelers coming from countries identified as having low potential for YF virus exposure. Because country entry requirements are subject to change at any time, CDC encourages travelers and their health care providers to check with the relevant embassy or consulate before departure.

To make its recommendations for preventing travel-associated YF virus infections, CDC uses a destination-specific risk classification for YF virus transmission: endemic, transitional, low potential for exposure, and no risk. CDC recommends YF vaccination for travel to endemic or transitional areas (Map 5-10 and Map 5-11). Recommendations are subject to revision at any time because of changes in YF virus circulation; before departure, check the CDC Travelers' Health website destination pages for current vaccine information and relevant Travel Health Notices (https://wwwnc.cdc.gov/travel/notices).

CDC website: www.cdc.gov/yellowfever

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ZIKA

Stacey Martin, J. Erin Staples

INFECTIOUS AGENT: Zika virus	
ENDEMICITY	Worldwide, periodic outbreaks in tropical and subtropical regions
TRAVELER CATEGORIES AT GREATEST RISK FOR EXPOSURE & INFECTION	Adventure tourists Long-term travelers and expatriates Travelers visiting friends and relatives
PREVENTION METHODS	Avoid insect bites Use condoms or abstain from sex if exposed (or possibly exposed)
DIAGNOSTIC SUPPORT	A clinical laboratory certified in high complexity testing; state health department; or contact CDC Arboviral Diseases Branch (www.cdc.gov/ncezid/dvbd/specimensub/arboviral-shipping.html; 970-221-6400; dvbid@cdc.gov)

INFECTIOUS AGENT

Zika virus is a single-stranded RNA virus of the *Flaviviridae* family, genus *Flavivirus*.

TRANSMISSION

Transmission occurs through the bite of an infected *Aedes* species mosquito. Intrauterine, perinatal, sexual, laboratory, and possible transfusion-associated transmission have been reported. Zika virus has been detected in breast milk, but the risk for transmission through breastfeeding is unknown.

EPIDEMIOLOGY

Zika virus occurs in tropical and subtropical regions. Since 2007, outbreaks of Zika virus disease have occurred throughout the Pacific Islands and in Southeast Asia. In 2015, Zika virus was identified in the Western Hemisphere, where large outbreaks occurred in Brazil. The virus then spread throughout much of the Americas, resulting in several hundred thousand cases. Since 2017, the number of reported Zika virus disease cases has declined worldwide, but occasional increases in cases have been noted from some countries. In 2020, only 4 Zika virus cases were reported in US international travelers. Current information on Zika virus transmission and travel guidance can be found at https://wwwnc.cdc.gov/travel/page/zika-travel-information.

CLINICAL PRESENTATION

Most Zika virus infections are either asymptomatic or result in mild clinical illness characterized by acute onset of fever, arthralgia, nonpurulent conjunctivitis, and maculopapular rash. Other symptoms can include edema, headache, lymphadenopathy, myalgia, retro-orbital pain, and vomiting. Severe disease requiring hospitalization and death are both uncommon. Guillain-Barré syndrome and rare reports of encephalopathy, meningoencephalitis, myelitis, uveitis, and severe thrombocytopenia have been associated with Zika virus infection, however. Vertical transmission of the virus leads to congenital Zika virus infection; sequelae include microcephaly with brain anomalies and other serious neurologic consequences, and fetal loss.

DIAGNOSIS

Consider Zika virus infection in patients with acute onset of fever, arthralgia, conjunctivitis, or maculopapular rash who, ≤2 weeks of illness onset, lived in or recently traveled to areas with ongoing Zika virus transmission or had sex with someone who lives in or traveled to those areas. Because Zika and dengue virus infections have similar clinical presentations, patients with suspected Zika virus infection also should be evaluated for possible dengue. Other considerations in the differential diagnosis include adenovirus, chikungunya, enterovirus, leptospirosis, malaria, measles, parvovirus, rickettsiosis, rubella, and group A streptococcal infections (see disease-specific chapters in this section).

Zika virus disease is a nationally notifiable condition. Report suspected cases of Zika virus infection to state or local health departments to facilitate diagnosis and mitigate the risk for local transmission in areas where *Aedes* species mosquitoes are active. State health departments should report laboratory-confirmed cases to the Centers for Disease Control and Prevention (CDC) according to the Council of State and Territorial Epidemiologists case definitions (https://ndc.services.cdc.gov).

Diagnostic Testing

Because Zika and dengue viruses share a similar global geographic distribution and cause infections that can be difficult to differentiate diagnostically, consider the global epidemiology of these 2 arboviruses when requesting testing and interpreting results. Zika virus testing guidance is updated as needed to address changes in the epidemiology. Current testing guidance is provided on the CDC website (www.cdc.gov/zika/hc-providers/testing-guidance.html). Some state health departments and many commercial laboratories perform Zika virus nucleic acid amplification testing (NAAT) and IgM testing. Confirmatory neutralizing antibody testing is available at CDC's Arboviral Diagnostic Reference Laboratory and selected health department laboratories.

NUCLEIC ACID AMPLIFICATION TESTING

NAAT is used to detect Zika viral RNA early in the course of infection and can be performed on amniotic fluid, whole blood, cerebrospinal fluid, semen, serum, tissues, and urine. Due to the temporal nature of Zika virus RNA in the body, a negative NAAT does not always exclude recent Zika virus infection. For this reason, Zika virus IgM antibody testing might be recommended in certain situations.

SEROLOGIC TESTING

Serum IgM antibody testing can detect Zika virus–specific IgM antibodies that typically develop toward the end of the first week of illness and can remain detectable for months to years after infection, making the determination of the timing of infection difficult. Serum IgM antibody testing can result in a false-positive result due to cross-reacting antibodies against related flaviviruses (e.g., dengue virus, yellow fever virus). Plaque reduction neutralization testing (PRNT) can be used to discriminate between cross-reacting antibodies in primary flavivirus infections, but neutralizing antibodies might still yield cross-reactive results in people who were previously infected with or vaccinated against a related flavivirus (secondary flavivirus infection).

TREATMENT

No specific antiviral treatment is available for Zika virus disease. Treatment is generally supportive and can include use of analgesics and antipyretics, fluids, and rest. Because aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) can increase the risk for hemorrhage in patients with dengue, avoid use of these medications until dengue can be ruled out.

Protect people infected with Zika, chikungunya, or dengue virus from further mosquito exposure during the first week of illness to decrease the possibility of local transmission. Carefully evaluate pregnant people with laboratory evidence of Zika virus infection; closely manage these cases for possible adverse pregnancy outcomes. Guidance for the diagnosis, evaluation, and management of infants with possible congenital Zika virus infections is available at www.cdc.gov/pregnancy/zika/testing-follow-up/evaluation-testing.html.

PREVENTION

No vaccine or preventive drug is available for Zika virus. All travelers to areas with Zika virus transmission should take steps to avoid mosquito

bites to prevent Zika virus and other vectorborne infections (see Sec. 4, Ch. 6, Mosquitoes, Ticks & Other Arthropods). Advise people with possible Zika virus exposure who want to reduce the risk for sexual transmission of Zika virus to an uninfected partner to follow current CDC recommendations (www.cdc.gov/zika/prevention/sexual-transmission-prevention.html). Although blood donations in the United States were previously screened for Zika virus RNA, the US Food and Drug Administration ceased this requirement in May 2021 because the virus no longer has sufficient incidence to affect the potential donor population.

Pregnancy

Pregnant people should not travel to areas with ongoing Zika outbreaks (https://wwwnc.cdc.gov/travel/page/zika-information). Before traveling to areas with current or past spread of Zika, pregnant people should discuss their travel plans with a health care provider. In deciding whether to travel, pregnant people should consider the destination, their reasons for traveling, and their ability to prevent mosquito bites. If used in accordance with the instructions on the product label, there are no restrictions on the use of insect repellents by people who are pregnant.

If a pregnant person or their partner travels to an area with current or past spread of Zika virus, advise the couple to use condoms or to abstain from sex for the entire pregnancy, even if the traveler does not have symptoms of Zika or feel sick. Couples trying to become pregnant who travel to areas with past or current Zika virus transmission should take steps to protect themselves from Zika and consider waiting to get pregnant according to the timeframes outlined in CDC guidance (www.cdc.gov/pregnancy/zika/women-and-their-partners.html).

Mothers are encouraged to breastfeed infants even after possible Zika virus exposure, because available evidence indicates the benefits of breastfeeding outweigh the theoretical risks associated with Zika virus infection transmission through breast milk.

CDC website: www.cdc.gov/zika

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PART 3: PARASITIC

AMEBIASIS

Jennifer Cope, Ibne Ali

INFECTIOUS AGENT: *Entamoeba histolytica*	
ENDEMICITY	Worldwide, especially in tropical countries with poor sanitation
TRAVELER CATEGORIES AT GREATEST RISK FOR EXPOSURE & INFECTION	Humanitarian aid workers Immigrants and refugees Long-term travelers and expatriates
PREVENTION METHODS	Practice good hand hygiene Follow safe food and water safety precautions Minimize fecal–oral exposures during sexual activity
DIAGNOSTIC SUPPORT	Contact CDC's Free-Living and Intestinal Amebas (FLIA) Laboratory for confirmatory diagnostic testing (www.cdc.gov/laboratory/specimen-submission/detail.html?CDCTestCode=CDC-10478)

INFECTIOUS AGENT

The protozoan parasite *Entamoeba histolytica*, and possibly other *Entamoeba* spp., causes amebiasis.

TRANSMISSION

Transmission occurs through the fecal–oral route, either by eating or drinking fecally contaminated food or water or through person-to-person contact (e.g., diaper changing, sexual activity).

EPIDEMIOLOGY

Amebiasis is distributed worldwide, particularly in the tropics, most commonly in areas of poor sanitation. *E. histolytica* is a common diarrheal pathogen in returned travelers. Long-term travelers (duration >6 months) are much more likely than short-term travelers (duration <1 month) to develop *E. histolytica* infection. Recent immigrants and refugees from these areas also are at risk. Outbreaks among men who have sex with men have been reported. People at greater risk for severe disease are pregnant, immunocompromised, or receiving corticosteroids; severe disease has also been reported among people with diabetes and those who consume alcohol.

CLINICAL PRESENTATION

Most patients have a gradual illness onset days or weeks after infection. Symptoms include cramps, bloody or watery diarrhea, and weight

loss, which might last several weeks. Occasionally, the parasite will spread to other organs (extraintestinal amebiasis), most commonly the liver. Amebic liver abscesses can be asymptomatic, but most patients present with right upper quadrant abdominal pain, fever, and weight loss, usually in the absence of diarrhea. Men are at greater risk of developing amebic liver abscess than are women for reasons not fully understood.

DIAGNOSIS

Microscopy does not distinguish between *E. histolytica* (known to be pathogenic), *E. bangladeshi*, *E. dispar*, and *E. moshkovskii*. Historically, *E. dispar* and *E. moshkovskii* have been considered nonpathogenic, but evidence is mounting that *E. moshkovskii* can cause illness; *E. bangladeshi* has only recently been identified, so its pathogenic potential is not well understood. ELISA or PCR are needed to confirm the diagnosis of *E. histolytica*. Additionally, serologic tests can help diagnose extraintestinal amebiasis.

The Free-Living and Intestinal Amebas (FLIA) laboratory of the Centers for Disease Control and Prevention (CDC) can make a specific diagnosis using a duplex real-time PCR capable of detecting and distinguishing *E. histolytica* and *E. dispar* in stool, liver aspirates, and tissue samples. More information about this testing and the CDC point of contact can be found at www.cdc.gov/laboratory/specimen-submission/detail.html; select test code CDC-10478 from the list.

The FLIA laboratory does not accept samples for routine screening purposes, and only accepts samples previously tested elsewhere but still requiring confirmatory testing. CDC requests that state public health officials assist clinical laboratories referring specimens for further testing, including providing information about testing, specimen submission forms, and shipping information.

TREATMENT

Treat patients with symptomatic intestinal infection and extraintestinal disease with metronidazole or tinidazole, then treat with iodoquinol or paromomycin. Also, treat asymptomatic patients infected with *E. histolytica* with iodoquinol or paromomycin, because they can infect others and because 4%–10% of asymptomatic patients develop disease within 1 year if untreated. In patients with large amebic liver abscesses (>5 cm in diameter), draining the abscess in addition to treating with metronidazole or tinidazole can aid in the early resolution of pain and tenderness.

PREVENTION

To reduce their risk for amebiasis, travelers should follow food and water precautions (see Sec. 2, Ch. 8, Food & Water Precautions), practice good hand hygiene, and avoid fecal exposure during sexual activity.

CDC website: www.cdc.gov/parasites/amebiasis

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ANGIOSTRONGYLIASIS

Rebecca Chancey, Anne Straily

INFECTIOUS AGENT: *Angiostrongylus cantonensis*	
ENDEMICITY	Southeast Asia and the Pacific Basin Australia The Caribbean
TRAVELER CATEGORIES AT GREATEST RISK FOR EXPOSURE & INFECTION	All travelers, but especially adventurous eaters
PREVENTION METHODS	Follow safe food precautions Avoid fresh produce, which can contain infected slugs or snails Avoid raw and undercooked freshwater crabs, frogs, shrimp, and snails
DIAGNOSTIC SUPPORT	Contact CDC's Parasitic Diseases Branch, (www.cdc.gov/parasites; 404-718-4745; parasites@cdc.gov)

INFECTIOUS AGENT

Angiostrongylus cantonensis, rat lungworm, a nematode parasite, causes angiostrongyliasis.

TRANSMISSION

Various species of rats are the definitive hosts of rat lungworm. Parasites from rats only infect slugs and snails, which are the intermediate hosts. Infective larvae also have been found in paratenic (transport) hosts (e.g., freshwater crabs, frogs, shrimp), which become infected by consuming infected slugs and snails. Transmission to humans occurs by ingesting infected intermediate or paratenic hosts contaminating raw produce or vegetable juices.

EPIDEMIOLOGY

A. cantonensis is considered the most common infectious cause of eosinophilic meningitis in humans. Most described cases have occurred in Asia and the Pacific Basin (e.g., parts of Australia, mainland China, Taiwan, Thailand, Hawaii, and other Pacific Islands); cases have been reported in many areas of the world, however, including Central and South America, the Caribbean, and parts of the continental United States. A review of the published literature in 2018 identified ≥77 cases of neuroangiostrongyliasis among travelers. All travelers are at risk, but adventure travelers might have more risky eating behaviors, predisposing them to exposure.

CLINICAL PRESENTATION

Incubation period is typically 1–3 weeks but ranges from 1 day to >6 weeks. Common manifestations include body aches, headache, fatigue, photophobia, stiff neck, abnormal skin sensations (e.g., tingling or painful feelings), nausea, and vomiting. Low-grade fever is possible. Symptoms are usually self-limited but might persist for weeks or months. Severe cases can be associated with blindness, paralysis, or death.

DIAGNOSIS

Diagnosis is typically presumptive, based on clinical and epidemiologic criteria in people with otherwise unexplained eosinophilic meningitis. Request PCR testing of cerebrospinal fluid through the Centers for Disease Control and Prevention's DPDx laboratory (www.cdc.gov/dpdx; dpdx@cdc.gov), or the Parasitic Diseases Hotline for Healthcare Providers (404-718-4745;

parasites@cdc.gov). Immunodiagnostic tests have been developed in research settings but are not approved or licensed for clinical use in the United States.

TREATMENT

A. cantonensis larvae die spontaneously, and supportive care usually suffices, including analgesics for pain and corticosteroids to limit inflammation. No anti-helminthic drugs have been effective in treatment. Although albendazole has been combined with corticosteroids in some cases, concern remains that anti-helminthic drugs will exacerbate symptoms due to a systemic response to dying worms. Lumbar puncture is required for etiological diagnosis of eosinophilic meningitis and can be repeated if clinically indicated to reduce intracranial pressure.

PREVENTION

Travelers can reduce their risk for infection by following safe food and water precautions. In particular, travelers should avoid eating raw or undercooked slugs, snails, and other possible hosts; and avoid eating raw produce (e.g., lettuce) unless it has been thoroughly washed with clean water, which might provide some protection but might not fully eliminate the risk. If a catchment tank is used as a source of water, travelers should ensure that the tank is covered to prevent intrusion by slugs and snails (see Sec. 2, Ch. 9, Water Disinfection) and keep their drink containers covered. In addition, travelers should wear gloves if they handle slugs or snails, and thoroughly wash hands afterwards.

CDC website: www.cdc.gov/parasites/angiostrongylus

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CRYPTOSPORIDIOSIS

Michele Hlavsa, Dawn Roellig

INFECTIOUS AGENT: *Cryptosporidium* spp.	
ENDEMICITY	Worldwide
TRAVELER CATEGORIES AT GREATEST RISK FOR EXPOSURE & INFECTION	Children aged 1–4 years and their caregivers
PREVENTION	Follow safe food and water precautions Minimize fecal–oral exposures during sexual activity Practice good hand hygiene
DIAGNOSTIC SUPPORT	A clinical laboratory certified in moderate complexity testing; or contact CDC's Waterborne Disease Prevention Branch (healthywater@cdc.gov) for clinical and diagnostic questions (does not conduct cryptosporidiosis diagnostic testing)

INFECTIOUS AGENT

Among the many protozoan parasites in the genus *Cryptosporidium*, *Cryptosporidium hominis* and *C. parvum* cause >90% of human infections.

TRANSMISSION

Cryptosporidium is transmitted via the fecal–oral route. Its low infectious dose, prolonged survival in moist environments, protracted communicability, and extreme chlorine tolerance make *Cryptosporidium* ideally suited for transmission through contaminated drinking or recreational water (e.g., swimming pools). Transmission also can occur through contact with fecally contaminated surfaces, by eating contaminated food, or through contact with infected animals (particularly pre-weaned bovine calves) or people (e.g., when providing direct care, during oral–anal sex).

EPIDEMIOLOGY

Cryptosporidiosis is endemic worldwide; the highest rates are found in low- and middle-income countries. An estimated 823,000 cryptosporidiosis cases occur in the United States each year, of which 9.9% are thought be due to international travel. The highest US rates of reported cryptosporidiosis are in young children aged 1–4 years and in people aged 15–44 years, particularly females (likely caregivers changing diapers and helping with toileting). International travel is a risk factor for sporadic cryptosporidiosis in the United States (population attributable risk is 11%) and other high-income nations; few studies, however, have assessed the prevalence of cryptosporidiosis in travelers.

One report identified a 6% prevalence of *Cryptosporidium* infection in North American travelers to Mexico; among travelers to Cuernavaca or Guadalajara who experienced travelers' diarrhea, longer visits were associated with an increased risk for *Cryptosporidium* infection compared with bacterial diarrhea. Approximately 30% of patients with cryptosporidiosis in New York City reported international travel during their incubation period, particularly among those aged <20 years.

CLINICAL PRESENTATION

Symptoms—most commonly, frequent, nonbloody, watery diarrhea—begin ≤2 weeks (typically 5–7 days) after infection and are generally self-limited. Other symptoms include abdominal pain, flatulence and urgency, nausea, vomiting, and low-grade fever. In immunocompetent people, symptoms typically resolve within 2–3 weeks,

although patients might experience a recurrence of symptoms after a brief period of recovery and before complete symptom resolution.

Clinical presentation in immunocompromised patients varies with the level of immunosuppression, ranging from no symptoms or transient disease to relapsing or chronic diarrhea or even cholera-like diarrhea, which can lead to dehydration and life-threatening wasting and malabsorption. Extraintestinal cryptosporidiosis in the biliary or respiratory tract, and rarely the pancreas, has been documented in children and immunocompromised people.

DIAGNOSIS

Routine testing for ova and parasites does not typically include *Cryptosporidium*; specifically request testing for this organism when *Cryptosporidium* infection is suspected. New molecular enteric panel assays generally include *Cryptosporidium* as a target pathogen. Because *Cryptosporidium* is intermittently excreted in the stool, collect multiple samples (i.e., collect specimens on 3 separate days) to increase test sensitivity.

Other diagnostic techniques include microscopy with direct fluorescent antibody (considered the gold standard), enzyme immunoassay kits, molecular assays, microscopy with modified acid-fast staining, and rapid immunochromatographic cartridge assays. Note that rapid immunochromatographic cartridge assays can generate false-positive results; consider confirmation with microscopy. The Centers for Disease Control and Prevention (CDC)'s Waterborne Disease Prevention Branch (healthywater@cdc.gov) can answer clinical and diagnostic questions but does not conduct cryptosporidiosis diagnostic testing. Health care professionals should contact their usual diagnostic laboratory for testing.

Infections caused by different *Cryptosporidium* species and subtypes can differ clinically. Most *Cryptosporidium* species, all with multiple subtypes, are indistinguishable by traditional diagnostic tests, however. To clarify cryptosporidiosis epidemiology and track infection sources, then, CDC coordinates CryptoNet (www.cdc.gov/parasites/crypto/cryptonet.html), which provides *Cryptosporidium* genotyping and subtyping services in collaboration with state public health agencies. CryptoNet recommends against using formalin to preserve stool for *Cryptosporidium* testing, because formalin impedes reliable genotyping and subtyping.

Cryptosporidiosis is a nationally notifiable disease in the United States.

TREATMENT

Most immunocompetent people recover from cryptosporidiosis without treatment; diarrhea can be managed by maintaining an adequate oral fluid intake. The US Food and Drug Administration has approved nitazoxanide as treatment for immunocompetent people aged ≥1 year with cryptosporidiosis (for details, see www.cdc.gov/parasites/crypto/treatment.html).

Nitazoxanide has not been shown to be effective in immunocompromised patients. Instead, reconstitution of the immune system can result in robust clinical improvement in the absence of specific treatment. Protease inhibitors might have anti-*Cryptosporidium* activity. All patients (immunocompromised and immunocompetent) might need rehydration and electrolyte replacement.

PREVENTION

Travelers can reduce their risk for cryptosporidiosis by carefully adhering to food and water precautions (see Sec. 2, Ch. 8, Food & Water Precautions) and using proper handwashing techniques (see www.cdc.gov/handwashing/when-how-handwashing.html and www.cdc.gov/parasites/crypto/gen_info/prevention-general-public.html). Alcohol-based hand sanitizers are not effective against this parasite.

Travelers can also decrease the risk for infection by filtering drinking water with an absolute 1-µm filter or heating drinking water to a rolling boil for 1 minute (see Sec. 2, Ch. 9, Water Disinfection, and www.cdc.gov/healthywater/drinking/travel/backcountry_water_treatment.html). *Cryptosporidium* oocysts are extremely tolerant of halogens (e.g., chlorine, iodine), so

CDC recommends filtering or boiling water in high-risk areas.

To protect themselves, swimmers should avoid ingesting recreational water. To protect others, people infected with cryptosporidiosis should not enter recreational water while ill with diarrhea, and for the first 2 weeks after symptoms have completely resolved, because of prolonged excretion of infectious oocysts.

Practicing safer sex (i.e., reducing contact with feces) can also decrease risk for infection.

CDC website: www.cdc.gov/parasites/crypto/index.html

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CUTANEOUS LARVA MIGRANS

Susan Montgomery, Mary Kamb

INFECTIOUS AGENT: *Ancylostoma* spp.	
ENDEMICITY	Worldwide
TRAVELER CATEGORIES AT GREATEST RISK FOR EXPOSURE & INFECTION	Travelers to tropical or subtropical regions who have unprotected skin contact with sand or soil
PREVENTION METHODS	Avoid direct skin contact with potentially contaminated sand or soil
DIAGNOSTIC SUPPORT	CDC's Parasitic Diseases Branch, (www.cdc.gov/parasites; 404-718-4745; parasites@cdc.gov) Parasitological diagnosis: DPDx (www.cdc.gov/DPDx)

INFECTIOUS AGENT

Larval stages of dog and cat hookworms (usually *Ancylostoma* spp.) can cause skin infections.

TRANSMISSION

Hookworm infections occur through direct skin contact with contaminated sand or soil.

EPIDEMIOLOGY

Zoonotic hookworms associated with cutaneous larva migrans (CLM)—also known as creeping eruption—have a worldwide distribution, but most cases are reported in travelers to Africa, South America, Asia, and the Caribbean. Beaches and sandboxes where free-roaming dogs and cats defecate are common sources of infection. Infection occurs in short-term and long-term travelers.

CLINICAL PRESENTATION

Creeping eruption usually appears 1–5 days after skin penetration, but the incubation period may be ≥1 month. Typically, a serpiginous, erythematous track appears in the skin and is associated with intense itching and mild swelling. Usual locations are the feet, lower legs, and buttocks, but any skin surface (e.g., trunk, upper extremities) that contacts contaminated soil can be affected (see Sec. 11, Ch. 8, Dermatologic Conditions).

DIAGNOSIS

CLM is diagnosed clinically based on a history of potential exposure and characteristic skin lesions. Biopsy is not recommended. Clinicians can obtain diagnostic assistance from the Centers for Disease Control and Prevention (CDC)'s Division of Parasitic Diseases and Malaria DPDx laboratory (www.cdc.gov/DPDx; dpdx@cdc.gov), or from the Parasitic Diseases Hotline for Healthcare Providers (404-718-4745; parasites@cdc.gov).

TREATMENT

CLM is self-limiting; migrating larvae usually die after 5–6 weeks. Albendazole is a very effective treatment. Ivermectin is effective but not approved by the US Food and Drug Administration for this indication. Symptomatic treatment can help relieve severe itching and reduce the chance of bacterial superinfection.

PREVENTION

Instruct travelers to reduce their contact with contaminated sand and soil by wearing shoes and protective clothing and using barriers (e.g., blankets, towels) when seated on the ground or sandy beaches, particularly in areas with free-roaming dogs and cats.

CDC website: www.cdc.gov/parasites/zoonotichookworm

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CYCLOSPORIASIS

Anne Straily, Rebecca Chancey

INFECTIOUS AGENT: *Cyclospora cayetanensis*	
ENDEMICITY	Tropical and subtropical regions
TRAVELER CATEGORIES AT GREATEST RISK FOR EXPOSURE & INFECTION	Any travelers to endemic regions who consume potentially contaminated fresh produce
PREVENTION METHODS	Follow safe food and water precautions
DIAGNOSTIC SUPPORT	A clinical laboratory certified in moderate complexity testing; or contact CDC's Parasitic Diseases Branch (www.cdc.gov/parasites; 404-718-4745; parasites@cdc.gov) Parasitological diagnosis: DPDx (www.cdc.gov/DPDx)

INFECTIOUS AGENT

Cyclospora cayetanensis, a coccidian protozoan parasite, causes cyclosporiasis.

TRANSMISSION

Transmission occurs through ingestion of infective *Cyclospora* oocysts, typically from contaminated food or water.

EPIDEMIOLOGY

Cyclosporiasis occurs in many countries around the world, but appears to be most common in tropical and subtropical regions. Outbreaks frequently are seasonal, but seasonality varies in different parts of the world. In Guatemala, detection rates increase during May–August. In Nepal, rates increase during the summer and rainy season (May–October). In Turkey, incidence rates are highest during July–November. No environmental conditions (e.g., temperature, rainfall) have yet been determined to be drivers for the seasonal variation in cyclosporiasis.

People typically become infected through the consumption of contaminated fresh produce or contaminated water. All travelers are at risk of infection, regardless of the purpose or length of their travel in an endemic area; even short-term travelers can become infected. Outbreaks in the United States and Canada typically occur during the spring and summer months; historically these have been linked to consumption of imported fresh produce. No commercially frozen or canned produce has yet been implicated as the source of an outbreak.

During 2011–2015, 415 cyclosporiasis cases were reported among US residents with a history of international travel during their incubation period. The most frequently reported destinations were in the Americas, including Mexico, the Caribbean, Central America, and South America; travel to Africa, Asia, and Europe was reported less frequently among identified case-patients.

CLINICAL PRESENTATION

The incubation period averages 1 week (range 2 days to ≥2 weeks). Symptom onset often is abrupt, but can be gradual; some people have an influenza-like prodrome. The most common symptom is watery diarrhea, which can be profuse. Other symptoms can include abdominal cramps, anorexia, bloating, body aches, low-grade fever, nausea, vomiting, and weight loss. If untreated, the illness can last for several weeks or months with a remitting–relapsing course.

DIAGNOSIS

Cyclosporiasis is diagnosed by detecting *Cyclospora* oocysts or DNA in stool specimens. Stool examinations for ova and parasites usually do not include methods for detecting *Cyclospora* unless testing for this parasite is specifically requested. Diagnostic assistance for *Cyclospora* and other parasitic diseases also is available from the Centers for Disease

Control and Prevention (www.cdc.gov/dpdx; 404-718-4745; parasites@cdc.gov). Cyclosporiasis is a nationally notifiable disease.

TREATMENT

Treatment includes trimethoprim-sulfamethoxazole; no highly effective alternatives have been identified. One case report documented resolution of symptoms after treatment with nitazoxanide in a patient with a sulfa allergy. Anecdotal data suggest that ciprofloxacin is ineffective.

PREVENTION

Travelers can reduce their risk for infection by following food and water precautions (see Sec. 2, Ch. 8, Food & Water Precautions), but using chlorine or iodine for water disinfection is unlikely to be effective because oocysts are extremely tolerant of halogens (see Sec. 2, Ch. 9, Water Disinfection).

CDC website: www.cdc.gov/parasites/cyclosporiasis

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CYSTICERCOSIS

Paul Cantey, Sharon Roy

INFECTIOUS AGENT: *Taenia solium*	
ENDEMICITY	Worldwide Most prominent where sanitary conditions are poor, and pigs have access to human feces
TRAVELER CATEGORIES AT GREATEST RISK FOR EXPOSURE & INFECTION	Immigrants and refugees Long-term travelers Travelers visiting friends and relatives
PREVENTION METHODS	Follow safe food precautions Avoid eating food cooked by someone who does not practice good hand hygiene Practice good hand hygiene
DIAGNOSTIC SUPPORT	Serologic testing: CDC's Parasitic Diseases Branch (www.cdc.gov/parasites; 404-718-4745; parasites@cdc.gov)

INFECTIOUS AGENT

Cysticercosis is caused by *Taenia solium*, a cestode parasite.

TRANSMISSION

Transmission occurs through ingestion of eggs excreted by a human carrier of the adult *T. solium* tapeworm via fecally contaminated food or through close contact with the carrier. Autoinfection is also possible. Larval cysts of *T. solium* infect brain, muscle, or other tissues. Eating undercooked pork containing cysticerci results in tapeworm infection (taeniasis), not human cysticercosis.

EPIDEMIOLOGY

Cysticercosis occurs globally and is common where sanitary conditions are poor and where pigs have access to human feces. Endemic areas include Latin America, sub-Saharan Africa, East Asia, and India. Cysticercosis is uncommon in travelers, but is more likely in long-term travelers, in immigrants and refugees from endemic regions, and in people who visit friends and relatives in endemic areas.

CLINICAL PRESENTATION

The latent period for cysticercosis ranges from months to decades. Symptoms depend on the number, location, and stage of cysts. The most important clinical manifestations are caused by cysts in the brain, where cysts can be parenchymal or extraparenchymal (ventricular, subarachnoid). The most common presentations are seizures and increased intracranial pressure. Other presentations include encephalitis, symptoms of space-occupying lesions (e.g., seizures), and hydrocephalus. Cysticercosis should be considered in any adult with new-onset seizures who comes from an endemic area or has had potential exposure to a tapeworm carrier.

DIAGNOSIS

Neuroimaging studies (e.g., CT, MRI) are required, and confirmatory serologic testing is often needed. Visualization of a scolex on neuroimaging is diagnostic. The most specific serologic test is the enzyme-linked immunotransfer blot (EITB), but results can be negative in ≥30% of patients with a single parenchymal lesion. The sensitivity of the test is also reduced in patients with only calcified lesions. The EITB is available through the Parasitic Diseases Branch at the Centers for Disease Control and Prevention (CDC). Instructions on how to submit a serum specimen for testing at CDC can be found at www.cdc.gov/laboratory/specimen-submission/index.html.

TREATMENT

Control of symptoms is the cornerstone of cysticercosis therapy. Anticonvulsants, corticosteroids, or both might be indicated. Urgently manage increased intracranial pressure, if present. Antiparasitic treatment (albendazole, praziquantel) is not indicated for all presentations of neurocysticercosis; carefully consider the risks and benefits before starting treatment and consider expert consultation. Recommendations vary depending on whether the lesion is parenchymal or extraparenchymal; viable, enhancing, or calcified; has associated perilesional edema; and by location and number of lesions. For some intraventricular lesions, surgical intervention could be the treatment of choice.

In complicated cases, the priority is neurologic management (e.g., corticosteroids, mannitol), neurosurgery, or both. In 2018, the Infectious Diseases Society of America and the American Society of Tropical Medicine and Hygiene published guidelines for the clinical management of neurocysticercosis, which are available at https://doi.org/10.1093/cid/cix1084. Clinicians can contact CDC Parasitic Diseases Inquiries at 404-718-4745 or parasites@cdc.gov to obtain more information about diagnosis and treatment.

PREVENTION

To reduce the risk for infection, travelers should follow food and water precautions (see Sec. 2, Ch. 8, Food & Water Precautions) and practice good hand hygiene to reduce the risk for possible autoinfection.

CDC website: www.cdc.gov/parasites/cysticercosis