COVID-19

The information included in this chapter was current as of August 2022. For the most recent information regarding coronavirus disease 2019 (COVID-19), see www.cdc.gov/coronavirus/2019-nCoV/index.html.

Sarah Anne Guagliardo, Cindy Friedman

INFECTIOUS AGENT: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)	
ENDEMICITY	Worldwide
TRAVELER CATEGORIES AT GREATEST RISK FOR EXPOSURE & INFECTION	All travelers
PREVENTION METHODS	Vaccination prevents hospitalization and deaths from COVID-19 Avoiding crowded, poorly ventilated spaces Hand hygiene Respiratory protection (wearing a well-fitting mask or respirator)
DIAGNOSTIC SUPPORT	A clinical laboratory certified in moderate complexity testing

INFECTIOUS AGENT

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the cause of coronavirus disease 2019 (COVID-19), is a single-stranded, positive-sense RNA virus that belongs to the family *Coronaviridae*, genus *Betacoronavirus*.

TRANSMISSION

SARS-CoV-2 is primarily transmitted from person to person following close (≤6 ft, ≈2 m) exposure to respiratory fluids carrying infectious virus. When an infected person breathes, sings, talks, coughs, or sneezes, they release infectious aerosol particles (droplet nuclei) into the air. Exposure can occur when aerosol particles and small respiratory droplets are inhaled or contact exposed mucous membranes. Infection from contaminated surfaces or objects (fomites) is possible but is unlikely to contribute significantly to new infections.

Infection through inhalation is most likely to occur at closer distances (≤6 ft), but transmission over distances >6 ft by inhalation of very fine aerosolized, infectious particles (airborne transmission) has been documented. The risk of transmission is enhanced in poorly ventilated indoor spaces.

EPIDEMIOLOGY

The first cases of COVID-19 were reported in December 2019 in Wuhan, China, and since then, the virus has spread to all continents. International travel has played an ongoing role in the epidemiology of the pandemic, facilitating the initial global spread of the virus as well as each successive SARS-CoV-2 variant. From January 2020 to April 2022, there were 5 major epidemic waves in the United States; as of April 2022, the most recent 3 corresponded to the Alpha, Delta, and Omicron variants.

Mortality Rates

As of April 2022, there were an estimated 400 million cases and 6 million deaths reported worldwide. Case counts and deaths are likely an underestimate, since only a small proportion of

infections are diagnosed and reported; in addition, self-testing options (for which positive results might go unreported) are now widely available. Estimates of the infection fatality rate (the mortality rate in infected individuals) among unvaccinated populations range from 0.15% to 1.7% Country-specific COVID-19 mortality rates can vary between destinations for multiple reasons, including differences in population-level immunity due to previous infection, vaccination rates, age distribution, prevalence of comorbidities, viral evolution, and access to health care. With the emergence of new variants, mortality rates may change.

Travel-Associated Risk

Reported travel-associated case counts and deaths also are likely an underestimate, and overall travel-related risk is difficult to ascertain. Investigating and identifying travel-associated cases of COVID-19 has unfortunately been hampered by a lack of complete passenger data for contact tracing, limited or incomplete reporting of contact tracing outcomes among exposed passengers, and difficulties in excluding non-travel–associated exposures. Tracking levels of transmission in countries globally is only one factor in determining travel-associated risk.

MODES OF TRANSPORTATION & TRANSMISSION RISK

Across all modes of transportation, not wearing a well-fitting mask or respirator (www.cdc.gov/coronavirus/2019-ncov/prevent-getting-sick/types-of-masks.htm]) within 6 ft of an infected person (e.g., sitting on a plane or train, sharing a cabin on a cruise) increases the risk for infection, underscoring the importance of prevention measures before and during travel.

AIR TRAVEL

Attack rates range from 0% to 8% on flights but can be as high as 60% in subsections of an aircraft, as was observed on a 10-hour flight in a business class cabin. The individuals affected in this outbreak were all seated within 6 feet of the index case; data regarding mask use were not available. The relationship between flight duration and attack rates is difficult to quantify due to other flight-specific variables (e.g., mask use among passengers and aircrew, passenger movement during the flight) that are not captured or difficult to measure. For more information about health concerns related to commercial air travel, see Sec. 8, Ch. 1, Air Travel.

CRUISE SHIP TRAVEL

Cruise ship travel facilitates the introduction and spread of respiratory viruses because of close indoor proximity and extensive social interactions between ever-changing cohorts of passengers from diverse geographic regions. Cruise ships were the source of many large COVID-19 outbreaks throughout the pandemic, with severe outcomes prior to COVID-19 vaccines.

In the earliest months of the pandemic (January–April 2020), attack rates on cruises were as high as 62%. Longer voyages were associated with more cases, and repeated outbreaks on the same ship (but different voyages) were common. Since then, the Centers for Disease Control and Prevention (CDC) has worked to develop guidance for the cruise ship industry to use to better manage risks associated with COVID-19 (www.cdc.gov/quarantine/cruise/index.html). See Sec. 8, Ch. 6, Cruise Ship Travel, for more details on health concerns related to cruises.

GROUND TRANSPORTATION

COVID-19 outbreaks on buses and trains have also been described. Attack rates on buses have been as high as 36%. On trains, attack rates among passengers within 3 rows of an index patient were lower, ranging from 0% to 10%, with an overall attack rate of <1%.

Sentinel Surveillance

In the context of declining global testing and reporting, determining country-level risk has become more challenging. Sentinel surveillance of international travelers may therefore be an important contribution to the global picture of disease burden and variant emergence. In September 2021, CDC launched a voluntary

traveler-based SARS-CoV-2 genomic surveillance program to detect variants among travelers arriving at major US international airports. Through this program, CDC scientists detected Omicron subvariants BA.2 and BA.3 in the United States 7 and 45 days earlier, respectively, than any other US report.

CLINICAL PRESENTATION

SARS-CoV-2 infection can present with an array of clinical findings (www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html), ranging from asymptomatic to severe (e.g., multiorgan involvement, respiratory failure, death). Most infections are mild, however; about 40% of people are asymptomatic. Among cases that do not result in severe disease or hospitalization, fatigue, headache, muscle aches, rhinitis, and sore throat are reported most often. Other reported symptoms and signs include fever, chills, cough, shortness of breath, loss of taste and smell, nausea, vomiting, and diarrhea.

There is evidence that clinical presentation and illness severity differ depending on the SARS-CoV-2 variant. For example, 34% of patients infected with the Delta variant experienced loss of taste and smell, as compared to 13% of patients infected with the Omicron variant. Omicron was also associated with proportionally less pneumonia and severe disease. For pre-Omicron variants, the median incubation period is 5 days with a range of 2–14 days after initial exposure; studies of the Omicron variant have estimated the incubation period to be 2–3 days.

Age and underlying medical conditions increase a person's risk for severe disease and death. The risk of severe disease and death increases significantly with age (≥50 years old), pregnancy, obesity, and with an increasing number of comorbidities (e.g., diabetes, hypertension, HIV infection). For a comprehensive list of risk factors, see www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/underlyingconditions.html. See Sec. 3, Ch. 1, Immunocompromised Travelers, and Sec. 7, Ch. 1, Pregnant Travelers, for additional information about these populations.

Long COVID

People infected with SARS-CoV-2 can continue to experience symptoms ≥4 weeks after initial infection. Reported symptoms include shortness of breath, fatigue, headache, and difficulty thinking or concentrating. Commonly known as "long COVID," this condition goes by several other names, including post-COVID syndrome or condition, post-acute sequelae of COVID-19 (PASC), and chronic COVID Syndrome (CCS). For the most up-to-date definition of long COVID and an associated list of symptoms, see www.cdc.gov/coronavirus/2019-ncov/long-term-effects/index.html. Researchers are investigating risk factors and manifestations of long COVID.

In addition to the above, there is growing evidence of long-term cardiovascular consequences of the disease, including cerebrovascular disorders, dysrhythmias, heart failure, ischemic and non-ischemic heart disease, myocarditis, pericarditis, and thromboembolic disease.

DIAGNOSIS

Viral tests that detect current infection with SARS-CoV-2 are used for COVID-19 diagnosis, and include nucleic acid amplification tests (NAATs, e.g., reverse transcription PCR [RT-PCR]) and antigen tests. Tests that detect antibody to SARS-CoV-2 can be used to identify previous infection and might be useful for surveillance purposes, but are not typically used for diagnosis, except for multisystem inflammatory syndrome in children and adults (www.cdc.gov/coronavirus/2019-ncov/hcp/testing.html).

Nucleic Acid Amplification Testing

NAATs detect SARS-CoV-2 RNA and are highly sensitive and specific. The most common NAAT is the RT-PCR test. A positive RT-PCR provides evidence of current infection. Residual shedding of non-infectious viral RNA also can result in a positive test result, as demonstrated by reports of patients whose RT-PCR tests remain positive ≥3 months post-infection (www.cdc.gov/coronavirus/2019-ncov/hcp/testing-overview.html).

Acceptable specimens for SARS-CoV-2 RT-PCR tests include saliva and swab samples collected from the upper respiratory tract (e.g.,

nasopharynx, nasal mid-turbinate, anterior nasal, oropharynx). As new tests are developed, other specimen types might be identified as being suitable for testing. Each test should be performed as specified by the manufacturer and authorized or approved by the US Food and Drug Administration (FDA). NAAT results usually take 1–3 days, but some rapid tests available in the United States can be useful for travelers who need proof of a negative test for entry to international destinations; travelers should confirm with their air carrier and their destination in advance to ensure the acceptability of the test used.

Antigen Testing

Antigen tests detect the presence of viral proteins (antigens). In general, they are less sensitive than NAATs but are less expensive and can yield rapid results (≈15 minutes). Antigen tests can be used in a laboratory, at the point of care, or self-administered. For more information on antigen testing, see www.cdc.gov/coronavirus/2019-ncov/lab/resources/antigen-tests-guidelines.html.

TREATMENT

Before travel, encourage patients to have a health care contingency plan in place, should they test positive for COVID-19 while abroad; some countries require proof of travel insurance for COVID-19 (see Sec. 6, Ch. 1, Travel Insurance, Travel Health Insurance & Medical Evacuation Insurance). For mild disease, medications such as acetaminophen or ibuprofen can provide symptomatic relief. Patients also should rest and stay well hydrated.

For people at greater risk for progression to severe disease, the FDA has issued Emergency Use Authorization for several postexposure treatments, including antiviral medications and monoclonal antibodies. As of August 2022, preferred antiviral medications include oral nirmatrelvir + ritonavir (Paxlovid) and intravenous remdesivir. If neither of these drugs is available or clinically appropriate, alternative therapeutic options include prophylaxis with the oral antiviral molnupiravir or with monoclonal antibodies. For maximal efficacy, administer medications as soon as possible after diagnosis. Emergence of future variants might impact future treatment options.

The National Institutes of Health regularly updates COVID-19 treatment guidelines. See www.covid19treatmentguidelines.nih.gov/ for the most up-to-date information.

PREVENTION

During the initial months of the pandemic, global travel virtually halted, with many countries closing their borders to international travelers. Since then, travel has gradually returned to near prepandemic levels. In response to newly emerging variants of concern, many countries instituted measures (e.g., mask use, testing, isolation, quarantine, vaccination requirements) to slow travel-associated transmission. Several countries, including the United States, instituted travel bans, although evidence is limited that these are an effective prevention measure.

Inhalation of virus particles and deposition of virus on mucous membranes can be prevented by wearing a well-fitting mask or respirator and avoiding crowded indoor spaces with poor ventilation. Handwashing can help prevent transmission from contact with contaminated surfaces (fomite transmission). Used in combination, layered interventions (e.g., mask wearing, avoiding crowded indoor spaces with poor ventilation, testing, isolation, quarantine, vaccination) are measures that can reduce risk of transmission.

Coronavirus Disease 2019 Information by Destination

Because the situation continues to evolve, travelers and health care providers should review the travel restrictions, requirements, recommendations, and resources for all destination countries and the United States before departure. Knowing the most up-to-date information about COVID-19 by destination can help travelers and clinicians make informed decisions about travel based on COVID-19 levels, the travelers' risk for developing severe illness, and the health care capacity at the destination.

CDC's COVID-19 travel page (www.cdc.gov/coronavirus/2019-ncov/travelers/index.html)

BOX 5-02 Coronavirus disease 2019 (COVID-19) international travel preparation: a checklist for travelers

- ☐ Be up to date with your COVID-19 vaccines before international travel (www.cdc.gov/coronavirus/2019-ncov/vaccines/index.html; www.cdc.gov/coronavirus/2019-ncov/vaccines/stay-up-to-date.html)
- ☐ Learn about destination-specific entry requirements (e.g., vaccination; documentation of vaccination; predeparture and postarrival testing) and the return requirements for the end of your trip (https://travel.state.gov/content/travel/en/traveladvisories/COVID-19-Country-Specific-Information.html)
- ☐ CDC recommends wearing a well-fitting mask or respirator (www.cdc.gov/coronavirus/2019-ncov/travelers/masks-public-transportation.html)
- ☐ Practice mitigation measures (e.g., avoiding crowded, indoor spaces with poor ventilation; hand hygiene; cleaning and disinfection; www.cdc.gov/coronavirus/2019-ncov/global-covid-19/global-urban-areas.html)
- ☐ Learn about transportation-associated risk factors (e.g., avoid poorly ventilated, crowded trains, buses)
- ☐ Purchase travel health insurance (some countries require proof of travel insurance for COVID-19)
- ☐ Have plans ready in case you get sick or are exposed while abroad (e.g., know where you can be tested for COVID-19 at your destination or bring rapid test kits in your luggage; identify health care facilities that can manage severe illness at your destination; set aside additional resources for lodging needs in the event you need to quarantine and/or isolate)
- ☐ Know the international travel requirements and recommendations for the United States (www.cdc.gov/coronavirus/2019-ncov/travelers/international-travel/index.html)

provides guidance for travelers. Each country's ministry of health website is another source for information about COVID-19 levels at the destination as well as current entry requirements, including proof of vaccination.

Vaccination

As of August 2022, everyone ≥6 months old in the United States is eligible and recommended to receive COVID-19 vaccination (see www.cdc.gov/coronavirus/2019-ncov/vaccines/index.html, and Sec. 7, Ch. 4, Vaccine Recommendations for Infants & Children). At present, there are 4 vaccines authorized for use in the United States: 2 mRNA-based vaccines (Moderna, Pfizer-BioNTech), a DNA-based, adenovirus-vectored vaccine (Johnson & Johnson's Janssen), and a protein vaccine (Novavax). In most circumstances the 2 mRNA vaccines are preferred.

All eligible travelers should be up to date with their COVID-19 vaccines (www.cdc.gov/coronavirus/2019-ncov/vaccines/stay-up-to-date.html) before travel. Interim clinical considerations for the use of COVID-19 vaccines in the United States (www.cdc.gov/vaccines/covid-19/clinical-considerations/covid-19-vaccines-us.html) provide additional details regarding vaccine schedules, vaccine safety, and vaccination recommendations for people who are moderately to severely immunocompromised.

Testing

Conducting both a pretravel and posttravel test is estimated to reduce the risk of viral spread by up to 75%. Predeparture testing results in the greatest reduction of risk when a specimen is collected closest to the time of travel. Conducting a posttravel test 3–5 days after return can help prevent spread in the community. For the most up-to-date testing guidance for travelers, see www.cdc.gov/coronavirus/2019-ncov/travelers/international-travel/index.html, and www.cdc.gov/coronavirus/2019-ncov/travelers/travel-during-covid19.html.

Isolation

Isolation is the physical separation of a person with a confirmed or suspected infectious disease from people who are not infected. People who have symptoms or who test positive for COVID-19 should follow the latest CDC guidance regarding isolating themselves from others and the precautions to take after ending isolation (www.cdc.gov/coronavirus/2019-ncov/your-health/quarantine-isolation.html). If a person is symptomatic, they should avoid travel

for 10 days after symptom onset; if asymptomatic, they should avoid travel for 10 days after the date the positive test was collected. Immunocompromised travelers (Sec. 3, Ch. 1, Immunocompromised Travelers) can be infectious for longer than 10 days and should consider longer isolation periods. For the most up-to-date information and guidance on isolation and travel, see www.cdc.gov/coronavirus/2019-ncov/travelers/index.html.

Quarantine

Quarantine is the physical separation from other people of a person who has had close contact with someone with confirmed or suspected infectious disease. A fundamental public health approach to disease containment, quarantine has been used throughout the COVID-19 pandemic (www.cdc.gov/coronavirus/2019-ncov/your-health/quarantine-isolation.html). For the most up-to-date information and guidance on quarantine and travel, see www.cdc.gov/coronavirus/2019-ncov/travelers/index.html.

Masks

Wearing a well-fitting mask or respirator that completely covers the nose and mouth reduces SARS-CoV-2 transmission. A properly fitted and appropriately worn respirator (e.g., N95 filtering facepiece respirator approved by the National Institute for Occupational Safety and Health) protects the wearer from inhaling airborne droplet nuclei. KN95s also offer a high level of protection. Well-fitting disposable surgical masks provide source control by helping reduce transmission from a person infected with SARS-CoV-2 to others within a shared space. Masks made from layered finely woven products afford some protection, with the least amount of protection being offered by loosely woven cloth products. For more details and updates on masking during travel, see www.cdc.gov/coronavirus/2019-ncov/travelers/face-masks-public-transportation.html.

CDC website: www.cdc.gov/coronavirus/2019-ncov/index.html

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DENGUE

Liliana Sánchez-González, Laura Adams, Gabriela Paz-Bailey

INFECTIOUS AGENT: Dengue virus 1, 2, 3, 4	
ENDEMICITY	Tropical and subtropical regions worldwide
TRAVELER CATEGORIES AT GREATEST RISK FOR EXPOSURE & INFECTION	All travelers, but increased risk for travelers on trips lasting >6 months
PREVENTION METHODS	Avoid insect bites Dengue is a vaccine-preventable disease (restrictions apply, see text for details)
DIAGNOSTIC SUPPORT	A clinical laboratory certified in high complexity testing; state health department; or CDC's Division of Vector-Borne Diseases, Dengue Branch (787-706-2399)

INFECTIOUS AGENT

Dengue, an acute febrile illness, is caused by infection with any of 4 related single-stranded RNA viruses of the genus *Flavivirus*, dengue virus 1, 2, 3, or 4 (DENV1–4). Infection with one DENV confers long-term immunity to that virus but conveys only short-lived protection against the other dengue viruses. The risk for severe dengue is greater during a second DENV infection; although severe dengue also can occur during the first, third, or fourth infection.

TRANSMISSION

Almost all DENV transmission occurs through the bite of infected *Aedes* species mosquitoes, primarily *Ae. aegypti* and *Ae. albopictus*. Because of the ≈7-day viremia in humans, bloodborne transmission is possible through exposure to infected blood, organs, or other tissues (e.g., bone marrow). In addition, perinatal DENV transmission occurs when the mother is infected near the time of birth; infection occurs via microtransfusions as the placenta detaches, or through mucosal contact with maternal blood during birth. No cases of congenital transmission have been documented, but it has been suggested. DENV can be transmitted through breast milk. DENV also has been detected in vaginal secretions and semen; sexual transmission has been reported but is considered rare.

EPIDEMIOLOGY

Dengue is endemic throughout the tropics and subtropics and occurs in >100 countries and destinations worldwide, including Puerto Rico, the US Virgin Islands, and US–affiliated Pacific Islands (Map 5-03, Map 5-04, and Map 5-05). The incidence of dengue among travelers to the tropics has increased in recent years, and dengue burden is expected to continue to grow in sub-Saharan Africa, Latin America, and Asia, with estimates of >50 million febrile illness cases per year.

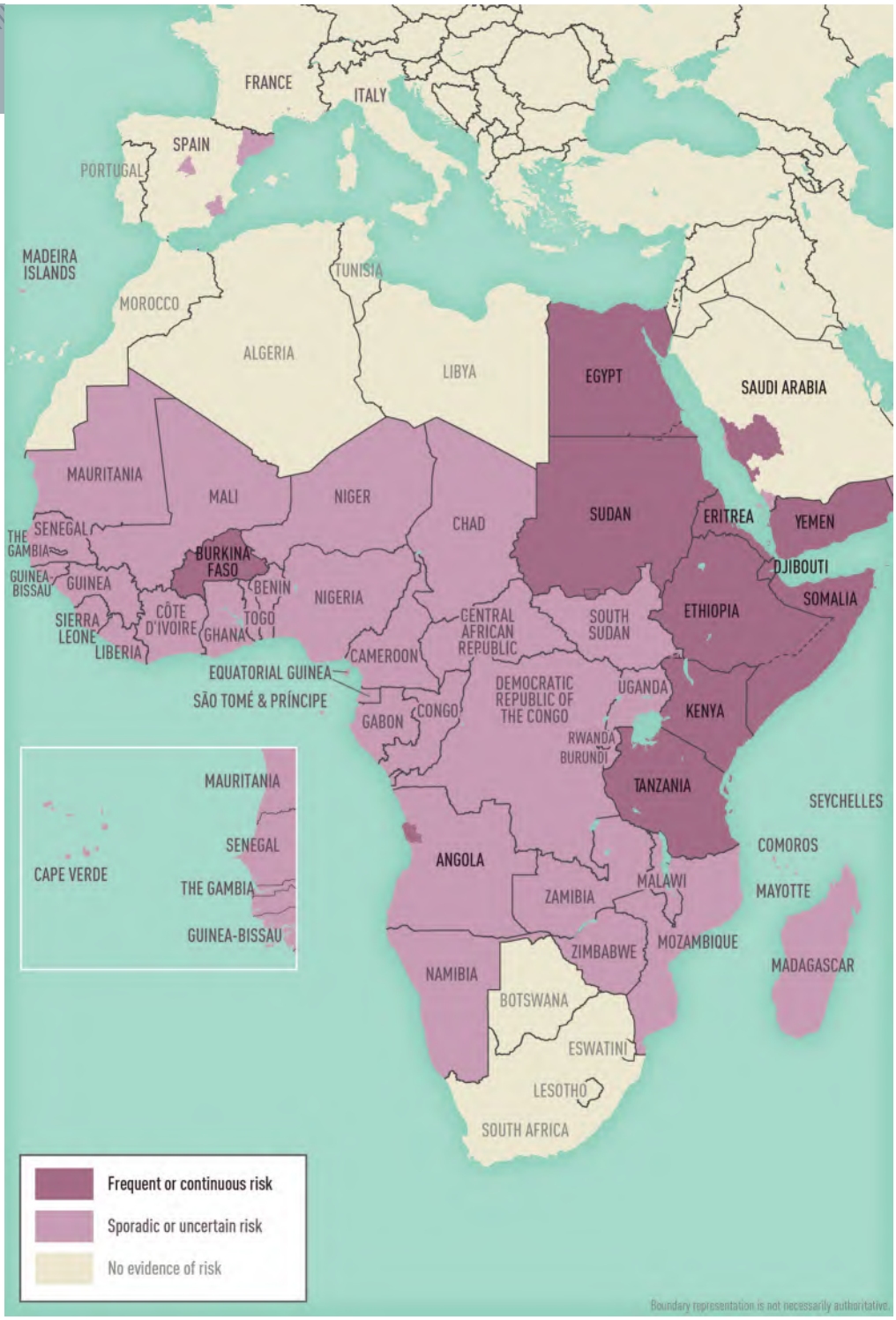
More than 5,000 travel-related dengue cases were reported in the United States during 2010–2017, with an annual average of 626 cases; a total of 2,119 patients with travel-related dengue required hospitalization, and 18 died. The most frequently reported regions of travel among US cases were the Caribbean, Central America, and Asia. Sporadic outbreaks with local transmission have occurred in Florida, Hawaii, and Texas. Although the geographic distribution of dengue is similar to that of malaria, dengue is more of a risk in urban and residential areas than is malaria.

CLINICAL PRESENTATION

An estimated 40%–80% of DENV infections are asymptomatic. Symptomatic dengue most commonly presents as a mild to moderate, nonspecific, acute febrile illness; ≤5% of all dengue

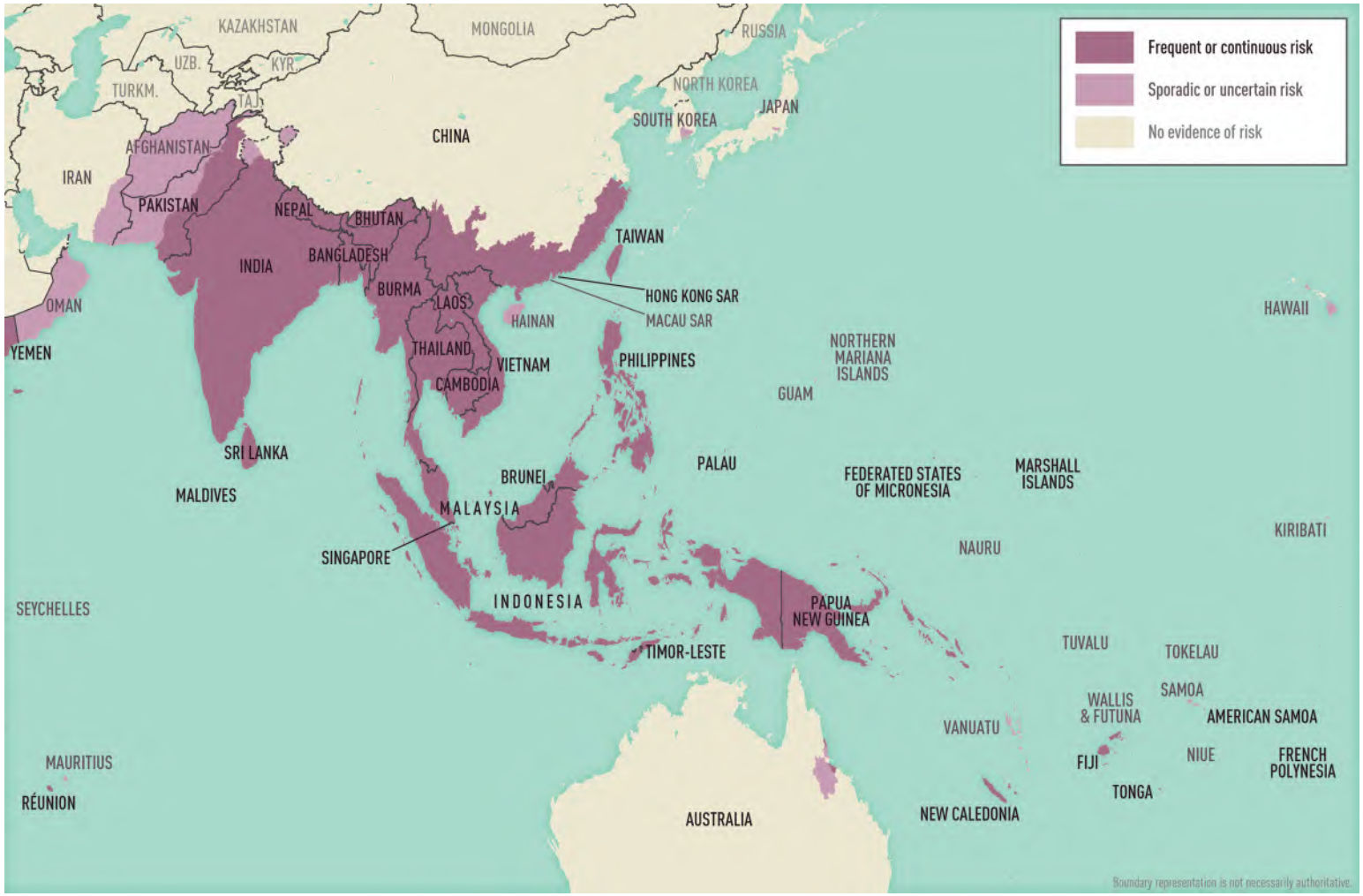
MAP 5-03 Dengue risk in the Americas & the Caribbean

Risk classification uses the methodology described in Jentes, et al. Evidence-based risk assessment and communication: a new global dengue-risk map for travellers and clinicians (www.ncbi.nlm.nih.gov/pmc/articles/PMC5345513/). *Frequent/continuous risk*: evidence of more than 10 dengue cases in at least 3 of the previous 10 years; *sporadic/uncertain risk*: evidence of at least 1 locally acquired dengue case during the last 10 years. Level of risk assigned to a destination reflects the highest risk level identified within that destination. Where data are available, subnational dengue risk levels are shown. Destination risk levels also are denoted using black (frequent/continuous risk) or gray (sporadic/uncertain risk) font for the place name.



MAP 5-04 Dengue risk in Africa, Europe, & the Middle East

Risk classification uses the methodology described in Jentes, et al. Evidence-based risk assessment and communication: a new global dengue-risk map for travellers and clinicians (www.ncbi.nlm.nih.gov/pmc/articles/PMC5345513/). *Frequent/continuous risk*: evidence of more than 10 dengue cases in at least 3 of the previous 10 years; *sporadic/uncertain risk*: evidence of at least 1 locally acquired dengue case during the last 10 years. Level of risk assigned to a destination reflects the highest risk level identified within that destination. Where data are available, subnational dengue risk levels are shown. Destination risk levels also are denoted using black (frequent/continuous risk) or gray (sporadic/uncertain risk) font for the place name.



MAP 5-05 Dengue risk in Asia & Oceania

Risk classification uses the methodology described in Jentes, et al. Evidence-based risk assessment and communication: a new global dengue-risk map for travellers and clinicians (www.ncbi.nlm.nih.gov/pmc/articles/PMC5345513/). *Frequent/continuous risk*: evidence of more than 10 dengue cases in at least 3 of the previous 10 years; *sporadic/uncertain risk*: evidence of at least 1 locally acquired dengue case during the last 10 years. Level of risk assigned to a destination reflects the highest risk level identified within that destination. Where data are available, subnational dengue risk levels are shown. Destination risk levels also are denoted using black (frequent/continuous risk) or gray (sporadic/uncertain risk) font for the place name.

Table 5-09 Dengue Clinical Classification

DENGUE	DENGUE WITH WARNING SIGNS	SEVERE DENGUE
Probable Dengue Live in/travel to endemic area. **Fever** and 2 of the following criteria • Nausea/vomiting • Rash • Aches and pains • Tourniquet test positive • Leukopenia • Any warning sign **Laboratory-confirmed dengue** • Molecular techniques/ IgM or IgG seroconversion	Presence of warning signs • Abdominal pain or tenderness • Persistent vomiting • Clinical fluid accumulation (ascites, pleural effusion) • Mucosal bleeding • Lethargy, restlessness • Postural hypotension • Liver enlargement >2 cm • Progressive increase in hematocrit	One of the following manifestations • Shock or respiratory distress due to severe plasma leakage • Severe bleeding (based on evaluation by attending physician) • Severe organ involvement (such as liver or heart)

Source: Dengue: Guidelines for Patient Care in the Region of the Americas. Washington, DC: Pan-American Health Organization (2016).

patients develop severe, life-threatening disease. Early clinical findings are nonspecific but require a high index of suspicion; recognizing early signs of shock and promptly initiating intensive supportive therapy can reduce risk for death among patients with severe dengue by ≥20-fold. See Table 5-09 for information regarding the World Health Organization guidelines for classifying dengue.

Phases of Symptomatic Dengue

FEBRILE PHASE

Symptomatic dengue begins abruptly after an incubation period of 5–7 days (range 3–10 days) and has a 3-phase clinical course: febrile, critical, and convalescent. Fever typically lasts 2–7 days and can be biphasic. Other signs and symptoms include severe headache; retro-orbital pain; bone, joint, and muscle pain; macular or maculopapular rash; and minor hemorrhagic manifestations, including ecchymosis, epistaxis, bleeding gums, hematuria, petechiae, purpura, or a positive tourniquet test result. Some patients have an injected oropharynx and facial erythema in the first 24–48 hours after onset. Warning signs of progression to severe dengue occur in the late febrile phase around the time of defervescence (i.e., temperature <100.4°F [38°C]) and can include severe abdominal pain, difficulty breathing, extravascular fluid accumulation, progressive increase in hematocrit (hemoconcentration), postural hypotension, lethargy or restlessness, liver enlargement, mucosal bleeding, and persistent vomiting.

CRITICAL PHASE

The critical phase of dengue begins at defervescence and typically lasts 24–48 hours. Most patients improve clinically during this phase, but those with substantial plasma leak (resulting from marked increase in vascular permeability) progress to severe dengue. Patients with substantial plasma leak can develop ascites or pleural effusions, hemoconcentration, and hypoproteinemia. Physiologic compensatory mechanisms narrow the pulse pressure as diastolic blood pressure increases, initially maintaining adequate circulation; patients might appear well despite early signs of shock.

Once hypotension develops, however, systolic blood pressure rapidly declines, and irreversible shock and death can ensue despite resuscitation efforts. Especially in cases of prolonged shock, patients can develop severe hemorrhagic manifestations, including hematemesis, melena, or menorrhagia. Uncommon manifestations during this phase include encephalitis, hepatitis, myocarditis, and pancreatitis. Laboratory findings commonly include elevated aspartate aminotransferase and alanine aminotransferase, hyponatremia,

leukopenia, lymphopenia, thrombocytopenia, and a normal erythrocyte sedimentation rate.

CONVALESCENT PHASE

As plasma leakage subsides, patients enter the convalescent phase and well-being improves; extravasated intravenous fluids and abdominal and pleural effusions are reabsorbed, hemodynamic status stabilizes (although bradycardia could manifest), and diuresis ensues. The patient's hematocrit stabilizes (or falls because of the dilutional effect of the reabsorbed fluid), and the white cell count usually starts to rise, after which the platelet count recovers. The convalescent phase rash might desquamate and be pruritic.

Dengue in Pregnancy

Data are limited on health outcomes of dengue in pregnancy and effects of maternal infection on the developing fetus. Perinatal transmission can occur, and peripartum maternal infection can increase the likelihood of symptomatic infection in the newborn. Signs and symptoms in perinatally infected neonates typically present during the first week of life and include ascites or pleural effusions, fever, hemorrhagic manifestations, hypotension, and thrombocytopenia. Placental transfer of maternal IgG against DENV from a previous maternal infection might increase risk for severe dengue among infants infected at 6–12 months of age when the protective effect of antibodies wanes.

DIAGNOSIS

Dengue is a nationally notifiable disease in the United States; report all suspected cases to the state or local health department. Consider dengue in the differential diagnosis of patients who develop onset of symptoms ≤2 weeks after returning from an endemic area. For patients presenting ≤7 days after fever onset, diagnostic testing should include a nucleic acid amplification test for DENV and IgM (Figure 5-01). For patients presenting >7 days after fever onset, IgM testing is recommended. In the United States, both IgM ELISA and real-time reverse transcription PCR (RT-PCR) are approved as in vitro diagnostic tests.

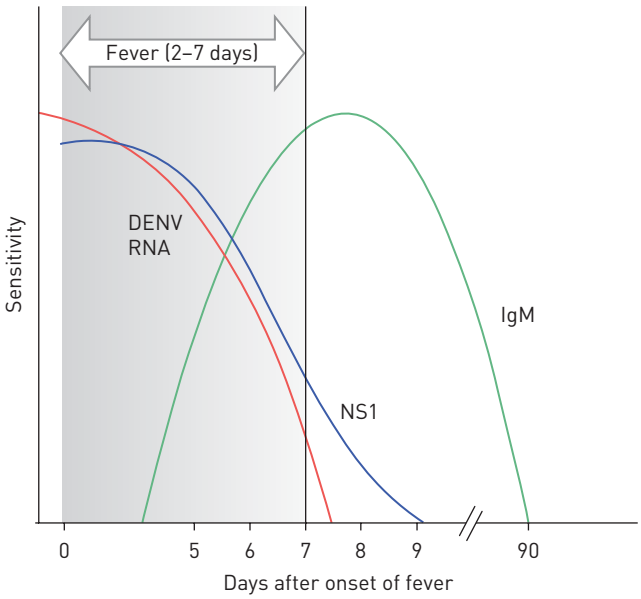


FIGURE 5-01 Relative sensitivity of detection of dengue virus nucleic acid, antigen, and IgM

Abbreviations: DENV, dengue virus; NS1, nonstructural protein 1

DENV RNA and NS1 are detectable during the first week of illness. DENV IgM is detectable starting ≈5 days after illness onset. Although most cases only have detectable DENV IgM for 14–20 days after illness onset, in some cases IgM might be detectable for up to 90 days. Routine testing of DENV IgG with a single sample is not useful in identifying patients with dengue.

Presence of virus by RT-PCR or DENV nonstructural protein 1 (NS1) antigen in a single diagnostic specimen is considered laboratory confirmation of dengue in patients with a compatible clinical and travel history. IgM in a single serum sample suggests a probable recent dengue infection. If a patient's travel history includes locations where other potentially cross-reactive flaviviruses circulate, perform both molecular and serologic diagnostic testing to detect DENV and other flaviviruses.

ELISA IgG in a single serum sample is not useful for routine diagnostic testing because IgG remains detectable for life after infection. In addition, people infected with or vaccinated against other flaviviruses (e.g., Japanese encephalitis, yellow fever) might produce cross-reactive flavivirus antibodies, yielding false-positive serologic dengue diagnostic test results.

Molecular and serologic DENV diagnostic testing are available from several commercial reference diagnostic laboratories, state public health laboratories, and the Centers for Disease Control and Prevention (CDC)'s Dengue Branch (www.cdc.gov/Dengue/clinicalLab/index.html). Clinicians can obtain consultation on dengue diagnostic testing from CDC at 787-706-2399 or by emailing dengue@cdc.gov.

TREATMENT

No specific antiviral agents exist for dengue. Depending on the clinical manifestations, patients might need only ambulatory care or might require hospitalization. Advise ambulatory patients to stay well hydrated and to avoid medications with anticoagulant properties, including aspirin (acetylsalicylic acid), aspirin-containing drugs, and other nonsteroidal anti-inflammatory drugs (e.g., ibuprofen). To control fever, advise patients to use acetaminophen and tepid sponge baths. Caution febrile patients to avoid mosquito bites to reduce risk for further community transmission.

Patients who develop severe dengue require hospitalization and close observation; monitoring in an intensive care unit might be required. Intravenous fluid therapy is the mainstay of treatment when plasma leakage is recognized. Prophylactic platelet transfusions in dengue patients are not beneficial and can contribute to fluid overload. Similarly, administration of corticosteroids has no demonstrated benefit and is potentially harmful. Avoid use of corticosteroids except in cases of autoimmune-related complications. CDC has additional dengue case management recommendations, available from www.cdc.gov/dengue/resources/DengueCheatSheet_ENG-P.pdf.

PREVENTION

In June 2021, the Advisory Committee on Immunization Practices (ACIP) recommended Dengvaxia for children aged 9–16 years with laboratory-confirmed previous dengue infection who are living in areas of the United States where dengue is endemic. These areas include the US territories of American Samoa, Puerto Rico, and the US Virgin Islands, and freely associated states including the Federated States of Micronesia, the Republic of Marshall Islands, and the Republic of Palau.

Dengvaxia is not approved for use in US travelers who are visiting but not living in areas where dengue is endemic. In people who have not already been infected with DENV, Dengvaxia can increase the risk for severe illness and hospitalization if the person gets dengue after vaccination. Serodiagnostic tests with acceptable performance (≥75% sensitivity and ≥98% specificity) recommended by health authorities are available to test people for evidence of previous dengue. Only people who test positive for previous DENV infection or who have other laboratory-confirmed evidence of a previous DENV infection are eligible for vaccination with Dengvaxia. Two other dengue vaccines are currently undergoing phase 3 clinical trials.

No specific medication is available to prevent dengue. Risk increases with duration of travel and disease incidence in the travel destination (e.g., during local epidemics or the rainy season). Travelers going to the tropics for any length of time should take steps to prevent mosquito bites by using the preventive measures listed below and in Sec. 4, Ch. 6, Mosquitoes, Ticks & Other Arthropods:

- Select accommodations with well-screened windows and doors or air conditioning, when possible. *Aedes* mosquitoes typically live indoors and often are found in dark, cool

places (e.g., in closets, under beds, behind curtains, in bathrooms, on porches).

- Wear clothing that covers the arms and legs, especially during the early morning and late afternoon, when risk of being bitten by *Aedes* species mosquitoes is greatest.
- Use insect repellent.
- For longer-term travelers, empty and clean or cover any standing water that can be a mosquito-breeding site in the local residence (e.g., water storage tanks, flowerpots).

CDC website: www.cdc.gov/dengue

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HAND, FOOT & MOUTH DISEASE

Eileen Yee

INFECTIOUS AGENT: Nonpolio enteroviruses	
ENDEMICITY	Worldwide, with outbreaks in the Asia-Pacific region
TRAVELERS CATEGORIES AT GREATEST RISK FOR EXPOSURE & INFECTION	Expatriates with children attending nursery school, daycare, elementary school Travelers with young children
PREVENTION METHODS	Practice hand hygiene Avoid close contact with infected people EV-A71 vaccine (licensed only in China)
DIAGNOSTIC SUPPORT	A clinical laboratory certified in moderate complexity testing; state health department; or CDC Polio and Picornavirus Laboratory (picornalab@cdc.gov)

INFECTIOUS AGENT

Hand, foot, and mouth disease (HFMD) is caused by nonpolio enteroviruses, a genus of the *Picornaviridae* family of nonenveloped RNA viruses (e.g., coxsackievirus A6, coxsackievirus A16, enterovirus A71). Enteroviruses that cause widespread outbreaks of HFMD worldwide can vary by type and region. In the Asia-Pacific region, enterovirus A71 (EV-A71) is the predominant etiologic agent, while in Europe and the United States, coxsackievirus viruses often are implicated in HFMD cases and outbreaks.

TRANSMISSION

Transmission occurs by direct person-to-person contact with the saliva, nose and throat secretions, vesicle fluid, or stool of an infected person and through contact with contaminated surfaces and objects (e.g., common diapering areas, shared toys, eating utensils).

EPIDEMIOLOGY

HFMD is a common infection among children worldwide and spreads quickly, causing large outbreaks that can lead to nursery, daycare, and school closures. Outbreaks often occur during summer and early fall in Australia and the United States, but seasonal patterns in the Asia-Pacific region can vary between climate zones. In the temperate climates, cases tend to peak during the early summer, whereas in tropical climates, including Hong Kong and Taiwan, outbreaks usually occur in late spring and fall.

Outbreaks also can happen sporadically throughout the year in other countries (e.g., Malaysia, Singapore, Thailand, Vietnam). Children <5 years old are most susceptible, but adults and adolescents also can become ill with HFMD. People traveling with young children should be aware of HFMD and any local outbreaks that might occur at their destinations and pay close attention to recommended preventive measures.

CLINICAL PRESENTATION

Incubation period is 3–6 days, and illness usually is self-limited, with recovery within 7–10 days. Patients usually present with fever and malaise; then sore throat and painful vesicles (herpangina) appear in the mouth, involving the buccal mucosa, tongue, or hard palate, and a peripheral rash, usually papulovesicular, appears on the hands (palms), feet (soles), or less often on the buttocks, genitals, elbows, and knees.

In rare cases, patients can develop brainstem encephalitis, aseptic meningitis, myocarditis, or pulmonary edema and can die from complications. Additionally, HFMD can have an atypical presentation, often in adults, beginning with a rash or lesion that enlarges and coalesces to form bullae; a thorough travel history or history of recent exposure to others with the infection is critical to making the diagnosis. Onychomadesis (shedding of the nails) and desquamation of the palms or soles can occur during convalescence.

DIAGNOSIS

Diagnosis is usually clinical, but confirmatory laboratory tests using reverse transcription PCR (RT-PCR) assays are available and performed for atypical or severe cases. Preferred samples for testing include vesicle fluid, throat or buccal swabs, or stool. Many commercial or reference laboratories can perform RT-PCR assays to detect enterovirus RNA.

The Centers for Disease Control and Prevention (CDC) Picornavirus Laboratory within the Division of Viral Diseases routinely performs qualitative pan-enterovirus molecular testing, after which the laboratory performs sequencing for enterovirus typing in consultation with state or local health departments in the United States. CDC can test nasopharyngeal or oropharyngeal swabs, nasal wash or aspirate samples, stool samples, rectal swabs, cerebrospinal fluid, serum, and tissue biopsy or autopsy specimens.

International laboratories seeking consultation can email the CDC laboratory, picornalab@cdc.gov. For information about specimen collection, storage, and shipping address, refer to CDC's Non-Polio Enterovirus website, www.cdc.gov/non-polio-enterovirus/lab-testing/index.html,

and email the laboratory (picornalab@cdc.gov) prior to shipping.

TREATMENT

HFMD treatment mainly involves supportive care to treat symptoms of fever or pain caused by mouth sores, and to prevent dehydration, especially in young children.

PREVENTION

Travelers can prevent HFMD by avoiding close contact (e.g., hugging, kissing, sharing food utensils or drinking cups) with infected people. Travelers also should maintain good hand hygiene (see www.cdc.gov/handwashing), and clean and disinfect potentially contaminated surfaces and soiled items, including diapering and child potty areas, doorknobs, eating areas, and toys. People traveling with infants and young children and those affected by local school or daycare outbreaks especially should follow these precautions.

Travelers should use frequent handwashing with soap and water rather than hand sanitizers, because alcohol-based sanitizers might be less effective against nonenveloped enteroviruses. Travelers should choose a US Environmental Protection Agency–registered disinfecting product or a comparable product that kills nonenveloped viruses (e.g., norovirus). The public health response to large outbreaks of HFMD, particularly in Asia, includes isolation of cases, social distancing, and closures of schools and daycare centers.

Licensed EV-A71 vaccines to prevent severe HFMD have been approved in China since 2015. This vaccine might not provide cross-protection against other enterovirus serotypes, however. The US Food and Drug Administration has not approved any enterovirus vaccines for use in the United States.

CDC website: www.cdc.gov/hand-foot-mouth

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HENIPAVIRUS INFECTIONS

Trevor Shoemaker, Mary Joung Choi

INFECTIOUS AGENT: *Henipavirus* spp.	
ENDEMICITY	Southeast Asia, Bangladesh, India (Nipah virus) Australia (Hendra virus) China (Langya virus)
TRAVELER CATEGORIES AT GREATEST RISK FOR EXPOSURE & INFECTION	Travelers exposed to infected animals (e.g., bats, pigs) or their body fluids Travelers who eat foods (e.g., fallen fruit, palm sap) contaminated by body fluids of infected animals Health care workers treating infected patients
PREVENTION METHODS	Avoid bat roosting areas Avoid unprotected contact with blood, fluids, tissues of potentially infected animals (e.g., sick or dead bats, pigs) Follow safe food precautions: avoid cooking, eating, handling raw or undercooked meat or animal products; avoid eating fallen fruit, raw date palm sap Use standard barrier precautions and personal protective equipment in medical settings
DIAGNOSTIC SUPPORT	State health department; or call the CDC Emergency Operations Center at 770-488-7100.

INFECTIOUS AGENT

Enveloped, single-stranded RNA viruses in the genus *Henipavirus*, family Paramyxovirus can infect humans. Of the 6 identified *Henipavirus* species, Hendra virus and Nipah virus are highly virulent emerging pathogens that cause outbreaks in humans and are associated with high case-fatality ratios. In August 2022, a new *Henipavirus* species (Langya virus, LayV) was identified among febrile human cases in eastern China. Phylogenetic analysis of Langya shows it to be most closely related to Mojiang virus. Mojiang virus, along with two other *Henipavirus* species—Cedar virus and Ghanaian bat virus—are not known to cause human disease.

TRANSMISSION

Pteropid fruit bats (flying foxes) are *Henipavirus* reservoir hosts. Hendra virus is transmitted to humans through direct contact with infected horses or body fluids or tissues of infected horses; horses are infected through exposure to bat urine. Hendra virus is not transmitted person-to-person or directly from bats to humans.

Nipah virus is transmitted through contact with infected pigs or bats; consumption of date palm sap or fallen fruit contaminated with bat excretions is another route of exposure. Person-to-person transmission of Nipah virus has been reported through close contact with infected people, including respiratory droplets. Nipah transmission is facilitated by cultural and health care practices in which friends and family members care for ill patients.

Initial sampling of small wild mammals detected Langya virus predominantly in shrews (71 of 262 [26%] sampled) belonging to the species *Crocidura lasiura* and *Crocidura shantungensis*. More research is needed to definitively determine the natural animal reservoir(s), susceptible species, and routes of transmission to humans. Preliminary evidence is not suggestive of person-to-person transmission of Langya virus.

EPIDEMIOLOGY

To date, no *Henipavirus* infections have been reported among travelers. Hendra virus outbreaks in Australia are caused by exposure to sick or dead infected horses. Since 1994, Hendra virus has been reported nearly annually in the eastern states of Australia. Nipah virus outbreaks in humans were reported in 1999 in Malaysia and Singapore and are reported almost annually in Bangladesh and India, typically resulting from direct or indirect bat exposure, but also less commonly through person-to-person spread or exposure to sick or dead pigs. Pteropid bats can be found throughout the tropics and subtropics, however, and henipaviruses have been isolated from these animals in East Africa, Central and South America, Asia, and Oceania.

As of August 2022, researchers have identified a total of 35 non-fatal human cases of Langya virus infection. Further research is needed to determine the geographic distribution of this newly identified virus.

CLINICAL PRESENTATION

Incubation period is ≈5–16 days (and rarely ≤2 months). Both Hendra and Nipah virus infections can cause a severe influenza-like illness with dizziness, headache, fever, and myalgias. The disease can progress to severe encephalitis with confusion, abnormal reflexes, seizures, and coma; respiratory symptoms also might be present. Relapsing or late-onset encephalitis can occur months or years after acute illness. The case-fatality ratio of Hendra virus is 57%; among 7 known human cases, 4 were fatal. Case-fatality ratios for Nipah virus infection are 40%–70% but have been 100% in some human outbreaks.

Most of the 35 known cases of Langya virus infection have reported non-specific clinical symptoms (e.g., anorexia, cough, fatigue, fever, headache, myalgia, nausea, vomiting). No deaths due to Langya virus have yet been identified.

DIAGNOSIS

Laboratory diagnosis is made by using a combination of tests, including ELISA of serum or cerebrospinal fluid (CSF); reverse transcription PCR of serum, CSF, or throat swabs; and virus isolation from CSF or throat swabs. The Centers for Disease Control and Prevention (CDC) can test specimens from patients suspected to be infected with a *Henipavirus*. Prior to submitting specimens to CDC, contact the state or local health department to arrange a clinical consultation, or call the CDC Emergency Operations Center at 770-488-7100.

TREATMENT

No specific antiviral treatment is available for *Henipavirus* infections. Therapy consists of supportive care and management of complications. Ribavirin has shown in vitro effectiveness, but its clinical usefulness is unknown. A monoclonal serotherapy has been proposed for Hendra in Australia.

PREVENTION

Travelers should avoid contact with bats, sick horses and pigs, and their excretions. Travelers should not consume fallen fruit, raw date palm sap, or products made from raw sap. A Hendra virus vaccine for horses has been licensed in Australia and has potential future benefit to prevent *Henipavirus* infections in humans, but no licensed vaccines for humans currently are available.

CDC websites: www.cdc.gov/vhf/hendra/index.html; www.cdc.gov/vhf/nipah/index.html

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HEPATITIS A

Noele Nelson, Mark Weng

INFECTIOUS AGENT: Hepatitis A virus	
ENDEMICITY	High endemicity: parts of Africa and Asia Intermediate endemicity: parts of Asia; also, Central and South America, and eastern Europe Low endemicity: Western Europe, United States
TRAVELER CATEGORIES AT GREATEST RISK FOR EXPOSURE & INFECTION	Travelers not vaccinated against Hepatitis A Travelers going to areas with inadequate sanitation and limited access to clean water
PREVENTION METHODS	Follow safe food and water precautions Hepatitis A is a vaccine-preventable disease
DIAGNOSTIC SUPPORT	A clinical laboratory certified in moderate complexity testing; state health department; or for testing at CDC www.cdc.gov/laboratory/specimen-submission/list.html

INFECTIOUS AGENT

Hepatitis A virus (HAV) is a nonenveloped RNA virus classified as a picornavirus.

TRANSMISSION

HAV is transmitted through direct person-to-person contact (fecal–oral transmission) or through ingestion of contaminated food or water. HAV can survive in the environment for prolonged periods at low pH. Freezing does not inactivate the virus, and HAV can be transmitted through ice and frozen foods. Heat inactivation must occur at temperatures >185°F (>85°C) for 1 minute. HAV can be transmitted from raw or inadequately cooked foods contaminated during growing, processing, or distribution, and through contamination by an infected food handler. Recent large-scale outbreaks have been caused by common-source food exposures (e.g., frozen berries, fresh fruit and vegetables, seafood) and through person-to-person spread among people experiencing homelessness and people who use injection and non-injection drugs.

Infected people shed HAV in their feces. People are most infectious 1–2 weeks before the onset of clinical signs and symptoms of jaundice or elevation of liver enzymes, when virus concentration is greatest in the stool and blood. Viral excretion and the risk for transmission diminish rapidly after liver dysfunction or symptoms appear, which is concurrent with the appearance of circulating antibodies to HAV. Infants and children can shed virus for up to 6 months after infection.

EPIDEMIOLOGY

Hepatitis A is among the most common vaccine-preventable infections acquired during travel. Cases of travel-related hepatitis A can occur in travelers to developed and developing countries and who have standard tourist accommodations, eating behaviors, and itineraries. Risk is greatest for those who live in or visit rural areas, trek in backcountry areas, or frequently eat or drink in settings with poor sanitation. Common-source food exposures are increasingly recognized as a risk for hepatitis A, and sporadic outbreaks have been reported in Australia, Europe, North America, and other regions with low levels of endemic transmission. Multinational hepatitis A outbreaks among men who have sex with men (MSM) have been described, including, since 2016, among MSM who travel to areas in

European Union countries with ongoing HAV transmission among MSM.

Hepatitis A is common in areas with inadequate sanitation and limited access to clean water. In highly endemic areas (e.g., parts of Africa and Asia), a large proportion of adults in the population are infected as children, are immune to HAV, and epidemics are uncommon. In areas of intermediate endemicity (e.g., Central and South America, eastern Europe, parts of Asia), childhood transmission is less frequent, more adolescents and adults are susceptible to infection, and outbreaks are more likely. In areas of low endemicity (e.g., western Europe, the United States), infection is less common, but disease occurs among people in high-risk groups and as communitywide outbreaks. Determining HAV endemicity globally is complex, however, and limited data are available on subpopulation variation of HAV antibody seroprevalence within regions (Map 5-06).

In the United States, the most frequently identified risk factors for HAV infection vary from year to year. The Advisory Committee on Immunization Practices (ACIP) recommends routine hepatitis A vaccination for all children, and vaccination for adults at increased risk for HAV infection or at increased risk for severe disease from HAV infection.

CLINICAL PRESENTATION

The incubation period averages 28 days (range 15–50 days). Infection can range from mild illness lasting 1–2 weeks to severely disabling disease lasting several months. Clinical manifestations include abrupt onset of fever, malaise, anorexia, nausea, and abdominal discomfort, followed by jaundice within a few days. The likelihood of having symptoms with HAV infection is related to the age of the infected person. In children aged <6 years, most (70%) infections are asymptomatic; jaundice is uncommon in symptomatic young children. Among older children and adults, the illness usually lasts <2 months, but ≈10%–15% of infected people have prolonged or relapsing symptoms over 6–9 months.

Severe hepatic and extrahepatic complications, including fulminant hepatitis and liver failure, are rare but more common in older adults and people with underlying liver disease. Chronic infection does not occur. The overall case-fatality ratio varies according to the population affected.

DIAGNOSIS

Hepatitis A cannot be differentiated from other types of viral hepatitis based on clinical or epidemiologic features. Diagnosis requires a positive test for HAV IgM in serum, which is detectable 2 weeks before the onset of symptoms to ≈6 months after symptom onset.

Serologic total HAV IgG and IgM tests are available commercially. The combination of a positive total HAV result and a negative HAV IgM result indicates past infection or vaccination, and hence immunity. Presence of serum HAV IgM usually indicates current or recent infection and does not distinguish between immunity derived from infection versus vaccination. Hepatitis A is a nationally notifiable disease.

Information on how to obtain HAV diagnostic support from the Centers for Disease Control and Prevention (CDC), including contact information, which samples to send, and how to send them is available at www.cdc.gov/laboratory/specimen-submission/list.html. For research use and for outbreak investigations, select "Hepatitis A NAT and Genotyping." For testing regulated by Clinical Laboratory Improvement Amendments, select "Hepatitis A Serology."

TREATMENT

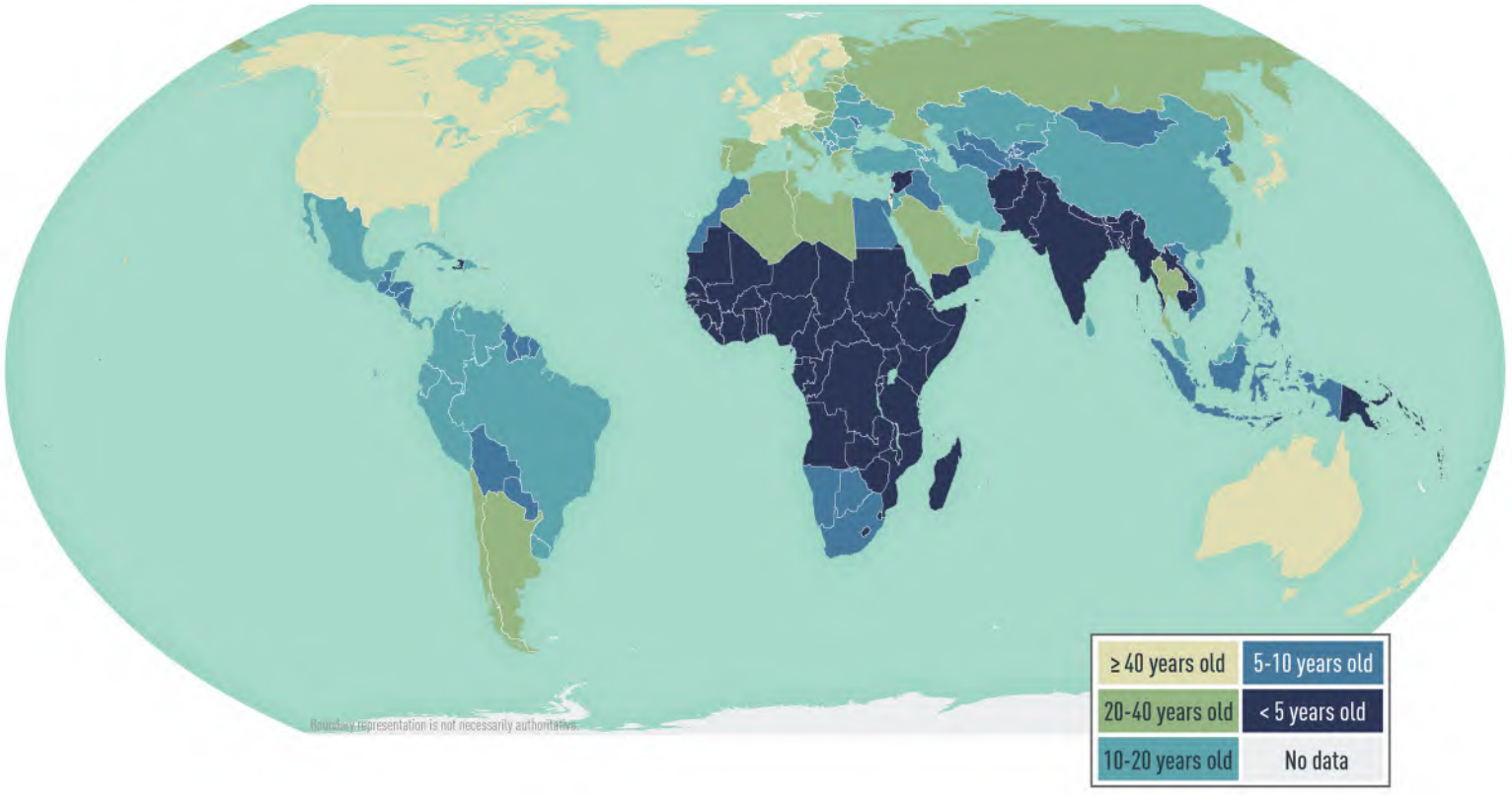
Provide supportive care.

PREVENTION

Travelers can prevent HAV through vaccination or immune globulin (IG), practicing food and water precautions, and maintaining standards of hygiene and sanitation.

Vaccine

Two single-antigen hepatitis A vaccines, Havrix (GlaxoSmithKline) and Vaqta (Merck), are approved for people ≥12 months of age in a 2-dose series. A combined hepatitis A and hepatitis B vaccine (Twinrix, GlaxoSmithKline) is approved for people ≥18 years of age in the United States (Table 5-10). The immunogenicity of the combination vaccine is equivalent to that of the single-antigen hepatitis A and hepatitis B vaccines when



MAP 5-06 Estimated age at midpoint of population immunity (AMPI) to hepatitis A, by country

Adapted from Jacobsen KH. Globalization and the changing epidemiology of hepatitis A virus. Cold Spring Harb Perspect Med. 2018;8(10).a031716. AMPI is the youngest age at which half of the birth cohort has serologic evidence of prior exposure to hepatitis A virus. As the AMPI increases, the endemicity level of hepatitis A generally decreases.

Table 5-10 Vaccines used to prevent hepatitis A virus (HAV) infection

VACCINE	TRADE NAME (MANUFACTURER)	AGE IN YEARS	DOSE / ROUTE	SCHEDULE	BOOSTER
Hepatitis A vaccine, inactivated	Havrix (GlaxoSmithKline)	1–18	0.5 mL (720 ELU) IM	DOSE 1: 1–18 years old DOSE 2: 6–12 months after DOSE 1	None
		≥19	1 mL (1,440 ELU) IM	DOSE 1: ≥19 years old DOSE 2: 6–12 months after DOSE 1	None
Hepatitis A vaccine, inactivated	Vaqta (Merck)	1–18	0.5 mL (25 U) IM	DOSE 1: 1–18 years old DOSE 2: 6–18 months after DOSE 1	None
		≥19	1 mL (50 U) IM	DOSE 1: ≥19 years old DOSE 2: 6–18 months after DOSE 1	None
Combined hepatitis A and hepatitis B vaccine[1]	Twinrix (GlaxoSmithKline)	≥18	1 mL (720 ELU HAV + 20 µg HBsAg) IM	**STANDARD** DOSE 1: ≥18 years old DOSE 2: 1 month after DOSE 1 DOSE 3: 6 months after DOSE 1	None
		≥18	1 mL (720 ELU HAV + 20 µg HBsAg) IM	**ACCELERATED** DOSE 1: ≥18 years old DOSE 2: 7 days after DOSE 1 DOSE 3: 21–30 days after DOSE 1	12 months after DOSE 1

Abbreviations: ELU, ELISA units inactivated HAV; HBsAg, hepatitis B surface antigen; IM, intramuscular; U, units of HAV antigen
[1]Combined hepatitis A and hepatitis B vaccine (Twinrix) should not be used for postexposure prophylaxis.

tested after completion of the recommended schedule. Postvaccination testing for serologic response is not indicated for healthy people, but is recommended for people whose subsequent clinical management depends on knowledge of their immune status and people for whom revaccination might be indicated (e.g., people with HIV and other immunocompromised people).

INDICATIONS FOR USE

All susceptible people traveling for any purpose, frequency, or duration to countries with high or intermediate hepatitis A endemicity should be vaccinated or receive IG before departure. Furthermore, prevalence patterns of HAV infection vary among regions within a country; in some areas, limited data result in uncertainty in endemicity maps, especially in low- and middle-income countries. Countries with decreasing prevalence of HAV infection have growing numbers of susceptible people and are at risk for hepatitis A outbreaks. In recent years, large hepatitis A outbreaks have been reported in high-income countries among people exposed to imported HAV-contaminated food, among MSM, among people who use drugs, and among people experiencing

homelessness. Considering the complexity of interpreting hepatitis A risk maps and potential risk for foodborne hepatitis A in low-endemicity countries, some experts advise people traveling outside the United States to consider hepatitis A vaccination regardless of destination.

Vaccination is also recommended for unvaccinated household members and other people (e.g., regular babysitters) who anticipate close personal contact with an international adoptee from a high- or intermediate-endemicity country ≤60 days after the child's arrival in the United States. The first dose of the 2-dose hepatitis A vaccine series should be administered as soon as adoption is planned, ideally ≥2 weeks before the arrival of the child (see Sec. 7, Ch. 5, International Adoption).

ADMINISTRATION

All susceptible people (i.e., those unvaccinated or never infected) traveling to or working in countries with high or intermediate hepatitis A endemicity are at risk for HAV infection. Before departure, these travelers should be vaccinated, or receive IG if they are too young or have contraindications for hepatitis A vaccination. For travelers already partially vaccinated (i.e., did not receive a full series of hepatitis A-containing vaccine), administer a dose prior to travel according to the routine immunization schedule.

INFANTS YOUNGER THAN 6 MONTHS OLD

Infants aged <6 months and travelers allergic to a vaccine component, or who elect not to receive vaccine, should receive IG, which provides effective temporary protection against HAV infection. For travel duration ≤1 month, the manufacturer recommends 1 dose of IG at 0.1 mL/kg; for travel >1 month but ≤2 months, 1 dose of IG at 0.2 mL/kg is recommended. A 0.2 mL/kg dose of IG should be repeated every 2 months for the duration of travel if the traveler remains in a high-risk setting; but encourage hepatitis A vaccination if not contraindicated.

INFANTS 6–11 MONTHS OLD

Administer hepatitis A vaccine to infants aged 6–11 months traveling outside the United States when protection against hepatitis A is recommended. Although hepatitis A vaccine is considered safe and immunogenic in infants, hepatitis A vaccine doses administered before 12 months of age could result in a suboptimal immune response, particularly in infants with passively acquired maternal antibody. Therefore, hepatitis A vaccine doses administered at <12 months of age are not considered to provide long-term protection, and the 2-dose hepatitis A vaccine series should be initiated at age 12 months according to the routine immunization schedule.

ADULTS OVER 40 YEARS OLD

Adults aged >40 years, immunocompromised people, and people with chronic liver disease should receive a single dose of hepatitis A vaccine as soon as travel is considered. People planning travel in <2 weeks can receive IG (0.1 mL/kg) in addition to vaccine at a separate injection site (i.e., separate limbs) based on provider risk assessment, including considerations of the traveler's age, immune status, underlying conditions, risk for exposure, and availability of IG. The hepatitis A vaccine series should be completed according to the routine immunization schedule.

TWINRIX

An alternative accelerated 4-dose schedule is available for Twinrix; doses can be administered at 0, 7, and 21–30 days, then a dose at 12 months. For more details, refer to NP Nelson et al. in the bibliography of this chapter. Although vaccinating an immune traveler is not contraindicated and does not increase the risk for adverse effects, screening for total HAV antibodies before travel can be useful in some circumstances to determine susceptibility and avoid unnecessary vaccination.

SAFETY & ADVERSE REACTIONS

Based on passive surveillance, the most frequently reported adverse events after single-antigen hepatitis A vaccination were fever, injection site reactions, and rash. The most frequently reported adverse events after Twinrix vaccination were dizziness, fever, headache, and injection site reactions. These findings are similar to those for other inactivated vaccines routinely administered among similar age groups.

PRECAUTIONS & CONTRAINDICATIONS

Hepatitis A vaccines should not be administered to travelers with a history of hypersensitivity to any vaccine component, including neomycin. Twinrix should not be administered to people with a history of hypersensitivity to yeast. The tip caps of prefilled syringes of Havrix and Twinrix and the vial stopper, syringe plunger stopper, and tip caps of Vaqta might contain dry natural rubber, which can cause allergic reactions in latex-sensitive people. Because hepatitis A vaccine consists of inactivated virus, and hepatitis B vaccine consists of a recombinant protein, no special precautions are needed for vaccination of immunocompromised travelers with single-antigen vaccines or Twinrix. Check precautions and contraindications before administering IG.

PREGNANCY

The ACIP recommends vaccinating selected groups of pregnant people if they have not been vaccinated previously (see www.cdc.gov/vaccines/schedules/hcp/imz/adult-conditions.html). These include people (e.g., travelers) at increased risk for HAV infection during pregnancy as well as those at risk for having a severe outcome from HAV infection (e.g., those with chronic liver disease or HIV).

OTHER CONSIDERATIONS

The best approach is to administer hepatitis A vaccine according to the routine immunization schedule; however, an interrupted series does not need to be restarted. Over 90% of vaccinated people develop levels of antibodies to HAV that correlate with protection 1 month after the first dose of hepatitis A vaccines. Given their similar immunogenicity, a series that has been started with one brand of hepatitis A single-antigen vaccine can be completed with another brand of single-antigen vaccine. For children and adults who complete a primary series of hepatitis A-containing vaccine, booster doses of vaccine are not recommended. Measles-mumps-rubella and varicella vaccines should not be administered <6 months after IG administration.

POSTEXPOSURE PROPHYLAXIS

Travelers exposed to HAV who are asymptomatic and who have not received hepatitis A vaccine should receive 1 dose of single-antigen hepatitis A vaccine or IG (0.1 mL/kg) as soon as possible, ideally ≤2 weeks following exposure. The efficacy of IG or vaccine when administered >2 weeks after exposure has not been established.

Hepatitis A vaccines should be administered as postexposure prophylaxis (PEP) for all people aged ≥12 months who have been exposed to HAV ≤2 weeks and have not previously completed the hepatitis A vaccine series. In addition to hepatitis A vaccine, administer IG (0.1 mL/kg) to people who are immunocompromised or who have chronic liver disease, and to people aged >40 years, depending on the risk assessment, which should include consideration of the exposed person's age, immune status, underlying conditions, exposure type (risk of transmission), and availability of IG.

Administer PEP as soon as possible. If giving both hepatitis A vaccine and IG (0.1 mL/kg), administer both simultaneously in different anatomic sites (i.e., separate limbs). If only 1 product is available, administer it as soon as possible and have the exposed person return for the other product if it becomes available ≤2 weeks following exposure. When the dose of hepatitis A vaccine given postexposure is the first dose the exposed person has ever received, administer a second dose 6 months after the first for long-term immunity; however, the second dose is not necessary for PEP.

Infants <12 months of age and people who are allergic to a vaccine component or who elect not to receive vaccine should receive a single dose of IG (0.1 mL/kg) as soon as possible ≤2 weeks of exposure.

Do not use Twinrix for PEP. Twinrix contains half of the single-antigen hepatitis A adult dose, and no data are available on the efficacy of combination vaccine for prophylaxis after exposure to HAV.

CDC website: www.cdc.gov/hepatitis/HAV

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HEPATITIS B

Aaron Harris

5

INFECTIOUS AGENT: Hepatitis B virus	
ENDEMICITY	Worldwide High prevalence in Africa and the Western Pacific
TRAVELER CATEGORIES AT GREATEST RISK FOR EXPOSURE & INFECTION	Expatriates Long-term development workers Medical tourists Missionaries and humanitarian aid workers Travelers not vaccinated against hepatitis B
PREVENTION METHODS	Ensure sterile medical and dental techniques Use safe injection practices Hepatitis B is a vaccine-preventable disease
DIAGNOSTIC SUPPORT	A clinical laboratory certified in moderate complexity testing; state health department; or contact CDC (www.cdc.gov/laboratory/specimen-submission/list.html). More information is available at www.cdc.gov/hepatitis/hbv/testingchronic.htm.

INFECTIOUS AGENT

Hepatitis B virus (HBV) is a small, circular, partially double-stranded DNA virus in the family *Hepadnaviridae*.

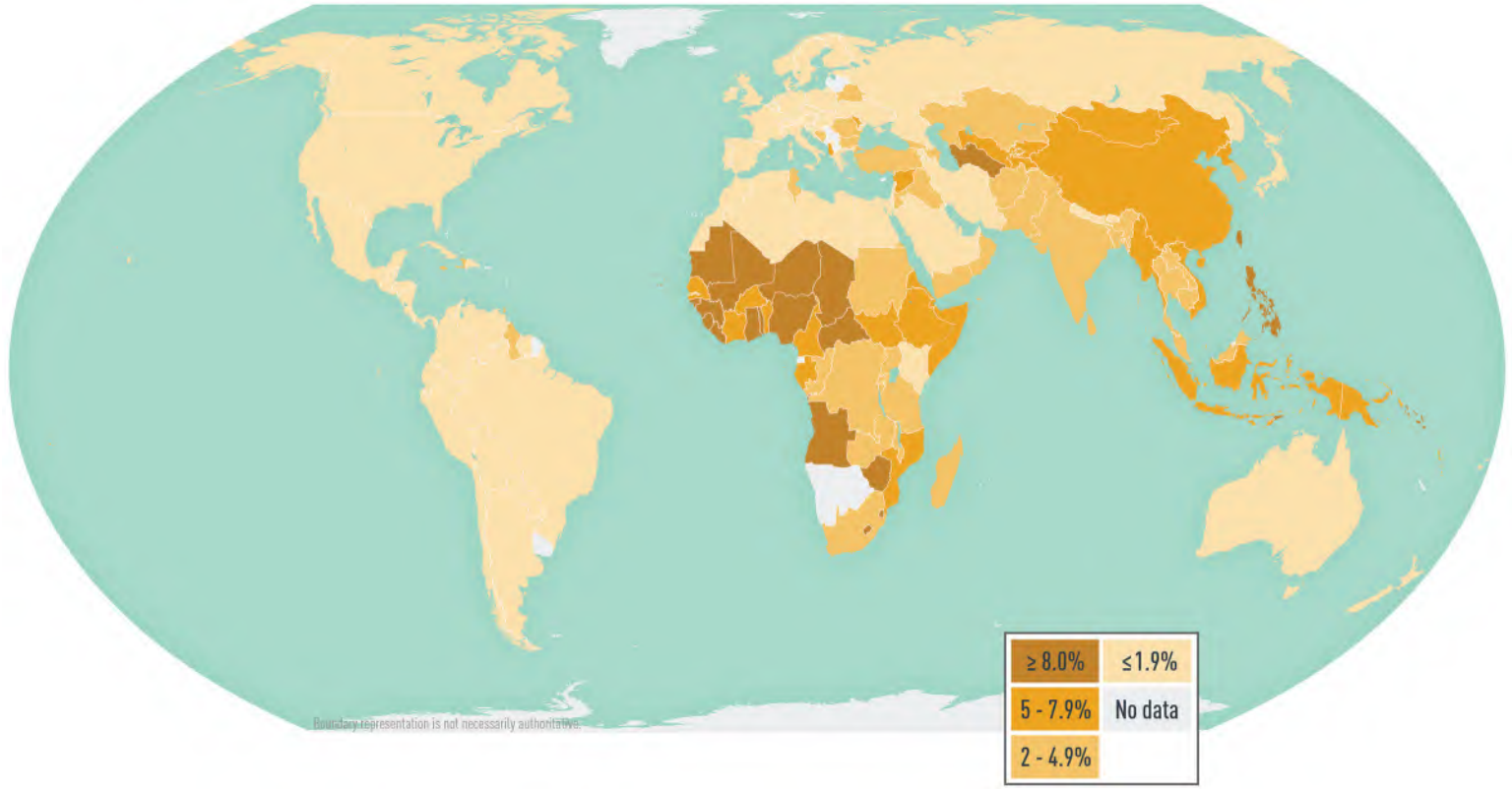
TRANSMISSION

HBV is transmitted by contact with contaminated blood, blood products, and other body fluids (e.g., semen). Travelers could be exposed to HBV through poor infection control during dental or medical procedures, receipt of blood products, injection drug use, tattooing or acupuncture, or unprotected sex.

EPIDEMIOLOGY

HBV is a leading cause of chronic hepatitis, liver cirrhosis, and hepatocellular carcinoma worldwide. In 2015, an estimated 257 million people globally were living with chronic HBV infection; that year, HBV caused an estimated 887,000 deaths. HBV infections are likely underestimated, however, because accurate data are lacking from many countries (Map 5-07).

Data demonstrating the specific risk to travelers are lacking; published reports of travelers acquiring hepatitis B are rare, however, and the risk for travelers who do not have high-risk



MAP 5-07 Worldwide prevalence of hepatitis B virus infection

Disease data source: 2021 estimates of hepatitis B virus disease burden. CDA Foundation Polaris Observatory. Available from: https://cdafound.org/polaris-countries-distribution/.

behaviors or exposures is low. The risk for HBV infection might be higher in countries where the prevalence of chronic HBV infection is ≥2% (e.g., in the western Pacific and African regions); expatriates, missionaries, and long-term development workers in those regions might be at increased risk for HBV infection. All travelers should be aware of how HBV is transmitted and take measures to minimize their exposures.

CLINICAL PRESENTATION

HBV infection primarily affects the liver. Typically, the incubation period for hepatitis B is 90 days (range 60–150 days). Newly acquired acute HBV infections only cause symptoms some of the time, and signs and symptoms vary by age. Most children <5 years of age and immunosuppressed adults are asymptomatic when newly infected, whereas 30%–50% of newly infected people aged ≥5 years have signs and symptoms. When present, typical signs and symptoms of acute infection include abdominal pain, anorexia, fatigue, fever, jaundice, joint pain, malaise, nausea and vomiting, light (clay-colored) stool, and dark urine. The overall case-fatality ratio of acute hepatitis B is ≈1%.

Some acute HBV infections resolve on their own, but some develop into chronic infection. The risk for acute hepatitis B to progress to chronic HBV infection depends on the age at the time of initial infection as follows: >90% of neonates and infants, 25%–50% of children aged 1–5 years, and <5% of older children and adults. Most people with chronic HBV infection are asymptomatic and have no evidence of liver disease. Fifteen percent to 40% of people with chronic HBV infection will, however, develop liver cirrhosis, hepatocellular carcinoma, or liver failure, and 25% of chronically infected people die prematurely from these complications. People infected with HBV are susceptible to infection with hepatitis D virus; coinfection increases the risk for fulminant hepatitis and rapidly progressive liver disease.

DIAGNOSIS

Hepatitis B is a nationally notifiable disease. The clinical diagnosis of acute HBV infection is based on signs or symptoms consistent with viral hepatitis and elevated hepatic transaminases and cannot be distinguished from other causes of acute hepatitis. Serologic markers specific for hepatitis B are necessary to diagnose HBV infection and for appropriate clinical management (Table 5-11). These markers can differentiate between acute, resolving, and chronic infection.

Information on how to obtain hepatitis B diagnostic support from the Centers for Disease Control and Prevention (CDC) Infectious Diseases Laboratories, including contact information, which samples to send, and how to send samples is available at www.cdc.gov/laboratory/specimen-submission/list.html. Select Hepatitis B Genotyping for research use only, and Hepatitis B Serology and Quantitative PCR if testing regulated by Clinical Laboratory Improvement Amendments is needed.

TREATMENT

No medications are available to treat acute HBV infection; treatment is supportive. Several antiviral medications are available for people with chronic HBV infection. People with chronic HBV infection should be under the care of a health professional and receive a thorough physical examination and laboratory testing to determine the need for antiviral therapy and ongoing monitoring for hepatocellular carcinoma and liver damage. American Association for the Study of Liver Diseases (AASLD) practice guidelines for the treatment of chronic HBV infection are available at www.aasld.org/publications/practice-guidelines-0.

PREVENTION

Vaccines

INDICATIONS FOR USE

Administer Hepatitis B vaccine to all unvaccinated people traveling to areas with intermediate to high prevalence of chronic HBV infection, namely, countries with HBV surface antigen positivity prevalence ≥2% (Map 5-07). Complete vaccination information and recommendations for the United States are available at www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/hepb.html.

Table 5-11 Interpretation of serologic test results for hepatitis B virus infection[1]

CLINICAL STATE	HBsAg	TOTAL ANTI-HBs	TOTAL ANTI-HBc	ACTION
Chronic infection	Positive	Negative	Positive	Link to hepatitis B-directed care[2]
Acute infection	Positive	Negative	Positive (HBc IgM)	Link to hepatitis B-directed care[2]
Resolved infection	Negative	Positive	Positive	Counseling, reassurance
Immune (immunization)	Negative	Positive[3]	Negative	Reassurance
Susceptible (never infected and no evidence of immunization)	Negative	Negative	Negative	Vaccinate
Isolated core antibody[4]	Negative	Negative	Positive	Depends on situation

Abbreviations: HBsAg, hepatitis B surface antigen; anti-HBc, antibody to hepatitis B core antigen; anti-HBs, antibody to hepatitis B surface antigen.

[1]Adapted from Abara WE, Qaseem A, Schillie S, McMahon BJ, Harris AM. Hepatitis B vaccination, screening, and linkage to care: best practice advice from the American College of Physicians and the Centers for Disease Control and Prevention. Ann Intern Med. 2017;167(11):794–804.
[2]Hepatitis B-directed care includes a physical examination and laboratory evaluation for liver transaminase, hepatitis B virus DNA, and hepatitis B e antigen.
[3]An anti-HBs titer of ≥10 mIU/mL correlates with protection only after a documented, complete hepatitis B vaccine series.
[4]If false-positive results are suspected, repeat testing. If results are from past infection or passive transfer to infants born to HBsAg-positive mother, no specific action is needed. If results could indicate occult hepatitis B virus infection, inform patient of risks from future chemotherapy, immunosuppression, or hepatitis C virus infection antiviral therapy, and consider checking hepatitis B virus DNA.

ADMINISTRATION

Several hepatitis B vaccines are available (Table 5-12). Hepatitis B vaccines are administered either as a 2-dose series at 0 and 1 month (Heplisav-B [Dynavax Technologies Corporation]), or as a 3-dose series at 0, 1, and 6 months (Engerix-B [GlaxoSmithKline], Recombivax HB [Merck], PreHevbrio [VBI], and the combined hepatitis A and hepatitis B vaccine, Twinrix [GlaxoSmithKline]). Heplisav-B is licensed for a 2-dose schedule for adults aged ≥18 years; the second dose should be given ≥1 month after the first dose.

Engerix B and Recombivax HB have also been licensed for use according to alternative vaccination schedules. Engerix-B can be administered using a 4-dose schedule, with the first 3 doses given within 2 months and a booster at 12 months (doses at 0, 1, 2, and 12 months). Recombivax HB can be given using a 2-dose schedule for children aged 11–15 years. Twinrix can be used on an accelerated 4-dose schedule (0, 7, and 21–30 days, with a booster at 12 months) to promote long-term immunity.

Always consult the prescribing information when administering alternative schedules and formulations. Whenever feasible, use the same manufacturer's vaccines to complete the patient's vaccine series; do not, however, defer vaccination when the manufacturer of previously administered doses is unknown or when the vaccine from the same manufacturer is unavailable. The 2-dose Heplisav-B vaccine series only applies when both doses in the series consist of Heplisav-B. Series consisting of a combination of 1 dose of Heplisav-B and a vaccine from a different manufacturer should adhere to the 3-dose schedule.

Table 5-12 Hepatitis B vaccines

VACCINE	TRADE NAME (MANUFACTURER)	AGE IN YEARS	DOSE & ROUTE	SCHEDULE	BOOSTER
Hepatitis B vaccine, recombinant with novel adjuvant (1018)	Heplisav-B (Dynavax Technologies)	≥18	0.5 mL (20 µg HBsAg and 3,000 µg of 1018) IM	DOSE 1: ≥18 years old DOSE 2: 1 month after DOSE 1	None
Hepatitis B vaccine, recombinant[1]	Engerix-B (GlaxoSmithKline)	0–19	0.5 mL (10 µg HBsAg) IM	**STANDARD** DOSE 1: 0–19 years old DOSE 2: 1 month after DOSE 1 DOSE 3: 6 months after DOSE 1	None
		0–10	0.5 mL (10 µg HBsAg) IM	**ACCELERATED** DOSE 1: 0–10 years old DOSE 2: 1 month after DOSE 1 DOSE 3: 2 months after DOSE 1	12 months after DOSE 1
		11–19	1 mL (20 µg HBsAg) IM	**ACCELERATED** DOSE 1: 11–19 years old DOSE 2: 1 month after DOSE 1 DOSE 3: 2 months after DOSE 1	12 months after DOSE 1
		≥20	1 mL (20 µg HBsAg) IM	**STANDARD** DOSE 1: ≥20 years old DOSE 2: 1 month after DOSE 1 DOSE 3: 6 months after DOSE 1	None
		≥20	1 mL (20 µg HBsAg) IM	**ACCELERATED** DOSE 1: ≥20 years old DOSE 2: 1 month after DOSE 1 DOSE 3: 2 months after DOSE 1	12 months after DOSE 1
Hepatitis B vaccine, recombinant[1]	Recombivax HB (Merck)	0–19	0.5 mL (5 µg HBsAg) IM	**STANDARD** DOSE 1: 0–19 years old DOSE 2: 1 month after DOSE 1 DOSE 3: 6 months after DOSE 1	None

Table 5-12 Hepatitis B vaccines (continued)

VACCINE	TRADE NAME (MANUFACTURER)	AGE IN YEARS	DOSE & ROUTE	SCHEDULE	BOOSTER
		11–15	1 mL (10 µg HBsAg) IM	**ADOLESCENT, ACCELERATED** DOSE 1: 11–15 years old DOSE 2: 4–6 months after DOSE 1	None
		≥20	1 mL (10 µg HBsAg) IM	**STANDARD** DOSE 1: ≥20 years old DOSE 2: 1 month after DOSE 1 DOSE 3: 6 months after DOSE 1	None
Hepatitis B vaccine, recombinant[1]	PreHevbrio (VBI)	≥18	1 mL (10 µg HBsAg) IM	DOSE 1: ≥18 years old DOSE 2: 1 month after DOSE 1 DOSE 3: 6 months after DOSE 1	None
Combined hepatitis A and B vaccine	Twinrix (GlaxoSmithKline)	≥18	1 mL (720 ELU HAV + 20 µg HBsAg) IM	**STANDARD** DOSE 1: ≥18 years old DOSE 2: 1 month after DOSE 1 DOSE 3: 6 months after DOSE 1	None
		≥18	1 mL (720 ELU HAV + 20 µg HBsAg) IM	**ACCELERATED** DOSE 1: ≥18 years old DOSE 2: 7 days after DOSE 1 DOSE 3: 21–30 days after DOSE 1	12 months after DOSE 1

Abbreviations: HBsAg, hepatitis B surface antigen; IM, intramuscular; ELU, ELISA units inactivated HAV; HAV, hepatitis A virus.

[1]Consult the prescribing information for differences in dosing for patients receiving hemodialysis, and other immunocompromised patients.

Protection from the standard vaccination series is robust, and >95% of healthy people achieve immunity after completion of the vaccination series. Serologic testing and booster vaccination are not recommended before travel for immunocompetent adults who have been previously vaccinated. Consider postvaccination serologic testing, however, for people whose subsequent clinical management depends on knowledge of their immune status, including health care personnel and public safety workers at risk for blood or body fluid exposure; those who require (or might require) outpatient hemodialysis; HIV-infected people; sex partners of HBsAg-positive people; and other immunocompromised people (e.g., hematopoietic stem-cell transplant recipients or people receiving chemotherapy).

SPECIAL SITUATIONS

The accelerated Twinrix vaccination schedule (0, 7, and 21–30 days, plus booster at 12 months) can be used for people traveling on short notice who face imminent HBV exposure or for emergency responders to disaster areas. Alternatively,

Heplisav-B can be used as a 2-dose series at 0 and 4 weeks to protect against hepatitis B alone. Ideally, vaccination with Heplisav-B should begin ≥1 month before travel so the full vaccine series can be completed before departure. When using vaccines other than Heplisav-B, begin vaccination ≥6 months before scheduled travel. Because some protection is provided by 1 or 2 doses, initiate the vaccine series, if indicated, even if the series cannot be completed before departure. Vaccines will not confer optimal protection, however, until after the series is completed; advise travelers to complete the vaccine series upon return.

SAFETY & ADVERSE REACTIONS

Safe hepatitis B vaccines are available for people of all ages, and serious adverse reactions are rare. The most common adverse reactions are soreness at the injection site (3%–29%) and low-grade fever (temperature >99.9°F [37.7°C]; 1%–6%). Hepatitis B vaccines should not be administered to people with a history of hypersensitivity to any vaccine component, including yeast. The vaccine contains a noninfectious recombinant protein (hepatitis B surface antigen) and an adjuvant (either 1018 [small synthetic immunostimulatory cytidine-phosphate-guanosine oligodeoxynucleotide motif for Heplisav-B] or aluminum [for Engerix-B, Recombivax HB, PreHevbrio, Twinrix]).

HBV infection affecting a pregnant person can result in serious disease for the mother and chronic infection for the newborn. Limited data indicate no apparent increased risk for adverse events to the mother (or the developing fetus) after maternal vaccination with Engerix-B, Recombivax HB, or Twinrix; no data are available on the use of Heplisav-B or PreHevbrio in pregnant or breastfeeding people. Until safety data are available for Heplisav-B and PreHevbrio, therefore, pregnant or breastfeeding people needing hepatitis B vaccination should receive Engerix-B, Recombivax HB, or Twinrix.

Personal Protective Measures

As part of the pretravel education process, educate all travelers about exposure risks for hepatitis B and other bloodborne pathogens, including activities or procedures that involve piercing the skin or mucosa; receiving blood products; contaminated equipment used during cosmetic (e.g., tattooing or piercing), dental, or medical procedures; injection drug use; and unprotected sexual activity. Caution travelers against providers who use inadequately sterilized or disinfected equipment, who reuse contaminated equipment, or who do not use safe injection practices (e.g., reusing disposable needles and syringes).

HBV and other bloodborne pathogens can be transmitted if medical equipment is not sterile or if personnel do not follow proper infection-control procedures. Travelers should consider the health risks when receiving dental or medical care overseas; US embassy country-specific websites might have information on medical concerns. Advise travelers to strongly consider health risks before obtaining a body piercing or a tattoo when traveling to destinations where adequate sterilization or disinfection procedures might not be available or practiced.

CDC website: www.cdc.gov/hepatitis/HBV

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HEPATITIS C

Philip Spradling

INFECTIOUS AGENT: Hepatitis C virus	
ENDEMICITY	Worldwide Regions of high prevalence in Africa, central, southern, and eastern Asia, and eastern Europe
TRAVELER CATEGORIES AT GREATEST RISK FOR EXPOSURE & INFECTION	Medical tourists Travelers to destinations with poor infection-control practices who participate in activities with high injury potential
PREVENTION METHODS	Practice bloodborne pathogen precautions Use safe injection practices and syringe service programs
DIAGNOSTIC SUPPORT	A clinical laboratory certified in moderate complexity testing, state health department, or contact CDC's Division of Viral Hepatitis Diagnostic Reference Laboratory, www.cdc.gov/hepatitis/hcv/labtesting.htm

INFECTIOUS AGENT

Hepatitis C virus (HCV) is a spherical, enveloped, positive-strand RNA virus. Seven distinct HCV genotypes and 67 subtypes have been identified, the distribution of which vary geographically worldwide.

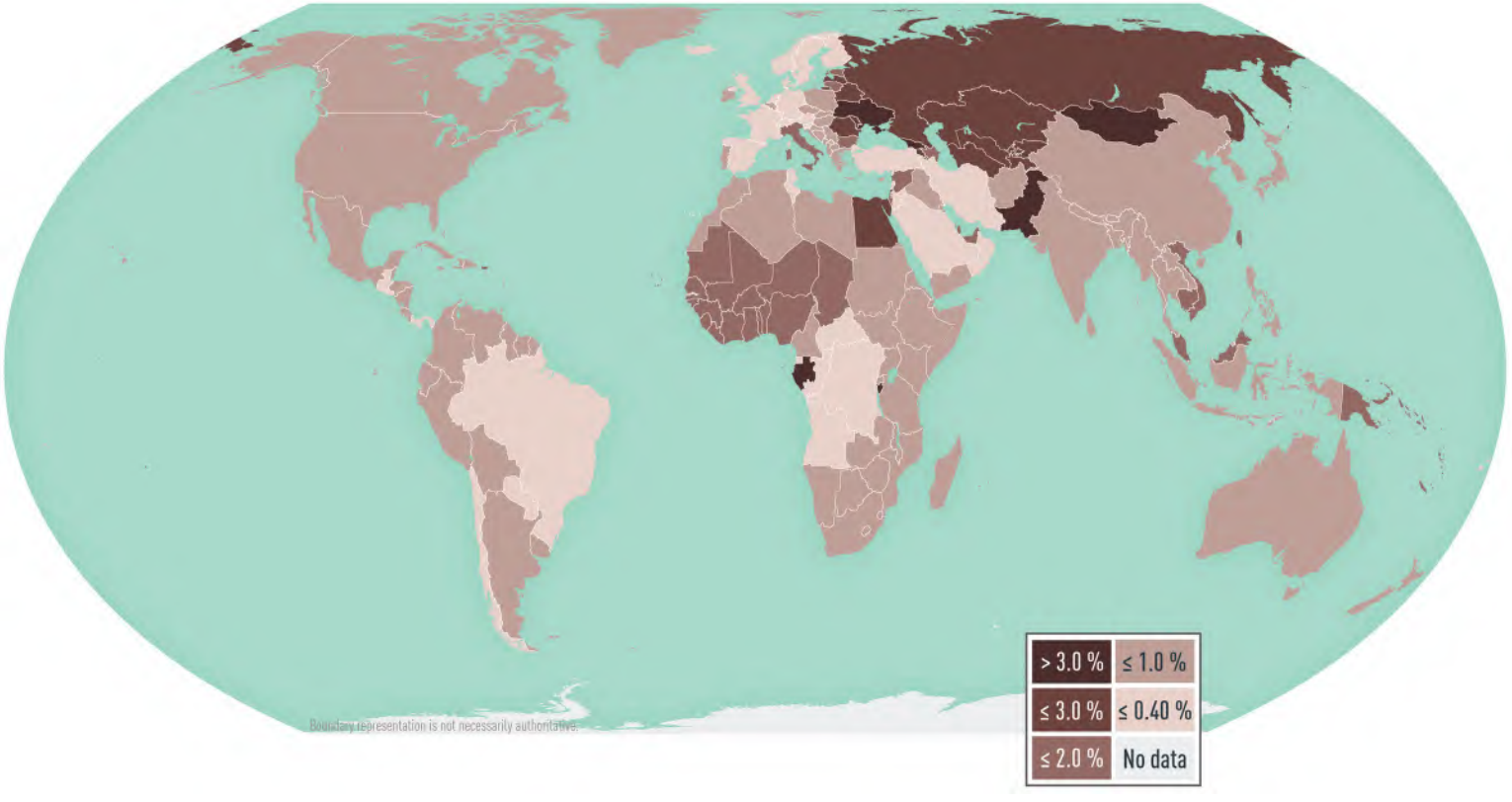
TRANSMISSION

HCV transmission is bloodborne and most often involves exposure to contaminated needles or syringes, or receipt of blood or blood products that have not been screened for HCV. Although infrequent, HCV can be transmitted through other procedures that involve blood exposure (e.g., tattooing, during sexual contact, perinatally from mother to child).

EPIDEMIOLOGY

Globally, an estimated 62 million people were living with HCV infection (chronically infected) in 2019. Although the quality of epidemiologic data and prevalence estimates vary widely across countries and within regions, the most recent global estimates from 2019 indicate that the viremic prevalence of HCV infection (prevalence of HCV RNA) is <1.0% in most developed countries, including the United States (Map 5-08). HCV prevalence is considerably higher in some countries in eastern Europe (3.1% in Ukraine, 2.9% in Russia, 2.9% in Moldova, 2.5% in Romania, 2.1% in Latvia) and certain countries in Africa (5.9% in Gabon, 3.6% in Burundi, 2.1% in Egypt), the Middle East (1.6% in Syria), and the South Caucasus and Central Asia (3.1% in Georgia, 3.0% in Uzbekistan, 2.7% in Tajikistan, 2.7% in Turkmenistan).

The most frequent mode of transmission in most high-, middle-, and low-income countries is sharing of drug preparation and drug-injection equipment. In countries where infection-control practices are poor, a predominant transmission mode is from unsafe injections and other health care exposures. Travelers' risk of contracting HCV infection is generally low, but they should exercise caution and avoid non-urgent dental or medical procedures, particularly in high-prevalence areas. Activities that can result in blood exposure include receiving blood transfusions that have not been screened for HCV; undergoing dental or medical procedures; participating in activities in which equipment has not been adequately sterilized or disinfected, or in which contaminated equipment is reused (e.g., acupuncture, injection drug use, shaving, and tattooing); and working in health care fields



MAP 5-08 Worldwide prevalence of hepatitis C viremia, 2019

Disease data source: 2019 estimates of hepatitis C virus disease burden. CDA Foundation Polaris Observatory. Available from https://cdafound.org/polaris-countries-distribution/.

(dental, laboratory, or medical) that entail direct exposure to human blood.

CLINICAL PRESENTATION

HCV infection is a major cause of cirrhosis and liver cancer and is the leading reason for liver transplantation in the United States. Most (80%) people with acute HCV infection have no symptoms. When they occur, symptoms are indistinguishable from other forms of acute viral hepatitis and could include abdominal pain, anorexia and nausea, fatigue, jaundice, and dark urine. Among infected people, over half will remain chronically infected unless treated with antiviral medications. Cirrhosis develops in ≈10%–20% of people after 20–30 years of chronic infection, and progression is often clinically silent; evidence of liver disease might not occur until late in the course of the disease.

DIAGNOSIS

In the United States, hepatitis C is a nationally notifiable disease. Hepatitis C testing is required for diagnosis. Testing is not routinely performed in many countries, however, and most HCV-infected people are unaware of their infection. Two types of tests are available: IgG assays for HCV antibodies, and nucleic acid amplification tests to detect HCV RNA in blood (viremia). Both tests are commercially available in the United States and most countries. IgM assays, to detect early or acute infection, are not available. Because a positive HCV antibody test cannot discriminate between a previously infected person who resolved or cleared the infection and someone with current infection, be certain that HCV RNA testing follows a positive HCV antibody test to identify people with current (recent and chronic) HCV infection.

In 2020, CDC updated recommendations to include ≥1 hepatitis C screening test for all adults ≥18 years of age during a lifetime, and hepatitis C screening for all pregnant people during each pregnancy. Information on how to obtain hepatitis C diagnostic support from the Centers for Disease Control and Prevention (CDC), including contact information, which samples to send, and how to send samples is available at www.cdc.gov/hepatitis/hcv/hcvfaq.htm or by calling 800-CDC-INFO (800-232-4636).

TREATMENT

Since 2014, several new all-oral direct-acting antiviral agents have been approved for use to treat hepatitis C. These new regimens require only 8–12 weeks of treatment, have few side effects, and eliminate HCV infection in ≈95% of people who complete treatment, regardless of HCV genotype, prior treatment status, HIV co-infection, and the presence of cirrhosis. Treatment guidelines, which are updated frequently, can be found at www.hcvguidelines.org.

PREVENTION

No vaccine or postexposure prophylaxis is available to prevent HCV infection, nor does immune globulin provide protection. Travelers should check with their health care provider to understand the potential risk for infection and any precautions they should take. If seeking dental or medical care, travelers should be alert to the use of instruments, tools, and other equipment that has not been adequately sterilized or disinfected; reuse of contaminated equipment; and unsafe injection practices (e.g., reuse of disposable needles and syringes). People who travel to undergo dental, medical, or surgical procedures should be cognizant of potential HCV exposure (see Sec. 6, Ch. 4, Medical Tourism).

HCV and other bloodborne pathogens can be transmitted when medical instruments are not sterile or providers do not follow proper infection-control procedures (e.g., washing hands, using latex gloves, cleaning and disinfecting surfaces and instruments). In some parts of the world (e.g., parts of sub-Saharan Africa), blood donors might not be screened for HCV infection. Advise travelers to avoid body piercing, tattooing, being shaved by a barber, or having an elective dental or medical procedure in destinations where adequate sterilization or disinfection practices might not be used. Furthermore, instruct travelers to seek testing for HCV infection upon return if they received blood transfusions or sustained blood exposures for which they could not assess the risks, and to seek immediate medical care if they have signs or symptoms of acute hepatitis.

CDC website: www.cdc.gov/hepatitis/HCV

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HEPATITIS E

Eyasu Teshale

5

INFECTIOUS AGENT: Hepatitis E virus	
ENDEMICITY	Worldwide
TRAVELER CATEGORIES AT GREATEST RISK FOR EXPOSURE & INFECTION	Humanitarian aid workers Immigrants and refugees People who are pregnant Severely immunocompromised travelers Travelers to low- and middle-income countries
PREVENTION METHODS	Practice safe food and water precautions
DIAGNOSTIC SUPPORT	A clinical laboratory certified in high complexity testing; state health department; or contact CDC's Division of Viral Hepatitis Diagnostic Reference Laboratory, www.cdc.gov/hepatitis/hev/labtestingrequests.htm

INFECTIOUS AGENT

Hepatitis E is caused by hepatitis E virus (HEV), a spherical, nonenveloped, single-stranded, single-serotype, RNA virus belonging to the *Hepeviridae* family. Five HEV genotypes (HEV1–4 and HEV-7) are known to cause human disease. HEV-3 and HEV-4 cause hepatitis E in high-income countries, whereas HEV-1, HEV-2, HEV-4, and HEV-7 are associated with disease in low- and middle-income countries. Globally, HEV-1 is the most prevalent cause of hepatitis E. HEV is relatively stable in the environment but can be inactivated by chlorination or by heating to ≥70°C (≈160°F) for 5 minutes.

TRANSMISSION

HEV transmission routes vary by genotype distribution. HEV-1 and HEV-2 are transmitted primarily by the fecal–oral route, mainly through drinking contaminated water. Zoonotic foodborne transmission of HEV-3 is associated with eating uncooked or undercooked meat and offal (including liver), of boar, deer, and pig. Consumption of shellfish was implicated in an outbreak of hepatitis E on a cruise ship. HEV-7 infection has been associated with consumption of camel meat and milk.

Transfusion-related hepatitis E increasingly is reported in Europe. Rare, domestically acquired

symptomatic disease has been observed in the United States, but its mode of transmission is generally unknown. Vertical transmission of HEV from people infected during pregnancy to their fetuses is common.

EPIDEMIOLOGY

Every year, ≈20 million HEV infections occur globally; ≈3.3 million cases are symptomatic hepatitis E, and ≈70,000 deaths occur. Large waterborne outbreaks have occurred in Africa, Central America, South and central Asia, and tropical East Asia. Many large outbreaks have occurred among refugees and in people living in camps for displaced persons. Sporadic illness is encountered in outbreak-prone areas, but also in regions not prone to outbreaks (e.g., North and South America, temperate East Asia [including China], Europe, the Middle East).

During hepatitis E outbreaks, clinical attack rates are highest among people aged 15–49 years. In areas endemic for HEV-1, infection in a pregnant person can progress to liver failure and death. Miscarriages and neonatal deaths are common complications of HEV infection during pregnancy. In areas where HEV-3 is prevalent, symptomatic disease occurs most frequently in adults aged >50 years. Among immunosuppressed people, particularly solid organ allograft recipients infected with HEV-3, hepatitis E can progress to chronic infection.

Due to the lack of systematic surveillance for hepatitis E, the incidence and characteristics of hepatitis E cases in the United States are unknown. Despite a lack of data on the risk for travel-associated HEV infections, US travelers are at greatest risk when they visit endemic countries and drink contaminated water. Most travel-associated hepatitis E cases have occurred among travelers returning from the Indian subcontinent. When traveling in countries where HEV-3 is found, eating raw or inadequately cooked boar, deer, or pig meat, or food products derived from any of these, can increase the risk for HEV infection.

CLINICAL PRESENTATION

The incubation period of HEV infection is 2–9 weeks (mean 6 weeks). The spectrum of illness ranges from asymptomatic to severe disease resulting in fulminant hepatitis and death. For most people, hepatitis E is a mild, self-limited disease. Infection with HEV-3 can progress to chronic infection, whereas infection with other genotypes results only in acute infection.

Signs and symptoms of acute hepatitis E include abdominal pain, anorexia, fever, jaundice, and lethargy, and are indistinguishable from other causes of viral hepatitis. Pregnant people with HEV-1 infection, especially those infected during the third trimester, might present with or progress to fulminant liver failure and death, and are at risk for spontaneous abortion and premature delivery. To date, no evidence shows severe outcomes associated with HEV-3 infection in people who are pregnant.

People with preexisting liver disease might have further hepatic decompensation with HEV superinfection. Recipients of solid organ transplants and people with severe immunosuppression tend to have asymptomatic acute HEV infection, but can develop chronic hepatitis E and progressive liver injury from HEV-3 infection.

DIAGNOSIS

Acute hepatitis E is diagnosed by detecting HEV IgM in serum. Detecting HEV RNA in serum or stool specimens further confirms the serologic diagnosis but seldom is required. Longer-term, serial detection of HEV RNA in serum or stool, regardless of the HEV antibody serostatus, suggests chronic HEV infection. No diagnostic test is approved by the US Food and Drug Administration (FDA) to detect HEV infection. Some commercial laboratories, however, perform both serologic and virologic tests upon request.

The Centers for Disease Control and Prevention (CDC), Division of Viral Hepatitis Diagnostic Reference Laboratory can provide diagnostic support for detecting HEV IgM and IgG in clinical samples by using commercially available kits, and offers a PCR assay for detection of HEV RNA in serum and stool samples. For information on sample handling and shipping to CDC's Division of Viral Hepatitis Diagnostic Reference Laboratory, see www.cdc.gov/hepatitis/hev/labtestingrequests.htm.

TREATMENT

Treatment for acute hepatitis E is supportive care. Oral ribavirin has been shown to be effective in the treatment of chronic hepatitis E.

PREVENTION

No FDA-approved vaccine or immune globulin is available to prevent HEV infection. Travelers should avoid drinking unboiled or unchlorinated water or any beverages containing unboiled water or ice. Travelers should eat only thoroughly cooked food, including seafood, meat, offal, and products derived from these.

CDC website: www.cdc.gov/hepatitis/HEV

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5

HUMAN IMMUNODEFICIENCY VIRUS / HIV

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INFECTIOUS AGENT: Human immunodeficiency virus	
ENDEMICITY	Worldwide
TRAVELER CATEGORIES AT GREATEST RISK FOR EXPOSURE & INFECTION	Immigrants and refugees who come from environments with high rates of HIV in their cohorts or who have been abused Travelers who have cosmetic or medical procedures using contaminated needles, syringes, or other items Travelers who inject drugs using nonsterile equipment Travelers who have unprotected sex
PREVENTION METHODS	Avoid invasive procedures in locations where proper sterilization of instruments might not be used Avoid nonsterile injection use Practice safe sex Take preexposure prophylaxis (for some travelers)
DIAGNOSTIC SUPPORT	A clinical laboratory certified in moderate complexity testing; self-tests are also available

INFECTIOUS AGENT

HIV is an enveloped positive-strand RNA virus in the family *Retroviridae*.

TRANSMISSION

HIV is transmitted through sexual contact, needle or syringe sharing, unsafe medical injection or blood transfusion, and organ or tissue transplantation. It can also be transmitted from mother to child during pregnancy, at birth, and postpartum through breastfeeding.

EPIDEMIOLOGY

HIV infection occurs worldwide. In 2000, an estimated 37.7 million people were living with HIV infection globally (see www.unaids.org/en/topic/data). Sub-Saharan Africa is the most affected part of the world (25.4 million cases, or 67% of all people living with HIV infection); central Asia and eastern Europe have experienced the largest increases in new HIV infections (47% increase from 2010 to 2020). Although the reported adult HIV prevalence in many regions of the world is low, certain populations are disproportionately affected (e.g., sex workers, people who inject drugs, men who have sex with men, transgender people, and incarcerated people). People with HIV face an intersection of stigma, discrimination, violence, and criminalization that causes health inequities; international travelers should be aware of how their travel affects local communities, including people with HIV.

The risk for HIV infection is generally low for international travelers. Risk for HIV exposure and infection is determined less by a traveler's geographic destination and more by the behaviors in which they engage while traveling (e.g., sex without a condom, nonsterile injection drug use). Travelers who might undergo scheduled or emergency medical procedures should be aware that HIV can be transmitted by unsafe nonsterile medical injection practices (e.g., reusing needles, syringes, or single-dose medication vials). Unsafe medical practices might be greater in low-income countries where the blood supply and organs and tissues used for transplantation might not be screened properly for HIV.

CLINICAL PRESENTATION

As many as 90% of infected people will recall experiencing symptoms during the acute phase of HIV infection. Acute HIV infection can present as an infectious mononucleosis-like or influenza-like syndrome, but the clinical features are highly variable. Symptoms typically begin a median of 10 days after infection and can include arthralgias and myalgias, fatigue, fever, headache, lymphadenopathy, maculopapular rash, malaise, oral ulcers, pharyngitis, and weight loss. Although none of these symptoms are specific for acute HIV infection, certain features (e.g., oral ulcers), suggest the diagnosis.

DIAGNOSIS

HIV can be diagnosed with laboratory-based or point-of-care assays that detect HIV antibodies, HIV p24 antigen, or HIV-1 RNA. In the United States, the recommended laboratory-based screening test for HIV is a combination antigen/antibody assay that detects antibodies against HIV, and the p24 antigen. The combination antigen/antibody assay becomes reactive approximately 2–3 weeks after HIV infection. Estimates suggest that 99% of people will develop a reactive combination antigen/antibody result within 6 weeks of infection, but in rare cases, it can take up to 6 months to develop a reactive test result.

HIV self-tests also are available for retail purchase in the United States, including an HIV antibody test performed on oral fluid instead of blood. Although oral swab HIV tests have a lower sensitivity for detecting recent HIV infection, these can be an important testing method for people and their partners who would not otherwise get an HIV test (see Sec. 11, Ch. 2, Rapid Diagnostic Tests for Infectious Diseases). Acute HIV infection is characterized by markedly elevated HIV RNA levels; perform an HIV RNA viral load test if acute infection is suspected. Travelers with potential HIV exposures abroad, including those with symptoms consistent with acute HIV infection, should consider testing for HIV during travel or upon return to the United States. Travelers can find detailed information on HIV testing locations at https://gettested.cdc.gov.

TREATMENT

With timely diagnosis, prompt medical care, and daily antiretroviral therapy (ART), people with HIV can now live longer, healthier lives. Owing to the advances of ART, people with HIV who start

treatment can have close to the same life expectancy as people of the same age without HIV. Effective treatment also substantially reduces the risk of transmitting HIV to others. People with HIV who achieve and maintain an undetectable viral load by taking ART daily as prescribed cannot sexually transmit the virus to others (undetectable = untransmittable [U = U]).

Detailed information on specific treatments is available from the Department of Health and Human Services AIDSinfo website (www.aidsinfo.nih.gov). Travelers can contact HIVinfo toll free at 800-448-0440 (English or Spanish) or 888-480-3739 (TTY).

PREVENTION

Travelers can reduce their risk for HIV infection by avoiding sexual encounters with people whose HIV status is unknown, using condoms consistently and correctly with all partners who have HIV or whose HIV status is unknown, and using HIV prophylaxis when indicated. Travelers going abroad for medical procedures should try to ensure in advance that all blood or blood products at the facility have been screened for bloodborne pathogens (including HIV) and that all invasive medical equipment is sterilized between uses or is sterile and single use only (see Sec. 6, Ch. 2, Obtaining Health Care Abroad, and Sec. 6, Ch. 4, Medical Tourism). Travelers who inject drugs should avoid sharing needles or other injection equipment and use only sterile, single-use syringes and needles that are safely disposed of after every injection.

Preexposure Prophylaxis

Preexposure prophylaxis (PrEP) is a highly effective method to prevent HIV acquisition and is used by people without HIV who are at risk of being exposed to HIV. Two medications have been approved by the US Food and Drug Administration for use as PrEP; each consists of 2 drugs combined in a single oral tablet taken daily. F/TDF (brand name Truvada) combines 200 mg emtricitabine with 300 mg tenofovir disoproxil fumarate. F/TAF (brand name Descovy) combines 200 mg emtricitabine with 25 mg tenofovir alafenamide.

People already on PrEP should continue its use during international travel. Travel medicine providers can consider initiating PrEP for people who have a greater risk for HIV acquisition during international travel (see www.cdc.gov/hiv/pdf/risk/prep/cdc-hiv-prep-guidelines-2017.pdf). A comprehensive prevention plan includes not only prescribing (or considering prescribing) PrEP, but also reinforcing careful adherence to the PrEP regimen, educating travelers on the importance of consistent condom use to protect against HIV as well other sexually transmitted infections, and discussing other HIV prevention methods (see www.cdc.gov/hiv/clinicians/prevention/prep.html).

Travelers taking PrEP should carry proper documentation and be aware that some countries (see below for further information) deny entry to people with evidence of HIV infection, which PrEP medications might mistakenly indicate to customs officials. Free, expert PrEP advice is available to health care professionals through the National Clinician Consultation Center's PrEPline (855-448-7737; https://nccc.ucsf.edu/clinician-consultation/prep-pre-exposure-prophylaxis/).

Postexposure Prophylaxis

Postexposure prophylaxis (PEP) with antiretroviral medications is another method to prevent HIV infection (see www.cdc.gov/hiv/clinicians/prevention/pep.html). PEP is recommended as a prevention option after a single high-risk exposure to HIV during sex, through sharing needles or syringes, through a needlestick, or from a sexual assault. PEP must be started within 72 hours of a possible exposure. Travelers who will be working in medical settings (e.g., nurse volunteers drawing blood, medical missionaries performing surgeries) could have contact with HIV-infected or potentially infected biological materials.

Under certain conditions, a clinician can prescribe PEP medications for travelers to use in emergency situations. Free, expert PEP advice is available to health care professionals through the National Clinician Consultation Center's PEPline (888-448-4911; https://nccc.ucsf.edu/clinician-consultation/pep-post-exposure-prophylaxis/). See Sec. 9, Ch. 4, Health Care Workers, Including Public Health Researchers & Medical Laboratorians, for detailed advice regarding management of postexposure prophylaxis in occupational settings.

HIV TESTING REQUIREMENTS FOR US TRAVELERS ENTERING FOREIGN COUNTRIES

Advise international travelers that some countries screen incoming travelers for HIV (usually those with an extended stay) and might deny entry to people with evidence of HIV infection. People intending to visit a country for an extended stay should review that country's policies and requirements. This information is usually available from the consular officials of the individual nations. The US Department of State has compiled a list of entry, exit, and visa requirements by country, available at https://travel.state.gov/content/travel/en/international-travel/International-Travel-Country-Information-Pages.html.

CDC website: www.cdc.gov/hiv

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INFLUENZA

Christine Szablewski, Michael Daugherty, Eduardo Azziz- Baumgartner

INFECTIOUS AGENT: Influenza virus	
ENDEMICITY	Worldwide
TRAVELER CATEGORIES AT GREATEST RISK FOR EXPOSURE & INFECTION	All travelers
PREVENTION METHODS	Influenza is a vaccine-preventable disease Practice hand hygiene Use appropriate personal protective equipment Use postexposure antiviral medication
DIAGNOSTIC SUPPORT	A clinical laboratory certified in moderate complexity testing; or contact CDC's Influenza Laboratory (404-639-2434)

INFECTIOUS AGENT

Influenza is caused by infection of the respiratory tract with influenza viruses, RNA viruses of the *Orthomyxovirus* genus. Influenza viruses are classified into 4 types: A, B, C, and D. Influenza A and B viruses commonly cause illness in humans and seasonal epidemics. Influenza A viruses are classified into subtypes based on the surface proteins hemagglutinin (HA) and neuraminidase (NA). Two influenza A virus subtypes, A(H1N1) and A(H3N2), and 2 influenza B virus lineages, B-Yamagata and B-Victoria, co-circulate in humans worldwide; the distribution of these viruses varies year to year and between geographic areas and time of year. Information about circulating seasonal viruses in various regions can be found on the Centers for Disease Control and Prevention (CDC) website (www.cdc.gov/flu/weekly) or World Health Organization website (www.who.int/teams/global-influenza-programme/surveillance-and-monitoring/influenza-updates/current-influenza-update).

Influenza type C infections generally cause mild illness and are not thought to cause human influenza epidemics. Influenza D viruses primarily affect cattle and are not known to infect or cause illness in people.

Novel influenza refers to viruses with a subtype different from seasonal influenza, and usually is caused by influenza A viruses that circulate among animals. Notably, avian influenza A(H5N1), A(H5N6), A(H7N9), and A(H9N2) viruses, and swine-origin variant viruses A(H1N1)v, A(H1N2)v, and A(H3N2)v have resulted in novel human influenza infections globally. An influenza virus that normally circulates in swine (but not people) but then is detected in a person is called a variant virus and is denoted with the letter *v*.

TRANSMISSION

Influenza viruses spread from person to person, primarily through respiratory droplets (e.g., when an infected person coughs or sneezes near a susceptible person). Transmission generally occurs via large particle droplets that require close proximity (≤6 feet) between the source and the recipient, but airborne transmission via small particle aerosols can occur within confined air spaces. Indirect transmission occurs when a person touches their face after touching a virus-contaminated surface (fomite).

The incubation period is usually 1–4 days after exposure. Most adults ill with influenza shed the virus in the upper respiratory tract and are infectious from the day before symptom onset to ≈5–7 days after symptom onset. Infectiousness is greatest within 3–4 days of illness onset and is correlated with fever. Children, immunocompromised people, and severely ill people might shed influenza virus for ≥10 days after symptom onset. Those who are asymptomatic can still shed the virus and infect others. Seasonal influenza viruses are rarely detected in blood or stool.

Influenza A virus transmission from animals to humans is rare but possible. Infected birds shed influenza virus in their droppings, mucus, and saliva, and transmission to humans can occur from direct contact with an animal (by touching an infected animal or by droplet spread) or contact with a sick animal's environment (by inhalation of airborne viruses or through fomite transmission). See CDC's Avian Influenza A Virus Infection in Humans website (www.cdc.gov/flu/avianflu/avian-in-humans.htm) for more details. Infected swine shed the virus in nasal secretions and can transmit viruses to humans in the same way seasonal influenza viruses spread among people. For more information, see CDC's website What People Who Raise Pigs Need to Know about Influenza (www.cdc.gov/flu/swineflu/people-raise-pigs-flu.htm).

EPIDEMIOLOGY

Seasonal Influenza

Influenza seasonality varies geographically. The risk for influenza exposure during travel depends on the time of year and destination. In temperate regions, influenza epidemics are more common during cooler months, October–March in the Northern Hemisphere and April–September in the Southern Hemisphere. In subtropical and tropical regions, seasonal influenza epidemics follow a similar pattern, but influenza illnesses can occur throughout the year. During the coronavirus disease 2019 pandemic in 2020 and 2021, there was a sharp decrease in global influenza activity. Although causality has not confirmed, the decrease has been attributed, in part,

to community and personal implementation of nonpharmaceutical interventions to mitigate severe acute respiratory syndrome coronavirus 2 transmission.

CDC estimates that 9–45 million (symptomatic) illnesses, 4–21 million outpatient visits, 140,000–810,000 hospitalizations, and 12,000–61,000 deaths associated with influenza occur each year in the United States (see www.cdc.gov/flu/about/disease/burden.htm). Globally, annual influenza epidemics result in an estimated 3–5 million cases of severe illness and 290,000–650,000 respiratory deaths.

AT-RISK POPULATIONS

Certain groups are at increased risk for influenza complications (see Box 5-03 and www.cdc.gov/flu/highrisk/index.htm). The incidence of influenza illness is greatest among children, especially those aged 0–4 years, and adults aged 50–64 years. Rates of hospitalization (a marker of severe illness) and death due to influenza are typically higher among older adults (≥65 years old) followed by adults aged 50–64 years, children aged <2 years, and people of any age with underlying medical conditions that place them at increased risk for complications.

Zoonotic Influenza

Influenza A viruses circulate among animal populations and occasionally infect humans. The primary reservoirs for influenza A viruses are wild birds, like waterfowl, but influenza A viruses are also common in domestic poultry and swine populations. Influenza A viruses can infect other animal species (e.g., bats, cats, dogs, ferrets, horses, sea lions, seals).

In the United States, the last large outbreak of H5 lineage avian influenza virus in birds occurred in 2022. Although 34 different avian influenza subtypes have been reported globally since 2005, 94% of outbreaks reported in birds were caused by H5 lineage viruses. Since 2005, 23,754 outbreaks of H5 lineage avian influenza in animals have been reported from 97 countries (Map 5-09). Avian influenza virus outbreaks do not have to be reported to the World Organisation for Animal Health (OIE) if the virus is endemic in a country; avian influenza A(H5N1) was declared endemic in Indonesia in 2006 and in Egypt in 2008. Swine influenza is not reportable to OIE.

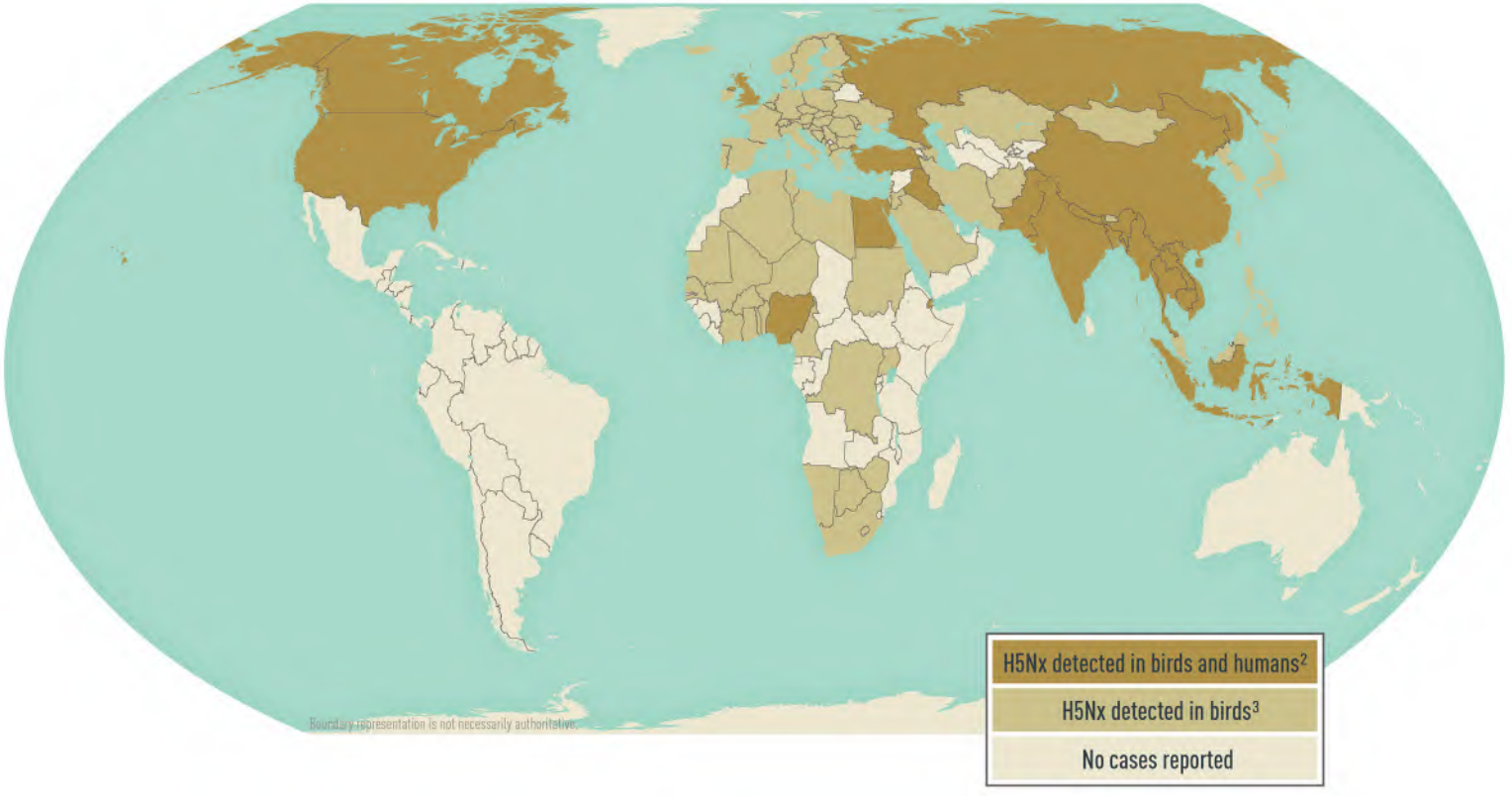
Novel Influenza A Viruses

Human infections with novel influenza A viruses are uncommon, but potentially could cause a pandemic if sustained human-to-human transmission occurs. Human infections with influenza A(H1N1)v, A(H1N2)v, and A(H3N2)v have been identified in the United States; the largest variant influenza outbreak occurred in 2012 and had a total of 309 infections and 1 death associated with an A(H3N2)v virus.

From 2011 through July 2021, 468 human infections with variant influenza viruses were identified in 24 US states. Most people identified with variant virus infections reported contact with swine preceding their illness, suggesting swine-to-human transmission. Limited cases of human-to-human transmission of variant viruses have also been reported. Seasonal human influenza viruses have infected swine, suggesting person-to-swine transmission. Agricultural fairs and swine farms are settings in which humans are exposed

BOX 5-03 Groups at increased risk for influenza complications

- Adults ≥65 years old
- Children <2 years old; although all children <5 years are considered at increased risk for serious influenza complications, the highest risk is for those <2
- Pregnant people and people ≤2 weeks post-partum
- People with certain medical conditions, including asthma, blood disorders, body mass index ≥40, chronic lung disease, endocrine disorders, heart disease, immunocompromise due to disease or medication, kidney disease, liver disorders, metabolic disorders, neurologic and neurodevelopment conditions, and history of stroke
- American Indians and Alaska Natives
- People living in nursing homes and other long-term care facilities



MAP 5-09 Global distribution of highly pathogenic avian influenza A (H5Nx) virus[1]

[1]Disease data source: Animal disease events. World Organisation for Animal Health, World Animal Health Information System (OIE-WAHIS). Available from: https://wahis.oie.int/#/events.

[2]H5Nx lineages include: H5N1, H5N6, and H5N8

[3]H5Nx lineages include: H5N1, H5N2, H5N3, H5N4, H5N5, H5N6, H5N8, H5N9, and H5Nx

to swine. Illnesses associated with variant virus infections are usually mild, with symptoms similar to those of seasonal influenza.

AVIAN INFLUENZA A(H5) LINEAGE VIRUSES

Avian influenza viruses do not commonly infect humans, but cases are reported globally each year (see www.cdc.gov/flu/avianflu/index.htm). During 2013–2020, 9 countries reported 281 human illnesses caused by avian influenza A(H5) lineage viruses, and a reported case-fatality ratio of ≈37% (Map 5-09). Most disease from A(H5) lineage viruses occurred after direct or close contact with sick or dead infected poultry. A(H5N1) and A(H5N6) viruses are widespread among poultry in some countries in Asia and the Middle East. Egypt and Indonesia account for 79% of A(H5N1) infections, and China accounts for 99% of A(H5N6) infections in humans globally. Instances of limited human-to-human A(H5N1) virus transmission have been reported. In February 2021, Russia reported 7 cases of human, asymptomatic infection with A(H5N8), the first report of influenza A(H5N8) infection in humans.

AVIAN INFLUENZA A(H7N9) VIRUS

Avian influenza A(H7N9) virus emerged in China in 2013; as of July 2021, it has caused 1,568 confirmed human infections. Most cases have been identified in mainland China, but several infections have been identified in Hong Kong Special Administrative Region (SAR), Macau SAR, Malaysia, and Taiwan, in travelers who reported exposure in mainland China. In 2014, Canada reported the first known imported influenza A(H7N9) virus infection in North America in a traveler returning from China. Most people with A(H7N9) infection were exposed to infected poultry or contaminated environments (e.g., live bird markets). The virus has been found in poultry and environmental samples collected in China. Most reported human A(H7N9) infections have been severe respiratory illnesses; the reported case-fatality ratio is 40%.

OTHER AVIAN INFLUENZA VIRUSES

Although uncommon, human infections with other avian influenza viruses, including A(H7N2), A(H7N3), and A(H9N2), have been reported globally in recent years, including 2 cases of A(H7N2) in humans exposed to infected cats in New York in 2016. And even though human infections with avian influenza viruses in the United States are rare, surveillance in domestic birds and people exposed to infected birds abides because of the low, but continued, risk for transmission to humans.

CLINICAL PRESENTATION

Physical Findings

Uncomplicated influenza illness, the most common presentation of seasonal influenza, is characterized by an abrupt onset of signs and symptoms that include nonproductive cough, fever, headache, malaise, muscle aches, rhinitis, sore throat, and vomiting, and, less commonly, rash. Illness without fever can occur, especially in older adults and infants. Children are more likely than adults to experience nausea, vomiting, or diarrhea when ill with influenza.

Physical findings are predominantly localized to the respiratory tract and include nasal discharge, pharyngeal inflammation without exudates, and occasionally rales on chest auscultation. Influenza illness typically resolves within 1 week for most previously healthy children and adults who do not receive antiviral medication, although cough and malaise can persist for >2 weeks, especially in older adults.

Humans infected with variant influenza viruses have a clinical presentation like seasonal influenza virus infections. Reported human infections with avian influenza A(H5N1) or A(H7N9) viruses often have severe pneumonia or respiratory failure and a high case-fatality ratio. These data might be skewed, however, because people with less severe illness often do not seek care for influenza or get tested for avian origin A(H5) or A(H7) viruses.

Complications

Complications of influenza virus infection include primary influenza viral pneumonia and secondary bacterial pneumonia; also, co-infections with other viral or bacterial pathogens, encephalopathy, exacerbation of underlying medical conditions (e.g., cardiac disease, pulmonary disease), Guillain-Barré syndrome (GBS), myocarditis, myositis, parotitis, seizures, and rarely, death.

DIAGNOSIS

Influenza can be difficult to distinguish from respiratory illnesses caused by other pathogens based on signs and symptoms alone. The positive predictive value of clinical signs and symptoms for influenza-like illness (fever with either cough or sore throat) for laboratory-confirmed influenza virus infection is 30%–88%, depending on host factors (e.g., age, community influenza activity levels).

Diagnostic Testing

Consider diagnostic testing for hospitalized patients with suspected influenza; patients for whom a diagnosis of influenza will inform clinical care decisions, including patients who do not improve on antiviral therapy and those with medical conditions that place them at increased risk for complications; and patients for whom results of influenza testing would affect infection control or management of close contacts, including other patients, such as in institutional outbreaks or other settings (e.g., cruise ships, tour groups).

For clinicians seeking laboratory confirmation of influenza, the Infectious Diseases Society of America recommends the use of rapid molecular assays in outpatients and nucleic acid amplification tests (e.g., reverse transcription PCR [RT-PCR]), in hospitalized patients. For suspected human infection with a novel influenza A virus of animal origin (e.g., avian influenza A virus, swine influenza A virus), contact the local and state health departments to perform RT-PCR for seasonal influenza viruses and novel influenza A viruses.

Other diagnostic tests available for influenza include antigen-based rapid influenza diagnostic tests, immunofluorescence assays, and viral culture (see www.cdc.gov/flu/professionals/diagnosis/overview-testing-methods.htm). Most patients with clinical illness consistent with uncomplicated influenza in communities where influenza viruses are circulating do not require diagnostic testing for empiric clinical management.

TEST SENSITIVITY

Nucleic acid assays are the most sensitive diagnostic assays. Thus, if infection with these viruses is suspected, contact the state health department in the United States or CDC outside the United States. Do not delay starting antiviral treatment while waiting for confirmatory laboratory testing results.

The sensitivity of antigen-based rapid influenza diagnostic tests varies but is substantially lower than RT-PCR or viral culture. Antigen-based rapid influenza diagnostic tests cannot distinguish between seasonal influenza A virus infections and animal-origin influenza A virus infections, and their sensitivity to detect these animal-origin influenza viruses can vary by test type and virus subtype. Therefore, a negative antigen-based rapid influenza diagnostic test result does not rule out influenza virus infection, and health care providers should not rely on a negative antigen-based rapid influenza diagnostic test result to make decisions about treatment.

TREATMENT

Antiviral Treatment

Early antiviral treatment (see Table 5-13) can shorten the duration of fever and other symptoms and reduce the risk for complications from influenza. Antiviral treatment is recommended as early as possible for any patient with confirmed or suspected influenza who is hospitalized; has severe, complicated, or progressive illness; or who is at increased risk for influenza-associated complications.

Treatment is most effective if it can be initiated ≤48 hours of symptom onset. For hospitalized patients, those with severe illness, or those at higher risk for complications, antiviral therapy might still be beneficial if started >48 hours after illness onset. Four antiviral agents are approved by the US Food and Drug Administration (FDA) for the treatment and prophylaxis of influenza (see www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm): oral oseltamivir, available as a generic (or as Tamiflu, Genentech); intravenous peramivir (Rapivab, BioCryst Pharmaceuticals); inhaled zanamivir (Relenza, GlaxoSmithKline); and oral baloxavir (Xofluza, Genentech).

Oseltamivir is the recommended treatment for people of all ages and is the preferred agent to treat patients with severe or complicated influenza illness who can tolerate oral medications. Peramivir is approved and recommended to treat patients aged ≥2 years and might be useful

Table 5-13 Treatment and prophylaxis for influenza A & B: approved and recommended antiviral medication dosing schedules

ANTIVIRAL	ROUTE	USE	PEDIATRIC DOSE	ADULT DOSE
Oseltamivir	Oral (PO)	Treatment[1]	**<1 year old**: 3 mg/kg PO, 2×/day ×5 days[2] ≥**1 year old (weight-based dosing schedule):** ≤15 kg: 30 mg PO, 2×/day ×5 days >15–23 kg: 45 mg PO, 2×/day ×5 days >23–40 kg: 60 mg PO, 2×/day ×5 days >40 kg: 75 mg PO, 2×/day ×5 days	75 mg PO 2×/day ×5 days
		Prophylaxis[1]	**<3 months old:** unless the situation is judged critical, oseltamivir is not recommended due to limited data in this age group ≥**3 months and <1-year old:** 3 mg/kg/dose PO 1×/day ×7 days[2] ≥**1 year old (weight-based dosing schedule):** ≤15 kg: 30 mg PO, 1×/day ×7 days >15–23 kg: 45 mg PO, 1×/day ×7 days >23–40 kg: 60 mg PO, 1×/day ×7 days >40 kg: 75 mg PO, 1×/day ×7 days	75 mg PO 1×/day ×7 days
Peramivir	Intravenous (IV)	Treatment[3]	**2–12 years old:** 12-mg/kg dose (up to 600 mg maximum) by IV infusion over ≥15 minutes ×1	≥**13 years old**: 600 mg by IV infusion over ≥15 minutes ×1
		Prophylaxis[4]	Not recommended	Not approved
Zanamivir	Inhaled	Treatment[5]	≥**7 years old**: 10 mg (2 5-mg inhalations) 2×/day ×5 days	
		Prophylaxis	≥**5 years old**: 10 mg (two 5-mg inhalations) 1×/day ×7 days	
Baloxavir	Oral (PO)	Treatment[6]	≥**12 year old (weight-based dosing schedule):** 40 to <80 kg: 40 mg PO ×1 ≥80 kg: 80 mg PO ×1	
		Postexposure prophylaxis	≥**12 year old (weight-based dosing schedule):** 40 to <80 kg: 40 mg PO ×1 ≥80 kg: 80 mg PO ×1	

[1]Oseltamivir is approved by the US Food and Drug Administration (FDA) for the treatment of acute uncomplicated influenza ≤48 hours of illness onset. Although not part of the FDA-approved indications, use of oseltamivir to treat influenza in infants <14 days old, and for prophylaxis in infants 3 months to 1 year of age, is recommended by the Centers for Disease Control and Prevention (CDC) and the American Academy of Pediatrics (AAP).
[2]AAP provides alternative dosing guidelines for infants aged 9–11 months and for premature infants.
[3]Peramivir is FDA-approved and recommended for treatment of acute uncomplicated influenza ≤48 hours of illness onset. Daily dosing for a minimum of 5 days was used in clinical trials of hospitalized patients with influenza.
[4]No data for use of peramivir for influenza chemoprophylaxis are available.
[5]Zanamivir is FDA-approved and recommended for treatment of acute uncomplicated influenza ≤48 hours of illness onset.
[6]Baloxavir marboxil is FDA-approved and recommended for treatment of acute uncomplicated influenza ≤48 hours of illness onset.