in patients unable to tolerate or absorb oral antiviral therapy. Zanamivir is approved and recommended to treat patients aged ≥7 years and for prophylaxis in people aged ≥5 years. Inhaled zanamivir is not recommended for use in people with underlying chronic respiratory disease. Baloxavir is indicated to treat acute uncomplicated influenza in patients ≥12 years of age who have been symptomatic for ≤48 hours.

Two other FDA-approved influenza antiviral medications, amantadine and rimantadine, are not recommended for treatment or prophylaxis of influenza because of widespread viral resistance. Discuss antiviral treatment options with people at increased risk for complications of influenza before they travel to areas with influenza activity.

5

Postexposure Prophylaxis

To complement hand washing, face covering, and social distancing, antiviral drugs can be used for prophylaxis to prevent infection after close contact with a confirmed case. CDC does not, however, recommend routine use of antiviral medications for prophylaxis except as one of multiple interventions to control institutional influenza outbreaks. Initiate postexposure prophylaxis ≤48 hours of exposure, but never >48 hours, because of the risk of treating infection with a subtherapeutic dose. Alternatively, exposed people can monitor for symptoms and initiate antiviral treatment early after symptoms begin.

CDC recommendations for antiviral use for variant influenza virus infections are like those for seasonal influenza virus infection (see www.cdc.gov/flu/professionals/antivirals/index.htm). CDC recommends antiviral treatment for all suspected cases of human infection with avian influenza viruses (see www.cdc.gov/flu/avianflu/severe-potential.htm). Recommendations for postexposure prophylaxis of close contacts of confirmed human infections of avian influenza A(H5N1) and A(H7N9) viruses are available at www.cdc.gov/flu/avianflu/novel-av-chemoprophylaxis-guidance.htm.

Consider postexposure prophylaxis for anyone exposed to birds infected with influenza A(H5N1), A(H7N9), A(H5N2), and A(H5N8). The decision to initiate prophylaxis, however, should be based on clinical judgment, with consideration given to the type of exposure and whether the exposed person is at increased risk for complications from influenza. If antiviral prophylaxis is initiated for people exposed to avian influenza A viruses, CDC recommends twice daily treatment dosing for oseltamivir or zanamivir instead of once daily prophylaxis dosing (see www.cdc.gov/flu/avianflu/guidance-exposed-persons.htm).

PREVENTION

Vaccines

Vaccination is the most effective way to prevent influenza and its complications. In the United States, CDC recommends annual seasonal influenza vaccination for people aged ≥6 months. Several influenza vaccines are approved for use in the United States (see www.cdc.gov/flu/prevent/different-flu-vaccines.htm) and can be grouped into 3 categories: inactivated influenza vaccine (IIV) including cell-based, high-dose, and adjuvanted influenza vaccines; live attenuated influenza vaccine (LAIV); and recombinant influenza vaccine (RIV).

For updates and recommendations, refer to www.cdc.gov/flu/professionals/acip/summary/summary-recommendations.htm. For people for whom >1 type of vaccine is approved, clinicians can provide any category of vaccine. Children aged 6 months–8 years who have never received an influenza vaccine, or who have not previously received a lifetime total of ≥2 doses, require 2 doses of age-appropriate influenza vaccine given ≥4 weeks apart during their first season of vaccination to induce sufficient immune response.

Travelers—including people at increased risk for complications of influenza—who did not receive the current seasonal influenza vaccine and who are traveling to parts of the world where influenza activity is ongoing, should consider influenza vaccination ≥2 weeks before departure.

ADMINISTRATION

IIVs are administered by intramuscular injection and labeled for use in people aged ≥6 months, but specific age indications vary by manufacturer and product; follow label instructions. Cell-based inactivated vaccines are licensed for people aged

≥2 years. High-dose and adjuvanted IIV vaccines, which can elicit higher levels of antibodies than standard-dose vaccines, are available for people aged ≥65 years. LAIV is administered as a nasal spray and is labeled for use in people aged 2–49 years who do not have contraindications. RIV is labeled for use in people aged ≥18 years.

ADVERSE REACTIONS

INACTIVATED INFLUENZA VACCINE

The most frequent side effects of vaccination with IIV in adults are soreness and redness at the vaccination site. These local injection-site reactions are slightly more common with high-dose IIV. Reactions generally are mild and rarely interfere with the ability to conduct usual, daily activities. Fever, headache, malaise, myalgia, and other systemic symptoms sometimes occur after vaccination; symptoms might be more frequent in people with no previous exposure to the influenza virus antigens in the vaccine (e.g., young children) and are generally short-lived.

GBS is associated with influenza-like illness and was associated with the 1976 swine influenza vaccine, which had an increased risk of 1 additional case of GBS per 100,000 people vaccinated. None of the studies of influenza vaccines other than the 1976 influenza vaccine have demonstrated a risk for GBS of similar magnitude. The increased risk for GBS after seasonal influenza vaccines generally is small, ≈1–2 additional cases per 1 million people vaccinated, whereas the estimated risk for GBS after influenza is ≈17.2 cases per 1 million patients hospitalized with influenza.

LIVE ATTENUATED INFLUENZA VACCINE

The most frequent side effects of LAIV reported in healthy adults include minor upper respiratory symptoms, runny nose, and sore throat, which are generally well tolerated. Some children and adolescents have reported fever, myalgia, vomiting, and wheezing. These symptoms, particularly fever, are more often associated with the first administered LAIV dose and are self-limited.

Children aged 2–4 years who have a history of wheezing in the past year or who have a diagnosis of asthma should not receive LAIV. People 2–49 years of age who have conditions that increase their risk for severe influenza (e.g., immunocompromising conditions, pregnancy) should receive IIV or RIV, not LAIV. To decrease the risk of transmitting live virus to severely immunocompromised people, their caretakers also should not receive LAIV, or should avoid contact for 7 days after receiving LAIV.

COMPOSITION

Influenza vaccine composition can be trivalent, protecting against 3 different influenza viruses (2 influenza A subtypes and 1 influenza type B lineage), or quadrivalent, with protection against 4 different influenza viruses (2 influenza A subtypes and 2 influenza type B lineages). Quadrivalent vaccine includes a representative strain from antigenically distinct B-Yamagata and B-Victoria lineages. All influenza vaccines in the United States are quadrivalent vaccines.

COVERAGE

No information is available about the benefits of revaccinating people before summer travel who were vaccinated during the preceding fall, and revaccination is not recommended. People at increased risk for influenza complications should consult with their health care provider to discuss the risk for influenza or other travel-related diseases before traveling during the summer.

Seasonal influenza vaccines are not expected to provide protection against human infection with animal-origin novel influenza viruses, including influenza A(H5N1) and A(H7N9) viruses. No commercially available influenza vaccines are available to protect against avian or swine viruses.

PRECAUTIONS & CONTRAINDICATIONS

Influenza vaccine is contraindicated in people who have had a previous severe allergic reaction to influenza vaccine, regardless of which vaccine component was responsible for the reaction. Immediate hypersensitivity reactions (e.g., hives, angioedema, allergic asthma, or systemic anaphylaxis) rarely occur after influenza vaccination. These reactions likely result from hypersensitivity to vaccine components, one of which is residual egg protein. People with a history of egg allergy

who have experienced only hives after exposure to eggs can receive any licensed and recommended influenza vaccine for their age and health status. Vaccine options are also available for people with a history of egg allergy with a history of severe reaction to egg, and are outlined at www.cdc.gov/flu/professionals/vaccination/vax-summary.htm#egg-allergy.

Personal Protective Measures

Measures that can help prevent influenza virus infection and other infections during travel include avoiding close contact with sick people and washing hands often with soap and water. In places where soap and a safe source of water are not available, CDC recommends using an alcohol-based hand sanitizer containing ≥60% alcohol. Face coverings are effective in preventing the spread of respiratory viruses, particularly among people in confined areas, and might have a role in the prevention of contagion during influenza epidemic periods. An ill person can help prevent the spread of illness to others by covering their nose and mouth with their elbow when coughing and sneezing and avoiding close contact with others. If symptomatic people cannot avoid contact with others, consider having them wear a mask when they are in close contact with others (see www.cdc.gov/flu/professionals/infectioncontrol/maskguidance.htm).

The best way to prevent infection with animal-origin influenza viruses, including A(H5N1) and A(H7N9), is to follow standard travel safety precautions, including using good hand hygiene, practicing food safety precautions, and avoiding contact with sources of exposure. Most human infections with animal-origin influenza viruses have occurred after direct or close contact with infected poultry or swine. In destinations where avian influenza virus outbreaks are occurring, travelers or those living abroad should avoid live animal markets and farms where animals are raised, avoid contact with sick or dead animals, avoid eating undercooked or raw animal products (including eggs), and avoid eating foods or drinking beverages that contain animal blood.

CDC website: www.cdc.gov/flu

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JAPANESE ENCEPHALITIS

Susan Hills, Nicole Lindsey, Marc Fischer

INFECTIOUS AGENT: Japanese encephalitis (JE) virus	
ENDEMICITY	Asia and parts of the western Pacific
TRAVELER CATEGORIES AT GREATEST RISK FOR EXPOSURE & INFECTION	Adventure tourists Long-term travelers and expatriates
PREVENTION MEASURES	Avoid insect bites Japanese encephalitis is a vaccine-preventable disease
DIAGNOSTIC SUPPORT	State health department; or contact CDC's Division of Vector-Borne Diseases, Arboviral Diseases Branch (970-221-6400; www.cdc.gov/ncezid/dvbd/specimensub/arboviral-shipping.html)

INFECTIOUS AGENT

Japanese encephalitis (JE) virus is a single-stranded RNA virus that belongs to the genus *Flavivirus* and is closely related to dengue, West Nile, and Saint Louis encephalitis viruses.

TRANSMISSION

JE virus is transmitted to humans through the bite of an infected mosquito, primarily *Culex* species. The virus is maintained in an enzootic cycle between mosquitoes and amplifying vertebrate hosts, primarily wading birds and pigs. Humans are incidental or dead-end hosts because they usually do not develop a level or duration of viremia sufficient to infect mosquitoes.

EPIDEMIOLOGY

JE virus is the most common vaccine-preventable cause of encephalitis in Asia, occurring throughout most of Asia and parts of the western Pacific. Transmission principally occurs in rural agricultural areas, often associated with rice cultivation and flood irrigation. In some areas of Asia, these ecologic conditions can occur near, or occasionally within, urban centers. In temperate areas of Asia, transmission is seasonal, and human disease usually peaks in summer and fall. In the subtropics and tropics, seasonal transmission varies with monsoon rains and irrigation practices and might be prolonged or even occur year round.

In endemic countries, where adults have acquired immunity through natural infection, JE is primarily a disease of children. Travel-associated JE can occur among people of any age, however. For most travelers to Asia, the risk for JE is extremely low but varies based on destination, accommodations, activities, and duration and season of travel.

Before 1973, >300 cases of JE were reported among soldiers from the United States, the United Kingdom, Australia, and Russia. During 1973–2020, 88 JE cases among travelers or expatriates from nonendemic countries were published or reported to the Centers for Disease Control and Prevention (CDC). Since 1993, when a JE vaccine became available in the United States, only 13 JE cases among US travelers have been reported to CDC (1993–2020).

The overall incidence of JE among people from nonendemic countries traveling to Asia is estimated to be <1 case per 1 million travelers. However, expatriates and travelers who stay for prolonged periods in rural areas with active JE virus transmission might be at similar risk as the susceptible, pediatric resident population, which is 6–11 cases per 100,000 children per year. Travelers,

even on brief trips, might be at increased risk if they have extensive outdoor or nighttime exposure in rural areas during periods of active transmission. Shorter-term (e.g., <1 month) travelers whose visits are restricted to major urban areas are at minimal risk for JE. In some endemic areas, few human cases occur among residents because of natural immunity among older people or vaccination, but JE virus is still maintained locally in an enzootic cycle between animals and mosquitoes. Therefore, susceptible visitors could be at risk for infection.

CLINICAL PRESENTATION

Most human infections with JE virus are asymptomatic; <1% of people infected with JE virus develop neurologic disease. Acute encephalitis is the most recognized clinical manifestation of JE virus infection. Milder forms of disease (e.g., aseptic meningitis, undifferentiated febrile illness) also can occur. The incubation period is 5–15 days. Illness usually begins with sudden onset of fever, headache, and vomiting. Mental status changes, focal neurologic deficits, generalized weakness, and movement disorders might develop over the next few days. The classical description of JE includes a parkinsonian syndrome with mask-like facies, tremor, cogwheel rigidity, and choreoathetoid movements. Acute flaccid paralysis, with clinical and pathological features like those of poliomyelitis, also has been associated with JE virus infection. Seizures are common, especially among children. The case-fatality rate is ≈20%–30%. Among survivors, 30%–50% have serious neurologic, cognitive, or psychiatric sequelae.

Common clinical laboratory findings include mild anemia, moderate leukocytosis, and hyponatremia. Cerebrospinal fluid (CSF) typically has a mild to moderate pleocytosis with a lymphocytic predominance, slightly elevated protein, and normal ratio of CSF to plasma glucose.

DIAGNOSIS

Suspect JE in a patient with evidence of a neurologic infection (e.g., encephalitis, meningitis, acute flaccid paralysis) who recently traveled to or resided in an endemic country in Asia or the western Pacific. Laboratory diagnosis of JE virus infection should be performed using a JE virus–specific IgM-capture ELISA on CSF or serum. JE virus–specific IgM can be measured in the CSF of most patients ≥4 days after symptom onset and in serum ≥7 days after symptom onset.

Plaque reduction neutralization tests can be performed to confirm the presence of JE virus–specific neutralizing antibodies and to discriminate between cross-reacting antibodies from closely related flaviviruses (e.g., dengue virus, West Nile virus). A ≥4-fold rise in JE virus–specific neutralizing antibodies between acute- and convalescent-phase serum specimens can be used to confirm recent infection. When interpreting laboratory results, clinicians must consider vaccination history, date of symptom onset, and information regarding other flaviviruses known to circulate in the geographic area that might cross-react in serologic assays.

Humans have low levels of transient viremia and usually have neutralizing antibodies by the time distinctive clinical symptoms are recognized. Virus isolation and nucleic acid amplification tests are insensitive in detecting JE virus or viral RNA in blood or CSF and should not be used for ruling out a diagnosis of JE. Contact the state or local health department or CDC's Arboviral Diseases Branch, Division of Vector-Borne Diseases (970-221-6400) for assistance with diagnostic testing. Instructions for submitting CSF and serum specimens to CDC for testing can be found at www.cdc.gov/ncezid/dvbd/specimensub/arboviral-shipping.html.

TREATMENT

No specific antiviral treatment for JE is available; therapy consists of supportive care and management of complications.

PREVENTION

Personal Protective Measures

Travelers can best prevent mosquito-borne diseases, including JE, by avoiding mosquito bites (see Sec. 4, Ch. 6, Mosquitoes, Ticks & Other Arthropods).

Vaccine

One JE vaccine is licensed and available in the United States, an inactivated Vero cell culture–derived vaccine, IXIARO, manufactured by Valneva Austria GmbH. IXIARO was approved

in March 2009 for use in people aged ≥17 years, and in May 2013 for use in children aged 2 months through 16 years. Other inactivated and live attenuated JE vaccines are manufactured and used in other countries but are not licensed for use in the United States.

INDICATIONS FOR TRAVELERS

Based on each traveler's planned itinerary, assess the risks for mosquito exposure and JE virus infection and discuss ways to reduce these risks. Advise all travelers going to JE-endemic countries of the importance of personal protective measures to reduce the risk for mosquito bites. The decision whether to vaccinate should be individualized and include consideration of the risks related to the specific travel itinerary, likelihood of future travel to JE-endemic countries, the high rate of death and disability when JE occurs, availability of an effective vaccine, the possibility but low probability, of serious adverse events after immunization, and the traveler's personal perception and tolerance of risk.

Travel location, duration, activities, accommodations, and seasonal patterns of disease in the areas to be visited each influence risk for exposure. Interpret the data in Table 5-14 cautiously, because JE virus transmission activity varies within countries and from year to year, and surveillance data are often incomplete. Additional information on factors that increase risk is provided in Japanese encephalitis vaccine: Recommendations of the Advisory Committee on Immunization Practices (www.cdc.gov/mmwr/volumes/68/rr/rr6802a1.htm).

The Advisory Committee on Immunization Practices (ACIP) recommends JE vaccine for people moving to a JE-endemic country, longer-term (e.g., ≥1 month) travelers to JE-endemic areas, and frequent travelers to JE-endemic areas. Consider JE vaccine for shorter-term (e.g., <1 month) travelers with an increased risk for JE based on planned travel duration, season, location, activities, and accommodations. In addition, consider vaccination for travelers going to JE-endemic areas but who are uncertain of specific destinations, activities, or duration of travel.

ACIP does not recommend JE vaccine for travelers with very low risk itineraries (e.g., shorter-term travel limited to urban areas, travel that occurs outside a well-defined JE virus transmission season).

EFFICACY & IMMUNOGENICITY

No efficacy data are available for IXIARO. The vaccine was licensed in the United States based on its ability to induce JE virus–specific neutralizing antibodies as a surrogate for protection. In pivotal immunogenicity studies, 96% of adults and 100% of children developed protective neutralizing antibodies 28 days after receiving a primary immunization series of 2 doses administered 28 days apart. In a trial among adults aged ≥65 years, 65% were seroprotected at 42 days after the 2-dose primary series. An accelerated primary series of 2 doses administered 7 days apart was studied among adults aged 18–65 years and was noninferior to the conventional dosing schedule.

In a study where a booster dose was administered to adults at 15 months, 96% of subjects were still seroprotected ≈6 years later. In a study conducted among 150 children in a JE-endemic country who received a booster dose at 11 months, 100% were seroprotected at 24 months after the booster dose.

ADMINISTRATION

The primary vaccination dose and schedule for IXIARO varies by age (Table 5-15). To administer a 0.25-mL dose, expel and discard half of the volume from the 0.5-mL prefilled syringe by pushing the plunger stopper up to the edge of the red line on the syringe barrel before injection. For all age groups, the 2-dose series should be completed ≥1 week before travel.

BOOSTER DOSES

A booster dose (third dose) should be given at ≥1 year after completion of the primary IXIARO series if ongoing exposure or reexposure to JE virus is expected.

Limited data are available on the use of IXIARO as a booster dose after a primary series with the mouse brain–derived inactivated JE vaccine. Three studies have been conducted, 2 in US military personnel and the other at 2 travel clinics in Europe. Results showed that among adults who had previously received at

Table 5-14 Risk areas & transmission season for Japanese encephalitis (JE), by destination[1,2,3]

COUNTRY	RISK AREAS	TRANSMISSION SEASON	COMMENTS
AUSTRALIA	Outer Torres Strait Islands New South Wales Queensland South Australia Victoria	December–May All human cases reported February–April	Four cases previously reported from Outer Torres Strait Islands and 1 case from Tiwi Islands On Australian mainland, 1 case reported from Far North Queensland (1998) In 2022, cases reported in the states of New South Wales, South Australia, Victoria
BANGLADESH	Widespread	Year round Most cases reported July–November	Disease incidence is greatest in northwest Bangladesh
BHUTAN	Presumed widespread in non-mountainous areas	Unknown	Risk likely greatest in southern districts that share similar ecologic conditions with bordering JE-endemic states of India
BRUNEI DARUSSALAM	Presumed widespread	Unknown	Limited data, but outbreak reported in 2013 Proximity to Sarawak, Malaysia, suggests ongoing transmission likely
BURMA (MYANMAR)	Widespread	Year round Most cases reported May–September	Greatest risk in delta and lowland areas
CAMBODIA	Widespread	Year round Peak season May–October	Cases reported from most provinces, so transmission likely countrywide
CHINA	All provinces except Xinjiang and Qinghai	Peak season June–October	
INDIA	Andhra Pradesh, Arunachal Pradesh, Assam, Bihar, Goa, Haryana, Jharkhand, Karnataka, Kerala, Maharashtra, Manipur, Meghalaya, Nagaland, Odisha, Punjab, Tamil Nadu, Telangana, Tripura, Uttar Pradesh, Uttarakhand, West Bengal	Peak season May–November, especially in northern India Season can be extended or year round in some areas, especially in southern India	
INDONESIA	Widespread	Year round Peak season varies by island	Cases reported from many islands, including Bali, Java, Kalimantan, Nusa Tenggara, Papua, Sumatra Transmission likely on all islands Several cases reported among travelers to Bali in recent years

Table 5-14 Risk areas & transmission season for Japanese encephalitis (JE), by destination (continued)

COUNTRY	RISK AREAS	TRANSMISSION SEASON	COMMENTS
JAPAN	All islands	June–October	Rare sporadic cases reported from all islands except Hokkaido Enzootic transmission without reported human cases on Hokkaido
LAO PEOPLE'S DEMOCRATIC REPUBLIC	Widespread	Year round Peak season June–September	
MALAYSIA	Widespread	Year round Peak season in Sarawak, October–December	Much higher rates of disease reported from Sarawak than peninsular Malaysia
NEPAL	Southern lowlands (Terai), some hill and mountain districts	Peak season June–October	Highest rates of disease reported from southern lowlands (Terai) Vaccine not routinely recommended for those trekking in high-elevation areas
NORTH KOREA	Presumed widespread	Unknown Proximity to South Korea suggests peak transmission May–November	
PAKISTAN	Unknown	Unknown	Very limited data Previous case report and serosurvey data suggest transmission possible at least in Sindh Province
PAPUA NEW GUINEA	Widespread	Presumed year round	Sporadic cases reported from Western Province Serologic evidence of disease from Gulf and Southern Highland Provinces 1 case reported from near Port Moresby Transmission likely countrywide
PHILIPPINES	Widespread	Year round Peak season April–August	Human, animal, and mosquito studies indicate transmission in 32 provinces Transmission likely on all islands
RUSSIA	Primorsky Krai	June–September	Cases previously reported from Primorsky Krai Vaccine not routinely recommended
SINGAPORE	Presumed in focal areas	Year round	Very rare sporadic cases reported Vaccine not routinely recommended

(*continued*)

Table 5-14 Risk areas & transmission season for Japanese encephalitis (JE), by destination (continued)

COUNTRY	RISK AREAS	TRANSMISSION SEASON	COMMENTS
SOUTH KOREA	Widespread	May–November	
SRI LANKA	Widespread, except in mountainous areas	Year round Peak season November–February	
TAIWAN	Widespread	Peak season May–October	
THAILAND	Widespread	Year round Peak season May–October, especially northern Thailand	Highest rates of disease reported from Chiang Mai Valley Several traveler cases reported in recent years from resort and coastal areas of southern Thailand
TIMOR-LESTE	Presumed widespread	No data Proximity to West Timor suggests year-round transmission	
VIETNAM	Widespread	Year round Peak season May–October, especially northern Vietnam	

[1]When making decisions on vaccination, consider destination and transmission season information in association with travel duration and activities.
[2]Data are based on published and unpublished reports. Perform risk assessments cautiously; risk can vary within areas and from year to year, and surveillance data regarding human cases and JE virus transmission are often incomplete. In some endemic areas, human cases among residents are limited because of vaccination or natural immunity among older people. Because JE virus is maintained in an enzootic cycle between animals and mosquitoes, susceptible visitors to these areas still might be at risk for infection.
[3]Outbreaks previously occurred in the Western Pacific Islands of Guam (1947–1948) and Saipan (1990), but these are no longer considered risk areas and are not included in the table.

least a primary series of mouse brain–derived inactivated JE vaccine, a single dose of IXIARO provided good protection through 12–23 months.

SAFETY & ADVERSE REACTIONS

IXIARO was licensed in the United States based on safety evaluations in almost 5,000 adults. Since licensure, >1 million doses of IXIARO have been distributed in the United States without any identified safety concerns. Local symptoms of pain and tenderness were the most reported symptoms in a safety study among 1,993 adult participants who received 2 doses of IXIARO. Fatigue, headache, and myalgia were each reported at a rate of >10%. In children, fever was the most reported systemic reaction in studies. Serious adverse events are reported only rarely.

PRECAUTIONS & CONTRAINDICATIONS

A severe allergic reaction after a previous dose of IXIARO or any other JE vaccine, or to any component of IXIARO, is a contraindication to administration of IXIARO. IXIARO contains protamine sulfate, a compound known to cause hypersensitivity reactions in some people.

Table 5-15 Administration information for the inactivated Vero cell culture–derived Japanese encephalitis vaccine, IXIARO

AGE	DOSE	ROUTE	SCHEDULE	BOOSTER[1]
2 months–2 years	0.25 mL	IM	0, 28 days	≥1 year after primary series
3–17 years	0.5 mL	IM	0, 28 days	≥1 year after primary series
18–65 years	0.5 mL	IM	0, 7–28 days	≥1 year after primary series
>65 years	0.5 mL	IM	0, 28 days	≥1 year after primary series

Abbreviations: IM, intramuscular; mL, milliliter

[1]Administer a booster when potential for Japanese encephalitis virus exposure continues (e.g., repeated travel to endemic areas).

No studies of IXIARO in pregnant people have been conducted. Pregnancy is a precaution against the use of IXIARO, however, and in most instances, clinicians should defer vaccinating pregnant people. Further discussion (including the possibility of delaying travel) is merited before recommending vaccination to the pregnant person who must travel to areas where the risk for JE infection outweighs the theoretical risk from immunization.

CDC website: www.cdc.gov/japaneseencephalitis

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MIDDLE EAST RESPIRATORY SYNDROME / MERS

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INFECTIOUS AGENT: Middle East respiratory syndrome coronavirus (MERS-CoV)	
ENDEMICITY (IN CAMELS)	Arabian Peninsula Parts of North, West, and East Africa
TRAVELER CATEGORIES AT GREATEST RISK FOR EXPOSURE & INFECTION	Travelers in or near the Arabian Peninsula who have contact with camels or patients with known MERS infection, or who visit health care facilities
PREVENTION METHODS	Practice general hygiene measures, including regular hand washing, especially after contact with camels and people who are ill Immunocompromised people and those with underlying health conditions should avoid close contact with camels Follow safe food and water precautions and avoid drinking raw camel milk or camel urine, or eating improperly cooked meat, including camel meat
DIAGNOSTIC SUPPORT	Contact state or local health department

INFECTIOUS AGENT

Middle East respiratory syndrome coronavirus (MERS-CoV) is a single-stranded, positive-sense RNA virus that belongs to the family *Coronaviridae*, genus *Betacoronavirus,* which causes Middle East respiratory syndrome (MERS).

TRANSMISSION

MERS-CoV is a zoonotic virus known to transmit sporadically from the host reservoir, camels (specifically dromedaries [*Camelus dromedarius*]), to humans. Limited human-to-human transmission chains can subsequently occur, usually via close contact in health care or household settings.

Camel-to-Human Transmission

Transmission from camels to humans occurs via direct contact (e.g., grooming, petting), and possibly via indirect contact (e.g., contact with camel feces or camel products, being in settings where camels are present). Precise transmission mechanisms are unknown, but camel handlers with prolonged direct contact with live camels are thought to have the greatest risk for infection.

MERS-CoV has been detected in camels in North, West, and East Africa, and in or near the Arabian Peninsula, but most camel-to-human transmission has been reported within the Arabian Peninsula. Limited recent evidence suggests acute (RNA positive) infection among camel workers in parts of East Africa, and evidence for past (antibody positive) infection in camel workers in parts of North and East Africa. The extent of camel-to-human transmission on the African continent is not fully understood, however, and no current evidence of subsequent human-to-human transmission in Africa has been reported.

Person-to-Person Transmission

After camel-to-human transmission, MERS-CoV can be spread from person to person, resulting in outbreaks in households and in health care settings. MERS-CoV does not seem to pass easily between people and generally requires very close contact (e.g., in households, including sharing a bedroom with or caring for a person known to be infected with MERS-CoV, or when providing unprotected patient care in health care settings).

Large health care–related outbreaks have been documented, with transmission to other patients, visitors, and health care personnel; transmission has been reported in emergency departments, inpatient wards, and outpatient dialysis units. Superspreading events in health care facilities (generally, a single case linked to ≥5 subsequent cases) often have involved severely ill patients and have been associated with late recognition of people infected with MERS-CoV, crowding, delayed implementation of infection-control practices, and performance of aerosol-generating procedures prior to adopting airborne precautions.

Some evidence shows that symptomatic people, especially those with more severe illness, play a major role in human-to-human transmission, but little evidence supports transmission from asymptomatic people. Sustained community transmission of MERS-CoV has not been shown. A few MERS cases have been reported without camel, health care, or known MERS case exposure, indicating that MERS-CoV transmission pathways are not fully understood.

EPIDEMIOLOGY

First reported in September 2012, illnesses with onset as early as April 2012 were subsequently documented. To date, all MERS cases reported to the World Health Organization (WHO) have been linked to travel to, or residence in, countries in or near the Arabian Peninsula where risk of infection is ongoing, including Bahrain, Iran, Jordan, Kuwait, Lebanon, Oman, Qatar, Saudi Arabia, United Arab Emirates, or Yemen.

Cases among travelers to the Arabian Peninsula have been reported from North Africa, Asia, and Europe; subsequent transmission to travelers' contacts also has been documented. More than 1,300 people in the United States have been evaluated for MERS after travel to the Arabian Peninsula. To date, only 2 patients in the United States have tested positive for MERS-CoV infection; both were travelers who arrived from the Arabian Peninsula in May 2014, and no secondary transmission was identified for either case.

Most reported MERS cases have been linked to human-to-human transmission within health care facilities; people who have direct contact with camels or close contact with symptomatic MERS patients are at risk for MERS-CoV infection.

Camel-Associated Risk

While recent evidence has highlighted the potential for camel-to-human transmission within parts of North and East Africa, no subsequent human-to-human transmission has been reported after such exposures. The risk for MERS-CoV infection in North, West, or East Africa is thought to be minimal, but travelers to the region who have direct camel contact, including those who work with camels, could be at risk.

Health Care–Associated Risk

Health care personnel and others who visit or work in facilities experiencing known MERS-CoV transmission are at risk for exposure and infection. In addition, depending on their activities, travelers to, in, or near the Arabian Peninsula, including tourists, medical tourists, or business travelers, also could be at risk for infection. Close contacts of ill travelers who come from the Arabian Peninsula represent another group at potential risk for infection.

One of the largest health care–associated outbreaks (186 cases, 38 deaths), occurred in the Republic of Korea in 2015 because of delayed recognition of a single infected business traveler returning home from the Arabian Peninsula. Health care–associated transmission also has occurred in France and the United Kingdom from cases exported from the Arabian Peninsula. Rapid detection and isolation of patients with MERS seeking medical care is critical to preventing secondary transmission in health care facilities.

CLINICAL PRESENTATION

MERS is associated with a spectrum of illness that ranges from asymptomatic infection to mild upper respiratory tract illness to severe acute respiratory failure and multiple organ dysfunction. High mortality has been observed with MERS; ≈35% of confirmed cases have been fatal. For people who develop symptomatic illness, the incubation period is ≈2–14 days; median incubation period is slightly more than 5 days. Disease is most often characterized by cough, fever, and shortness of breath. Other nonspecific symptoms include abdominal pain, nausea, vomiting, and diarrhea; arthralgias and myalgias; chills; headache; and sore throat. Initial symptoms can progress to pneumonia. Chest radiographs have shown variable pulmonary involvement.

In addition to acute and often severe respiratory compromise, serious complications of MERS include acute renal injury and cardiovascular collapse. Abnormal laboratory findings can include elevated liver function tests, lymphopenia, and thrombocytopenia.

More severe illness and poorer outcomes have been observed in older adults, people who are immunocompromised, and people with underlying medical conditions (e.g., cardiovascular disease [including hypertension], diabetes mellitus, chronic kidney disease, chronic lung disease). Individuals with >1 underlying condition are at increased risk for poor outcomes.

DIAGNOSIS

Several diagnostic assays have been developed to detect acute infection with MERS coronavirus, including real-time reverse transcription PCR (rRT-PCR). These assays can reliably distinguish MERS coronavirus from other human coronaviruses, including severe acute respiratory syndrome coronavirus 2, the virus that causes coronavirus disease 2019 (COVID-19). Notably for MERS, specimens collected from the lower respiratory tract (e.g., bronchoalveolar lavage, endotracheal aspirates, sputum) are the priority for testing, although upper respiratory tract and serum specimens also can be used. To increase the likelihood of detecting MERS coronavirus, collect specimens from multiple sites and at multiple time points over the course of the illness.

In the United States, most state public health laboratories are approved to test for MERS-CoV using an rRT-PCR assay developed by the Centers for Disease Control and Prevention (CDC). Coordinate testing through state and local health departments, who will, in turn, contact CDC for additional diagnostic support as needed. For details on who should be evaluated as a person under investigation for MERS-CoV infection, see Box 5-04 and the CDC website, www.cdc.gov/coronavirus/mers/interim-guidance.html. Consult with public health

BOX 5-04 Patients in the United States who should be evaluated for Middle East respiratory syndrome coronavirus (MERS-CoV) infection

SEVERE ILLNESS: criteria for evaluation
Patient has fever and pneumonia or fever and acute respiratory distress syndrome, no alternative diagnosis, and ≥1 of the following epidemiologic risk factors

- Within 14 days before symptom onset, a history of travel from countries in or near the Arabian Peninsula

OR

- Within 14 days before symptom onset, history of close contact with a person who themselves developed fever and acute respiratory illness within 14 days of travel to countries in or near the Arabian Peninsula

OR

- Is a member of a cluster of patients with severe acute respiratory illness of unknown etiology

MILDER ILLNESS: criteria for evaluation
Patient has fever and symptoms of respiratory illness (e.g., cough and/or shortness of breath, not necessarily pneumonia), no alternative diagnosis, and ≥1 of the following epidemiologic risk factors

- Within 14 days of symptom onset, a history of being in a health care facility in a country or territory in or near the Arabian Peninsula where recent health care–associated cases of MERS have been identified

OR

- Within 14 days of symptom onset, a history of direct camel contact in or near the Arabian Peninsula

OR

- Within 14 days of symptom onset, a history of close contact with a person with confirmed MERS-CoV infection case while that person was ill

departments for case-patients with equivocal clinical presentations or exposure histories (e.g., uncertain health care exposure).

Because the risk for MERS-CoV transmission from camels in North, West, and East Africa is not yet fully understood, consider MERS evaluation for travelers coming from these regions who develop severe respiratory illness (fever and pneumonia or acute respiratory distress syndrome) ≤14 days of direct camel contact.

TREATMENT

Treatment is currently limited to supportive care; no specific therapies for patients with MERS have yet been approved. As of April 2022, antiviral and monoclonal antibody therapies are in development or under investigation for potential use. In preclinical trials, some FDA-approved therapeutic options for adult patients with COVID-19 are also demonstrating efficacy against MERS-CoV.

PREVENTION

Although no vaccine or preventive drug has been approved for use in humans, several are under investigation. Because of the risk for nosocomial transmission resulting in sizeable hospital outbreaks, rapid detection and isolation of patients with MERS is critical. Standard, contact, and airborne infection-control precautions are recommended for hospitalized patients being evaluated for or diagnosed with MERS.

Travelers should practice general hygiene precautions (e.g., frequent handwashing; avoiding touching their eyes, noses, and mouths; avoiding contact with sick people). Additionally, WHO recommends as a general precaution that anyone visiting places where camels are present practice general hygiene measures, including regular handwashing before and after touching animals. In line with food hygiene practices, WHO recommends people avoid drinking raw camel milk or camel urine or eating meat (including camel meat) that has not been properly cooked. WHO also recommends that people at higher risk for severe MERS illness avoid close contact with camels.

CDC website: www.cdc.gov/coronavirus/mers

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MUMPS

Mariel Marlow, Jessica Leung

INFECTIOUS AGENT: Mumps virus	
ENDEMICITY	Worldwide
TRAVELER CATEGORIES AT GREATEST RISK FOR EXPOSURE & INFECTION	All travelers, especially those not vaccinated against mumps
PREVENTION METHODS	Mumps is a vaccine-preventable disease
DIAGNOSTIC SUPPORT	A clinical laboratory certified in moderate complexity testing; or see CDC's Division of Viral Diseases (www.cdc.gov/mumps/lab/index.html)

INFECTIOUS AGENT

Mumps virus is an enveloped, single-stranded, negative-sense RNA virus of the family *Paramyxoviridae*, genus *Rubulavirus*.

TRANSMISSION

Transmission occurs by respiratory droplets or saliva from a person infected with mumps and usually requires close contact for spread. Transmission is most likely to occur 2 days before through 5 days after the onset of parotitis.

EPIDEMIOLOGY

Mumps is endemic throughout the world. On average >500,000 mumps cases are reported to the World Health Organization annually; global mumps incidence is challenging to estimate, however, because mumps is not a notifiable disease in many countries. As of 2018, mumps-containing vaccine is routinely used in 122 countries. Since the mid-2000s, large mumps outbreaks have been reported among populations with high 2-dose measles-mumps-rubella (MMR) vaccine coverage in countries with routine mumps immunization programs. Despite these outbreaks, mumps incidence is still much higher in countries that do not have routine mumps vaccination. The risk for potential exposure among travelers is unknown but could be high in many countries.

CLINICAL PRESENTATION

The average incubation period is 16–18 days (range 12–25 days). Mumps is an acute systemic illness that classically presents with parotitis (acute onset of unilateral or bilateral tender, self-limited swelling of the parotid) or other salivary gland swelling, usually lasting 5 days. Nonspecific prodromal symptoms of anorexia, low-grade fever, headache, malaise, and myalgias can occur several days before the onset of parotitis. Infections also can be asymptomatic or limited to nonspecific respiratory symptoms. Complications include aseptic meningitis, encephalitis, hearing loss, mastitis, oophoritis, orchitis, and pancreatitis, any of which can occur in the absence of parotitis. Fully vaccinated people can get mumps but are at much lower risk for mumps and mumps complications.

DIAGNOSIS

Mumps is usually clinically defined as acute parotitis or other salivary gland swelling or oophoritis or orchitis, without other apparent cause. Laboratory confirmation of mumps involves detecting mumps virus by real-time reverse

transcription PCR (rRT-PCR) or virus isolation by culture. Laboratory confirmation of mumps can be challenging; therefore, mumps cases should not be ruled out by negative laboratory results.

Serologic testing for the presence of IgM antibodies in serum also can aid in the diagnosis of mumps but is not confirmatory. Mumps laboratory testing can be performed by commercial labs, most state and local public health laboratories, and the Centers for Disease Control and Prevention (CDC). For further information on laboratory testing, including optimal timing for specimen collection, see www.cdc.gov/mumps/lab/index.html. Mumps is a nationally notifiable disease.

TREATMENT

Supportive care is the mainstay of treatment for mumps.

PREVENTION

Before departure from the United States, travelers aged ≥12 months who do not have acceptable evidence of mumps immunity (as documented by 2 doses of a mumps virus–containing vaccine, laboratory evidence of immunity, laboratory confirmation of disease, or birth before 1957) should be vaccinated with 2 doses of MMR vaccine ≥28 days apart, or 1 dose of MMR if they previously received 1 MMR dose. Measles-mumps-rubella-varicella (MMRV) vaccine is licensed for children aged 12 months through 12 years and can be used if vaccination for measles, mumps, rubella, and varicella is indicated for this age group. There is no recommendation for infants aged <12 months to receive vaccination against mumps before international travel; the Advisory Committee on Immunization Practice (ACIP) recommends, however, that infants aged 6–11 months receive 1 dose of MMR vaccine before departure to protect against measles. There is no recommendation for a third dose of MMR vaccine for travelers to countries experiencing mumps outbreaks.

CDC website: www.cdc.gov/mumps

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NOROVIRUS

Sara Mirza, Aron Hall

INFECTIOUS AGENT: Norovirus	
ENDEMICITY	Worldwide
TRAVELER CATEGORIES AT GREATEST RISK FOR EXPOSURE & INFECTION	All travelers
PREVENTION METHODS	Practice good hand hygiene with soap and water Carefully clean and disinfect surfaces and toilet areas contaminated with fecal material or vomit
DIAGNOSTIC SUPPORT	A clinical laboratory certified in moderate complexity testing; state health departments during outbreak investigations

INFECTIOUS AGENT

Norovirus infection is caused by nonenveloped, single-stranded RNA viruses of the genus *Norovirus*, which have also been referred to as Norwalk-like viruses, Norwalk viruses, and small round-structured viruses. Norovirus is a cause of viral gastroenteritis, sometimes referred to as stomach flu; however, norovirus has no biologic association with influenza or influenza viruses.

TRANSMISSION

Norovirus transmission occurs primarily through the fecal–oral route, either through direct person-to-person contact or indirectly via contaminated food or water. Norovirus also is spread through fomites and aerosols of vomitus.

EPIDEMIOLOGY

Norovirus outbreaks frequently occur in settings where people live in close quarters and can easily infect each other. Norovirus is a commonly reported cause of diarrhea among travelers in confined spaces (e.g., on cruise ships, and in camps, dormitories, hotels). Risk for infection is present anywhere food is prepared in an unsanitary manner and can be contaminated, or where drinking water is inadequately treated. Ready-to-eat cold foods (e.g., salads, sandwiches) are a particular risk. Raw shellfish, especially oysters, are a frequent source of infection because viral particles in contaminated water concentrate in the gut of these filter feeders. Contaminated ice has also been implicated in outbreaks.

Viral contamination of fomites can persist during and after outbreaks and be a source of infection. On cruise ships, for instance, environmental contamination has caused recurrent norovirus outbreaks on successive cruises with newly boarded passengers. Transmission of norovirus on airplanes has been reported during domestic and international flights and likely results from contamination of lavatories or from symptomatic passengers in the cabin.

Norovirus infections are common throughout the world. Globally, most children will have ≥1 infection by the time they are 5 years old. Norovirus infections can occur year round, but in temperate climates, activity peaks during the winter. Noroviruses are common in low-, middle-, and high-income countries. Globally, norovirus causes ≈18% of acute gastroenteritis cases and could be responsible for ≈200,000 deaths annually. In the United States, norovirus is the leading cause of medically attended gastroenteritis in young children and of outbreaks of gastroenteritis; norovirus

causes ≈19–21 million illnesses a year and ≈50% of all foodborne disease outbreaks.

CLINICAL PRESENTATION

Infected people usually experience acute onset of vomiting and non-bloody diarrhea. The incubation period is 12–48 hours. Other symptoms include abdominal cramps, nausea, and sometimes a low-grade fever. Illness is generally self-limited, and most patients fully recover in 1–3 days. In some cases, especially among the very young or elderly, dehydration can occur and require medical attention.

DIAGNOSIS

Norovirus infection is generally diagnosed based on symptoms. Diagnostic testing is not widely performed to guide clinical management of individual patients, but laboratory testing is used to identify disease clusters during outbreak investigations.

PCR-based multipathogen diagnostic panels are increasingly available for clinical and research purposes. These panels have good sensitivity and specificity to detect norovirus. The most common diagnostic test used at state public health laboratories and at the Centers for Disease Control and Prevention (CDC) is real-time reverse-transcription quantitative PCR (RT-qPCR), which rapidly and reliably detects the virus in stool specimens. Several commercial enzyme immunoassays (EIAs) also are available to detect the virus in stool specimens, but the specificity and sensitivity of EIAs are relatively poor compared with RT-qPCR.

CDC recommends contacting local health departments for outbreak investigation and specimen testing. Whole stool specimens are preferred for testing; vomitus specimens might be acceptable. For more information on laboratory diagnostic testing and specimen collection, see www.cdc.gov/norovirus/lab-testing/index.html and www.cdc.gov/laboratory/specimen-submission/detail.html.

TREATMENT

Supportive care is the mainstay of norovirus treatment, especially oral or intravenous rehydration. Antidiarrheals and antiemetics are not recommended for the routine management of acute gastroenteritis in children. For adults, antiemetic, antimotility, and antisecretory agents can be useful adjuncts to rehydration. Antibiotics are not useful in treating patients with norovirus disease.

PREVENTION

No norovirus vaccine is currently available, but vaccine development is advancing. Noroviruses are common and highly contagious, but travelers can minimize their risk for infection by frequently and properly washing hands and avoiding possibly contaminated food and water. Washing hands with soap and water for ≥20 seconds is considered the most effective way to reduce norovirus contamination; alcohol-based hand sanitizers might be useful between handwashings, but should not be considered a substitute for soap and water.

In addition to handwashing, people traveling together can use measures to prevent transmission of noroviruses, including carefully cleaning up fecal material or vomit and disinfecting contaminated surfaces and toilet areas. Travelers should use products approved by the US Environmental Protection Agency for norovirus disinfection; alternatively, they can use a dilute bleach solution (5–25 tablespoons bleach per gallon of water). Travelers should wash soiled articles of clothing for the maximum available cycle length and machine dry clothing on high heat.

To help prevent the spread of noroviruses, consider isolation for ill people on cruise ships and in institutional settings, including hospitals, long-term care facilities, and schools.

CDC website: www.cdc.gov/norovirus

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POLIOMYELITIS

Concepción Estívariz, Janell Routh, Steven Wassilak

5

INFECTIOUS AGENT: Poliovirus (serotypes 1, 2, 3)	
ENDEMICITY	Type 1 wild poliovirus (WPV): endemic to Afghanistan and Pakistan only Circulating vaccine-derived poliovirus (cVDPV): countries in Africa and Asia (see www.polioeradication.org and https://wwwnc.cdc.gov/travel/notices)
TRAVELER CATEGORIES AT GREATEST RISK FOR EXPOSURE & INFECTION	Any unvaccinated or under-vaccinated traveler to countries with current or recent poliovirus circulation
PREVENTION METHODS	Polio is a vaccine-preventable disease
DIAGNOSTIC SUPPORT	CDC Emergency Operations Center (770-488-7100; ask to speak to the on-call polio subject matter expert) CDC's Polio and Picornavirus Laboratory (picornalab@cdc.gov) CDC's Poliovirus Laboratory Testing (www.cdc.gov/polio/what-is-polio/lab-testing/)

INFECTIOUS AGENT

Polioviruses (genus *Enterovirus*) are small, non-enveloped viruses with a single-stranded RNA genome. Polioviruses are rapidly inactivated by chlorine, formaldehyde, heat, and ultraviolet light. Poliovirus has 3 serotypes, 1, 2, and 3, that evoke minimal heterotypic immunity between them.

TRANSMISSION

Transmission occurs when the virus enters through the mouth and multiplies in the throat and gastrointestinal tract. Virus can be excreted in nasopharyngeal secretions for 1–2 weeks and in stool for 3–6 weeks, even in people who develop no symptoms after infection. Transmission occurs from person to person through the oral and fecal–oral routes.

EPIDEMIOLOGY

Before a vaccine was available, infection with wild poliovirus (WPV) was common worldwide and had seasonal peaks and epidemics

in the summer and fall in temperate areas. The incidence of poliomyelitis (polio) in the United States declined rapidly after the licensure of inactivated poliovirus vaccine (IPV) in 1955 and live oral poliovirus vaccine (OPV) in the 1960s. The last cases of indigenously acquired polio in the United States occurred in 1979 and in the Americas in 1991.

Built on the success achieved in the Americas, the Global Polio Eradication Initiative (GPEI) began in 1988 and has made great progress in interrupting WPV transmission globally. Type 2 WPV was last isolated in 1999 and was declared eradicated in 2015; type 3 WPV was last detected in November 2012 and was declared eradicated in 2019. In 2021, type 1 WPV endemic circulation persisted in only 2 countries, Afghanistan and Pakistan. Despite achievements in eradicating WPV globally, polio-free countries with low vaccination coverage remain at risk for poliomyelitis outbreaks after importation of WPV. In February 2022, for example, a person in Malawi (onset of paralysis, November 2021) was identified with type 1 WPV, 18 months after Africa was certified free of indigenous WPV (in August 2020). The virus isolated from this patient was genetically linked to a type 1 WPV lineage last detected in Pakistan in 2019.

Countries that have low OPV coverage in routine immunization also are at risk of experiencing poliomyelitis cases and outbreaks caused by circulating vaccine-derived poliovirus (cVDPV). The live attenuated poliovirus strains contained in the Sabin OPV can circulate in areas with inadequate OPV coverage and revert to having wild-like characteristics. Rarely, OPV can cause paralytic poliomyelitis in vaccine recipients or their close contacts, known as vaccine-associated paralytic poliomyelitis (VAPP).

Because >90% of cVDPV cases detected between 2006 and 2014 were serotype 2, all OPV-using countries conducted a synchronized switch from trivalent OPV (tOPV, containing serotypes 1, 2, and 3) to bivalent OPV (bOPV, containing serotypes 1 and 3) in April 2016. Despite this effort, during 2019–2020, serotype 2 cVDPV caused 1,445 cases of poliomyelitis in 26 countries, whereas serotype 1 cVDPV caused 46 cases in 5 countries, and WPV caused 316 cases in 2 countries. In 2021, cVDPV serotypes 1 or 2 were isolated from 659 cases of poliomyelitis in 23 countries (data as of April 5, 2022).

Travelers to countries with current or recent WPV or cVDPV outbreaks can be at risk for exposure to poliovirus. The last documented case of WPV-associated paralysis in a US resident traveling abroad occurred in 1986 in a 29-year-old vaccinated adult who had been traveling in South and Southeast Asia. In 2005, an unvaccinated US adult traveling abroad acquired VAPP after contact with an infant recently vaccinated with OPV. Of special concern are people with underlying primary immunodeficiencies that prevent an adequate antibody response to viruses; they are at a greater risk for prolonged poliovirus infection and paralysis from WPV, cVDPV, or from exposure to people recently vaccinated with OPV.

For additional information on the status of polio eradication efforts, countries or areas with active WPV or VDPV circulation, and vaccine recommendations, consult the GPEI website (www.polioeradication.org) and the polio travel health notices on the Centers for Disease Control and Prevention (CDC)'s Travelers' Health website (https://wwwnc.cdc.gov/travel/notices).

CLINICAL PRESENTATION

Most poliovirus infections are asymptomatic; ≈25% cause minor illness with full recovery. Depending on poliovirus type, ≈1 in 200 to ≈1 in 2000 infections are associated with paralysis. Paralysis affects ≥1 limbs, and in severe cases can result in quadriplegia, respiratory failure, and rarely, death. Residual paralysis occurs in ≈2/3 cases, and for many people with residual deficits, and even for some who recover fully, worsening of weakness or paralysis can occur 20–30 years later, known as post-polio syndrome. Adults who develop paralysis usually have more severe disease and a worse prognosis than children.

DIAGNOSIS

Information on diagnostic testing for poliovirus is available from CDC's Polio Laboratory Testing website (www.cdc.gov/polio/what-is-polio/lab-testing) and Test Directory: Submitting Specimens to CDC (www.cdc.gov/laboratory/specimen-submission/list.html).

Poliovirus can be detected in clinical specimens (usually stool) obtained from an acutely ill patient. Shedding in fecal specimens can be intermittent and declines over time, but poliovirus can be detected for up to 60 days after onset of paralysis. During the first 3–10 days after paralysis onset, poliovirus also can be detected from oropharyngeal specimens, but stool specimens are the preferred source for diagnosis. Poliovirus rarely can be detected in the blood or cerebrospinal fluid; in most cases, blood antibody titers are not useful for diagnosis.

Poliovirus is detected by virus isolation in cultured cells. PCR testing of poliovirus isolates can identify the serotype and whether it is WPV, VDPV, or the vaccine (Sabin) strain. Genomic sequencing of poliovirus isolates can determine the geographic origin of WPV and the estimated time of circulation since the original OPV dose for VDPV.

Paralytic polio is designated an immediately notifiable, extremely urgent disease, which requires state and local health authorities to notify CDC within ≤4 hours of identification. Because of new safety requirements in handling polioviruses, CDC is the only laboratory in the United States permitted to test specimens from a suspected paralytic polio case. Notify CDC through the Emergency Operations Center (EOC, 770-488-7100) or through state health authorities. CDC's EOC will connect callers with polio subject matter experts who can provide consultation regarding the collection of clinical specimens and procedures.

TREATMENT

No licensed treatment exists for poliovirus infection, and only supportive care for symptoms is available. Two antiviral agents are undergoing clinical testing for the treatment of people with immunodeficiencies who are infected with and excreting VDPV.

PREVENTION

Vaccine

HEALTH PROTECTION RECOMMENDATIONS

Since 2000, IPV is the only polio vaccine available in the United States, but bivalent OPV is used in most low- and middle-income countries for routine immunization series and for global polio eradication activities. In response to cVDPV serotype 2 outbreaks, the population should be immunized with genetically stabilized novel OPV2, monovalent OPV2, or trivalent OPV when serotype co-circulation occurs, as in Afghanistan and Pakistan. For complete information on recommendations for poliomyelitis vaccination, consult the Advisory Committee on Immunization Practices (ACIP) website (www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/polio.html) and the March 2016 World Health Organization (WHO) position paper on poliovirus vaccines (https://cdn.who.int/media/docs/default-source/immunization/position_paper_documents/polio/who-pp-polio-mar2016-references.pdf?sfvrsn=f4e72554_2).

Before they go to areas where WPV or VDPV is circulating, ensure travelers have completed the recommended age-appropriate polio vaccine series (see Infants & Children, later in this chapter). Adults who have completed a primary series should receive a single lifetime IPV booster dose if traveling to those areas. CDC also recommends a single lifetime IPV booster dose for adult travelers going to some countries that border areas with WPV circulation based on evidence of historical cross-border transmission. These recommendations apply only to travelers going to bordering countries with a high risk for exposure to someone with imported WPV infection (e.g., people who will be working in health care settings, refugee camps, or other humanitarian aid settings).

Countries are considered to have WPV or VDPV circulation if they have evidence of poliovirus circulation during the previous 12 months, either endemic circulation of WPV, active WPV, or cVDPV outbreaks, or environmental isolation through sewage sampling. Because poliovirus circulation is dynamic, refer to CDC's Travelers' Health website destination pages for the most

up-to-date polio vaccine recommendations by country (https://wwwnc.cdc.gov/travel/destinations/list).

COUNTRY REQUIREMENTS

In May 2014, the Director General of the WHO declared the international spread of poliovirus to be a public health emergency of international concern under the authority of the International Health Regulations (IHR). To prevent further spread of virus, WHO issued temporary polio vaccine recommendations for travelers staying >4 weeks and residents departing from countries with risk for poliovirus spread. The IHR emergency committee on polio meets every 3 months and updates the list of countries that must continue the temporary polio vaccine recommendations to reduce the risk for international spread of poliovirus. Updated IHR reports are available at www.who.int/news.

The polio vaccine must be received 4 weeks to 12 months before the date of departure from the polio-affected country. Be aware that long-term travelers and residents might be required to show proof of polio vaccination when departing from these countries, and document all polio vaccination administration on an International Certificate of Vaccination or Prophylaxis (ICVP). Country requirements might change, so check for updates on the CDC Travelers' Health website (https://wwwnc.cdc.gov/travel/notices) for a list of affected countries and guidance on meeting the vaccination requirements. For ordering information and instructions on how to fill out the ICVP, see https://wwwnc.cdc.gov/travel/page/icvp.

ADULTS

Before traveling to areas where WPV or VDPV is circulating, adults who are unvaccinated, incompletely vaccinated, or whose vaccination status is unknown should receive a series of 3 doses: 2 doses of IPV administered 4–8 weeks apart, and a third dose administered 6–12 months after the second dose. If 3 doses of IPV cannot be administered within the recommended intervals, alternative dosing schedules are available (see Table 5-16).

IMMUNOCOMPROMISED PEOPLE

IPV can be safely administered to immunocompromised travelers and their household contacts. Although a protective immune response cannot be ensured, IPV might confer some protection to people who are immunocompromised. Those with certain primary immunodeficiency diseases should not be given OPV and should avoid contact with children vaccinated with OPV overseas in the previous 6 weeks.

INFANTS & CHILDREN

In the United States, all infants and children should receive 4 doses of IPV, given at ages 2, 4, and 6–18 months, and 4–6 years. The final dose should be administered at ≥4 years of age, regardless of the number of previous doses, and should be given ≥6 months after the previous dose. A fourth dose in the routine IPV series is not necessary if the third dose was administered at ≥4 years of age and ≥6 months after the previous dose. If the routine series cannot be administered within the recommended intervals before protection is

Table 5-16 Alternative adult polio vaccine dosing schedules

TIME BEFORE TRAVEL	NUMBER OF DOSES[1]	INTERVAL BETWEEN DOSES
<4 weeks	1	Not Applicable
4–8 weeks	2	4 weeks
>8 weeks	3	4 weeks

[1]If <3 doses are administered, the remaining doses required to complete a 3-dose series should be administered when feasible—at the recommended intervals described in this chapter—if the person remains at risk for poliovirus exposure.

needed, CDC recommends the following alternative: give the first dose to infants at ≥6 weeks of age, give the second ≥4 weeks after dose 1, and the third dose ≥4 weeks after dose 2, then give the fourth dose ≥6 months after dose 3.

If the age-appropriate series is not completed before international travel, administer the remaining IPV doses to complete a full series when feasible, at the intervals recommended above. In addition, children completing the accelerated schedule should still receive a dose of IPV at ≥4 years of age, provided ≥6 months have passed since the last dose.

CHILDREN WHO RECEIVED POLIOVIRUS VACCINE OUTSIDE THE UNITED STATES

Vaccines administered outside the United States generally can be accepted as valid doses if the schedule is similar to that recommended in the United States. Vaccination against polio is also valid for children from countries that use an accelerated schedule. Only written, dated records are accepted as evidence of previous vaccination. Please see Guidance for Assessment of Poliovirus Vaccination Status and Vaccination of Children Who Have Received Poliovirus Vaccine Outside the United States (www.cdc.gov/mmwr/volumes/66/wr/mm6601a6.htm and its erratum, www.cdc.gov/mmwr/volumes/66/wr/mm6606a7.htm?s_cid=mm6606a7_w) for information on interpreting international poliovirus vaccination documentation.

Children with full vaccination status who received only bOPV in the primary series because they were born after April 2016, or who received a combination of tOPV and bOPV, should be revaccinated with a full IPV series to ensure protection against all 3 poliovirus types. If the child has documentation of receipt of an IPV dose, this can be considered the first dose in the US dosing schedule. In accordance with the age-appropriate US IPV schedule, vaccinate or revaccinate children <18 years old without adequate documentation of poliovirus vaccination.

International adoption from countries or areas where WPV or VDPV is actively circulating is a special situation. International adoptees might not have completed a primary polio vaccination series nor received a polio vaccine dose before departure. Thus, although the risk is small, they could be infected with WPV or VDPV and remain infectious upon entry into the United States, and potentially transmit to US household members and caregivers. As a measure of prudence, the polio vaccination status of all household members and caregivers of international adoptees from a country with active WPV or VDPV circulation should be assessed before the child enters the United States (see Sec. 7, Ch. 5, International Adoption). People who are unvaccinated, incompletely vaccinated, or whose vaccination status is unknown should be brought up to date.

PREGNANCY & BREASTFEEDING

If a pregnant person is unvaccinated or incompletely vaccinated and requires immediate protection against polio because of planned travel to a country or area where WPV or VDPV is actively circulating, IPV can be administered as recommended for adults. In addition, neither is breastfeeding a contraindication to receiving polio vaccine.

PRECAUTIONS & CONTRAINDICATIONS

IPV can be administered to people with diarrhea. Minor upper respiratory illnesses with or without fever, mild to moderate local reactions to a previous dose of IPV, current antimicrobial therapy, and the convalescent phase of acute illness are not contraindications to vaccination. IPV can be coadministered with other vaccines.

SAFETY & ADVERSE REACTIONS

Minor local reactions (pain and redness) can occur after IPV administration. Do not administer IPV to people who have experienced a severe allergic reaction (e.g., anaphylaxis) after a previous dose of the vaccine. Because IPV contains trace amounts of neomycin, polymyxin B, or streptomycin, hypersensitivity reactions can occur after IPV administration among people allergic to these antibiotics.

CDC website: www.cdc.gov/polio

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RABIES

Ryan Wallace, Brett Petersen, David Shlim

INFECTIOUS AGENT: Rabies virus	
ENDEMICITY	Worldwide, except Antarctica Some countries categorized as rabies virus–free are endemic for related viruses (e.g., Australian Bat Lyssavirus)
TRAVELER CATEGORIES AT GREATEST RISK FOR EXPOSURE & INFECTION	Primarily travelers with bat or dog contact (although a wide range of mammals can transmit virus)
PREVENTION METHODS	Avoid direct animal contact and animal bites If bitten, seek immediate medical attention and appropriate postexposure prophylaxis Rabies is a vaccine-preventable disease
DIAGNOSTIC SUPPORT	State health department; rabies@cdc.gov; or www.cdc.gov/rabies/specific_groups/hcp/ante_mortem.html

INFECTIOUS AGENTS

Rabies is a fatal, acute, progressive encephalomyelitis caused by neurotropic viruses in the family Rhabdoviridae, genus *Lyssavirus*. Numerous, diverse lyssavirus variants are found in various animal species throughout the world, all of which can cause fatal human rabies. Rabies virus is by far the most common *Lyssavirus* infection in humans. Tens of millions of potential human exposures and

tens of thousands of deaths from rabies occur each year.

TRANSMISSION

The normal and most successful mode of rabies virus transmission is via the bite of a rabid animal. Rabies virus is neurotropic; it gains access to the nervous system through exposed peripheral nerve synapses in bite wounds. The virus travels from its point of entry along peripheral nerves to the central nervous system (CNS), where viral replication increases exponentially. Rabies virus then migrates from the CNS back to the peripheral nervous system (PNS) into, among other tissues, the salivary glands. Rabies virus secreted in saliva allows the transmission cycle to repeat. Viral shedding typically occurs just days prior to onset of clinical signs in infected animals and humans; early clinical signs can be nonspecific, however, and public health professionals should conduct a thorough risk assessment to determine if medical care is indicated.

Exposure of highly innervated tissues (e.g., those in the face and hands) can increase the risk for successful infection, and exposures occurring closer to the CNS (e.g., head, neck) can potentially shorten the incubation period. In addition to saliva, rabies virus can be found in CNS and PNS tissue, and in tears. Infection from non-bite exposures (e.g., organ transplantation from infected humans) has occurred, but human-to-human transmission generally does not occur otherwise.

All mammals are believed to be susceptible to rabies virus infection, but terrestrial mesocarnivores and bats are major rabies virus reservoirs. Dogs are the main reservoir in many low- and middle-income countries, and the epidemiology of the disease differs between regions and countries. All patients with mammal bites should be medically evaluated to ascertain if rabies postexposure prophylaxis is indicated.

> Bat exposure anywhere in the world is a cause for concern and an indication to consider rabies postexposure prophylaxis.

EPIDEMIOLOGY

Lyssaviruses, the causative agent for rabies, have been found on all continents except Antarctica. Rabies virus is classified into 2 major genetic lineages: canine and New World bat. These 2 lineages can be further classified into rabies virus variants based on genetic differentiations and on the reservoir species in which they circulate. Regionally, different viral variants are adapted to various mammalian hosts and perpetuate in dogs and wildlife (e.g., bats, foxes, jackals, mongooses, raccoons, skunks).

Canine rabies remains enzootic in many areas of the world, including Africa, parts of Central and South America, and Asia. In addition to rabies virus, the *Lyssavirus* genus includes 14 other viruses that all cause rabies disease. Non–rabies *lyssaviruses* are found in Africa, Asia, Australia, and Europe; although non–rabies *lyssaviruses* have caused human deaths, these viruses contribute relatively little to the global rabies burden compared to rabies virus.

Timely and specific information about the global occurrence of rabies is often difficult to find. Surveillance levels vary, and reporting status can change suddenly because of disease reintroduction, emergence, or disruptions in surveillance operations. The rate of rabies exposures in travelers is an estimate, at best, and might range from 16–200 per 100,000 travelers.

CLINICAL PRESENTATION

After viral invasion of the PNS and then CNS, clinical illness in humans culminates in an acute, fatal encephalitis. After infection, the asymptomatic incubation period is variable, but signs and symptoms most commonly develop within several weeks to months after exposure.

Pain and paresthesia at the site of exposure are often the first symptoms of disease. The disease then progresses rapidly from a prodromal phase (fever and nonspecific, vague symptoms) to a neurologic phase characterized by anxiety, paralysis, paresis, and other signs of encephalitis. Swallowing muscle spasm can be stimulated by the sight, sound, or perception of water (hydrophobia). Delirium and convulsions can develop, followed soon thereafter by coma and death.

Approximately 80% of people with rabies will manifest with classic encephalitic disease in which fever, hydrophobia, hyperactivity, and spasms eventually progress to paralysis and coma; this progression corresponds to “furious”

rabies in animals. Another 20% of people can present with paralytic rabies, in which paralysis often first involves the bitten extremity and then progresses as an ascending paralysis, ultimately leading to coma; this is the equivalent of paralytic or "dumb" rabies in animals. Once clinical signs appear, patients die quickly in the absence of intensive supportive care.

DIAGNOSIS

Diagnosis can be made in a patient with a compatible exposure history and a classic clinical presentation (Box 5-05). Clinical suspicion and prioritization of differential diagnoses can be complicated by variations in clinical presentation and a lack of exposure history, however. Because several weeks to months could have elapsed since exposure, and an accurate exposure history can be difficult to elicit, patients might not discuss potential rabies virus exposures with friends or family, and clinicians might not initially consider the possibility. As a result, rabies diagnosis in the United States is almost always missed at the first clinical encounter.

Definitive antemortem diagnosis requires use of specialized diagnostic methods on multiple specimens, including cerebrospinal fluid (CSF), saliva, serum, and skin biopsies taken from the nape of the neck. Because the probability of virus and antibody detection varies over the course of illness, sequential sample collection is indicated if initial testing is negative but clinical suspicion remains high. Finding rabies virus antigen or nucleic acid in any antemortem sample confirms the diagnosis.

A thorough review of all medical care provided to patients prior to sample collection is necessary to correctly interpret some diagnostic test results. Recent reports, for example, have described how human-derived products (e.g., intravenous immune globulin [IVIG]) administered to patients can be a passive source of high concentrations of donor-derived *Rabies lyssavirus*–neutralizing antibodies (RLNAs); in the absence of an accurate history of prior, recent IVIG administration, finding RLNAs in serum can incorrectly suggest a diagnosis of rabies. In unvaccinated encephalitic patients, however, the presence of rabies virus–neutralizing antibodies (particularly in CSF samples) confirms the diagnosis. For more information on diagnostic testing, see www.cdc.gov/rabies/specific_groups/hcp/ante_mortem.html.

Rabies is a nationally notifiable disease. The Centers for Disease Control and Prevention (CDC) is designated as the national rabies reference laboratory for the United States, along with the World Health Organization (WHO) Collaborating Center for Rabies and World Organisation for Animal Health (OIE) Rabies Reference Laboratory. In this capacity, CDC performs public health testing for domestic and international health agencies, for both human and animal rabies diagnoses. Clinicians submitting samples to CDC for rabies testing must first consult with program staff, obtain approval, and complete the requisite paperwork; step-by-step instructions are available from www.cdc.gov/rabies/resources/specimen-submission-guidelines.html.

BOX 5-05 World Health Organization, human rabies case definitions

CLINICAL CASE DEFINITION

A person presenting with an acute neurologic syndrome (encephalitis) dominated by forms of hyperactivity (furious rabies) or paralytic syndromes (paralytic rabies) progressing toward coma and death, usually by cardiac or respiratory failure, typically within 7–10 days after the first symptom if no intensive care is instituted.

Symptoms include any of the following: aerophobia, dysphagia, hydrophobia, nausea or vomiting, paresthesia or localized pain, localized weakness.

HUMAN RABIES: SUSPECTED

A case compatible with the clinical case definition.

HUMAN RABIES: PROBABLE

A suspected case plus a reliable history of contact with a suspected, probable, or confirmed rabid animal.

HUMAN RABIES: CONFIRMED

A suspected or probable case confirmed in the laboratory.

TREATMENT

No evidence-based "best practices" approach to treating rabies patients is available. Most cases are managed with symptomatic and palliative supportive care. Survival after the clinical phase of rabies virus infection is incredibly rare, but case reports continue to provide insight into potential therapeutic options, and experimental treatment regimens continue to be investigated. To date, early and robust production of rabies virus–neutralizing antibodies has been the primary factor associated with rare reports of survival. Rabies is still considered universally fatal for practical purposes; not getting bitten in the first place is therefore the most important prevention measure. For those who are (or who suspect they might have been) bitten by a rabid animal, urgently taking the other prevention measures described next is the only way to optimize survival.

PREVENTION

Travelers can best prevent rabies by learning about infection risks and the need to avoid bites from mammals, especially high-risk rabies reservoir species; consulting with travel health professionals to determine whether preexposure vaccination is recommended; knowing how to prevent rabies after a bite; and knowing how to obtain postexposure prophylaxis (PEP), which might involve urgent importation of rabies biologics or travel to somewhere PEP is available. Not seeking PEP or receiving inadequate care likely will result in death from rabies. See https://wwwnc.cdc.gov/travel/diseases/rabies for a list of pretravel rabies precautions.

Avoid Animal Bites

Avoiding bites is truly the best prevention measure for rabies. Although rabies can be completely prevented by appropriate postexposure care, obtaining that care and worrying about its effectiveness can be nerve-racking for patients. Warn travelers going to rabies-enzootic countries about the risks for rabies exposure. Counsel them to stay away from all free-roaming mammals, including puppies and kittens, and to avoid contact with bats and other wildlife.

Children are at greater risk for rabies exposure and subsequent illness because of their inquisitive nature and inability to read behavioral cues from dogs and other animals. The smaller a child's stature, the more likely they are to experience severe bites to high-risk areas (e.g., the head and face). Also contributing to the higher risk for children is their attraction to animals and the possibility that they might not report an exposure.

BATS & OTHER WILDLIFE

Besides rabies virus, other bat-associated pathogens include *Histoplasma* spp., coronaviruses, and viral hemorrhagic fever viruses (see Sec. 4, Ch. 7, Zoonotic Exposures: Bites, Stings, Scratches & Other Hazards). Educate travelers to avoid handling bats or other wildlife and to consider using personal protective equipment (PPE) before entering caves where bats are found. Many bats have tiny teeth, and the wounds they inflict might not be readily apparent. Warn travelers that any suspected or documented bite or wound from a bat should be grounds for seeking PEP.

DOGS

In many low- and middle-income countries, dogs stray freely in cities; encourage travelers to remain vigilant. Inadvertently approaching puppies when the mother is near, stepping on sleeping dogs, walking into dogs, or getting too close to dogs fighting or protecting food sources can provoke biting behavior.

Travelers bitten by a dog once are almost never bitten a second time, validating the observation that with proper awareness, bites can be avoided. Scanning for dogs on the street can become second nature for experienced travelers and expatriates. Knowledgeable travelers (even those never bitten) can travel for decades without ever having a dog bite.

NONHUMAN PRIMATES

Although nonhuman primates (NHPs) are rarely rabid, they are a common source of bites, mainly on the Indian subcontinent. In most instances, wild NHPs cannot be followed up for rabies assessments, and PEP is recommended for bite victims. Awareness of this risk and simple prevention are particularly effective: advise travelers not to approach or otherwise interact with NHPs or carry food while NHPs are near, especially those

that have become habituated to tourists (see Sec. 4, Ch. 7, Zoonotic Exposures: Bites, Stings, Scratches & Other Hazards).

Preexposure Prophylaxis

Preexposure prophylaxis (PrEP) does not eliminate the need for additional medical attention after a rabies exposure, but it simplifies PEP (see Postexposure Prophylaxis later in this chapter). PrEP might also provide some protection when an exposure to rabies virus goes unrecognized, or PEP is otherwise delayed. Travelers who complete a recognized PrEP immunization series (see Revised Vaccine Schedule later in this chapter) or who receive full PEP are considered previously vaccinated and do not require routine boosters. Routine testing for rabies virus–neutralizing antibody is not recommended for international travelers who do not otherwise fall into the frequent or continuous risk categories (Table 5-17).

RECOMMENDED TRAVELER CATEGORIES

Recommendations for preexposure rabies vaccination can be made for certain international traveler categories based on multiple factors: the occurrence of animal rabies in the destination country; the availability of anti-rabies biologics; the traveler's intended activities, especially in remote areas; and the traveler's duration of stay. A decision to receive preexposure rabies immunization might also be based on the likelihood of repeat travel to at-risk destinations or long-term travel to a high-risk destination. Consider PrEP for animal handlers, field biologists, cavers, missionaries, veterinarians, and some laboratory workers. Table 5-17 provides criteria for PrEP. Regardless of whether PrEP is administered, encourage travelers to purchase medical evacuation insurance if they are going to areas where the risk for rabies is high (see Sec. 6, Ch. 1, Travel Insurance, Travel Health Insurance & Medical Evacuation Insurance).

REVISED VACCINE SCHEDULE

In the United States, PrEP previously consisted of a series of 3 intramuscular (deltoid) injections of human diploid cell rabies vaccine (HDCV) or purified chick embryo cell (PCEC) vaccine given on days 0, 7, and 21 or 28. Based on recent changes in WHO recommendations and the availability of empirical studies, the US Advisory Committee on Immunization Practices (ACIP) reviewed its own recommendations for PrEP and approved a 2-dose preexposure regimen, given on days 0 and 7 (Table 5-18).

The advantages of the revised schedule are that it is less expensive and easier to complete prior to travel. There are no data on how long this 2-dose series provides protection, however. Because of this uncertainty, travelers with a sustained risk for rabies exposure should either have a titer drawn or receive a third dose of vaccine within 3 years of the initial series. Travelers unlikely to visit an at-risk destination after 3 years require no further titers or boosters unless they have a subsequent exposure.

VACCINE SAFETY & ADVERSE REACTIONS

Advise travelers they might experience local reactions after vaccination (e.g., erythema, itching at the injection site, pain, swelling), or mild systemic reactions (e.g., abdominal pain, dizziness, headache, muscle aches, nausea). Approximately 6% of people receiving booster vaccinations with HDCV experience systemic hypersensitivity reactions characterized by malaise, pruritis, and urticaria. The likelihood of these reactions is less with PCEC vaccine.

Wound Management

If wounded by an animal, travelers should clean all animal bites and scratches with copious amounts of soap and water, povidone iodine, or other products with virucidal activity. Inform travelers that cleaning bite wounds immediately (or as soon as possible) substantially reduces the risk for rabies virus infection, especially when followed by timely administration of PEP. For unvaccinated patients, delay suturing any wounds for a few days. If suturing is necessary to control bleeding or for functional or cosmetic reasons, inject rabies immune globulin (RIG) into all exposed tissues before closing the wound. Use of local anesthetics is not contraindicated in wound management.

Table 5-17 Rabies preexposure prophylaxis recommendations—United States, 2022[1]

RISK CATEGORY	EXPOSURE TYPE[2]	TYPICAL POPULATION[2]	DISEASE BIOGEOGRAPHY[3]	RECOMMENDATIONS	
				PRIMARY PrEP VACCINE SERIES[4]	BOOSTERS[5]
CATEGORY 1 Elevated risk for unrecognized[6] and recognized[7] exposures, including unusual or high-risk exposures	Often high viral concentration exposures Could be recognized or unrecognized Could be unusual (e.g., aerosolized virus)	People working with live rabies virus in research or vaccine production facilities People performing testing for rabies in diagnostic laboratories	Laboratory	IM rabies vaccine DOSE 1: Day 0 DOSE 2: 7 days after DOSE 1	Check titers q6 months Provide booster for titers <0.5 IU/mL[8]
CATEGORY 2 Elevated risk for unrecognized[6] and recognized[7] exposures	Typically recognized Could be unrecognized Unusual exposures unlikely	People with frequent bat contact[9] People who perform animal necropsies	All geographic regions (domestic and international) where any rabies reservoir is present	IM rabies vaccine DOSE 1: Day 0 DOSE 2: 7 days after DOSE 1	Check titers q2 years Provide booster for titers <0.5 IU/mL[8]
CATEGORY 3 Elevated risk for recognized[7] exposures or sustained risk[10]	Exposure nearly always recognized Exposure risk exceeds that of the general population Duration of risk >3 years after primary 2-dose PrEP vaccine series	People who interact with animals that could be rabid[11] People whose occupational or recreational activities typically involve contact with animals[12] Selected travelers[13]	All domestic and international regions where any rabies reservoir is present International regions with rabies virus reservoirs, particularly where rabies virus is endemic in dog populations	IM rabies vaccine DOSE 1: Day 0 DOSE 2: 7 days after DOSE 1	One-time titer check during years 1–3 after the primary 2-dose PrEP vaccine series Provide booster for titers <0.5 IU/mL[8] **OR** Provide booster ≥21 days but <3 years after primary 2-dose PrEP vaccine series[14]

CATEGORY 4 Elevated risk for recognized[7] exposure, no sustained risk[10]	Exposure nearly always recognized Exposure risk exceeds that of the general population Duration of risk expected to be ≤3 years after primary 2-dose PrEP vaccine series	Same at-risk populations as CATEGORY 3 **BUT** Risk duration ≤3 years[15]	Same disease biogeography as CATEGORY 3	IM rabies vaccine DOSE 1: Day 0 DOSE 2: 7 days after DOSE 1	None
CATEGORY 5 Low risk for exposure	Exposure uncommon	Typical resident of the United States	Not applicable	None	None

Abbreviations: IM, intramuscular; IU, international units; PrEP, preexposure prophylaxis

[1]Source: Rao AK, Briggs D, Moore SM, et al. Use of a Modified Preexposure Prophylaxis Vaccination Schedule to Prevent Human Rabies: Recommendations of the Advisory Committee on Immunization Practices—United States, 2022. MMWR Morb Mortal Wkly Rep 2022;71:619–27 (www.cdc.gov/mmwr/volumes/71/wr/mm7118a2.htm).
[2]Exposure type and nature of work or travel are the most important variables to consider when determining a person's risk category. Perform risk categorization on a case-by-case basis; examples provided are intended as a guide only.
[3]Consult local or state health departments about local disease biogeography.
[4]Primary immunogenicity peaks 2–4 weeks after completing the recommended primary 2-dose PrEP vaccine series. People who are immunocompetent are expected to mount an appropriate response, and checking titers is not routinely recommended. Before people with altered immunity participate in high-risk activities, confirm a rabies antibody titer ≥0.5 IU/mL ≥1 week after booster vaccination (but ideally, 2–4 weeks after completing the recommended series). Individual facilities set their own rules regarding laboratory-confirmation of acceptable antibody titers for personnel.
[5]Need for boosters is based on long-term immunogenicity, the ability to mount an anamnestic response to rabies virus >3 years after completion of the primary 2-dose PrEP vaccine series.
[6]Unrecognized exposures: exposures that a person might not know occurred (e.g., a small scratch sustained during an inconspicuous breach in personal protective equipment might go unnoticed by a laboratorian testing neural tissue from rabid animals or by a field biologist conducting ecologic studies on bats).
[7]Recognized exposures: bites, scratches, splashes, etc., that are unusual for a person (e.g., bat contact) or painful (e.g., raccoon bite or scratch).
[8]Provide a booster dose of rabies vaccine when rabies antibody titers are <0.5 IU/mL. For people who are immunocompetent, checking antibody titers to verify booster response is not recommended. For people with altered immunity, verify antibody titers ≥1 week (ideally, 2–4 weeks) after each booster dose of vaccine administered.
[9]Includes people who: handle bats; have regular contact with bats; enter high-density bat environments (e.g., biologists who enter bat roosts or collect suspected rabies samples); perform animal necropsies (e.g., veterinary pathologists who frequently perform necropsies on mammals suspected to have had rabies). People for whom the frequency of handling rabies virus–infected tissues is low, or the procedures performed do not involve contact with neural tissue or opening of a suspected rabid animal's calvarium, could consider following the recommended immunization schedule for RISK CATEGORY 2 rather than RISK CATEGORY 1.
[10]Sustained risk: elevated risk for rabies virus exposure >3 years after the completion of the primary 2-dose PrEP vaccine series.
[11]Rabies virus is unlikely to persist outside a dead animal's body for an extended time due to virus inactivation by desiccation, ultraviolet irradiation, and other factors. Risk of transmission to people who handle animal products (e.g., hunters, taxidermists) is unknown but presumed to be low (RISK CATEGORY 5); direct skin contact with saliva and neural tissue of mammals should be avoided regardless of profession.
[12]Includes veterinarians, technicians, animal control officers, and their students/trainees; people who handle wildlife reservoir species (e.g., wildlife biologists, rehabilitators, trappers); spelunkers.
[13]PrEP considerations for travelers include: (1) Will the person be participating in occupational or recreational activities that increase their risk for exposure to potentially rabid animals (particularly dogs)? and (2) Will the person have difficulty getting prompt access to safe postexposure prophylaxis (PEP)? For example, will they be in rural areas or visiting destinations where PEP is not readily available (www.cdc.gov/rabies/resources/countries-risk.html).
[14]Unless the recipient has altered immunity, checking titers after recommended booster doses is not indicated.
[15]For example, short-term hands-on animal care volunteers, or infrequent travelers with no expected high-risk travel >3 years after their primary 2-dose PrEP vaccine series.

Table 5-18 Preexposure immunization for rabies[1]

VACCINE	DOSE (mL)	NUMBER OF DOSES	SCHEDULE (DAYS)[2]	ROUTE
HDCV, Imovax (Sanofi)	1.0	2	0 and 7	IM
PCEC, RabAvert (Novartis)	1.0	2	0 and 7	IM

Abbreviations: HDCV, human diploid cell vaccine; IM, intramuscular; PCEC, purified chick embryo cell

[1]People who are immunocompromised by disease or medications should postpone preexposure vaccinations and consider avoiding activities for which rabies preexposure prophylaxis is indicated during the period of expected immune compromise. If this is not possible, immunocompromised people at risk for rabies should have their antibody titers checked after vaccination.
[2]Every attempt should be made to adhere to recommended schedules; for most minor deviations (e.g., delays of a few days for individual doses), vaccination can be resumed as though the traveler were on schedule. Travelers with a sustained risk for rabies exposures should either have a titer drawn or receive a third dose of vaccine within 3 years of the initial series. Travelers unlikely to visit an at-risk destination after 3 years require no further titers or boosters unless they have an exposure.

Postexposure Prophylaxis

TRAVELERS WHO RECEIVED PREEXPOSURE PROPHYLAXIS

For previously vaccinated people, PEP consists of 2 doses of modern cell culture vaccine given 3 days apart (days 0 and 3), ideally initiated shortly after the exposure. The booster doses do not have to be the same brand as the one used for the original preexposure immunization series. RIG should not be administered to people who were previously vaccinated, because it can lead to a diminished immune response to vaccine and provides no benefit to the recipient.

TRAVELERS WHO DID NOT RECEIVE PREEXPOSURE PROPHYLAXIS

RABIES IMMUNE GLOBULIN + RABIES VACCINE

For unvaccinated people, PEP consists of RIG administration (20 IU/kg for human RIG [HRIG] or 40 IU/kg for equine RIG) and a series of 4 injections of rabies vaccine over 14 days; immunocompromised patients should receive 5 doses over a 1-month period (Table 5-19). After cleaning the wound, inject as much of the dose-appropriate volume of RIG (Table 5-19) as is anatomically feasible at wound sites. The intent is to put RIG anywhere saliva might have contaminated the wounded tissue.

Once initiated, rabies PEP should not be interrupted or discontinued because of local or mild systemic reactions to the vaccine. If an adverse event occurs with one of the vaccine types, consider switching to the alternative cell culture vaccine for the remainder of the series. Antihistamines or nonsteroidal anti-inflammatory medications taken before vaccination can help reduce mild adverse reactions in people with a history of such reactions.

RABIES IMMUNE GLOBULIN: AVAILABILITY & TIMING

HRIG is manufactured by plasmapheresis of blood from hyperimmunized volunteers. The total quantity of commercially produced HRIG falls short of worldwide demand, and it is not available in many low- and middle-income countries (www.cdc.gov/rabies/resources/countries-risk.html). Equine RIG, purified fractions of equine RIG, and rabies monoclonal antibody products might be available in some countries where HRIG is not. Such products are preferable to no RIG.

If access to RIG is delayed but modern cell culture vaccine is available, start the vaccine series as soon as possible, and add RIG to the regimen ≤7 days after the first dose of vaccine was administered. After day 7, RIG is unlikely to provide benefit, because antibodies from the patient's own vaccine-derived immune response should be present.

Because rabies virus can persist in tissue for a long time before invading a peripheral nerve, a previously unimmunized traveler who sustained a bite suspicious for rabies should receive full PEP, including RIG, even if a considerable length of time has passed since the initial exposure. If there is a scar, or the patient remembers where the bite

Table 5-19 Postexposure immunization for rabies[1]

IMMUNIZATION STATUS	PRODUCT	DOSE	NUMBER OF DOSES	SCHEDULE (DAYS)[2]	ROUTE
Not previously vaccinated[3]	RIG	20 IU/kg body weight	1	0	Infiltrate bite site (if possible) Give remainder IM
	Vaccine (HDCV or PCEC)	1.0 mL	4[4]	0, 3, 7, 14 (and 28 if immunocompromised)[5]	IM
Previously vaccinated[6,7]	Vaccine (HDCV or PCEC)	1.0 mL	2	0, 3	IM

Abbreviations: HDCV, human diploid cell vaccine; IM, intramuscular; PCEC, purified chick embryo cell; RIG, rabies immune globulin

[1]Begin all postexposure prophylaxis with immediate, thorough cleansing of all wounds with soap and water, povidone iodine, or other substances with virucidal activity.
[2]Every attempt should be made to adhere to recommended schedules; for most minor deviations (e.g., delays of a few days for individual doses), vaccination can be resumed as though the traveler were on schedule. When substantial deviations occur, assess immune status by serologic testing 7–14 days after the final dose is administered.
[3]For people not previously vaccinated against rabies, PEP consists of both RIG and a series of rabies vaccine injections.
[4]Immunocompromised patients should receive 5 vaccine doses. The first 4 vaccine doses are given on the same schedule as for an immunocompetent patient, and the fifth dose is given on day 28; patient follow-up should include monitoring antibody response. For more information, see Rupprecht et al., www.cdc.gov/mmwr/preview/mmwrhtml/rr5902a1.htm.
[5]The Centers for Disease Control and Prevention recommends 4 postexposure vaccine doses, on days 0, 3, 7, and 14, unless the patient is immunocompromised, in which case a fifth dose is given at day 28.
[6]Defined as preexposure immunization with HDCV or PCEC, prior postexposure prophylaxis with HDCV or PCEC, or prior vaccination with any other type of rabies vaccine and a documented history of positive rabies virus–neutralizing antibody response to that vaccination.
[7]RIG not recommended.

occurred, an appropriate amount of RIG should be injected in the area.

RABIES IMMUNE GLOBULIN: DILUTION

If the wound is small and on a distal extremity (e.g., a finger, toe), use clinical judgment to decide how much RIG to inject to avoid complications (e.g., ischemia) due to local distention of the digit or digits. Administer any remaining dose intramuscularly at a site distant from the site of vaccine administration. If wounds are extensive, do not exceed the dose-appropriate volume of RIG. If the indicated volume is inadequate to inject all wounds, dilute the RIG with dextrose 5% in water (D5W) to ensure sufficient volume to inject all wounds. Previous advice recommended normal saline as a diluent, but its use is incompatible with new formulations of HRIG. RIG dilution is particularly important in children whose body weight might be small in relation to the size and number of wounds.

RABIES IMMUNE GLOBULIN: SAFETY & ADVERSE EVENTS

The incidence of adverse events after the use of modern equine-derived RIG is low (0.8%–6.0%), and most reactions are minor. Because such products are not regulated by the US Food and Drug Administration, however, their use cannot be recommended unequivocally. In addition, unpurified anti-rabies serum of equine origin might still be used in some countries where neither human nor equine RIG is available.

CONTRAINDICATIONS & PRECAUTIONS

Pregnancy is not a contraindication to receiving PEP. In infants and children, the dose of HDCV or PCEC for PrEP or PEP is the same as that recommended for adults. The PEP RIG dose is based on body weight (Table 5-19).

Rabies vaccines were once manufactured from viruses grown in animal brains; some of these vaccines are still in use in low- and middle-income

countries. Typically, travelers can identify brain-derived vaccines, also known as nerve tissue vaccines, if they are offered a daily large-volume injection (5 mL) for approximately 14–21 days. Because of variability in the potency in these preparations, which might limit their effectiveness, and the risk for severe adverse reactions, advise travelers to decline these vaccines and to travel to a location where acceptable vaccines and RIG are available.

VARIATIONS IN POSTEXPOSURE PROPHYLAXIS

Different PEP schedules, alternative routes of administration, and other rabies vaccines besides HDCV and PCEC might be used abroad. For example, commercially available purified Vero cell rabies vaccine is an acceptable alternative, if available. Other rabies vaccines or PEP regimens could require additional prophylaxis or confirmation of adequate rabies virus–neutralizing antibody titers. Encourage travelers to take photos of the rabies PEP products they receive and to be conscious of the vaccine storage conditions and corresponding administration schedule. This information is necessary for health care providers to determine whether additional vaccines or titers are indicated. Clinicians can obtain assistance managing complicated PEP scenarios from experienced travel medicine professionals, health departments, and CDC (rabies@cdc.gov).

Health care providers are justifiably concerned about getting everything right when trying to prevent a disease that is virtually 100% fatal, leading to overconcern about small variations in the administration of rabies vaccines. Modern-day cell culture rabies vaccines are highly immunogenic, however, and postexposure rabies vaccine schedules have been developed to provide the quickest onset of endogenous antibodies, which is why these vaccines are given on such a short schedule.

Make every effort to adhere to a recognized ACIP or WHO schedule. Variations of days to weeks are unlikely to diminish the immune response to vaccination but could delay the onset of protection. Numerous schedules and routes of administration have been recognized by international health authorities and have been shown to be highly effective at preventing rabies.

CDC website: www.cdc.gov/rabies

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RABIES IMMUNIZATION

David Shlim

Prior to the coronavirus disease 2019 (COVID-19) pandemic, few topics in travel medicine prompted more concern and questions than the prevention of rabies in travelers. Rabies prevention presents unique issues for the travel medicine clinician, because it is the one infectious disease that can be prevented, either through a combination of pre- and postexposure immunizations or through postexposure treatment with rabies immune globulin (RIG) and vaccine. Prevention is possible because the time of the bite can almost always be recognized, and immunoprophylactic intervention can stop clinical disease from developing. The seeming complexity of the issues surrounding wound care, timing of administration, deviations from standard schedules, the cost of preexposure immunization, and the difficulty of finding vaccine and RIG while traveling can make the travel medicine practitioner's head spin.

The good news is that we have developed a method of preventing rabies encephalitis that is virtually 100% effective. The challenges that remain are the lack of availability of RIG in many areas of the world, the expense of both pre- and postexposure care, and the ongoing endemicity of rabies in street dogs in many areas. To keep the travel medicine approach to rabies prevention in perspective, 1–2 cases of rabies are reported in travelers per year, in contrast to >50,000 rabies deaths in resource-poor, low- and middle-income countries.

THE 2-DOSE PREEXPOSURE RABIES VACCINE SCHEDULE

World Health Organization Recommendations

In 2017—partly to address the lack of progress in decreasing rabies in the world—a World Health Organization (WHO) expert committee endorsed a 2-dose rabies preexposure immunization schedule in place of the previous 3-dose schedule. The committee was hoping to make preexposure immunization more affordable and convenient for local people, and more desirable and feasible for travelers. The seemingly sudden announcement spurred national health agencies to do their own research and decide whether to harmonize with WHO, or stick to their own recommendations. Conclusions so far have varied around the world.

WHO also endorsed the use of wound-only administration of RIG, in which an anatomically appropriate dose (not to exceed the weight-calculated amount) of RIG is injected around the wound, but where the remaining calculated dose is not administered intramuscularly. This idea was based on the thinking that RIG is most valuable at the site of the wound, and little additional RIG makes its way into the bloodstream. The further rationale behind this approach is that it leaves hard-to-obtain and expensive RIG available to treat more people. But measurable amounts of RIG are detected in the blood after its intramuscular administration, and whether this is critical to prevention of rabies encephalitis is not really known.

Advisory Committee on Immunization Practices Guidance

In the United States, the Advisory Committee on Immunization Practices (ACIP) convened a working group to evaluate similar questions to those considered by WHO. In 2021, ACIP voted to approve a 2-dose preexposure rabies immunization series, with the proviso that either a third dose be given within 3 years, or a serological

(continued)

test be performed to document seroconversion. Although the working group felt that "boostability" likely will extend beyond 3 years, there were no data yet available to support this.

In addition, and in contrast to WHO recommendations, ACIP elected to retain the current guidance of calculating RIG dose based on patient weight, administering an amount feasible around the wound and delivering the rest into muscle. This raises the question of whether Americans will receive the ACIP-recommended full RIG dose in countries that have adopted WHO's wound-only RIG administration guidance. This might be yet another reason for recommending preexposure prophylaxis.

After a high-risk exposure, travelers who received 2 (or 3) doses of rabies vaccine before travel need to receive 2 more doses of rabies vaccine, 3 days apart. Conversely, unimmunized travelers exposed to rabies and other lyssaviruses will require—according to US standards—a series of 4 or 5 doses of rabies vaccine intramuscularly over a 2- to 4-week period, and infiltration of RIG. Because human and equine RIG often are unavailable in low- and middle-income countries, preexposure rabies immunization can facilitate the traveler's access to adequate postexposure rabies prophylaxis.

In the United States, however, where a single dose of rabies vaccine can exceed $400, cost has been a deterrent to preexposure prophylaxis. Although the new ACIP guidelines have reduced the associated inconvenience of 3 pretravel clinic visits extending over several weeks to just 2 visits 7 days apart, the high price might influence a traveler's decision about whether to accept preexposure prophylaxis. Even when modern cell-culture rabies vaccine was first introduced in the early 1980s, at approximately $45 per dose, many people already considered the vaccine too expensive.

INTRADERMAL PREEXPOSURE RABIES IMMUNIZATION

Intradermal (ID) rabies immunization began almost as soon as the intramuscular (IM) human diploid cell vaccine (HDCV) was manufactured. By reconstituting the 1.0 mL of vaccine in the vial, practitioners could draw up approximately eight 0.1-mL doses. One problem was that the entire vial had to be used within a few hours of reconstituting, meaning that a provider had to either be working in a busy clinic or lining up groups of people (e.g., families) for rabies immunization all at the same time.

Early studies of the immune response to ID rabies vaccine, using HDCV and later, other rabies vaccines, were uniformly encouraging. Virtually 100% of vaccinees seroconverted. A 1982 statement by ACIP reviewed data on >1,500 vaccinees and declared, "It appears that, with this vaccine, the 0.1-mL ID regimen is an acceptable alternative to the currently approved 1.0-mL IM regimen for preexposure prophylaxis." ACIP called upon manufacturers to produce a product with appropriate packaging and labeling.

In 1986, the Mérieux Institute (now Sanofi Pasteur) received approval to market a 0.1-mL dose in an individual syringe. Sharing reconstituted vials of 1.0 mL between patients remained off-label. Although the new product solved the logistical problem of providing individual travelers with an ID dose, the cost of the prepackaged ID dose was still 75% of the full 1.0-mL IM dose.

ACIP continued to endorse the concept of ID preexposure rabies immunization in a 1999 statement on rabies prevention. Three lots of a prepackaged rabies ID vaccine were recalled in 2000, however, for having a potency that fell below the specification level before the expiration date. In 2001, the ID rabies vaccine was withdrawn from the market. Since then, authorities in the United States have not recommended sharing 1.0-mL vials for ID rabies immunization because the manufacturer has not applied to the US Food and Drug Administration for the appropriate packaging and labeling. This lack of endorsement of ID preexposure immunization has frustrated some travel medicine professionals.

With 2 decades more experience in using ID preexposure rabies immunization, the concept

is now well accepted and routinely used in many parts of the world; ID administration remains off-label in the United States, however, due to the aforementioned packaging issues. Some clinics relying on preexposure ID dosing require vaccinated travelers to have a titer drawn after the series is completed to confirm seroconversion. This may save some money, but requires an additional clinic visit and even more time before travel.

POSTEXPOSURE PROPHYLAXIS

A wide variety of postexposure vaccine regimens are now used around the world, some of which use multisite intradermal vaccine doses. From the point of view of the traveler, perhaps the best strategy would be to try to use postexposure regimens that are approved in the traveler's home country, which could create the most confidence and make it easier to complete at home any regimens initiated abroad.

PREVENTION: THE BEST MEDICINE

I recently noticed that travelers are almost never bitten a second time in their entire lives, and experienced travelers and expatriates, including most travel medicine professionals, are never bitten at all. This led me to believe that it might be possible to educate travelers on how to avoid bites by making them better aware of animal behaviors and to keep their distance.

Perhaps greater emphasis on bite prevention should become a priority during the pretravel visit. As travel medicine professionals, we can analyze our own behaviors in avoiding bites and transmit that information to travelers. Avoiding bites altogether would be the best way to help reduce anxiety-ridden travel and urgent telephone calls to obtain postexposure immunization in resource-poor settings.

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

RUBELLA

Michelle Morales, Tatiana Lanzieri, Susan Reef

INFECTIOUS AGENT: Rubella virus	
ENDEMICITY	Worldwide
TRAVELER CATEGORIES AT GREATEST RISK FOR EXPOSURE & INFECTION	Unvaccinated travelers
PREVENTION METHODS	Rubella is a vaccine-preventable disease
DIAGNOSTIC SUPPORT	A clinical laboratory certified in moderate complexity testing; state health department; or CDC Rubella Laboratory Testing (www.cdc.gov/rubella/lab/index.html)

INFECTIOUS AGENT

Rubella is a spherical, positive-sense, single-stranded RNA virus of the family *Matonaviridae*, genus *Rubivirus*.

TRANSMISSION

Rubella virus is transmitted through person-to-person contact or droplets shed from the respiratory secretions of infected people. People can shed virus from 7 days before the onset of the rash to ≈5–7 days after rash onset. Transmission from mother to fetus also can occur, with the highest risk for congenital rubella syndrome (CRS) if infection occurs in the first trimester. Infants with CRS can transmit virus for ≤1 year after they are born.

EPIDEMIOLOGY

In 2015, the World Health Organization Region of the Americas became the first in the world to be declared free of endemic rubella virus transmission. Rubella virus continues to circulate widely, however, especially in Africa, East Asia, and South Asia; ≈49,000 cases were reported worldwide in 2019, and ≈10,000 cases were reported in 2020. Globally, >100,000 infants are born each year with CRS; >80% are born in Africa and some countries in South and Southeast Asia. In the United States, endemic rubella virus transmission was interrupted in 2001 and elimination verified in 2004, but imported cases of rubella and CRS continue to occur. During 2016–2019, a median of 5 (range, 1–7) imported rubella cases were reported annually in the United States, and 8 CRS cases were reported during the same period.

CLINICAL PRESENTATION

The average incubation period is 14 days (range 12–23 days). Rubella usually presents with generalized lymphadenopathy, slight or no fever, and a mild, nonspecific, maculopapular, generalized rash that lasts up to 3 days. The rash usually starts on the face, becoming generalized within 24 hours. Appearance of the rash can sometimes be preceded by anorexia, mild conjunctivitis, low-grade fever, malaise, runny nose, and sore throat. Adolescents and adults, especially women, also can present with transient arthritis. Rare complications include encephalitis and thrombocytopenic purpura, but ≈25%–50% of infections are asymptomatic. Infection during early pregnancy can lead to miscarriage, fetal death, or an infant born with CRS, a constellation of birth defects.

DIAGNOSIS

Clinical diagnosis of rubella virus is unreliable and should not be considered in assessing immune

status; ≤50% of all infections are subclinical or unapparent. Many rubella infections are not recognized because the rash resembles many other rash illnesses.

Diagnosis is based on serologic demonstration of specific rubella IgM or significant increase in rubella IgG in acute- and convalescent-phase specimens. Reverse transcription PCR (RT-PCR) can be used to detect virus infection; viral culture also is acceptable but is time consuming and expensive. Rubella is a nationally notifiable disease in the United States.

TREATMENT

Treatment of rubella involves supportive care. Counsel patients to isolate, and encourage household contacts to get tested and vaccinated.

PREVENTION

Unless contraindicated, vaccinate all travelers aged ≥12 months who do not have acceptable evidence of immunity to rubella (documented by ≥1 dose of rubella-containing vaccine on or after the first birthday, laboratory evidence of immunity, or birth before 1957) with measles-mumps-rubella (MMR) vaccine. Before departure from the United States, infants aged 6–11 months should receive 1 dose of MMR vaccine (for measles protection), and children aged ≥12 months and adults should receive 2 doses of MMR vaccine ≥28 days apart.

MMR vaccine is contraindicated during pregnancy. Advise pregnant people who do not have acceptable evidence of rubella immunity to avoid travel to countries where rubella is endemic or to areas with known rubella outbreaks, especially during the first 20 weeks of pregnancy. In addition, they should receive an MMR vaccination immediately postpartum. Ensure that all people of childbearing age and recent immigrants are up to date on immunization against rubella or have evidence of immunity to rubella, because these groups are at the greatest risk for maternal–fetal transmission of rubella virus, which can result in CRS.

CDC website: www.cdc.gov/rubella

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RUBEOLA / MEASLES

Paul Gastañaduy, James Goodson

INFECTIOUS AGENT: Measles virus	
ENDEMICITY	Worldwide
TRAVELER CATEGORIES AT GREATEST RISK FOR EXPOSURE & INFECTION	All travelers, especially unvaccinated travelers
PREVENTION METHODS	Rubeola is a vaccine-preventable disease
DIAGNOSTIC SUPPORT	A clinical laboratory certified in moderate complexity testing; state health department; or CDC Measles Virus Laboratory, www.cdc.gov/measles/lab-tools/measles-virus-lab.html

INFECTIOUS AGENT

Measles virus is a member of the genus *Morbillivirus* of the family *Paramyxoviridae*.

TRANSMISSION

Measles is transmitted from person to person via respiratory droplets and by the airborne route as aerosolized droplet nuclei. Infected people are usually contagious from 4 days before until 4 days after rash onset. Measles is among the most contagious viral diseases known; secondary attack rates are ≥90% among susceptible household and institutional contacts. Humans are the only natural host for sustaining measles virus transmission, which makes global eradication of measles feasible.

EPIDEMIOLOGY

Measles was declared eliminated (defined as the absence of endemic measles virus transmission in a defined geographic area for ≥12 months in the presence of a well-performing surveillance system) from the United States in 2000. Measles virus continues to be imported into the country from other parts of the world, however, and recent prolonged outbreaks in the United States resulting from measles virus importations highlight the challenges faced in maintaining measles elimination.

Given the large global measles burden and high communicability of the disease, travelers could be exposed to the virus in any country they visit where measles remains endemic or where large outbreaks are occurring. Most measles cases imported into the United States occur in unvaccinated US residents who become infected while traveling abroad, often to the World Health Organization (WHO)–defined Western Pacific and European regions. These travelers become symptomatic after returning to the United States and sometimes infect others in their communities, causing outbreaks.

Nearly 90% of imported measles cases are considered preventable by vaccination (i.e., the travelers lacked recommended age- and travel-appropriate vaccination). Furthermore, observational studies in travel clinics in the United States have shown that 59% of pediatric and 53% of adult travelers eligible for measles-mumps-rubella (MMR) vaccine at the time of pretravel consultation were not vaccinated at the visit, highlighting a missed opportunity to reduce the likelihood of measles introductions and subsequent spread. Encourage all eligible travelers to receive appropriate MMR vaccination. Outbreak investigations are costly and resource intensive, and infected people—in addition to productivity losses—can incur direct costs for the management of their illness, including treatment, quarantine, and caregiving.

CLINICAL PRESENTATION

The incubation period averages 11–12 days from exposure to onset of prodrome; rash usually appears ≈14 days after exposure. Symptoms include fever, with temperature ≤105°F (≤40.6°C); conjunctivitis; coryza (runny nose); cough; and small spots with white or bluish-white centers on an erythematous base appearing on the buccal mucosa (Koplik spots). A characteristic red, blotchy (maculopapular) rash appears 3–7 days after onset of prodromal symptoms. The rash begins on the face, becomes generalized, and lasts 4–7 days.

Common measles complications include diarrhea (8%), middle ear infection (7%–9%), and pneumonia (1%–6%). Encephalitis, which can result in permanent brain damage, occurs in ≈1 per 1,000–2,000 cases of measles. The risk for serious complications or death is highest for children aged ≤5 years, adults aged ≥20 years, and in populations with poor nutritional status or that lack access to health care.

Subacute sclerosing panencephalitis (SSPE) is a progressive neurologic disorder caused by measles virus that usually presents 5–10 years after recovery from the initial primary measles virus infection. SSPE manifests as mental and motor deterioration, which can progress to coma and death. SSPE occurs in ≈1 of every 5,000 reported measles cases; rates are higher among children <5 years of age.

DIAGNOSIS

Measles is a nationally notifiable disease. Laboratory criteria for diagnosis include a positive serologic test for measles-specific IgM, IgG seroconversion, or a significant rise in measles IgG level by any standard serologic assay; isolation of measles virus; or detection of measles virus RNA by reverse transcription PCR (RT-PCR) testing. The Centers for Disease Control and Prevention's Measles Virus Laboratory is the national reference laboratory; it provides serologic and molecular testing for measles and technical assistance to state public health laboratories for the collection and shipment of clinical samples for molecular diagnostics and genetic analysis. Detailed information on diagnostic support can be found at www.cdc.gov/measles/lab-tools/measles-virus-lab.html.

A clinical case of measles illness is characterized by generalized maculopapular rash lasting ≥3 days; temperature ≥101°F (38.3°C); and cough, coryza, or conjunctivitis. A confirmed case is one with an acute febrile rash illness with laboratory confirmation or direct epidemiologic linkage to a laboratory-confirmed case. In a laboratory-confirmed or epidemiologically linked case, the patient's temperature does not need to reach ≥101°F (38.3°C) and the rash does not need to last ≥3 days.

TREATMENT

Treatment is supportive. The WHO recommends vitamin A for all children with acute measles, regardless of their country of residence, to reduce the risk for complications. Administer vitamin A as follows: for infants <6 months old, give 50,000 IU, once a day for 2 days; for infants 6 months old and older, but younger than 12 months, give 100,000 IU once a day for 2 days; for children ≥12 months old give 200,000 IU once a day for 2 days. For children with clinical signs and symptoms of vitamin A deficiency, administer an additional (i.e., a third) age-specific dose of vitamin A 2–4 weeks following the first round of dosing.

PREVENTION

Measles has been preventable through vaccination since a vaccine was licensed in 1963. People who do not have evidence of measles immunity should be considered at risk for measles, particularly during international travel. Acceptable presumptive evidence of immunity to measles includes birth before 1957; laboratory confirmation of disease; laboratory evidence of immunity; or written documentation of age-appropriate vaccination with a licensed, live attenuated measles-containing vaccine[1], namely, MMR or measles-mumps-rubella-varicella (MMRV). For infants 6 months old and older, but younger than 12 months, this includes documented administration of 1 dose of MMR; for people aged ≥12 months, documentation should

[1] From 1963–1967, a formalin-inactivated measles vaccine was available in the United States and was administered to ≈600,000–900,000 people. It was discontinued when it became apparent that the immunity it produced was short-lived. Consider people who received this vaccine unvaccinated.

include 2 doses of MMR or MMRV (the first dose administered at age ≥12 months and the second dose administered no earlier than 28 days after the first dose). Verbal or self-reported history of vaccination is not considered valid presumptive evidence of immunity.

Vaccination

Measles vaccine contains live, attenuated measles virus, which in the United States is available only in combination formulations (e.g., MMR and MMRV vaccines). MMRV vaccine is licensed for children aged 12 months–12 years and can be used in place of MMR vaccine if vaccination for measles, mumps, rubella, and varicella is needed.

International travelers, including people traveling to high-income countries, who do not have presumptive evidence of measles immunity and who have no contraindications to MMR or MMRV, should receive MMR or MMRV before travel per the following schedule.

Infants (6 months old and older, but younger than 12 months): 1 MMR dose. Infants vaccinated before age 12 months must be revaccinated on or after the first birthday with 2 doses of MMR or MMRV separated by ≥28 days. MMRV is not licensed for children aged <12 months.

Children (aged ≥12 months): 2 doses of MMR or MMRV separated by ≥28 days.

Adults born in or after 1957: 2 doses of MMR separated by ≥28 days.

One dose of MMR is ≈85% effective when administered at age 9 months; MMR and MMRV are 93% effective when administered at age ≥1 year. Vaccine effectiveness of 2 doses is 97%.

ADVERSE REACTIONS

In rare circumstances, MMR vaccination has been associated with anaphylaxis (≈2–14 occurrences per million doses administered); febrile seizures (≈1 occurrence per 3,000–4,000 doses administered, but overall, the rate of febrile seizures after measles-containing vaccine is much lower than the rate with measles disease); thrombocytopenia (≈1 occurrence per 40,000 doses during the 6 weeks after immunization); or joint symptoms (arthralgia develops among ≈25% of nonimmune postpubertal females from the rubella component of the MMR vaccination, and ≈10% have acute arthritis-like signs and symptoms that generally persist for 1–21 days and rarely recur; chronic joint symptoms are rare, if they occur at all). No evidence supports a causal link between MMR vaccination and autism, type 1 diabetes mellitus, or inflammatory bowel disease.

CONTRAINDICATIONS

ALLERGY

People who experienced a severe allergic reaction (difficulty breathing, hives, hypotension, shock, swelling of the mouth or throat) following a prior dose of MMR or MMRV vaccine, or who had an anaphylactic reaction to topically or systemically administered neomycin, should not be vaccinated or revaccinated. People who are allergic to eggs can receive MMR or MMRV vaccine without prior routine skin testing or the use of special protocols.

IMMUNOSUPPRESSION

Enhanced replication of live vaccine viruses can occur in people who have immune deficiency disorders. Death related to vaccine-associated measles virus infection has been reported among severely immunocompromised people; thus, severely immunosuppressed people should not be vaccinated with MMR or MMRV vaccine. For a thorough discussion of recommendations for immunocompromised travelers, see Sec. 3, Ch. 1, Immunocompromised Travelers.

HIV

MMR vaccination is recommended for all people with HIV infection aged ≥12 months who do not have evidence of measles, mumps, and rubella immunity, and who do not have evidence of severe immunosuppression. The assessment of severe immunosuppression can be based on CD4 values (count or percentage); absence of severe immunosuppression is defined as CD4 ≥15% for ≥6 months for children aged ≤5 years, or CD4 ≥15% and CD4 count ≥200 cells/mL for ≥6 months for people aged >5 years.

LEUKEMIA

People with leukemia in remission and off chemotherapy, who were not immune to measles when

diagnosed with leukemia, may receive MMR vaccine. At least 3 months should elapse after termination of chemotherapy before administering the first dose of vaccine.

STEROIDS & OTHER IMMUNOSUPPRESSIVE THERAPIES

Avoid vaccinating people who have received high-dose corticosteroid therapy (in general, considered to be ≥20 mg or 2 mg/kg body weight of prednisone, or its equivalent, daily for ≥14 days) with MMR or MMRV for ≥1 month after cessation of steroid therapy. Corticosteroid therapy usually is not a contraindication when administration is short-term (<14 days) or a low to moderate dose (<20 mg of prednisone or equivalent per day).

In general, withhold MMR or MMRV vaccine for ≥3 months after cessation of other immunosuppressive therapies and remission of the underlying disease. See Sec. 3, Ch. 1, Immunocompromised Travelers, for more details.

PREGNANCY

MMR vaccines should not be administered to pregnant people or people attempting to become pregnant. Because of the theoretical risk to the fetus, people should be counseled to avoid becoming pregnant for 28 days after receiving a live-virus (e.g., MMR) vaccine.

PRECAUTIONS

PERSONAL OR FAMILY HISTORY OF SEIZURES OF ANY ETIOLOGY

Compared with administration of separate MMR and varicella vaccines at the same visit, use of MMRV vaccine is associated with a higher risk for fever and febrile seizures 5–12 days after the first dose among children aged 12–23 months. Approximately 1 additional febrile seizure occurs for every 2,300–2,600 MMRV vaccine doses administered. Use of separate MMR and varicella vaccines avoids this increased risk for fever and febrile seizures.

THROMBOCYTOPENIA

The benefits of primary immunization are usually greater than the potential risks for vaccine-associated thrombocytopenia. Avoid giving subsequent doses of MMR or MMRV vaccine, however, if an episode of thrombocytopenia occurred ≤6 weeks after a previous dose of vaccine.

Postexposure Prophylaxis

Measles-containing vaccine or immune globulin (IG) can be effective as postexposure prophylaxis. MMR or MMRV administered ≤72 hours after initial exposure to measles virus might provide some protection. If the exposure does not result in infection, the vaccine should induce protection against subsequent measles virus infection.

When administered ≤6 days of exposure, IG can be used to confer temporary immunity in a susceptible person. If the exposure does not result in modified or typical measles, vaccination with MMR or MMRV is still necessary to provide long-lasting protection. Six months after receiving intramuscularly administered IG, or 8 months after receiving intravenously administered IG, administer MMR or MMRV vaccine, provided the patient is aged ≥12 months and the vaccine is not otherwise contraindicated.

CDC website: www.cdc.gov/measles

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5

SMALLPOX & OTHER ORTHOPOXVIRUS-ASSOCIATED INFECTIONS

The information included in this chapter was current as of August 2022. For the most recent information regarding monkeypox and the 2022 monkeypox outbreak, see www.cdc.gov/poxvirus/monkeypox/index.html.

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SMALLPOX

INFECTIOUS AGENT: Variola virus	
ENDEMICITY	Eradicated worldwide Bioterrorism threat exists
TRAVELER CATEGORIES AT GREATEST RISK FOR EXPOSURE & INFECTION	None
PREVENTION METHODS	Smallpox is a vaccine-preventable disease (restrictions apply, see text below for details)
DIAGNOSTIC SUPPORT	CDC Poxvirus Inquiries (poxvirus@cdc.gov) CDC Emergency Operations Center (770-488-7100)

COWPOX, VACCINIA & SIMILAR ORTHOPOXVIRUSES

INFECTIOUS AGENTS: Cowpox virus, Vaccinia virus, Akhmeta virus	
ENDEMICITY	Cowpox virus: Europe and the Caucuses Vaccinia virus: the Americas (Argentina, Brazil, Colombia); Asia (Bangladesh, India) Akhmeta virus: Georgia
TRAVELER CATEGORIES AT GREATEST RISK FOR EXPOSURE & INFECTION	Travelers who come into direct contact with animals, specifically bovids
PREVENTION METHODS	Avoid agricultural bovids with signs of disease Wear appropriate personal protective equipment
DIAGNOSTIC SUPPORT	CDC Poxvirus Inquiries (poxvirus@cdc.gov) CDC Emergency Operations Center (770-488-7100)

MONKEYPOX

INFECTIOUS AGENT: Monkeypox virus	
ENDEMICITY	West and Central Africa, esp. Congo Basin, Nigeria
TRAVELER CATEGORIES AT GREATEST RISK FOR EXPOSURE & INFECTION	Travelers to monkeypox-endemic regions who have direct exposures to wild mammals, products derived from wild mammals, or monkeypox patients or their biological samples Travelers who have close skin-to-skin contact (including that which occurs during sex) with people infected with monkeypox virus
PREVENTION METHODS	Avoid sick or dead wild small mammals, tissues of wild mammals, and products made from wild mammals Avoid people with monkeypox Wear appropriate personal protective equipment Monkeypox is a vaccine-preventable disease (restrictions apply, see text below for details)
DIAGNOSTIC SUPPORT	CDC Poxvirus Inquiries (poxvirus@cdc.gov) CDC Emergency Operations Center (770-488-7100)

INFECTIOUS AGENT

Smallpox is caused by variola virus, genus *Orthopoxvirus*. Other members of this genus that can infect humans include cowpox virus, vaccinia virus, and monkeypox virus.

TRANSMISSION

Smallpox & Vaccinia

In 1980, the World Health Organization (WHO) officially declared smallpox eradicated; however, the threat of reemergence by intentional introduction (e.g., bioterrorism) persists. Before smallpox was eradicated, it spread from person to person principally through respiratory droplets. Contact with infectious skin lesions or scabs was a less common mode of transmission but sometimes occurred (e.g., when caregivers cared for patients or washed contaminated clothing). Rarely, smallpox spread through air in enclosed settings (airborne transmission).

Vaccinia virus is the live virus component of contemporary smallpox vaccines. One of these vaccines, ACAM2000, is a replication competent vaccinia virus; occasionally, infection occurs from touching the fluid or crust material from the inoculation lesion of someone recently vaccinated against smallpox, or from touching contaminated materials like sheets and towels. Human infections with vaccinia virus have occurred in Brazil, Colombia, and India after contact with agricultural animals, often bovids, infected with sylvatic vaccinia-like viruses.

Cowpox

Contrary to the disease name, wild rodents are considered the reservoirs for cowpox virus. Mammals (e.g., cats, cows, humans) are incidental hosts. Cowpox virus infection occurs after direct contact with infected animals including incidental hosts. Person-to-person transmission has not been observed.

Monkeypox

Small mammals, not monkeys, are the suspected reservoir for monkeypox virus. Historically, people at increased risk for transmission have had contact with infected wildlife or wildlife products, infected humans, or the bodily fluids or respiratory droplets from infected wildlife or people. Person-to-person spread of monkeypox virus can occur through exposure to respiratory secretions and through direct skin-to-skin contact with a lesion or lesions (including scabs). Contact with infectious materials (e.g., shared towels, bedding) is another, albeit less common, means of interpersonal spread. In 2022, a global, multinational monkeypox outbreak began; through August 2022, most cases had occurred among men who have sex with men and were predominately due to close skin-to-skin contact (including that which occurs during sex).

EPIDEMIOLOGY

Smallpox & Vaccinia

The last documented case of naturally occurring (endemic) smallpox was in 1977. A single confirmed case of smallpox today could be the result of an intentional act (bioterrorism) and would be considered a global public health emergency.

Infections with wild vaccinia-like viruses have been reported among cattle and buffalo herders in India and among dairy workers in southern Brazil and Colombia. Travelers touching affected bovines might acquire a localized, cutaneous infection. Immunosuppressed people or people with certain skin conditions are at an increased risk for developing systemic illness.

Cowpox

Human infections with cowpox virus and cowpox-like viruses have been reported in Europe and the Caucasus (e.g., cowpox and Akhmeta viruses in Georgia). Travelers having direct contact with infected bovines, felines, rodents (including pet rats), or captive exotic animals (e.g., zoo animals) can be at risk for cutaneous infection.

Monkeypox

Monkeypox is endemic to the tropical forested regions of West and Central Africa, notably the Congo Basin. Most cases are reported from the Democratic Republic of the Congo (DRC), where monkeypox was first recognized as a human disease in 1970. Travelers (including immigrants and refugees) leaving the DRC could be infected with monkeypox virus, but reports of disease imported from the DRC are rare.

In 2003, small mammals imported from Africa were the source of a human monkeypox outbreak in the United States. The infected, imported animals were housed with domestic prairie dogs being sold as pets. At least 37 people were infected.

Increases in human monkeypox cases across multiple African countries have occurred over the last few years in Cameroon, Central African Republic, Côte d'Ivoire, Gabon, Liberia, Nigeria, Republic of the Congo, and Sierra Leone. In many of these countries, decades had passed before new cases were detected. During 2018–2021, Nigeria was implicated as the country of origin for 8 cases of exported monkeypox in humans: 4 cases were diagnosed in people who traveled to the United Kingdom; 2 others traveled to the United States; 1 to Singapore; and 1 to Israel. In the United Kingdom, secondary cases occurred among family members of one of the patients and in a health care provider.

Most recently, a global monkeypox outbreak began in May 2022. On July 23, the WHO declared the outbreak a Public Health Emergency of International Concern, and on August 4, the United States declared the ongoing spread of the virus to be a public health emergency. As of August 2022, the outbreak had caused tens of thousands of cases in >90 countries, predominately among men who have sex with men; as previously noted, transmission has been associated with close skin-to-skin contact.

CLINICAL PRESENTATION

Table 5-20 summarizes key clinical characteristics of orthopoxvirus infections in humans. Immunocompromised patients or people with exfoliative skin conditions (e.g., atopic dermatitis or eczema) are at greater risk for severe illness or death. Ocular infections, although rare, have caused permanent corneal scarring. Poor pregnancy outcomes, including fetal death, have been observed when pregnant people have had variola or monkeypox virus infections.

Smallpox

Clinical signs and symptoms include acute onset of fever >101°F (38.3°C), head and body aches, malaise, and sometimes vomiting, then a characteristic, disseminated rash of firm, deep-seated vesicles or pustules in the same stage of development on

Table 5-20 Clinical characteristics of smallpox, cowpox, vaccinia (naturally occurring) and similar orthopoxviruses, and monkeypox

CLINICAL CHARACTERISTIC	SMALLPOX	COWPOX, VACCINIA, OR SIMILAR ORTHOPOXVIRUSES	MONKEYPOX	
			CLASSICAL	2022 OUTBREAK
INCUBATION PERIOD (DAYS)	7–19	2–4	4–17	Subject to change as the outbreak evolves
FEVER	Yes Febrile prodrome before lesions	Yes Often coincides with lesions	Yes Febrile prodrome before lesions	Not consistently reported
MALAISE	Yes	Yes	Yes	Not consistently reported
HEADACHE	Yes	Yes	Yes	Not consistently reported
LYMPHADENOPATHY	No	Yes	Yes	Not consistently reported
LESION DISTRIBUTION	Centrifugally disseminated Often present on palms/soles	Often localized to hands, face, and neck due to contact transmission	Centrifugally disseminated Present on the palms/soles	Often affecting anogenital region but also affecting face and extremities Sometimes present on palms/soles
LESION CHARACTERISTICS	Deep-seated, profound, well circumscribed, often with a central point of umbilication Rash progresses slowly from macule to papule to vesicle to pustule to crust, over 2–4 weeks			