Medical Summary

RABIES

GENERAL INFORMATION

Introduction

Rabies is an acute, progressive infection of the central nervous system caused by neurotropic viruses in the family Rhabdoviridae, genus *Lyssavirus*. Human rabies is characterized by fever, anxiety, hydrophobia, muscular spasms, and coma (furious rabies); alternatively, the patient becomes lethargic and paralyzed (paralytic rabies). Once symptoms develop, rabies is nearly always fatal. (See "Clinical Presentation" for information on 3 non-fatal cases of bat rabies.) The rabies virus is present in the saliva and nervous tissue of rabid animals and humans.

The most common mode of transmission is via penetrating bites by rabid animals. All mammals are susceptible to infection, but the main reservoirs are carnivores and bats. Dogs are the main source of infection for humans worldwide. Bites to the face and hands carry especially high risk. Canine rabies has been eliminated from a few countries, but bat rabies occurs worldwide, with the exception of New Zealand. Timely immunization is protective when given before and/or after exposure.

Mode of Transmission

Rabies virus is present in the saliva of a rabid animal, even those that do not exhibit features of disease. Saliva must be inoculated through intact skin or licked onto preexisting abrasions or scratches or onto mucosal surfaces. Bites from dogs are the most common source for humans. Other sources include canines (foxes, wolves, jackals, coyotes), raccoons, skunks, cats, and, occasionally, cattle (in farmers); monkeys are a potential but uncertain source. Bat rabies is transmitted by bat bites or scratches (which may not be noticed) or more rarely by inhalation of aerosolized bat saliva in caves where numerous bats congregate. Rare routes of transmission include corneal grafting and organ transplantation. Rabies has never been transmitted from a patient to a family member or health care worker.

Travelers usually become infected with rabies as a result of handling or being attacked by stray dogs or cats, which bite, lick, or dribble saliva on them. Of 39 cases of rabies (with identified animal contact) imported into Europe, the United States, Russia, and Japan between 1990 and 2010, 37 had contact with dogs, 1 with a fox, and 1 with a bat.

Epidemiology

Lyssavirus genotype 1 causes rabies in terrestrial mammals and in bats in the Americas; genotypes 2-7 cause rabies-like infection in bats throughout the rest of the world.

Rabies is a zoonosis of wild mammals (sylvatic rabies) and is endemic in most of the world. Raccoons and skunks are important reservoirs in the U.S. and mongooses in southern Africa, Central America, and the Caribbean islands. All mammals are susceptible, but dogs and other canines are the most important vectors because they bite readily, eat small mammals that may be naturally infected, infect other dogs by fighting, and have daily contact with humans. The saliva of rabid dogs is highly infectious.

Bats are infected with a rabies-like *Llyssavirus* worldwide, except in New Zealand. Insectivorous, fruit, and vampire bats may be infected. In the U.S., insectivorous bats, notably silver-haired and Mexican free-tailed bats, cause more than 90% of human rabies cases. In Central and South America, rabies transmitted by vampire bats causes significant mortality in cattle and occasional outbreaks in humans.

The Indian subcontinent, North Africa, West Africa, Central Asia, Mexico, Haiti, and the Philippines have been the main destinations at which travelers from the U.S. and Europe have acquired rabies.

A number of countries (e.g., New Zealand and many in Western Europe) are considered to be free of terrestrial rabies. Check Travax destinations for country-specific information.

Risk

A bite, a scratch, or a lick from a dog or other mammal in a rabies-endemic country or a bite or scratch from a bat in any country presents a risk of rabies to an unvaccinated traveler.

Risk of developing rabies increases with severity (number and depth) of bites and proximity to the head, because the incubation period of clinical rabies depends on the time it takes for the virus to enter nerves in the damaged tissue and travel to the brain.

Clinical Presentation

The incubation period ranges from 4 days to 4 years (or longer), according to the severity and site of the bite, but most commonly ranges from 20 to 90 days. Tingling at the site of the bite heralds a prodromal illness characterized by fever, myalgia, anxiety, depression, irritability, and sometimes respiratory or gastrointestinal symptoms, which progress to the classical features of either furious or paralytic rabies.

- Patients with furious rabies, which is common after dog bites, are terrified of water (hydrophobia) and develop severe spasms of inspiratory muscles of respiration, which may lead to asphyxia, generalized convulsions, and ultimately coma and death.
- Patients with paralytic rabies, which is common after bat bites, become lethargic, dribble saliva, and develop an ascending flaccid paralysis.

Human rabies of canine origin is uniformly fatal. The American bat rabies virus may be less virulent, and 3 human cases are known to have survived after prolonged intensive care.

Prevention

Preexposure

Non-Vaccine

- Avoid contact with all dogs and other biting mammals in a country with canine rabies.
- Avoid contact with all wild mammals that are potential reservoirs–especially an animal that is behaving abnormally–in a country with endemic sylvatic rabies.
- Advise travelers not to touch or feed monkeys, especially those in temples and national parks, as they often show little fear of humans.
- Advise travelers to seek advice if planning to visit bat-infested caves.
- Children are at high risk for exposure and may not report bites, scratches, or other incidents if they occur, so travelers with children should be especially vigilant.

Vaccine: Rabies vaccine is available and may be indicated for travelers to any country with rabies (especially canine rabies).

- Risk of rabies varies widely between countries, and there is emerging evidence that bat lyssavirus/rabies infection is now presumed to exist in all countries (except New Zealand).
- Travax country-specific recommendations for preexposure rabies vaccination take into account destination, duration of stay, likelihood of activities (recreational or occupational) with potential

exposure to rabid animals, whether the traveler is a young child, and likely availability of vaccine and rabies immune globulin for postexposure care.
- See "Indications for Vaccination" and Travax destinations for country-specific recommendations.

Postexposure

Non-Vaccine

- Postexposure care should begin with *immediate* thorough cleansing of all wounds with soap or detergent and water under a running tap if possible, for a minimum of 15 minutes.
- If available, a virucidal agent (such as povidone iodine) should be used to irrigate the wounds.
- Deep wounds should be explored, debrided, and irrigated in hospital, under an anesthetic if necessary, and not closed or sutured.

Vaccine/Vaccine + HRIG

- Vaccine (without HRIG) is given to persons who have completed a primary series.
- Both vaccine *and* HRIG are given to persons without a complete primary series (3 or more doses of rabies vaccine). HRIG provides rapid, passive, short-term immunity.

Need for Medical Assistance

A traveler who has been bitten, scratched, or licked by a mammal in a rabies-endemic country or by a bat anywhere in the world should *urgently* seek advice on postexposure prophylaxis. National, state, or local health authorities should be consulted by the traveler or the medical provider for recent information on rabies risk according to the particular exposure.

INDICATIONS FOR VACCINATION

Note: Shoreland's vaccine recommendations focus primarily on the risk to the individual traveler and reflect a synthesis and reconciliation of available advice from CDC, ACIP, AAP, and WHO, as well as prominent travel medical authorities, global surveillance, and published literature. These recommendations may differ from those of individual countries' public health authorities. Significant differences between Shoreland and other authorities (e.g., CDC) are noted, when they occur.

Preexposure Prophylaxis

Routine

Rabies vaccination is routinely indicated for:

- Persons who may be at risk due to occupations or activities such as workers in rabies research, diagnostic, or biologics production facilities; spelunkers; veterinarians, veterinary students, and staff; and animal control and wildlife workers in areas in which rabies occurs

Travel

Rabies vaccination is recommended for:

- Long-stay travelers in high-risk destinations
- Shorter-stay travelers in high-risk destinations if > 24 hours from reliable source of modern cell-culture rabies vaccine and RIG
- Travelers with extensive outdoor exposure in high-risk destinations where immediate access to

appropriate medical care may be limited, regardless of length of stay
- Risk-averse travelers to high-risk destinations, especially those engaging in high-risk activities

Note: Preexposure immunization does not eliminate the need for further immunization after an exposure incident; however, it reduces the postexposure vaccine schedule to 2 injections and eliminates the need for RIG, which is often very difficult to access abroad.

Booster (or Testing)

Booster or testing is indicated for:

- Persons at continuous risk (e.g., rabies research lab or biologics production workers)
- Persons at frequent risk (e.g., rabies diagnostic lab workers, veterinarians and staff, spelunkers, animal control and wildlife workers in epizootic areas)

Postexposure Prophylaxis (PEP)

Recommended

PEP is recommended for:

- Bite exposures: any penetration of the skin by teeth
    - PEP need not be initiated for dogs, cats, and ferrets that are healthy and available for 10 days' observation. If PEP has been initiated and the animal remains healthy, PEP can be discontinued.
    - Skunks, raccoons, foxes, and most other carnivores and bats should be considered rabid unless proven negative by testing.
    - Livestock, small and large rodents (rats, mice, hamsters, gerbils, guinea pigs, woodchucks, beavers), lagomorphs (rabbits, hares), and other mammals almost never require initiation of PEP.
- Non-bite exposures: scratches or contamination of open wounds, abrasions, or mucous membranes with saliva or other potentially infectious material
    - See above for presumption of rabies infection by animal type.

May Be Indicated

PEP may be indicated for:

- Bat exposures if it is *not certain that exposure did not occur* even if evidence of exposure is not visible.

Not Indicated

PEP is not indicated for:

- Bat exposures if the person is *reasonably certain exposure did not occur* or if the bat is available for testing and is negative for rabies virus.

Note: PEP is indicated regardless of the time interval between exposure and initiation of PEP, even if the interval is a year or longer.

VACCINES

Vaccines and Immune Globulin-U.S.

Rabies Inactivated-Virus Cell-Culture Vaccines

RabAvert (Purified Chick Embryo Cell Vaccine; PCECV) is a freeze-dried vaccine grown in chicken fibroblasts.

- Available in single-dose vials of freeze-dried vaccine and single-dose vials of diluent
- Contains gelatin, ovalbumin, human serum albumin, neomycin, chlortetracycline, amphotericin B
- Preservative-free
- Thimerosal-free
- Latex-free

Imovax Rabies (Human Diploid Cell Vaccine; HDCV) is a freeze-dried vaccine harvested from infected human diploid cells.

- Available in single-dose vials of freeze-dried vaccine and single-dose syringes of diluent
- Contains human albumin, neomycin
- Preservative-free
- Thimerosal-free
- Latex-free

Human Rabies Immune Globulin (HRIG)

HyperRAB S/D (solvent/detergent treated) is prepared from plasma of donors hyper-immunized with rabies vaccine.

- Available in 2 mL (300 IU) and 10 mL (1,500 IU) single-dose vials
- Preservative-free
- Thimerosal not listed in the package insert
- Latex-free

Imogam Rabies-HT (heat treated) is prepared from pooled venous plasma of persons immunized with rabies vaccine (HDCV).

- Available in 2 mL (300 IU) and 10 mL (1,500 IU) single-dose vials
- Contains glycine
- Preservative-free
- Thimerosal not listed in the package insert
- Latex-free

Vaccines and Immune Globulin-Available Outside the U.S.

Rabies Inactivated-Virus Cell-Culture Vaccines

Modern cell-culture vaccines for preexposure and postexposure use produced by multinational manufacturers include:

VeroRab (Sanofi Pasteur) is a freeze-dried Purified Vero-Cell Vaccine (PVRV).

- Sold in some countries as Rabies Vero or TRC VeroRab
- Available in single-dose vials of vaccine with diluent in syringes
- Contains human albumin and trace amount of neomycin and streptomycin

RabiPur (Novartis): PCECV (Purified Chick Embryo Cell Vaccine)

- Called RabAvert in the U.S. (see above) and Canada and RabiPur elsewhere (> 70 countries)

- RabiPur is also manufactured in India under license by a contractor solely for the Indian market and is a Good Manufacturing Practice (GMP) vaccine; this vaccine is also acceptable for use.

Rabivac (Novartis): HDCV (Human Diploid Cell Vaccine)

- Widely available outside the U.S.

Imovax Rabies (Sanofi Pasteur): HDCV (Human Diploid Cell Vaccine)

- Inactivated vaccine available in Canada
- Available in Australia and New Zealand as MIRV
- Available in single-dose vials (lyophilized vaccine) and single-use syringes (diluent)
- Contains neomycin and phenol
- Preservative-free

Note: The cell-culture vaccines listed above are acceptable for preexposure use and are considered equivalent in quality and potency to U.S.-licensed rabies vaccines.

If a traveler returns to the U.S. after starting any of the above licensed cell-culture vaccines for postexposure treatment, the schedule may be continued using any U.S.-licensed cell-culture vaccine.

- Brain and nerve cell tissue vaccines are available in some countries but have a high rate of severe side effects and should not be used. Travelers should avoid these types of vaccine.
- If a traveler returns after starting a brain or nerve cell tissue vaccine, the vaccine series should be restarted using a modern cell-culture vaccine.

Rabies Immune Globulin

While human rabies immune globulin (HRIG) is the preferred RIG product (given its relatively slow clearance), it is in short supply, particularly in developing countries. Where HRIG is unavailable or not affordable, purified equine rabies immune globulin (ERIG) should be used. Most of the new ERIG products are potent, highly purified, safe, and much less expensive than HRIG. However, they are of heterologous origin and carry a small risk of hypersensitivity reactions.

HRIG

- **Imogam Rabies-HT (Sanofi Pasteur):** human rabies immune globulin (HRIG), heat-treated
  - Available in Canada, Europe, and other countries
  - See U.S. vaccines above.
- **BeriRab P (ZLB Behring AG)**: human rabies immine globulin, pasteurized
  - Available in Argentina, Austria, Egypt, El Salvador, Germany, Hong Kong, India, Iran, Israel, Jordan, Kuwait, Mexico, Pakistan, Philippines, Sri Lanka, Switzerland, Syria, and Thailand.
  - Available in 2 mL ampules with 300 IU rabies antibodies, 5 mL ampules with 750 IU rabies antibodies, and 10 mL ampules with 1500 IU rabies antibodies
  - Preservative free

ERIG

- **FaviRab (Sanofi Pasteur):** purified equine origin immune globulin (ERIG)
  - FaviRab (ERIG) is widely distributed and acceptable for postexposure prophylaxis if HRIG is unlikely to be available for ≥ 48 hours.
  - The product contains pre-digested equine antibodies that do not contain the portion that usually causes the allergic reactions seen with whole equine serum. Nevertheless, instructions for a test dose, per package insert, should be followed closely, and epinephrine should be immediately available.
  - Available in multi-dose 5 mL vials (200 IU/mL per vial); recommended dose: 40 IU/kg

- Contains polysorbate 80

ADMINISTRATION: RABIES PREEXPOSURE IMMUNIZATION

U.S. health care providers should provide the patient (or parent/legal guardian of a child) with the most current *Vaccine Information Statement (VIS)* prior to giving each dose of this vaccine.

Intradermal (ID) dosing of cell-culture vaccine is highly economical but off-label in the U.S. and Western countries. While ID regimens (0.1 mL/dose using the standard IM schedule) are endorsed by WHO, neither Shoreland nor CDC supports the use of ID regimens in Western travelers because of liability issues.

Pediatric

- Vaccine may be given as young as needed.

Dose/Route

1.0 mL, intramuscular, avoid buttocks (may result in suboptimal immune response)

Schedule

Primary: PCECV, HDCV: 3 doses, 1 each on days 0, 7, and 28

- The third dose may be advanced towards day 21 if time is short.

Booster: PCECV, HDCV: 1 dose (if indicated)

A booster dose is routinely recommended *only* for:

- Persons at continuous risk: test for rabies antibody every 6 months; boost if the titer falls below 0.5 IU/mL
- Persons at frequent risk: boost or test every 2 years

Adult

Dose/Route

1.0 mL, intramuscular, avoid buttocks (may result in suboptimal immune response)

Schedule

Primary: PCECV, HDCV: 3 doses, 1 each on days 0, 7, and 28

- The third dose may be advanced towards day 21 if time is short.

Booster: PCECV, HDCV: 1 dose (if indicated)

A booster dose is routinely recommended *only* for:

- Persons at continuous risk: test for rabies antibody every 6 months; boost if the titer falls below 0.5 IU/mL
- Persons at frequent risk: boost or test every 2 years

ADMINISTRATION: RABIES POSTEXPOSURE TREATMENT

U.S. health care providers should provide the patient (or parent/legal guardian of a child) with the most

current *Vaccine Information Statement (VIS)* prior to giving each dose of this vaccine.

Also see Table RAB-1, "Rabies Postexposure Treatment."

Pediatric

Dose/Route/Schedule

- Vaccine and HRIG may be given as young as needed.
- Use same dosage and schedule as for adults (see below).
- Avoid buttocks (may result in suboptimal immune response)

Adults Who Have Completed the Preexposure Series

- Administer vaccine only.

Vaccine

Dose/Route

1.0 mL, intramuscular, avoid buttocks (may result in suboptimal immune response)

Schedule

Give 2 doses: 1 each on days 0 and 3.

- Give the first dose as soon as possible after exposure.

RIG: not needed

Adults Who Have Not Completed the Preexposure Series

- Administer both vaccine and RIG.

Vaccine

Dose/Route/Schedule

Give 4 IM doses (**1.0 mL** each): 1 each on days 0, 3, 7, and 14.

- Give the first dose as soon as possible after exposure.
  - This regimen applies only to healthy, fully immune competent persons with access to wound care, high-quality RIG, and cell-culture vaccine.
  - See "Compromised Immunity" for immunocompromised persons.
- A fifth dose of vaccine should be given (on day 28) for travelers in resource-limited situations where administration of RIG (either human or equine) is not possible.
- Also see "WHO-Approved PEP Regimens."

RIG

Dose/Route/Schedule

Administer 20 IU/kg body weight. If anatomically feasible, the full dose should be infiltrated around the wound(s) and any remaining volume should be administered IM at a site anatomically distant from the vaccine administration site.

Note: A decision to *vaccinate* is a decision to give *RIG* no matter how long it has been since the actual bite or non-bite exposure actually occurred.

- RIG must be given within 7 days of *initiating the vaccine series*.
    - RIG should not be given if more than 7 days have elapsed since vaccine initiation, as it may interfere with vaccine response.

Lapsed and Altered Schedules

Lapsed Preexposure Schedule

Because of the lack of data for extended lapsed intervals with rabies vaccine, some experts recommend restarting a rabies preexposure series when there are more than minor variations from the published 0, 7, and 28-day schedule.

- Delay of the second dose (the day 7 dose) for more than 3 days requires restarting the vaccine series.
    - A less time-efficient approach would be to resume the series but obtain rabies titers 7-14 days after the third dose and give an additional dose if titers are inadequate.
- The third dose should be given on day 28 but may be advanced towards day 21 (but no earlier) if time is short.
- Delay of the third dose beyond day 28 is permissible, even up to 1 year or longer.

Note: Persons who have had < 3 preexposure doses are considered to be unimmunized in the event of exposure.

WHO-Approved PEP Regimens

IM: The following regimens are commonly used in many rabies-endemic countries.

- 5-dose (classic/Essen) regimen: days 0, 3, 7, 14, and 28
- 4-dose (shortened Essen) regimen: days 0, 3, 7, and 14
    - This regimen applies only to healthy, fully immune competent persons with access to wound care, high-quality RIG, and cell-culture vaccine.
- 4-dose (Zagreb) regimen: 2 doses (at separate sites) given on day 0 and 1 dose each on days 7 and 21
- Returned travelers may be started on one of these regimens in the exposure country.

ID:WHO recommends a 2-site ID regimen (days 0, 3, 7, and 28) in countries where the ID route has been approved. Shoreland does not recommend use of the ID regimen in Western travelers.

SIDE EFFECTS

Local reactions for rabies vaccines may include: injection site pain (21-77% of HDCV recipients and 2-23% of PCECV recipients), induration, erythema, swelling, and itching.

Mild systemic reactions (e.g., fever, headache, dizziness, and GI symptoms) occur in 7-56% of HDCV recipients and 0-31% of PCECV recipients; nausea, abdominal pain, myalgia, and localized lymphadenopathy may also occur.

Systemic hypersensitivity reactions (e.g., urticaria, pruritus, malaise) have been reported in up to 6% of vaccinees receiving booster vaccination with HDCV, while < 1% of vaccinees receiving the HDCV primary series showed these side effects. These reactions have not been reported in persons receiving PCECV.

- Rarely, neurologic adverse events have been reported, but causality was not established in these cases and all resolved spontaneously.

- Serious systemic, anaphylactic, or neuroparalytic reactions are rare; however, if they do occur, seek expert advice to decide if the series can be continued. The risk of acquiring rabies must be weighed carefully before the decision is made to discontinue immunization.

Once initiated, rabies postexposure prophylaxis should not be interrupted or discontinued because of local or mild systemic reactions to rabies vaccine. These reactions usually can be managed with anti-inflammatory, antihistaminic, and antipyretic agents (e.g., aspirin).

When it is necessary to revaccinate a person who has a history of hypersensitivity to a previous dose of rabies vaccine, empiric intervention such as pre-treatment with antihistamines might be considered. Epinephrine should be readily available to counteract anaphylactic reactions, and the individual should be carefully observed immediately after immunization.

Suspected allergic or adverse effects or medical care required after any immunization should be reported.

PRECAUTIONS AND CONTRAINDICATIONS

General

Consider postponing preexposure vaccination (if feasible) until recovery in persons with moderate or severe illness, with or without a fever, to minimize potential adverse effects.

Persons with a history of serious hypersensitivity to components of rabies vaccine should be revaccinated with caution. (See "Side Effects.")

- A history of anaphylactic reaction to egg or egg protein is a contraindication to PCECV.

Preferably, the same vaccine (HDCV or PCECV) should be used throughout the vaccination series; however, it may be advisable to switch to the alternate vaccine to complete the series if severe allergic reactions occur.

Bleeding Disorders

This is an IM injection and may pose a risk for persons with bleeding disorders. See *Bleeding Disorders and Vaccination*.

Compromised Immunity

Preexposure: Avoid preexposure vaccination in immunosuppressed persons when feasible and advise them to consider avoiding activities for which rabies preexposure prophylaxis is indicated.

- When this course is not possible, immunosuppressed persons at risk for rabies should be vaccinated by the IM route, should be aware that immune response may be inadequate, and should have antibody titers checked after completion of the preexposure series.
- Corticosteroids and other immunosuppressive agents, antimalarials, and immunosuppressive illnesses can interfere with the development of active immunity after vaccination.
- Failure to seroconvert after the third dose should be managed in consultation with the traveler's physician and appropriate public health officials.

Postexposure:

- Both vaccine and RIG should be given to immunocompromised persons, regardless of previous vaccination status.

- Five doses of vaccine (instead of 4) should be given IM on days 0, 3, 7, 14, and 28.
- It is especially important that a serum sample be sent for rabies antibody testing to ensure that an acceptable antibody response has developed.
- Immunosuppressive agents should not be administered during postexposure therapy unless essential for the treatment of other conditions.

Pregnancy

Because of the potential consequences of inadequately treated rabies exposure, pregnancy is not considered a contraindication to *postexposure prophylaxis*.

- Several studies have shown no indication of increased incidence of abortion, premature birth, or fetal abnormality associated with rabies vaccination.

If the risk of exposure to rabies is substantial, *preexposure prophylaxis* might also be indicated during pregnancy.

COMPATIBILITY

Corticosteroids, chemotherapy agents, and immunosuppressive agents can interfere with the development of active immunity after immunization. In these patients, consider testing for antibody response after immunization.

Chloroquine phosphate and mefloquine do not appear to weaken the antibody response to HDCV administered intramuscularly.
