Rabies Vaccine

AHFS Class: 80:12 — Vaccines (tofc-80)

Rabies Vaccine *(AHFS DI)*

Rabies Vaccine, Human Diploid-Cell **Rabies Vaccine, Purified Chick Embryo Cell Culture**
Synonym: Human Diploid-Cell Rabies Vaccine
Synonym: HDCV
Synonym: HDCS
Synonym: Purified Chick Embryo Cell Culture Rabies Vaccine
Synonym: PCEC
Synonym: PCECV

Introduction

Rabies vaccine is an inactivated virus vaccine that contains rabies virus antigens and is used to stimulate active immunity to rabies infection.[208,234,236,] Rabies vaccine is commercially available in the US as human diploid-cell rabies vaccine (HDCV; Imovax®) and purified chick embryo cell culture rabies vaccine (PCECV; RabAvert®).[208,234,249,]

Uses

Rabies vaccine is used to stimulate active immunity to rabies in adults, adolescents, and children.[208,234,236,250,253,] Rabies vaccine is used for *preexposure* vaccination in individuals at increased risk of exposure to the disease or virus and also is used for *postexposure* prophylaxis as part of a regimen that includes local wound treatment and *active* immunization with rabies vaccine and may also include *passive* immunization with rabies immune globulin (RIG) in certain patients.[208,234,236,250,253,]

There currently are 2 types of rabies vaccine commercially available in the US: human diploid-cell rabies vaccine (HDCV; Imovax®) and purified chick embryo cell culture rabies vaccine (PCECV; RabAvert®).[208,234,236,] While experience with HDCV (Imovax®) is more extensive than that with PCECV (RabAvert®), clinical trials have demonstrated that the immunogenicity of PCECV is equivalent to that of HDCV.[236,]

▪ Risks of Exposure and Infection

Rabies is a viral infection transmitted by the saliva of infected mammals, most commonly wild, terrestrial carnivores (e.g., skunks, raccoons, foxes, coyotes) or bats.[236,] In the US, the greatest risk for naturally acquired rabies is from contact with and bites from insectivorous bats.[222,236,242,] The likelihood that a domestic dog or cat is infected with rabies varies from region to region.[236,] In the continental US, rabies among dogs is reported most frequently along the US-Mexican border and sporadically in areas of the US with enzootic wildlife rabies.[236,]

Small rodents (e.g., squirrels, chipmunks, rats, mice, hamsters, guinea pigs, gerbils) and lagomorphs (e.g., rabbits, hares) are almost never infected with rabies virus and have not been known to transmit rabies to humans in the US.[236,] However, from 1990–1996 in areas of the US where raccoon rabies was enzootic, woodchucks (groundhogs) accounted for 93% of rabies cases among rodents reported to the US Centers for Disease Control and Prevention (CDC).[236,]

During January 2000 to December 2020, 52 cases of human rabies were diagnosed in the US, 38 were indigenously acquired.[253,] None of these infections were in individuals who had previously received preexposure prophylaxis. [253,] Rabies prevention and control strategies and elimination of canine rabies virus variants and enzootic transmission among dogs have lowered the number of rabies cases in the US to an average of 1–2 per year.[250,] However, worldwide, rabies is much more common, with more than 59,000 rabies-related deaths occurring annually.[249,]

In the US, individuals at high risk of exposure to rabies include veterinarians, animal handlers, and certain laboratory workers.[236,] Other individuals at risk are those whose activities bring them into frequent contact with rabies virus or potentially rabid bats, foxes, raccoons, skunks, cats, dogs, or other species at risk for having rabies.[236,]

Travelers to areas where rabies is endemic may be at risk, especially if they are likely to come in contact with animals in areas where dog or other animal rabies is enzootic and immediate access to appropriate medical care (including rabies vaccine and RIG) is unlikely.[212,236,249,] Rabies is found on all continents (except Antarctica)[212,] and the World Health Organization (WHO) states that rabies occurs mainly in underserved populations, both rural and urban, with documented existence for more than 4000 years.[249,] Dogs are the principal vector of rabies and the source of 99% of human rabies cases in rabies-endemic regions globally, primarily in Asia and Africa.[249,] Canine rabies remains highly endemic in parts of Africa, Asia, and Central and South America.[212,] The CDC states that travelers to these areas who will have extensive unprotected outdoor exposure (e.g., while bicycling, camping, hiking, or engaging in certain occupational activities) may be at an increased risk, even if their trip is brief.[212,] In areas enzootic for rabies, children are considered at particular risk of acquiring rabies[212,249,] because of their tendencies to play with animals and not to report bites.[212,] Casual exposure to cave air is not a concern, but cavers (spelunkers) should be warned not to handle bats.[212,]

The US Public Health Service Advisory Committee on Immunization Practices (ACIP) has redefined risk categories dependent upon the level of an individual's risk for rabies exposure, with risk level 1 involving activities with the highest risk and level 5 involving those with the lowest risk.[253,] (For ACIP definitions of risk categories and recommendations regarding *preexposure* vaccination for each category, see Table 1).

▪ Preexposure Vaccination Against Rabies in High-risk Groups

The ACIP recommends a 2-dose (0 and 7 days) intramuscular rabies vaccine series (either HDCV or PCECV) for immunocompetent individuals for whom rabies *preexposure* prophylaxis is indicated.[253,] Additionally, all individuals in risk category 1 (the highest risk level) should have rabies antibody titers checked every 6 months, and those in risk category 2 should have rabies antibody titers checked every 2 years.[253,] A booster dose should be given if titers are <0.5 IU/mL.[253,] Those individuals in risk category 3 should have rabies antibody titers checked during years 1-3 after completion of the 2-dose primary rabies vaccine series, with a booster administered if the titer is <0.5 IU/mL, or preemptively receive a one-time booster dose of the vaccine during day 21 to year 3 after completion of the 2-dose primary series.[253,]

Preexposure vaccination does not eliminate the need for prompt postexposure prophylaxis if an exposure to rabies occurs.[208,234,236,250,253,] However, *preexposure* vaccination may provide protection in individuals with inapparent exposure to rabies; may protect individuals in whom *postexposure* prophylaxis might be delayed; and simplifies prophylaxis after rabies exposure by eliminating the need for passive immunization with RIG and reducing the number of rabies vaccine doses needed.[208,234,236,250,253,] Ensuring a simplified *postexposure* prophylaxis regimen is particularly important for individuals at high risk of being exposed to rabies in areas where immunizing agents may not be readily available or where available preparations may carry a high risk of adverse effects.[208,234,236,]

The need for *preexposure* vaccination against rabies, serologic monitoring, and booster doses of rabies vaccine depends on the nature and category of rabies risk associated with the potential exposure.[236,253,] *Preexposure* vaccination is indicated for individuals whose risk of rabies exposure is greater than that of the general population (e.g., veterinarians and their staff, animal-control and wildlife workers, field biologists, spelunkers, missionaries, rabies researchers, certain laboratory workers) and for those whose activities bring them into frequent contact with rabies virus or potentially rabid bats, raccoons, skunks, cats, dogs, or other species at risk for having rabies.[236,253,] (For ACIP definitions of risk categories and recommendations regarding *preexposure* vaccination for each category, see Table 1.)

Table 1. US Rabies Risk Categories and Recommendations for Preexposure Vaccination[253,]

Category of Rabies Risk	Nature of Exposure	Typical Population	Preexposure Vaccination
1. Elevated risk for unrecognized[a] and recognized[b] exposures including unusual or high-risk exposures	Exposure, often in high concentrations, might be recognized or unrecognized, might be unusual (e.g., aerosolized virus)	Rabies research laboratory workers, rabies vaccine production workers, individuals who perform testing for rabies in diagnostic laboratories	Yes; then perform serologic testing every 6 months and give booster dose if antibody titer <0.5 IU/mL[c]
2. Elevated risk for unrecognized[a] and recognized[b] exposures	Exposure typically recognized but could be unrecognized; unusual exposures unlikely	Individuals who frequently handle bats, have contact with bats, enter high-density bat environments, or perform animal necropsies	Yes; then perform serologic testing every 2 years and give booster dose if antibody titer <0.5 IU/mL[c]
3. Elevated risk for recognized[b] exposures, sustained risk[d]	Exposure nearly always recognized; risk for recognized exposures higher than that for the general population and duration exceeds 3 years after the primary vaccination	Individuals who interact with animals that could be rabid and selected travelers who will be performing occupational or recreational activities that increase risk for exposure and might have difficulty getting prompt access to safe postexposure prophylaxis	Yes; then perform a one-time titer check during years 1-3 after the 2-dose primary series; booster if antibody titer <0.5 IU/mL[c] OR booster no sooner than day 21 and no later than year 3 after the 2-dose primary series[e]
4. Elevated risk for recognized[b] exposures, risk not sustained[d]	Exposure nearly always recognized; risk for exposure higher than for general population but expected to be time-limited	Same as for above risk category but risk duration ≤3 years (e.g., short-term volunteer providing hands-on animal care)	Yes
5. Low risk for exposure	Exposure uncommon	Typical individual in the US	No

[a] Unrecognized exposures are those that recipients might not know occurred.

[b] Recognized exposures are bites, scratches, and splashes that are usually identified by the individual because the exposure is unusual.

[c] When antibody titers <0.5 IU/mL, a booster vaccination should be provided. There is no need to verify booster response in immunocompetent individuals. For immunocompromised individuals, the antibody titer should be verified ≥1 week (ideally, 2-4 weeks) after booster administration.

[d] Sustained risk is elevated risk for rabies >3 years after completion of the primary rabies preexposure prophylaxis vaccination schedule.

Travelers

For travelers, the CDC recommends *preexposure* vaccination against rabies based on the local incidence of rabies in the country to be visited, availability in that location of appropriate agents for rabies *postexposure* prophylaxis, and the intended activities and expected duration of stay.[212,] *Preexposure* vaccination is particularly important for travelers at risk of rabies exposure in countries where locally available rabies vaccines are associated with a high risk of adverse effects.[212,] *Preexposure* vaccination may also provide protection when there is an inapparent or unrecognized exposure to rabies and when *postexposure* prophylaxis might be delayed.[212,]

▪ Postexposure Prophylaxis of Rabies

Postexposure prophylaxis of rabies is recommended for previously *vaccinated* and *unvaccinated* children, adolescents, and adults following potential exposure to rabies disease or virus.[208,234,236,250,]*A history of previous vaccination against rabies simplifies the postexposure prophylaxis regimen, but does not eliminate the need for prompt postexposure prophylaxis if an exposure to rabies occurs.* [208,234,236,250,]

Whenever a possible human exposure to rabies occurs, the risk of infection must be accurately assessed to determine the need for *postexposure* prophylaxis.[236,250,] Decisions regarding the need for *postexposure* prophylaxis should be based on the vaccination status of the exposed individual (see Table 2), type of exposure (bite, nonbite), information about the animal involved (type, vaccination status, condition at time of attack) (see Table 3), and rabies epidemiology in the specific geographic region.[234,236,250,] Local or state public health officials may be consulted for assistance when evaluating rabies exposures and the need for *postexposure* prophylaxis.[236,]

Regardless of immunization status, the ACIP and American Academy of Pediatrics (AAP) recommend that *postexposure* prophylaxis of rabies begin immediately with thorough cleansing of all bite wounds and scratches using soap and water and, if available, irrigation with a virucidal agent such as povidone-iodine solution.[236,250,] Local wound treatment is an essential *initial* step in rabies *postexposure* prophylaxis in all individuals.[236,250,]

In previously *unvaccinated* adults, adolescents, and children, rabies *postexposure* prophylaxis includes both *active* immunization with rabies vaccine (4- or 5-dose regimer of vaccine) and *passive* immunization with a single dose of RIG as soon as possible.[208,234,236,250,]

In previously *vaccinated* individuals, rabies *postexposure* prophylaxis includes *active* immunization with a 2-dose booster regimen of rabies vaccine (without RIG) as soon as possible.[236,250,]

Table 2. US Rabies Postexposure Prophylaxis Schedule for Adults, Adolescents, or Children[250,]

Vaccination Status	Treatment	Regimen
Not previously vaccinated	Wound cleansing	Immediately cleanse all wounds thoroughly with soap and water; if available, irrigate wounds with virucidal agent (e.g., povidone-iodine solution)
	RIG	Administer 20 international units/kg of RIG; if anatomically feasible, infiltrate full RIG dose around and into wound(s) and give any remaining portion of the dose IM at an anatomical site distant from site of rabies vaccine administration
	Rabies vaccine	Administer 4-dose regimen of rabies vaccine[b] ; give 1 mL (human diploid-cell vaccine [HDCV; Imovax®] or purified chick embryo cell culture vaccine [PCECV; RabAvert®]) IM[c] once on days 0[d] , 3, 7, and 14
Previously vaccinated[a]	Wound cleansing	Immediately cleanse all wounds thoroughly with soap and water; if available, irrigate wounds with virucidal agent (e.g., povidone-iodine solution)
	RIG	RIG should *not* be administered
	Rabies vaccine	Administer 2-dose regimen of rabies vaccine; give 1 mL (HDCV or PCECV) IM[c] once on days 0[d] and 3

[a] Any person with a history of a complete preexposure or postexposure vaccination regimen with HDCV, PCECV, or rabies vaccine adsorbed (RVA; not commercially available in the US), or previous vaccination with any other type of rabies vaccine and a documented history of antibody response to the prior vaccination

[b] Individuals with immunosuppression should receive a 5-dose regimen of rabies vaccine; give 1 mL (HDCV or PCECV) IM once on days 0[c] [d] , 3, 7, 14, and 28.

[c] Deltoid area is the preferred site for IM administration of rabies vaccine in adults, adolescents, and older children (3 to 10 years of age). For younger children, the anterolateral thigh is preferred. Never administer in gluteal area.

[d] Day 0 is the day the first dose of rabies vaccine is administered.

When *postexposure* prophylaxis is indicated, it should be initiated immediately.[236,] However, because the incubation period of rabies in humans can range from days to years (usually 1–3 months),[234,236,250,]*postexposure* prophylaxis should be initiated regardless of the length of delay if a documented or likely exposure has occurred and there are no clinical signs of rabies present in the exposed individual.[236,]

Since the availability and routine use of cell culture-derived rabies vaccines began in the US in 1990, there have been no reported cases of rabies *postexposure* prophylaxis failures in the US when the recommended *postexposure* prophylaxis regimen was used in previously unvaccinated individuals (i.e., proper wound care followed by a single dose of RIG and a 4- or 5-dose regimen of a cell culture-derived rabies vaccine).[234,236,] There have been rare reports of *postexposure* prophylaxis failures in other countries.[234,236,] In most of these cases, there was some deviation from recommended *postexposure* prophylaxis procedures (e.g., *postexposure* prophylaxis not given or substantially delayed, wounds not adequately cleansed, rabies vaccine given IM into the gluteal rather than deltoid region, failure to passively immunize with RIG by infiltrating the wound site, use of less than the recommended dose of RIG, use of less than the number of recommended doses of rabies vaccine).[208,234,236,250,]

Wound Treatment

Because rabies virus may remain localized at the site of inoculation for a variable time before entering neural tissue, all bites and scratches should immediately be washed with soap and water and, if available, irrigated with a virucidal agent (e.g., povidone-iodine solution). [208,234,236,250,] Studies in animals indicate that thorough wound cleansing alone (without other *postexposure* prophylaxis) markedly reduces the likelihood of rabies.[234,236,] Tetanus prophylaxis and measures to control secondary infection also should be instituted as indicated. [208,234,236,] The decision to suture large wounds should take into account cosmetic factors and the potential for bacterial infection.[236,] AAP states that, if possible, the wound should not be sutured.[213,]

Whenever RIG is indicated as part of the *postexposure* prophylaxis regimen (i.e., in previously unvaccinated individuals), the dose should be infiltrated around the wound(s) if anatomically feasible.[234,236,]For information on use of RIG for postexposure prophylaxis following exposure to rabies, see Rabies Immune Globulin 80:04. (381041?viewMode=detailed#uses)

Evaluation of the Possible Animal Vector

Since rabies cannot be diagnosed in humans prior to the onset of symptoms, evaluation and diagnosis of rabies in the animal vector is an important guide to whether *postexposure* prophylaxis should be initiated.[249,] In the US, a healthy domestic dog, cat, or ferret that bites a human should be confined and observed by a veterinarian for 10 days.[236,] Any illness in the animal should be evaluated by a veterinarian and reported immediately to the local health department.[236,] If signs suggestive of rabies develop, the animal should be euthanized immediately and the head carefully removed and shipped under refrigeration to a qualified laboratory for examination.[236,] Any stray dog or cat that bites a human should either be observed for 10 days or euthanized immediately and the head shipped to a laboratory for examination.[236,] However, a vaccinated dog, cat, or ferret is unlikely to be infected with rabies.[236,]

Table 3. US Rabies Postexposure Prophylaxis Guide Based on Type and Status of Animal Involved[236,]

Animal Type	Evaluation and Disposition of Animal	Postexposure Prophylaxis Recommendations
Dogs, cats, ferrets	Healthy and available; confine for 10 days of observation	Do not begin prophylaxis unless animal develops clinical signs of rabies[a]
	Rabid or suspected rabid	Immediately begin postexposure prophylaxis
	Unknown (e.g., escaped)	Consult public health officials
Skunks, raccoons, foxes, and most other carnivores; bats[b]	Regard as rabid unless animal proven negative by laboratory tests[c]	Consider immediate postexposure prophylaxis
Livestock, small rodents, lagomorphs (rabbits, hares), large rodents (woodchucks, beavers), other mammals	Consider individually	Consult public health officials. Bites from squirrels, hamsters, guinea pigs, gerbils, chipmunks, rats, mice, other small rodents, rabbits, and hares almost never require rabies postexposure prophylaxis

[a] During the 10-day observation period, begin postexposure prophylaxis in the exposed individual at the first sign of rabies in a dog, cat, or ferret that has bitten them. If the animal exhibits clinical signs of rabies, euthanize it immediately and perform appropriate testing.

[b] Initiate postexposure prophylaxis as soon as possible following exposure to such wildlife, unless animal is available for testing and public health authorities are facilitating expeditious laboratory testing or it is already known that brain material from the animal has tested negative. Other factors that might influence urgency of decision-making regarding initiation of postexposure prophylaxis before diagnostic results are known include the animal species, general appearance and behavior of the animal, whether encounter was provoked by a human, and the severity and location of bites. Discontinue postexposure prophylaxis if appropriate laboratory tests (i.e., direct fluorescent antibody test) are negative.

[c] Euthanize the animal and test as soon as possible. Holding for observation is not recommended.

Bite exposures include any penetration of the skin by teeth and all bite exposures (regardless of bite location) from an animal known or suspected to be rabid pose a potential risk of rabies transmission and require *postexposure* prophylaxis.[236,] Nonbite exposures include contamination of preexisting open wounds, abrasions, mucous membranes, or scratches with saliva or other potentially infectious material (e.g., neural tissue) from an animal known or suspected to be rabid.[236,] Although nonbite exposures only rarely cause rabies, such exposures require assessment to determine if sufficient reasons exist to consider *postexposure* prophylaxis.[236,] Nonbite exposures of highest risk occur in surgical recipients of corneas, solid organs, and vascular tissue transplanted from patients who died of rabies and individuals exposed to large amounts of aerosolized rabies virus.[236,]

After any potential human exposure involving bats, the bat in question should be safely collected if possible and submitted for rabies diagnosis.[236,] *Postexposure* prophylaxis is not necessary if the individual can be reasonably certain that a bite, scratch, or mucous membrane exposure did not occur or if the bat is available for testing and is negative for rabies virus.[236,] However, the greatest risk for naturally acquired rabies in the US is from contact with and bites from insectivorous bats.[236,242,] A rabies-virus variant associated with 2 small-bodied bats (the eastern pipistrelle bat [*Pipistrellus subflavus*] and silver-haired bat [*Lasionycteris noctivagans*]) has been identified in 69% (20/29) of US patients tested for the virus.[242,] In addition, because signs of rabies in wild animals cannot be interpreted reliably, any wild animal that bites or scratches a human should be euthanized immediately (without unnecessarily damaging the head) and the brain submitted for rabies testing.[236,] If examination of the brain by direct fluorescent antibody testing does not show rabies, the saliva can be assumed to contain no virus and the person bitten does not need *postexposure* prophylaxis.[236,] If *postexposure* prophylaxis has already been initiated in the exposed individual, it can be discontinued when direct fluorescent testing shows that the exposing animal is not rabid.[236,]

In *all* instances of potential human exposure involving bats when the bat is not available for rabies testing, *postexposure* prophylaxis might be appropriate even when a bite, scratch, or mucous membrane exposure is not apparent but there is a reasonable probability that such exposure might have occurred.[236,] *Postexposure* prophylaxis can be considered for individuals who were in the same room as the bat and who possibly may be unaware that a bite or direct contact occurred (e.g., if a sleeping individual finds a bat in the room upon awakening or an adult observes a bat in the room with a previously unattended child or individual who is mentally disabled or intoxicated).[236,] Other household members who did not have direct contact with the bat or were awake and aware when in the room with the bat should not be considered as having exposure to rabies.[236,]

Previously Unvaccinated Individuals

Postexposure prophylaxis of rabies in previously *unvaccinated* adults, adolescents, and children involves thorough cleansing of all bite and nonbite wounds followed by *active* immunization with a 4- or 5-dose regimen of HDCV (Imovax®) or PCECV (RabAvert®) rabies vaccine and *passive* immunization with RIG.[208,212,234,236,250,] Rabies vaccine (in conjunction with RIG) is indicated in all unvaccinated individuals following bite or nonbite exposure from known or suspected rabid animals or from bats or wild carnivorous animals.[236,] If subsequent testing shows that the exposing animal is not rabid, prophylaxis can be discontinued.[236,] Concomitant use of both active immunization with rabies vaccine and passive immunization with RIG is indicated regardless of the interval between exposure and initiation of treatment since incubation periods of longer than 1 year have been reported in humans exposed to rabies.[236,]

The ACIP states that rabies pathogenesis data, animal data, clinical studies, and epidemiologic surveillance indicate that a 4-dose series of HDCV (Imovax®) or PCECV (RabAvert®) is as effective as a 5-dose vaccine series when used for *postexposure* prophylaxis in conjunction with wound management and RIG.[250,] However, in individuals with altered immunocompetence, the ACIP states that a 5-dose series of HDCV (Imovax®) or PCECV (RabAvert®) should be used in conjunction with wound management and RIG since the immune response to the vaccine may be reduced.[250,]

RIG is administered only once (i.e., on day 0) to provide immediate antibodies until the patient responds to the vaccine by actively producing antibodies.[236,] If RIG is not administered when vaccination is begun, it can be given through the seventh day after the first dose of vaccine but is not indicated beyond the seventh day since an antibody response to rabies vaccine is presumed to have occurred.[236,250,] If anatomically feasible, RIG should be thoroughly infiltrated in the area around and into the wound.[236,250,] RIG should never be administered in the same syringe or simultaneously in the same anatomical site as rabies vaccine.[236,250,]For additional information on use of RIG for postexposure prophylaxis following exposure to rabies, see Rabies Immune Globulin 80:04. (381041?viewMode=detailed#uses)

Previously Vaccinated Individuals

In previously *vaccinated* children, adolescents, and adults following potential rabies exposure, a 2-dose booster regimen of HDCV (Imovax®) or PCECV (RabAvert®) rabies vaccine (without RIG) is recommended as soon as possible.[236,250,] RIG should *not* be administered to these individuals since initial passive immunization is not necessary.[236,]

This 2-dose booster regimen also can be used in individuals who previously received a *preexposure* or *postexposure* vaccination regimen with HDCV (Imovax®), PCECV (RabAvert®), Imovax® Rabies I.D. (no longer commercially available in the US), or rabies vaccine adsorbed (RVA; no longer commercially available in the US) or those who previously received *preexposure* vaccination with some other vaccine and had documented adequate concentrations of antirabies antibody.[208,234,236,250,]

Individuals Performing Autopsies

Transmission of rabies to individuals performing autopsies has not been reported to date;[251,] there have been no confirmed cases of rabies reported in individuals performing postmorten examinations of humans or animals.[251,] The CDC recommends that personnel performing autopsies on decedents with confirmed or suspected rabies use appropriate personal protective equipment, wear heavy or chain mail gloves, minimize aerosol generation by using a handsaw rather than an oscillating saw, limit the number of individuals participating in the procedure and collection of specimens, and use ample amounts of 10% sodium hypochlorite solution during and after the procedure to ensure decontamination of all exposed surfaces.[251,] The CDC states that *preexposure* vaccination against rabies usually is not required for individuals performing autopsies and that rabies *postexposure* prophylaxis is recommended in autopsy personnel only if a wound or mucous membrane gets contaminated with the patient's saliva or other potentially infectious material (e.g., neural tissue) during the procedure.[251,]

Travelers

In travelers, *preexposure* vaccination does not eliminate the need for additional medical attention after a rabies exposure, but simplifies *postexposure* prophylaxis by eliminating the need for RIG (which may not be available in some countries) and by decreasing the number of doses of vaccine required.[212,]

Travelers to rabies-endemic countries should be warned about the risk of acquiring rabies and educated in bite prevention strategies (e.g., avoiding contact with bats, avoiding stray dogs, monkeys, or cats).[212,] Because appropriate preparations of RIG or rabies vaccine may be not available for *postexposure* prophylaxis in the destination country, the CDC recommends that travelers to such countries have a preplanned strategy in place that may involve identifying a different country where appropriate *postexposure* prophylaxis can be obtained if necessary.[212,] The CDC states that rabies vaccines grown in animal brains (nerve tissue vaccine; NTV) still may be used in some developing countries; if offered such a vaccine (identified by a regimen that requires 5-mL injections once daily for 14–21 days), travelers should refuse the vaccine and travel to a country where an acceptable rabies vaccine preparation and RIG are available.[212,]

Travelers should be advised that any animal bite or scratch should receive immediate wound treatment including thorough cleansing of the wound with copious amounts of soap and water[212,249,] and, if available, a povidone-iodine solution; such treatment will markedly reduce the risk of rabies.[212,]

Individuals who are exposed to rabies while traveling outside the US in areas where rabies is endemic might receive *postexposure* prophylaxis with regimens and/or preparations not recommended by the ACIP (or used in the US), resulting in the need for additional therapy following return to the US.[212,236,] Although *postexposure* prophylaxis failures have not been reported in the US, failures have occurred in other countries when some deviation was made from the recommended *postexposure* prophylaxis regimen (e.g., *postexposure* prophylaxis not given or substantially delayed, wounds not adequately cleansed, rabies vaccine given IM into the gluteal rather than deltoid region, failure to passively immunize with RIG by infiltrating the wound site, use of less than the recommended dose of RIG, use of less than the recommended number of vaccine doses).[208,234,236,250,] If *postexposure* prophylaxis is initiated outside the US using regimens other than those recommended by the ACIP or with NTV it may be necessary to provide additional therapy when the individual returns to the US.[236,] Local or state public health officials should be consulted for specific advice in such cases.[236,] Serologic testing should be considered in these travelers to verify efficacy of the regimen used and to ensure an adequate immune response.[236,]

Children

Children are at higher risk of rabies exposure compared with adults because of increased potential for animal contact and because they are more likely to be bitten on the head, face, and neck leading to more severe injuries.[212,249,]

Pregnant Females

Because of the potential risks of inadequately treated rabies exposure and because fetal abnormalities have not been associated with rabies vaccination, the manufacturers, CDC, ACIP, AAP, and the American College of Obstetricians and Gynecologists (ACOG) state that pregnancy is not a contraindication to *postexposure* immunization with HDCV (Imovax®) or PCECV (RabAvert®) rabies vaccine.[204,208,212,234,236,] However, ACOG recommends that each pregnant woman be considered individually and that public health authorities be consulted.[204,] In addition, if the risk of exposure to rabies is substantial, *preexposure* vaccination might be indicated during pregnancy.[208,236,]

Individuals with Altered Immunocompetence

The ACIP states that recommendations concerning use of rabies vaccine in patients with altered immunocompetence generally are the same as those for patients who are not immunocompromised.[233,236,250,253] Therefore, if indicated, the vaccine may be used in patients with human immunodeficiency virus (HIV) infection; patients who are severely immunocompromised because of congenital immunodeficiency, leukemia, lymphoma, aplastic anemia, generalized malignancy, or therapy with alkylating agents, antimetabolites, radiation, or corticosteroids; patients with solid organ transplants or chronic immunosuppressive therapy; or patients with asplenia, renal failure, diabetes, alcoholism, or alcoholic cirrhosis.[233,236,250] However, immunocompromised individuals (including those receiving corticosteroids or other immunosuppressive agents) may have a reduced immunologic response to vaccination.[212,234,236,250,253] Therefore, the ACIP states that a 5-dose vaccine series (not a 4-dose series) of HDCV (Imovax®) or PCECV (RabAvert®) should be used when rabies *postexposure* prophylaxis is indicated in previously unvaccinated individuals with altered immunocompetence.[250]

Preexposure vaccination (2-dose primary series) against rabies generally should be postponed in immunocompromised individuals and such individuals should be advised to avoid activities for which rabies *preexposure* vaccination is indicated.[212,236,250,253] If this is not possible, the rabies vaccine can be administered, but antibody titer should be checked no sooner than 1 week (ideally, 2 to 4 weeks) after completion of the 2-dose *preexposure* series and all appropriate booster doses (including those given within 3 years of the primary series and in response to a low titer during the serial titer checks recommended for risk categories 1 and 2).[253] If the titer is <0.5 IU/mL, a booster dose should be administered, followed by a subsequent titer check.[253] If 2 such booster doses fail to elicit an appropriate antibody response, local or state public health authorities should be consulted for guidance.[253]

Use of immunosuppressive agents should be avoided during rabies *postexposure* prophylaxis unless considered essential for the treatment of other conditions.[233,234,236]

If rabies *postexposure* prophylaxis is indicated in an immunocompromised individual, serologic testing is considered essential after completion of the *postexposure* prophylaxis regimen to confirm than an adequate antibody response is obtained.[234,236,250] If an acceptable antibody response is not detected after the final vaccine dose of the *postexposure* prophylaxis series, the patient should be managed in consultation with their clinician and appropriate public health officials.[216,250]

▪ Pre- and Postvaccination Serologic Testing

Serum concentrations of antirabies neutralizing antibody are used to assess the immune response to rabies vaccine and are considered a reasonable surrogate indicator of protection or immunity against rabies.[236,249] However, although antirabies antibodies are believed to have a primary role in preventing rabies infection, other immune effectors also may be involved and a definitive "protective" concentration of antibody cannot be identified for all rabies exposure scenarios.[236,249]

The minimum antibody level historically recommended by ACIP is one that results in complete neutralization of rabies virus at a 1:5 serum dilution by the rapid flouorescent focus inhibition test.[253] This is approximately equivalent to a titer of 0.1 to 0.3 IU/mL.[253] Although no infections among vaccinated individuals have occurred with this cut-off titer, most published studies use 0.5 IU/mL as a correlate of protection.[253] Therefore, this level is now endorsed by ACIP and replaces the previous minimum acceptable rabies antibody titer.[253]

Serologic confirmation of adequate antibody concentrations following *preexposure* vaccination (2-dose primary series) is not necessary in most individuals because of the high rate of response in immunocompetent adults, adolescents, and children when the recommended vaccine regimen is used.[208,212,234,236,253] However, if *preexposure* vaccination is performed in immunocompromised individuals, serologic testing should be done to document seroconversion.[212,236,253] Individuals who fail to seroconvert after the second vaccine dose and appropriate booster doses should be managed in consultation with their clinician and appropriate public health officials.[253]

To determine the need for *preexposure* booster doses of rabies vaccine in individuals who received *preexposure* vaccination with a primary vaccine series, see Table 1 under Uses.

Serologic testing is not indicated *prior* to *postexposure* prophylaxis in previously vaccinated individuals who are exposed to rabies.[236] Such testing is inappropriate because it would delay *postexposure* prophylaxis and, although antirabies neutralizing antibodies are an important component of immunity, other immune effectors also play a role in disease prevention.[236]

Serologic confirmation of adequate antibody concentrations following *postexposure* prophylaxis (4- or 5-dose series of rabies vaccine and a single dose of RIG) is not necessary in most individuals because of the high rate of vaccine response among immunocompetent adults, adolescents, and children when the recommended regimen is used.[208,212,236] However, *postvaccination* serologic testing is considered essential in immunocompromised individuals since these individuals may have impaired immune response to vaccination.[208,234,236]

Serologic testing to confirm an adequate antibody response was obtained should be considered in travelers who received rabies *postexposure* prophylaxis with regimens and/or preparations not currently recommended by ACIP.[236]

Dosage and Administration

▪ Reconstitution and Administration

Human diploid-cell rabies vaccine (HDCV; Imovax®) and purified chick embryo cell culture rabies vaccine (PCECV; RabAvert®) are administered *only* by IM injection for *preexposure* vaccination (primary immunization) or *postexposure* prophylaxis.[208,234,236]

Reconstituted HDCV (Imovax®) and PCECV (RabAvert®) should be inspected visually for particulate matter and discoloration prior to administration whenever container and solution or suspension permit.[208,234]

HDCV (Imovax®) and PCECV (RabAvert®) do not contain preservatives and should be used immediately after reconstitution.[208,234]

Rabies vaccine should *not* be mixed with any other vaccine or solution.[252]

Human Diploid-cell Rabies Vaccine (HDCV; Imovax®)

HDCV (Imovax®) is reconstituted by adding the entire contents of the syringe containing the diluent provided by the manufacturer to a single-dose vial of lyophilized

vaccine to provide a solution containing at least 2.5 international units per mL of rabies antigen.[208] *Only* the diluent supplied by the manufacturer should be used.[208]

The reconstitution needle and plunger should be attached to the syringe and the diluent injected into the vaccine vial.[208] The vial should be gently swirled until the vaccine is completely dissolved.[208] The lyophilized vaccine is creamy white to orange; the reconstituted suspension is pink to red.[208]

Because the vaccine vial contains negative pressure that may impede withdrawal of the full dose of reconstituted vaccine, the manufacturer recommends that the syringe be disconnected from the needle after reconstitution to allow any remaining vacuum to exhaust.

The reconstitution needle should be removed and discarded.[208] A suitable needle should then be used for IM administration.[208] The entire volume of reconstituted vaccine (approximately 1 mL) is administered for each dose.[208] Use immediately after reconstitution.[208]

Purified Chick Embryo Cell Vaccine (PCECV; RabAvert®)

PCECV (RabAvert®) is reconstituted by adding the entire contents of the syringe containing the diluent provided by the manufacturer to a single-dose vial of lyophilized vaccine to provide a suspension containing at least 2.5 international units per mL of rabies antigen.[234] *Only* the diluent supplied by the manufacturer should be used.[234]

The reconstitution needle (the longer of the 2 needles provided by the manufacturer) should be attached to the diluent syringe, inserted into the vaccine vial at a 45° angle, and the entire contents of the diluent syringe should be slowly injected into the vaccine vial.[234] The vial should be gently mixed to avoid foaming.[234] The lyophilized vaccine is white; the reconstituted suspension is clear to slightly opalescent, colorless to slightly pink.[234] The entire amount of dissolved vaccine should be withdrawn intc the syringe and the long needle should be replaced with the smaller needle for IM injection.[234] The injection should be used immediately after reconstitution.[234]

Because the vaccine vial contains negative pressure that may impede withdrawal of the full dose of reconstituted vaccine, the manufacturer recommends that the syringe be disconnected from the needle after reconstitution to allow any remaining vacuum to exhaust; however, creating positive pressure (e.g., by injecting air into the vial) is not recommended since over-pressurization may interfere with withdrawal of the proper vaccine dose.[234]

IM Injection

Depending on patient age, rabies vaccine should preferably be administered IM into the deltoid muscle or anterolateral thigh.[208,212,234,236,250,252] In adults, adolescents, and older children (3 to 10 years of age), the deltoid is the preferred IM injection site for rabies vaccine; for younger children, the anterolateral thigh is preferred.[208,212,234,236,250,252]

IM injections of rabies vaccine should *not* be made in the gluteal area because the immunologic response to rabies vaccine may be lower than when administered IM into the deltoid muscle.[208,209,210,212,216,221,234]

Rabies vaccine should *not* be injected into or near blood vessels or nerves.[208,234] Although the manufacturers and some experts recommend that aspiration be performed after the needle has been inserted to ensure that a blood vessel has not been entered,[208,234] the US Public Health Service Advisory Committee on Immunization Practices (ACIP) and American Academy of Pediatrics (AAP) state that aspiration (i.e., pulling back on the syringe plunger after needle insertion and before injection) is not required because large blood vessels are not present at recommended IM injection sites..[252]

To ensure delivery into muscle, IM injections should be made at a 90° angle to the skin using a needle length appropriate for the individual's age and body mass, the thickness of adipose tissue and muscle at the injection site, and the injection technique.[252]

Syncope may occur following vaccination.[234,252] Syncope may be accompanied by transient neurologic symptoms (e.g., visual disturbances, paresthesia, tonic-clonic movements).[234] Procedures should be in place to avoid falling injury and to restore cerebral perfusion following syncope.[234,252] Syncope and secondary injuries may be averted if vaccinees sit or lie down during and for 15 minutes after vaccination.[252] If syncope occurs, the patient should be observed until symptoms resolve.[252]

▪ Dosage

Whenever possible, the rabies vaccine (HDCV; Imovax® or PCECV; RabAvert®) used for the initial dose should be used for subsequent doses in the vaccine series in the same individual.[234,236] Although only limited data are available to date, most experts state that rabies vaccines available in the US may be considered interchangeable.[234,236] The ACIP states that clinical studies are not available to date showing differences in efficacy or safety if the vaccine series is completed with a different preparation.[236]

The recommended vaccination schedule should be adhered to as closely as possible.[236] If a minor deviation from the schedule occurs (e.g., a dose is delayed by a few days), the dose should be given and the vaccination schedule should be resumed using the same interval between doses.[236] If a substantial deviation from the schedule occurs, serologic testing should be performed 7–14 days after the final vaccine dose to assess immune status.[236] For the 2-dose *preexposure* prophylaxis vaccine series, when substantial delays occur (2 weeks or more) from the recommended date of the second dose, local and state public health authorities should be consulted for guidance.[253]

Preexposure Vaccination Against Rabies in High-risk Groups

Primary Immunization.

For *preexposure* vaccination in adults, adolescents, or children, HDCV (Imovax®) or PCECV (RabAvert®) rabies vaccine is administered IM in a primary series of two 1-mL doses per ACIP recommendations; the first dose is administered on a selected date, and the second dose is given 7 days later.[253] Completion of the primary series before an expected exposure to rabies virus ensures the highest level of protection.[208,234]

Because the antibody response to HDCV (Imovax®) or PCECV (RabAvert®) usually is satisfactory when the recommended *preexposure* vaccination regimen is used, routine serologic testing to confirm seroconversion is not necessary in most individuals after the 2-dose primary series.[253] However, postvaccination antibody titers should be checked following *preexposure* vaccination in immunocompromised individuals, including individuals receiving immunosuppressive agents, since these individuals may have an impaired immunologic response to vaccination.[208,234,236,253] In immunocompromised individuals, failure to seroconvert after the initial 2-dose vaccine series and appropriate boosters should be managed in consultation with appropriate public health officials.[253]

Booster Doses.

When booster doses are necessary for *preexposure* vaccination in adults, adolescents, or children to ensure continuous protection against rabies, HDCV (Imovax®) or PCECV (RabAvert®) is administered IM in 1-mL doses.[208,234,236,]

The need for booster doses of rabies vaccine depends on the nature and category of risk associated with the potential exposure.[208,234,236,249,253,] (See Table 1.)

Postexposure Prophylaxis of Rabies

Exposure to rabies must be individually evaluated before prophylaxis is begun and factors such as species of the biting animal, circumstances of the biting incident, vaccination status of the biting animal, presence of rabies in the geographic region, and *preexposure* vaccination status of the individual must be considered to determine if *postexposure* prophylaxis is necessary.[236,250,] (See Table 2 under Uses.) *Local or state public health officials should be consulted if questions regarding the need for rabies prophylaxis arise.* [236,250,]

Previously Unvaccinated Individuals.

For rabies *postexposure* prophylaxis in previously *unvaccinated* adults, adolescents, or children, *active* immunization with a series of 4 or 5 doses of HDCV (Imovax®) or PCECV (RabAvert®) rabies vaccine is used in conjunction with wound management and *passive* immunization with a single dose of rabies immune globulin (RIG).[208,234,236,250,]

Although the manufacturers recommend a 5-dose regimen of HDCV (Imovax®) or PCECV (RabAvert®) used in conjunction with wound management and a single dose of RIG for *postexposure* prophylaxis in all previously unvaccinated individuals,[208,234,] the ACIP states that a 4-dose regimen of HDCV (Imovax®) or PCECV (RabAvert®) used in conjunction with wound management and a single dose of RIG is sufficient for previously unvaccinated individuals who are immunocompetent.[250,] However, the ACIP states that individuals with altered immunocompetence should receive a 5-dose regimen of HDCV (Imovax®) or PCECV (RabAvert®) in conjunction with wound management and a single dose of RIG.[250,]

For immunocompetent adults, adolescents, and children, the ACIP recommends that the first vaccine dose be given IM as soon as possible after exposure (day 0) and that the 3 remaining vaccine doses be given IM on days 3, 7, and 14, respectively, after the first dose.[250,250,] Each dose consists of the entire contents (1 mL) of a reconstituted single-dose vial.[208,234,236,250,]

For immunocompromised adults, adolescents, and children, the ACIP recommends that the first vaccine dose be given IM as soon as possible after exposure (day 0) and that the 4 remaining doses be given IM on days 3, 7, 14, and 28, respectively, after the first dose.[250,] Each dose consists of the entire contents (1 mL) of a reconstituted single-dose vial.[208,234,236,250,]

In all previously unvaccinated individuals, passive immunization with a single dose of RIG should always be administered in conjunction with the first dose of HDCV (Imovax®) or PCECV (RabAvert®).[208,234,236,250,] Rabies vaccine should *not* be given in the same syringe as RIG *nor* injected simultaneously at the same site since neutralization of the vaccine may occur.[234,236,250,] If rabies vaccine is not immediately available, the dose of RIG should be given immediately and the vaccine series started as soon as possible.[250,] If RIG is not immediately available, it may be administered at any time through day 7 following the first vaccine dose.[236,250,] RIG is not necessary after day 7 since sufficient vaccine-induced rabies antibody will be present in most vaccine recipients.[236,250,]

Previously Vaccinated Individuals.

For *postexposure* prophylaxis in previously *vaccinated* adults, adolescents, or children who have received the recommended 2-dose primary *preexposure* regimen of HDCV (Imovax®) or PCECV (RabAvert®) or previously received a recommended *postexposure* regimen using one of these IM vaccines, the ACIP and manufacturers recommend a 2-dose *postexposure* booster regimen of HDCV (Imovax®) or PCECV (RabAvert®) rabies vaccine (without RIG).[208,234,236,250,] Each booster dose consists of the entire contents (1 mL) of a reconstituted single-dose vial.[208,234,236,250,] The first dose is administered IM as soon as possible after exposure (day 0) and the second dose is given IM 3 days later.[208,234,236,250,] RIG should not be administered to these individuals since initial passive immunization is not necessary and may interfere with the desired anamnestic response to rabies vaccine.[234,236,]

This same 2-dose *postexposure* prophylaxis regimen can be used in individuals who previously received a *preexposure* or *postexposure* vaccination regimen with Imovax® Rabies I.D. (no longer commercially available in the US) or rabies vaccine adsorbed (RVA; no longer commercially available in the US) or those who previously received *preexposure* vaccination with some other vaccine and had documented antirabies antibody titers.[208,234,236,250,] All other individuals should be considered *unvaccinated* and should receive the usual 4- or 5-dose IM regimen of rabies vaccine (in conjunction with RIG) as recommended for *postexposure* vaccination in previously unvaccinated individuals.[208,234,236,] In these cases, if serologic testing is performed using a serum sample obtained before the *postexposure* prophylaxis regimen is started, the 5-dose regimen can be discontinued after the second dose.[208,234,]

Cautions

Human diploid-cell rabies vaccine (HDCV; Imovax®) and purified chick embryo cell culture rabies vaccine (PCECV; RabAvert®) usually are well tolerated and adverse effects reported with the vaccines generally are mild or moderate adverse local or systemic effects.[208,234,] Once initiated, *postexposure* prophylaxis with rabies vaccine should not be interrupted or discontinued because of mild or moderate adverse effects.[208,234,236,] However, serious systemic, anaphylactic, or neuroparalytic reactions have been reported rarely with HDCV (Imovax®) and PCECV (RabAvert®) and pose a therapeutic dilemma for the clinician.[208,234,236,] State health departments or the US Centers for Disease Control and Prevention (CDC) should be contacted for advice and assistance on managing these individuals as well as deciding whether to discontinue the vaccine series.[208,236,]

▪ Local Effects

Following IM administration of HDCV (Imovax®), local reactions (e.g., pain, swelling, erythema) occur at the site of injection in about 25% of individuals.[208,]

Following IM administration of PCECV (RabAvert®), local reactions such as induration, swelling, and erythema have been reported more frequently than systemic adverse effects.[234] In several comparative studies, pain at the injection site was reported in 34–84% of individuals who received PCECV (RabAvert®).[234] Extensive limb swelling has been reported during postmarketing surveillance.[234]

Precautions and Contraindications

The manufacturer of PCECV (RabAvert®) states that *preexposure* vaccination with the vaccine is contraindicated in individuals with a history of anaphylaxis to the vaccine or any of the vaccine components.[234] The manufacturer of Imovax® states that *preexposure* vaccination with the vaccine is contraindicated in individuals with a history of a life-threatening systemic hypersensitivity reaction to the vaccine or any of the vaccine components.[208]

Because of the almost invariably fatal outcome of rabies, the manufacturers of HDCV (Imovax®) and PCECV (RabAvert®) state that there are no known contraindications to *postexposure* rabies vaccination, including pregnancy, when such prophylaxis is indicated.[208,234] The patient's risk of developing rabies should be carefully considered before deciding to discontinue the vaccine series and state health departments or the CDC should be contacted for advice and assistance regarding the management of such patients.[234]

Local or mild systemic adverse reactions to HDCV (Imovax®) or PCECV (RabAvert®) *do not contraindicate* continuing rabies vaccination and, once initiated, rabies *postexposure* prophylaxis should *not* be interrupted or discontinued because of such reactions.[208,234,236] These reactions usually can be managed with nonsteroidal anti-inflammatory agents (NSAIAs) or antipyretic agents (e.g., ibuprofen, acetaminophen).[208,234,236] However, serious systemic, neurologic, or anaphylactic adverse effects during rabies vaccination pose a serious therapeutic dilemma for the clinician, and the individual's risk of acquiring rabies must be weighed carefully before deciding to discontinue vaccination.[208,236] State health departments or the CDC should be contacted for advice and assistance on managing these individuals as well as deciding whether to discontinue the vaccine series.[208,236] In addition, all such serious reactions should be reported promptly to the manufacturer and to the US Vaccine Adverse Event Reporting System (VAERS) at 800-822-7967or http://www.vaers.hhs.gov/ (http://www.vaers.hhs.gov/) .[208,234,236]

Careful attention must be paid to recommended *postexposure* rabies prophylaxis protocols.[236] Use of both *active* immunization with rabies vaccine and *passive* immunization with rabies immune globulin (RIG) is necessary for *postexposure* prophylaxis following an exposure to rabies in previously unvaccinated individuals or individuals without serologic evidence of adequate rabies antibody after previous vaccination using preparations other than HDCV (Imovax®) or PCECV (RabAvert®).[236] Fatal rabies paralysis and encephalitis have occurred in several individuals who received *postexposure* prophylaxis with appropriate doses of HDCV and RIG; vaccine failure in these patients appeared to result from an inadequate immune response to HDCV, which may have occurred secondary to poor absorption of the vaccine from the gluteal area.[210,216,221] Several other cases of *postexposure* rabies prophylaxis failure have been reported in individuals who received cell culture-derived rabies vaccine other than those commercially available in the US and RIG or antirabies serum.[236] However, in most cases of *postexposure* failure to date, there has been some deviation from the recommended *postexposure* regimen (e.g., postexposure prophylaxis not given or substantially delayed, wounds not adequately cleansed, rabies vaccine given IM into the gluteal rather than deltoid region, failure to passively immunize with RIG by infiltrating the wound site, use of less than the recommended dose of RIG, use of less than the recommended number of doses of rabies vaccine).[208,234,236,250]

Sensitivity Reactions.

Allergic reactions, including anaphylaxis, have been reported in association with HDCV (Imovax®) and PCECV (RabAvert®).[208,234] Such reactions pose a therapeutic dilemma.[208,236] The individual's risk of acquiring rabies should be carefully considered when deciding whether to discontinue the vaccination series.[208,236] State health departments or the CDC should be contacted for advice and assistance regarding management of these individuals.[208,236]

When rabies vaccine is indicated in an individual with a history of hypersensitivity to the vaccine or any ingredient in the vaccine, the patient should be observed closely following each dose and appropriate therapy (e.g., epinephrine, corticosteroids, oxygen) should be readily available to treat a reaction if it occurs.[208,234,236] The use of prophylactic antihistamines is acceptable.[234,236] All serious anaphylactic reactions associated with rabies vaccine should be reported to the manufacturer and VAERS at 800-822-7967 or http://www.vaers.hhs.gov/ (http://www.vaers.hhs.gov/) .[234,236]

Allergy to Neomycin or Other Anti-infectives

The possibility of an allergic reaction to the small amounts of anti-infectives or other excipients present in HDCV (Imovax®) and PCECV (RabAvert®) should be considered and weighed in light of the potential risk of contracting rabies if the vaccine is not given.[208,234] Each dose of HDCV (Imovax®) contains <150 mcg of neomycin sulfate.[208] Each dose of PCECV (RabAvert®) contains no more than 10 mcg of neomycin and trace amounts of chlortetracycline (no more than 200 ng) and amphotericin B (no more than 20 ng).[234] Caution should be used in individuals sensitive to these anti-infectives.[234]

Neomycin allergy usually results in delayed-type (cell-mediated) hypersensitivity reactions manifested as contact dermatitis. [252] The US Public Health Service Advisory Committee on Immunization Practices (ACIP) states that a history of delayed-type allergic reaction to neomycin is not a contraindication to administration of vaccines containing trace amounts of neomycin; individuals with a history of anaphylactic reaction to neomycin should be evaluated by an allergist before receiving a neomycin-containing vaccine.[252]

Gelatin Allergy

PCECV (RabAvert®) contains <12 mg of polygeline (bovine gelatin);[234] therefore, the possibility of allergic reactions in individuals sensitive to bovine gelatin should be considered. [234] ACIP states that individuals with a history of anaphylactic reaction to gelatin should be evaluated by an allergist before receiving a gelatin-containing vaccine.[252] The bovine components used in the vaccine originate only in the US, Australia, and New Zealand.[234]

Allergy to Egg-related Antigens

PCECV (RabAvert®) rabies vaccine is produced in chick embryo cell culture and may contain minimal amounts of chicken protein (ovalbumin).[234] The manufacturer of PCECV (RabAvert®) rabies vaccine states that if the vaccine is used in individuals with a history of anaphylaxis involving symptoms such as urticaria, angioedema or swelling, brochospasm, lightheadedness, hypotension, or shock following exposure to egg or chicken protein, it should be administered in an inpatient or outpatient medical setting (including but not necessarily limited to hospitals, clinics, health departments, and physician offices) under supervision of a healthcare provider able to recognize and manage severe allergic reactions.[234]

HDCV (Imovax®) rabies vaccine is produced in human diploid cells and does not contain chicken protein.[208,]

Nervous System Effects.

Neurologic effects, sometimes serious (e.g., Guillain-Barré syndrome, transient neuroparalysis, myelitis, retrobulbar neuritis, multiple sclerosis, subacute peripheral and focal CNS disorders) have been temporally associated with HDCV (Imovax®) and PCECV (RabAvert®).[208,234,] If neurologic effects occur, the individual's risk of acquiring rabies should be carefully considered when deciding whether to discontinue the vaccination series.[208,234,] State health departments or the CDC should be contacted for advice and assistance regarding management of these individuals.[208,236,]

The fact that use of corticosteroids to treat life-threatening neuroparalytic reactions may interfere with the immunologic response to the vaccine should be considered.[208,234,] In these cases, it is especially important that serologic testing be done to verify seroconversion following rabies vaccination.[208,] All serious vaccine-associated neuroparalytic reactions should be reported to the manufacturer and to VAERS at 800-822-7967 or http://www.vaers.hhs.gov/ (http://www.vaers.hhs.gov/).[208,]

Administration Precautions.

Care must be taken to ensure that HDCV (Imovax®) and PCECV (RabAvert®) are administered only by IM injection for *preexposure* vaccination or *postexposure* prophylaxis.[208,234,236,] IM injections of rabies vaccine should preferably be made into the deltoid muscle in adults, adolescents, and older children (3 to 10 years of age); the anterolateral thigh is preferred in infants and young children.[252,236,]

Use of the gluteal area for IM administration of rabies vaccine should be avoided since administration in this area may result in an impaired immunologic response.[208,209,210,212,216,221,234,250,252,] Reasons for a suboptimal response are unclear, but may occur because of inadvertent subcutaneous injection or administration into fatty tissue instead of muscle.[209,210,221,] Fatal rabies paralysis and encephalitis have been reported in several individuals who received HDCV (Imovax®) by IM injection into the gluteal area.[210,216,221,]

Inadvertent intravascular injection of PCECV (RabAvert®) may result in systemic reactions, including shock.[234,]

RIG should *not* be administered in the same syringe and should *not* be administered simultaneously at the same injection site as rabies vaccine.[236,246,250,]

Individuals with Altered Immunocompetence.

Rabies vaccine may be administered to individuals immunosuppressed as the result of disease or immunosuppressive therapy.[211,233,236,250,253,] However, clinicians should consider the possibility that the antibody response to rabies vaccine and efficacy may be reduced in these individuals.[208,212,234,236,250,253,]

The ACIP states that recommendations concerning use of rabies vaccine in individuals with altered immunocompetence (e.g., patients with HIV infection, congenital immunodeficiency, leukemia, lymphoma, aplastic anemia, generalized malignancy, solid organ transplant, asplenia, renal failure, diabetes, alcoholism, or alcoholic cirrhosis, or in those receiving therapy with alkylating agents, antimetabolites, radiation, corticosteroids, or other chronic immunosuppressive therapy) are the same as those for patients who are not immunocompromised.[233,236,250,253,] However, the ACIP states that a 5-dose vaccine series (not a 4-dose series) of HDCV (Imovax®) or PCECV (RabAvert®) should be used when rabies *postexposure* prophylaxis is indicated in previously unvaccinated individuals with altered immunocompetence.[250,]

Preexposure vaccination (2-dose series) should be postponed in immunocompromised individuals and these individuals should be advised to avoid activities for which rabies *preexposure* vaccination is indicated.[212,236,253,] If this is not possible, the rabies vaccine can be administered, but antibody titer should be checked no sooner than 1 week (ideally, 2 to 4 weeks) after completion of the 2-dose preexposure series and all booster doses (including those administered within 3 years of the primary series anc in response to a low titer during the serial titer checks recommended for risk categories 1 and 2).[253,] If the titer is <0.5 IU/mL, a booster dose should be administered, followed by a subsequent titer check.[253,] If 2 such booster doses fail to elicit an appropriate antibody response, local or state public health authorities should be consulted for guidance.[253,]

If rabies *postexposure* prophylaxis is indicated in an immunocompromised individual, serologic testing is considered essential after completion of the *postexposure* prophylaxis regimen to confirm than an adequate antibody response is obtained.[234,236,250,] If an acceptable antibody response is not detected after the final vaccine dose of the *postexposure* prophylaxis series, the patient should be managed in consultation with their clinician and appropriate public health officials.[216,250,]

Use of immunosuppressive agents should be avoided during rabies *postexposure* prophylaxis, unless considered essential for the treatment of other conditions.[233,234,236,250,]

Risk of Transmissible Agents in Preparations Containing Albumin.

HDCV (Imovax®) and PCECV (RabAvert®) contain albumin human.[208,234,] Since albumin is prepared from pooled human plasma, it is a potential vehicle for transmission of human viruses, including the causative agents of viral hepatitis and HIV infection, and theoretically may carry a risk of transmitting the causative agent of Creutzfeldt-Jakob disease (CJD) or variant CJD (vCJD).[234,245,] Improved donor screening, viral-inactivation procedures (e.g., solvent/detergent treatment), and/or filtration procedures have reduced, but not completely eliminated, risk of pathogen transmission with plasma-derived preparations.[234,]

Concomitant Illness.

A decision to administer or delay vaccination in an individual with current or recent febrile illness depends on the severity of symptoms and etiology of the illness.[211,] The ACIP states that minor acute illness, such as mild diarrhea or mild upper respiratory tract infection (with or without fever) generally does not preclude vaccination.[211,]

The manufacturers and ACIP state that *preexposure* rabies vaccination (but not *postexposure* prophylaxis) with HDCV (Imovax®) or PCECV (RabAvert®) generally should be deferred in individuals with moderate or severe acute illness until improvement of the condition is noted.[211,234,]

Limitations of Vaccine Effectiveness.

HDCV (Imovax®) and PCECV (RabAvert®) may not protect all vaccine recipients against rabies.[234,] In addition, rabies vaccination may not prevent rabies in individuals who do not achieve adequate rabies antibody titers.[234,236,]

Duration of Immunity.

The duration of immunity following the recommended 2-dose *preexposure* vaccine series (primary immunization) of HDCV (Imovax®) or PCECV (RabAvert®) is unclear.[253] Clinical data show that an anamnestic response after the 2-dose series occurs at 3 years; however, such a response >3 years after the series has not been evaluated.[253]

The need for additional (booster) doses after primary immunization depends on the nature and category of rabies risk associated with the potential exposure.[236,253]

Individuals with Bleeding Disorders.

Because bleeding may occur following IM administration in individuals with thrombocytopenia or a bleeding disorder (e.g., hemophilia) or in those receiving anticoagulant therapy, caution should be used in such individuals.[211]

The ACIP states that vaccines may be given IM to individuals who have bleeding disorders or are receiving anticoagulant therapy if a clinician familiar with the patient's bleeding risk determines that the vaccine can be administered with reasonable safety.[211] In these cases, a fine needle (23 gauge) should be used to administer the vaccine and firm pressure should be applied to the injection site (without rubbing) for 2 minutes or longer.[211] If the patient is receiving antihemophilia therapy, the IM vaccine should be administered shortly after a scheduled dose of such therapy.[211] The individual and/or their family should be advised about the risk of hematoma from IM injections.[211]

Improper Storage and Handling.

Improper storage or handling of vaccines may result in loss of vaccine potency and reduced immune response in vaccines.[211]

HDCV (Imovax®) or PCECV (RabAvert®) that has been mishandled or has not been stored at the recommended temperature should not be administered.[208,211,234]

All vaccines should be inspected upon delivery and monitored during storage to ensure that the appropriate temperature is maintained.[211] If there are concerns about mishandling, the manufacturer or state or local health departments should be contacted for guidance on whether the vaccine is usable.[211]

Pediatric Precautions

HDCV (Imovax®) has been shown to be safe and effective in children.[208]

Only limited data are available regarding safety and efficacy of PCECV (RabAvert®) in pediatric patients.[234] PCECV (RabAvert®) has been used effectively for *preexposure* vaccination in children 2 years of age or older and also has been used effectively for *postexposure* prophylaxis in children 1 year of age or older.[234] At least 1 neonate has received 5 doses of RabAvert® rabies vaccine (given on days 0, 3, 7, 14, and 30) without unusual adverse effects.[234]

Geriatric Precautions

Experience in those 65 years of age or older is insufficient to determine whether they respond differently to rabies vaccine than younger adults.[234] Clinical experience with PCECV (RabAvert®) rabies vaccine reveals no overall differences in safety between geriatric individuals and younger patients.[234]

Mutagenicity and Carcinogenicity

Studies have not been performed to date to evaluate the mutagenic or carcinogenic potential of HDCV (Imovax®) or PCECV (RabAvert®) rabies vaccine.[234]

Pregnancy, Fertility, and Lactation

Pregnancy.

The manufacturers state that rabies vaccine should be given to pregnant females only if clearly needed.[208,234] However, because of the potential risks of inadequately treated rabies exposure and because limited data indicate that fetal abnormalities have not been associated with rabies vaccine, the ACIP, CDC, AAP, American College of Obstetricians and Gynecologists (ACOG), and the manufacturers state that pregnancy is *not* considered a contraindication for *postexposure prophylaxis*.[204,208,212,234,236] ACOG recommends that each pregnant female be considered individually and that public health authorities be consulted.[204] In addition, when a substantial risk of rabies exposure is present, *preexposure* vaccination may be indicated during pregnancy.[208,234,236] Animal reproduction studies have not been performed with HDCV (Imovax®) or PCECV (RabAvert®) rabies vaccine.[208,234]

Fertility.

It is not known if HDCV (Imovax®) or PCECV (RabAvert®) rabies vaccine affects fertility.[208,234]

Lactation.

It is not known if antigens contained in rabies vaccine are distributed into milk.[212,234] The CDC states that use of rabies vaccine in nursing females should follow the same guidelines as other adults.[212] Because inactivated vaccines do not multiply within the body, the ACIP states that they should not pose any unusual problems for nursing females or their infants.[211]

The manufacturer of PCECV (RabAvert®) rabies vaccine states that nursing is not a contraindication to rabies *postexposure* prophylaxis because of the possible consequences of inadequately treated rabies exposure.[234] *Preexposure* vaccination with the vaccine in nursing females may also be indicated if the risk of rabies exposure is substantial.[234]

▪ Systemic Effects

Systemic reactions to HDCV (Imovax®) occur in about 20% of individuals receiving the vaccine and include mild to moderate constitutional manifestations such as nausea, vomiting, abdominal pain, diarrhea, headache, fatigue, sore throat, low grade fever (up to 38.3°C), chills, muscle aches, arthralgia, myalgia, fainting, and dizziness.[208]

The most common adverse systemic effects reported with PCECV (RabAvert®) are influenza-like symptoms, including mild to moderate asthenia, fatigue, fever, myalgia (53%), malaise (15–20%), and headache (10–52%).[234] Other common adverse effects include arthralgia, localized lymphadenopathy (15%), dizziness (15%), nausea, and rash.[234] In addition, GI complaints, severe headache, fatigue, circulatory reactions, palpitations, hot flush, sweating, chills, monoarthritis, and urticaria pigmentosa have

been reported rarely.[234,]

Sensitivity Reactions

An immune complex (serum-sickness)-like (type III hypersensitivity) reaction has been reported in up to 7% of individuals receiving IM booster doses of HDCV (Imovax®).[208,219,236,] These reactions generally have occurred 2–21 days after a booster dose of HDCV (Imovax®), were not life-threatening, and were characterized by generalized urticaria with or without arthralgia, arthritis, angioedema, nausea, vomiting, fever, and malaise.[208,219,236,] These reactions also have been reported in individuals receiving primary immunization with HDCV (Imovax®), but less frequently than with booster doses.[219,236,] There is limited evidence that these type III hypersensitivity reactions to HDCV (Imovax®) may be caused by β-propiolactone-altered albumin human used during manufacture of the vaccine; β-propiolactone is thought to render the albumin allergenic and the development of immunoglobulin E (IgE) antibodies to this allergen have been reported.[236,]

Allergic reactions, including serious systemic anaphylactic reactions, have been reported rarely in association with PCECV (RabAvert®) rabies vaccine.[234,] At least 2 cases of anaphylactic shock have been reported.[234,] Bronchospasm, edema, pruritus, and urticaria also have been reported during postmarketing surveillance.[234,] Type III hypersensitivity reactions have been reported during postmarketing surveillance in individuals receiving PCECV (RabAvert®), which contains albumin human in concentrations <0.3 mg per dose.[234,]

When rabies vaccine is indicated in an individual who has had a serious hypersensitivity reaction to the vaccine, prophylactic antihistamines may be given and appropriate therapy (e.g., epinephrine, corticosteroids, oxygen) should be readily available to treat a reaction if it occurs.[208,234,236,]

Drug Interactions

▪ Rabies Immune Globulin

If rabies *postexposure* prophylaxis requires active immunization with rabies vaccine and passive immunization with rabies immune globulin (RIG), a single dose of RIG should be administered simultaneously with the first vaccine dose in previously unvaccinated individuals.[208,234,236,250,] When anatomically feasible, the full RIG dose should be infiltrated around and into the wound(s) and any remaining portion of the RIG dose should be administered IM (using a different syringe and different injection site than rabies vaccine) at a site distant from vaccine administration.[234,236,250,] Neutralization of rabies vaccine may occur if RIG and the vaccine are mixed in the same syringe or administered into the same injection site.[211,236,] During *postexposure* prophylaxis, if the vaccine regimen is initiated without RIG, RIG may be administered through the seventh day after the first dose of vaccine.[234,236,] However, RIG is not indicated beyond the seventh day since an antibody response to rabies vaccine is presumed to have occurred.[234,236,249,]

RIG is not indicated for *postexposure* prophylaxis in individuals who previously received recommended *preexposure* or *postexposure* regimens of human diploid-cell rabies vaccine (HDCV; Imovax®) or purified chick embryo cell culture (PCECV; RabAvert®) or in those who previously received other rabies vaccines and have documented adequate antirabies antibody titers.[236,]

Passively acquired antibody to rabies antigen, which is present in rabies immune globulin (RIG), may partially suppress the active immune response to rabies vaccine;[234,236,250,] however, there is evidence that a single RIG dose of 20 international units/kg given at the same time as the first dose of rabies vaccine provides maximum circulating antirabies antibody with minimal interference with the active immune response to the vaccine.[246,] To minimize potential suppression of the active immune response to the vaccine, RIG should not be given in doses greater than 20 units/kg and repeated RIG doses should not be given.[234,236,250,]

▪ Vaccines

Data are not available regarding the concurrent administration of HDCV (Imovax®) or PCECV (RabAvert®) and other vaccines.[211,] However, rabies vaccines commercially available in the US are inactivated vaccines and administration of these vaccines should not interfere with the antibody response to other inactivated vaccines, live vaccines, recombinant vaccines, or toxoids.[211,] Inactivated vaccines can be administered either simultaneously with or at any time before or after inactivated or live vaccines.[211,] However, each vaccine should be administered using a different syringe and a different injection site.[211,]

▪ Immunosuppressive Agents

Immunosuppressive therapy (e.g., corticosteroids, other immunosuppressive agents, radiation therapy) can interfere with the active antibody response to rabies vaccine.[208,212,233,234,236,250,]

Preexposure vaccination with rabies vaccine should be postponed in individuals receiving immunosuppressive therapy, and activities for which vaccination against rabies is indicated should be avoided until such therapy is discontinued.[212,236,250,] If it is necessary to administer *preexposure* vaccination against rabies to an individual receiving immunosuppressive therapy, serologic testing should be performed following completion of the vaccine series to document an acceptable antibody titer.[236,250,253,]

Immunosuppressive therapy should be avoided during *postexposure* prophylaxis against rabies, unless such therapy is considered essential for the treatment of other serious conditions.[208,233,234,236,250,] If rabies *postexposure* prophylaxis is indicated in a previously unvaccinated individual who is receiving immunosuppressive therapy that cannot be discontinued, the ACIP states that a 5-dose series (not a 4-dose series) of HDCV (Imovax®) or PCECV (RabAvert®) should be used.[250,] In addition, it is important that serologic testing for rabies antibody be performed after completion of the *postexposure* prophylaxis regimen to ensure that an adequate antibody response was attained in individuals receiving corticosteroids or immunosuppressive agents or when corticosteroids are used to treat individuals who develop life-threatening neuroparalytic reactions to rabies vaccine.[208,233,234,236,250,]

Pharmacology

Rabies vaccine is used to stimulate active immunity to rabies in individuals exposed to the disease or virus.[208,229,230,231,234,235,236,] Inactivated rabies virus, which is present in human diploid-cell rabies vaccine (HDCV; Imovax®) or purified chick embryo cell culture (PCECV; RabAvert®) rabies vaccine, stimulates active immunity to rabies by inducing production of antirabies neutralizing antibodies.[208,234,236,]

▪ Rabies Virus and Infection

Rabies virus is an RNA virus classified in the Rhabdovirus family.[212,236,249,] Rabies is a viral infection transmitted by the saliva of infected mammals.[234,236,249,] Following exposure and infection, rabies virus appears to remain close to the wound for an indeterminate time and can be partially neutralized with rabies immune globulin (RIG) while at this site. Unimpeded, the virus usually moves along a neural pathway via the peripheral nerves toward the CNS.[249,] Once the virus enters the CNS of the host, it replicates and disseminates rapidly via the nervous system to many different tissues, including the salivary glands.[249,] At this stage the virus is unlikely to be affected by antibodies, and a fatal encephalomyelitis almost invariably ensues.[234,236,249,] The incubation period in humans can range from days to years (usually 1–3 months);[212,234,249,250,] after severe bites to the face, neck, or arms, the incubation period may be as short as 10 days.[246,] The length of the incubation period depends on factors such as the amount of viral inoculum, the degree of innervation at the site of viral entry, and the proximity of the bite to the CNS.[249,]

Rabies may present as a furious or a paralytic form.[234,] Common prodromal symptoms of rabies include malaise, anorexia, fatigue, headache, and fever followed by pain or paresthesia at the site of exposure.[234,249,] Anxiety, agitation, and irritability may occur during the prodromal stage, followed by hyperactivity, disorientation, seizures, aerophobia, hydrophobia, hypersalivation, and eventually paralysis, coma, and death.[212,234,249,] Following the appearance of clinical symptoms of rabies, use of rabies vaccine or RIG will not improve the prognosis and may be detrimental; there is no specific proven effective treatment for rabies once symptoms develop.[212,236,249,]

In the US, approximately 16,000–39,000 individuals receive rabies *postexposure* prophylaxis each year.[234,236,250,] Rabies prevention and control strategies and elimination of canine rabies virus variants and enzootic transmission among dogs have lowered the number of rabies cases in the US to an average of 1–2 per year.[250,] However, worldwide, rabies is much more common and more than 59,000 rabies-related deaths occur each year.[249,250,]

Types of Exposure

Rabies is transmitted via the saliva of infected mammals and transmission of the virus usually only occurs when it is introduced into bite wounds or open cuts in skin or onto mucous membranes.[208,212,236,] There are 2 categories of exposure that are considered when evaluating possible transmission of rabies virus to humans: bite exposures and nonbite exposures.[208,236,] Bite exposures include any penetration of the skin by teeth and all bites, regardless of location, have a potential risk of rabies transmission.[208,236,] Unfortunately, bites by some animals (e.g., bats) can inflict minor injury and may be undetected.[236,] Although nonbite exposures from terrestrial animals only rarely cause rabies, the fact that there have been occasional reports of transmission by nonbite exposures suggest that such exposures should be considered for *postexposure* prophylaxis.[236,] Nonbite exposures include contamination of preexisting open wounds, abrasions, mucous membranes, or scratches with saliva or other potentially infectious material (e.g., neural tissue) from a rabid animal.[208,236,] Because rabies virus is inactivated by desiccation and UV irradiation, if material containing the virus is dry, the virus can be considered noninfectious.[236,] Other forms of contact (in the absence of a bite or nonbite exposure), such as petting a rabid animal or contact with the blood, urine, or feces (e.g., guano) of a rabid animal is *not* considered exposure and *postexposure* prophylaxis is *not* necessary.[208,236,]

An unprovoked attack by an animal is more likely than a provoked attack to indicate that the animal is rabid.[236,] Bites inflicted on an individual attempting to feed or handle an apparently healthy animal generally should be regarded as provoked.[236,] A dog, cat, or ferret that has been vaccinated against rabies is unlikely to become infected with rabies.[236,]

Nonbite exposures that are considered the highest risk occur in individuals exposed to large amounts of aerosolized rabies virus and surgical recipients of organs or tissues (e.g., corneas) transplanted from patients who died of rabies (human-to-human transmission).[208,234,236,] In the US, stringent guidelines for acceptance of donor corneas have been implemented to reduce this risk.[208,234,236,] Transmission of rabies virus from the bite of a human with rabies or a nonbite exposure to individuals infected with rabies is theoretically possible, but no such case has been documented to date.[208,236,] Routine delivery of health care to a patient with rabies is not an indication for *postexposure* rabies prophylaxis in health-care personnel, unless they have been bitten by the patient or if they have mucous membranes or nonintact skin (e.g., open wounds) that were contaminated with the patient's saliva or other potentially infectious material (e.g., neural tissue).[236,]

▪ Response to Rabies Vaccine

Development of immunity and protection from rabies infection are evaluated by the appearance of antirabies antibody in serum.[236,] However, the actual serum titer of rabies antibody indicating immunity and protection against rabies has not been definitely established to date and reported values for antibody titers vary among laboratories and are influenced by the type of test performed.[236,]

The minimum antibody level historically recommended by US Public Health Service Advisory Committee on Immunization Practices (ACIP) is one that resulted in complete neutralization of rabies virus at a 1:5 serum dilution by the rapid fluorescent focus inhibition test.[253,] This is approximately equivalent to a titer of 0.1-0.3 IU/mL.[253,] Although no infections among vaccinated individuals occurred with this cut-off titer, most published studies use 0.5 IU/mL as a correlate or protection.[253,] Therefore, this antibody titer level is now endorsed by ACIP.[253,]

Response following IM Injection

Antirabies antibodies neutralize rabies virus and are believed to have a primary role in preventing rabies infection.[236,] Following IM administration of rabies vaccine, antirabies antibody levels are detectable in serum within 7–10 days and persist for several years.[236,]

RIG has been reported to partially suppress the active antibody response to rabies vaccines.[234,236,250,] Once vaccination with rabies vaccine has been initiated, administration of larger than usual doses of RIG (e.g., greater than 20 international units/kg) or repeated administration of RIG may interfere with the immune response to the vaccine.[234,236,250,]

The immunologic response to rabies vaccine appears to vary with the IM injection site.[209,210,216,221,227,] IM injection of the vaccine in the gluteal area may result in a lower response rate than IM injection into the deltoid,[208,209,211,216,221,227,234,249,] and fatal rabies paralysis and encephalitis have occurred in several individuals who received HDCV IM into the gluteal area.[210,216,221,] Although the reasons for this have not been determined to date, it has been suggested that rabies vaccine injections

given into the gluteal area may inadvertently be given subcutaneously or into fatty tissue instead of muscle and that uptake of the vaccine may therefore be impaired.[208,209,210,211,221,234,]

Duration of Response

The duration of rabies antibody following administration of rabies vaccine is variable.[236,]

Following administration of the historical 3-dose *preexposure* vaccine series (primary immunization) using HDCV (Imovax®) or PCECV (RabAvert®), protective concentrations of rabies neutralizing antibody decline gradually, but appear to persist for about 2 years or longer.[234,236,] There is some evidence that adequate concentrations of rabies neutralizing antibody are present in 94–100% of individuals tested at 6, 12, 21, and 26 months after a 3-dose primary immunization series of HDCV or PCECV.[236,] Following administration of a 1- or 2-dose booster regimen of HDCV or PCECV in individuals who previously received primary immunization with one of these vaccines, an anamnestic response occurred and adequate concentrations of antirabies antibody were present 1 year after the booster doses.[236,]

Following administration of the 2-dose primary *preexposure* vaccine series, clinical data show that an anamnestic response occurs at 3 years; however, an anamnestic response >3 years after this series has not been evaluated.[253,]

Chemistry and Stability

▪ Chemistry

Rabies vaccine is commercially available in the US as human diploid-cell rabies vaccine (HDCV; Imovax®) or purified chick embryo cell culture rabies vaccine (PCECV; RabAvert®).[208,234,236,] These 2 vaccines contain rabies virus antigen, but are prepared using different virus strains and different types of cell cultures to propagate the virus.[208,234,236,] Previously, a sterile preparation of rabies antigen obtained from rhesus diploid-cells (rabies vaccine adsorbed; RVA)[236,] and a killed, fixed rabies virus obtained from infected duck embryos were available in the US. Rabies vaccine also is available outside the US as other cell-culture derived vaccines (e.g., purified VERO cell rabies vaccine) and as vaccines of nerve tissue origin (e.g., nerve tissue vaccine, NTV).[236,249,]

Rabies vaccines commercially available in the US meet standards established by the Center for Biologics Evaluation and Research of the US Food and Drug Administration and contain not less than 2.5 International Units of rabies antigen per mL.[208,234,236,]

Human Diploid-Cell Rabies Vaccine (HDCV; Imovax®)

HDCV (Imovax®) is a sterile, concentrated, lyophilized suspension of rabies virus antigen for IM administration.[208,] The antigen is prepared from the Wistar Institute Pitman-Moore strain (PM-1503-3M) of rabies virus[208,] that has been propagated in MRC-5 strain of human diploid-cell tissue culture, concentrated by ultrafiltration, and inactivated with β-propiolactone.[208,]

HDCV (Imovax®) is a creamy white to orange-colored lyophilized powder for IM injection.[208,] Following reconstitution with the sterile water for injection diluent provided by the manufacturer, the vaccine is pink to red in color.[208,]

Each 1-mL dose of HDCV (Imovax®) for IM injection contains at least 2.5 units of rabies antigen and also contains less than 100 mg of albumin human, less than 150 mcg of neomycin sulfate, and 20 mcg of phenol red indicator.[208,] The vaccine does not contain thimerosal or any other preservative.[208,]

Purified Chick Embryo Cell Culture Rabies Vaccine (PCECV; RabAvert®)

PCECV (RabAvert®) is a sterile, lyophilized powder for IM injection containing rabies virus antigen.[234,] The antigen is prepared from the fixed-virus strain Flury low egg passage (LEP) of rabies virus propagated in primary cultures of chicken fibroblasts.[234,] The virus is harvested, inactivated with β-propiolactone, purified and concentrated using zonal centrifugation in a sucrose density-gradient, and stabilized with buffered polygeline (processed bovine gelatin) and potassium glutamate.[234,]

Traces of antibiotics (neomycin, chlortetracycline, amphotericin B) used during chicken fibroblast cell culture and virus propagation steps in the manufacture of PCECV (RabAvert®) rabies vaccine may be present in the final reconstituted vaccine.[234,] Minimal amounts of chicken protein may be present in the final product.[234,] Bovine components originate only from the US, Australia, and New Zealand.[234,]

PCECV (RabAvert®) for IM injection is a lyophilized, white powder.[234,] Following reconstitution with the sterile water for injection diluent provided by the manufacturer, the vaccine is a clear to slightly opalescent, colorless to slightly pink suspension.[234,] Each 1-mL dose of PCECV (RabAvert®) for IM injection contains at least 2.5 units of rabies antigen and also contains less than 0.3 mg of human albumin, less than 12 mg of polygeline (processed bovine gelatin), 1 mg of potassium glutamate, 0.3 mg of sodium EDTA, less than 10 mcg of neomycin, less than 200 ng of chlortetracycline, less than 20 ng of amphotericin B, and less than 3 ng of ovalbumin.[234,] The vaccine does not contain thimerosal or any other preservative.[234,]

▪ Stability

Human Diploid-Cell Vaccine (HDCV; Imovax®)

HDCV (Imovax®) lyophilized powder for IM injection should be refrigerated at 2–8°C; freezing should be avoided.[208,] Following reconstitution, the vaccine should be used immediately.[208,]

Purified Chick Embryo Cell Culture Rabies Vaccine (PCECV; RabAvert®)

PCECV (RabAvert®) lyophilized powder for IM injection should be stored at 2–8°C and protected from light.[234,] Following reconstitution, the vaccine should be used immediately.[234,]

Advice to Patients

The following information contains important points for the clinician to discuss with patients during counseling. For more comprehensive monographs suitable for distribution to the patient, please refer to the *AHFS Patient Medication Information* monographs available from MedlinePlus (https://vsearch.nlm.nih.gov/vivisimo/cgi-bin/query-meta?v:project=medlineplus) (in English and Spanish; written at a 6th- to 8th-grade reading level).

Prior to administration of each vaccine dose, provide a copy of the appropriate CDC Vaccine Information Statement (VIS) to the patient or patient's legal representative as required by the National Childhood Vaccine Injury Act (VISs are available at http://www.cdc.gov/vaccines/pubs/vis/default.htm (http://www.cdc.gov/vaccines/pubs/vis/default.htm)).[244,]

Advise the patient and/or patient's parent or guardian of the risks and benefits of vaccination with rabies vaccine.[208,234,]

Advise the patient and/or patient's parent or guardian that rabies vaccine is used to prevent rabies and is given to persons at high risk of exposure to rabies as a result of employment, travel, or hobbies (e.g., certain laboratory workers, veterinarians, animal control and wildlife workers, spelunkers, hunters).[208,234,]

Advise the patient and/or patient's parent or guardian that rabies vaccine is also used to prevent rabies in individuals who have been bitten, scratched, or licked on an open wound by an animal known or suspected of having rabies.[208,234,]

When rabies *preexposure* vaccination is indicated, importance of completing the 2-dose primary vaccination series.[253,]

When rabies *postexposure* prophylaxis is indicated in previously unvaccinated individuals, importance of completing a 4- or 5-dose series of rabies vaccine and receiving a single dose of RIG as soon as possible following rabies exposure.[208,213,234,236,]

When rabies *postexposure* prophylaxis is indicated in previously vaccinated individuals, importance of receiving a 2-dose regimen of rabies vaccine as soon as possible following rabies exposure.[213,208,234,236,]

Importance of informing clinicians if the patient has a weakened immune system (e.g., cancer, HIV/AIDS) or receives treatment that may weaken the immune system (e.g., corticosteroids, cancer treatment).[208,234,]

Importance of informing clinicians if a patient has a fever or serious illness.[208,234,] Advise patient that *preexposure* vaccination may be deferred if they are moderately or severely ill, but that rabies *postexposure* prophylaxis will still be administered, regardless of any other illness they may have.[244,]

Importance of informing clinicians if any serious adverse reactions (e.g., hypersensitivity, neurologic reactions) occur.[208,234,] Clinicians or individuals can report any adverse reactions that occur following vaccination to the Vaccine Adverse Event Reporting System (VAERS) at 800-822-7967 or https://vaers.hhs.gov/index (https://vaers.hhs.gov/index) .[208,213,234,]

Importance of informing clinicians of existing or contemplated concomitant therapy, including prescription and OTC drugs, and any concomitant illnesses.[208,234,]

Importance of females informing clinicians if they are or plan to become pregnant or plan to breast-feed.[208,234,]

Importance of informing patients of other important precautionary information.[208,234,]

Additional Information

The American Society of Health-System Pharmacists, Inc. represents that the information provided in the accompanying monograph was formulated with a reasonable standard of care, and in conformity with professional standards in the field. Readers are advised that decisions regarding use of drugs are complex medical decisions requiring the independent, informed decision of an appropriate health care professional, and that the information contained in the monograph is provided for informational purposes only. The manufacturer's labeling should be consulted for more detailed information. The American Society of Health-System Pharmacists, Inc. does not endorse or recommend the use of any drug. The information contained in the monograph is not a substitute for medical care.

Preparations

Excipients in commercially available drug preparations may have clinically important effects in some individuals; consult specific product labeling for details.

Rabies Vaccine (Human Diploid-cell) (https://www.accessdata.fda.gov/scripts/cder/ndc/default.cfm?sugg=NonProprietaryName&ApptName=Rabies+Vaccine+%28Human+Diploid-cell%29&collapse=1)

Parenteral

For injectable suspension, for IM use only

≥2.5 units (of rabies antigen)

Imovax® Rabies, Sanofi Pasteur (https://www.accessdata.fda.gov/scripts/cder/ndc/default.cfm?sugg=LabelerName&ApptName=Sanofi+Pasteur&collapse=1)

Rabies Vaccine (Purified Chick Embryo Cell Culture) (https://www.accessdata.fda.gov/scripts/cder/ndc/default.cfm?sugg=NonProprietaryName&ApptName=Rabies+Vaccine+%28Purified+Chick+Embryo+Cell+Culture%29&collapse=1)

Parenteral

For injectable suspension, for IM use only

≥2.5 units (of rabies antigen)

RabAvert®, GlaxoSmithKline (https://www.accessdata.fda.gov/scripts/cder/ndc/default.cfm?sugg=LabelerName&ApptName=GlaxoSmithKline&collapse=1)

Related Resources

AHFS Patient Medication Information (https://vsearch.nlm.nih.gov/vivisimo/cgi-bin/query-meta?v:project=medlineplus&query=Rabies%20Vaccine) and other related patient health topics (MedlinePlus)
ASHP Drug Shortages Resource Center (https://www.ashp.org/Drug-Shortages)
CCRIS (https://toxnet.nlm.nih.gov/cgi-bin/sis/search2/r?dbs+ccris:%%22Rabies%20Vaccine%%22) (Chemical Carcinogenesis Research Information System)
ChemID*plus* (https://chem.nlm.nih.gov/chemidplus/name/Rabies%20Vaccine)
Biochemical Data Summary (http://www.drugbank.ca/unearth/q?utf8=%%E2%%9C%%93&query=Rabies%20Vaccine&searcher=drugs&approved=1&vet_approved=1&nutraceutical=1&illicit=1&withdrawn=1&investigational=1 (US and Canada)
Clinical Trials (https://www.clinicaltrials.gov/ct/search?submit=Search&term=Rabies%20Vaccine)
DailyMed (https://dailymed.nlm.nih.gov/dailymed/search.cfm?query=Rabies%20Vaccine) (drug labels)
DART (https://toxnet.nlm.nih.gov/cgi-bin/sis/search2/r?dbs+dart:%%22Rabies%20Vaccine%%22) (Developmental and Reproductive Toxicology Database)
Drugs@FDA (https://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.SearchAction&SearchType=BasicSearch&SearchTerm=Rabies%20Vaccine) (approval information)
European Medicines Agency (https://www.ema.europa.eu/en/search/search?search_api_views_fulltext=Rabies%20Vaccine)
FDA National Drug Code Directory (https://www.accessdata.fda.gov/scripts/cder/ndc/default.cfm?sugg=NonProprietaryName&ApptName=Rabies%20Vaccine&collapse=1)
FDA Recalls, Market Withdrawals, and Safety Alerts (https://www.fda.gov/Safety/Recalls/default.htm)
HSDB (https://toxnet.nlm.nih.gov/cgi-bin/sis/search2/r?dbs+hsdb:%%22Rabies%20Vaccine%%22) (Hazardous Substances Data Bank)
Inxight Drugs (https://drugs.ncats.io/substances?q=%%22Rabies%20Vaccine%%22) (National Center for Advancing Translational Sciences)
LactMed (drug effects on breastfeeding) (https://toxnet.nlm.nih.gov/cgi-bin/sis/search2/r?dbs+lactmed:@or+%%28@na+%%22Rabies%20Vaccine%%22+%%29)
New Drug Approvals (https://ahfs.ashp.org/drug-assignments.aspx)
Orange Book (https://www.accessdata.fda.gov/scripts/cder/ob/default.cfm?panel=0&drugname=Rabies%20Vaccine) (therapeutic equivalence)
PharmGKB (https://www.pharmgkb.org/search?connections&gaSearch=Rabies%20Vaccine&query=Rabies%20Vaccine&type=chemical) (Pharmacogenomic data from PharmGKB)
Pillbox (*beta*) (https://pillbox.nlm.nih.gov/pillimage/search_results.php?submit=Search&splid=&getingredient=Rabies%20Vaccine) (drug identification and images)
PubMed (https://www.ncbi.nlm.nih.gov/pubmed?DB=pubmed&term=Rabies%20Vaccine%%5BAll+Fields%%5D) (scientific journals)
Safety-related Labeling Changes (https://www.accessdata.fda.gov/scripts/cder/safetylabelingchanges) (FDA/CDER)
ToxLine (https://toxnet.nlm.nih.gov/cgi-bin/sis/search2/r?dbs+toxline:%%22Rabies%20Vaccine%%22) (Toxicology Literature Online)

† Use is not currently included in the labeling approved by the US Food and Drug Administration.

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