

Rabies Pre-Exposure Vaccination for Humans

Pre-exposure vaccination should be offered to persons in continuous or frequent-risk groups, such as veterinarians, animal handlers, and certain laboratory workers. Pre-exposure vaccination also should be considered for other persons 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. In addition, international travelers might be candidate for pre-exposure vaccination if they are likely to come in contact with animals where canine rabies is endemic and immediate access to appropriate medical care, including rabies biologics, might be limited.

Pre-exposure prophylaxis is administered for several reasons. First, although pre-exposure vaccination does not eliminate the need for additional therapy following a rabies exposure, it simplifies therapy by eliminating the need for RIG administration and decreasing the number of doses of vaccine needed – a point of particular importance for person at high risk for being exposed to rabies in areas where immunizing products might not be available or where they might be at high risk for adverse reactions. Second, pre-exposure prophylaxis might protect persons whose post-exposure therapy is delayed. Finally, it might provide protection to persons at risk for unapparent exposures to rabies.

Rabies pre-exposure prophylaxis guide – U.S. 2008

Risk category	Nature of risk	Typical populations	Pre-exposure recommendations
Continuous	Virus present continuously, often in high concentrations. Specific exposures likely to go unrecognized. Bite, nonbite, or aerosol exposure.	Rabies research laboratory workers; rabies biologics production workers.	Primary course. Serologic testing every 6 months; booster vaccination if antibody titer is below acceptable level.*
Frequent	Exposure usually episodic, with source recognized, but exposure also might be unrecognized. Bite, nonbite, or aerosol exposure.	Rabies diagnostic laboratory workers, cavers, veterinarians and staff, and animal-control and wildlife workers in areas where rabies is enzootic. All persons who frequently handle bats.	Primary course. Serologic testing every 2 years; booster vaccination if antibody titer is below acceptable level.*
Infrequent (greater than population at large)	Exposure nearly always episodic with source recognized. Bite or nonbite exposure.	Veterinarians and animal-control staff working with terrestrial animals in areas where rabies is uncommon to rare. Veterinary students. Travelers visiting areas where rabies is enzootic and immediate access to appropriate medical care including biologics is limited.	Primary course. No serologic testing or booster vaccination.
Rare (population at large)	Exposure always episodic with source recognized. Bite or nonbite exposure.	U.S. population at large, including persons in areas where rabies is epizootic.	No vaccination necessary.

* Minimum acceptable antibody level is complete virus neutralization at a 1:5 serum dilution by the rapid fluorescent focus inhibition test. A booster dose should be administered if the titer falls below this level.

Pre-exposure vaccination consists of two regimens: a primary vaccination regimen and a booster regimen. The primary vaccination regimen consists of three 1.0 mL injections of HDCV or PCEC that are administered intramuscularly (IM) in the deltoid area. One injection should be given per day on days 0, 7, and 21 or 28. Day 0 is defined as the day the first dose of vaccination is administered. If a booster vaccination is recommended, a single 1.0 mL injection of HDCV or PCEC should be administered intramuscularly (IM) in the deltoid area. For more information please refer to the *2008 Compendium of Animal Rabies Prevention and Control*.

Rabies Pre-exposure Prophylaxis

Rabies Vaccine	3 doses, 1 mL, IM, days 0, 7, and 21
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Post-exposure Therapy for Previously Vaccinated Persons

For people exposed to rabies and have been previously vaccinated with either the recommended pre-exposure OR post-exposure regimen should receive two 1.0 mL doses IM of vaccine, immediately after exposure on day 0, followed by an additional dose on day 3. HRIG is not necessary and should not be administered.

Rabies Post-exposure Prophylaxis (PEP) for Previously Immunized People

Treatment	Regimen
Wound Cleansing	Clean immediately with soap and water. If possible, irrigate wound with a anti-virus agent, like povidine-iodine
HRIG	Do not administer
Rabies Vaccine	2 doses, 1 mL, IM, days 0 and 3

Serologic Response and Pre-Exposure Booster Doses of Vaccine

Although virus neutralizing antibody levels might not definitively determine a person's susceptibility or protection from a rabies virus exposure, titers in persons at risk for exposure are used to monitor the relative rabies immune status over time. To ensure the presence of a primed immune response over time among persons at higher than normal risk for exposure, titers should be checked periodically, with booster doses administered only as needed. Two years after primary pre-exposure vaccination, a complete neutralization of challenge virus at a dilution of 1:5 (by the RFFIT) was observed among 93%-98% of persons who received the 3-dose pre-exposure series intramuscularly and 83%-95% of persons who received the 3-dose series intradermally. If the titer falls below the minimum acceptable antibody level of complete neutralization at a serum dilution of 1:5, a single pre-exposure booster dose of vaccine is recommended for persons at continuous or frequent risk for exposure to rabies. The following guidelines are recommended for determining when serum testing should be performed after primary pre-exposure vaccination:

- A person in the continuous-risk category should have a serum sample tested for rabies virus neutralizing antibody every 6 months.
- A person in the frequent-risk category should have a serum sample tested for rabies virus neutralizing antibody every 2 years.

The Alabama Department of Public Health can provide the names and addresses of laboratories performing appropriate rabies virus neutralizing serologic testing.

Human Diploid Cell Vaccine (HDCV)

Studies of HDCV recipients reported local reactions (i.e., pain at the injection site, redness, swelling, induration) among 60-89.5% of recipients. Most local reactions were mild and resolved spontaneously within a few days. Local pain at the injection site was the most frequently reported adverse reaction occurring in 21-77% of those receiving the vaccine. Mild

systemic reactions (i.e., fever, headache, dizziness, gastrointestinal symptoms) were reported in 6.8-55.6% of recipients.

Immediate systemic hypersensitivity reactions were observed in 1.2% of recipients in one study involving boosters of HDCV one year after primary vaccination with HDCV. Immediate hypersensitivity reactions have been reported in as many as 6% of persons receiving booster vaccination with HDCV following primary rabies prophylaxis; 3% occurring within one day of receiving boosters and 3% occurring 6-14 days after boosters. Systemic allergic reactions have been associated with the presence of betapropiolactone-altered human albumin in HDCV and the development of antibodies to this allergen. No deaths resulting from these reactions have been reported.

Purified Chick Embryo Cell Vaccine (PCEC)

In studies of PCEC use, local reactions (i.e., pain at the injection site, redness, and swelling) were reported among 11-57% of recipients. Local pain at the injection site, the most common local reaction, was reported in 2-23% of those receiving the vaccine. Systemic reactions were less common, and have been reported in 0-31% of vaccine recipients. In one study, 7% of children administered PCEC experienced mild to moderate clinical reactions.

In another study reviewing adverse events following the administration of PCEC using data from the United States Vaccine Adverse Events Reporting System (VAERS), approximately 1.1 million doses of PCEC were distributed (from 1997-2005) and 331 reports describing adverse events following PCEC administration were received by VAERS. A total of 196 reported adverse events (3% serious) occurred following administration of PCEC alone, and 135 (10% serious) occurred following post-exposure prophylaxis (PCEC co-administered with HRIG) or PCEC administered concomitantly with another vaccine. A total of 20 reports, three serious, were classified as anaphylaxis. One patient was found to be allergic to gelatin, a vaccine component. Among the 309 non-serious adverse events, the most frequently reported were headache, fever, myalgia, nausea, and weakness. A limitation of VAERS is that causality between vaccine administration and reported adverse events cannot be established. No deaths or rabies cases were reported following the administration of PCEC.

Human Rabies Immune Globulin (HRIG)

In a clinical trial involving 16 volunteers, participants receiving HRIG alone (no vaccine) commonly reported local reaction (100% in conventional HRIG group, 75% in heat-treated HRIG group), including pain/tenderness (100% conventional HRIG group, 50% heat-treated HRIG group), erythema (63% conventional HRIG, 25% heat-treated HRIG), and induration (50% conventional, 31% heat-treated). Systemic reactions were reported in 75% of participants in the conventional HRIG group and 81% in the heat-treated group. Headache was the most commonly reported systemic reaction (50% conventional, 69% heat-treated). Most of the reported local and systemic reactions were mild, and there were no significant differences in the frequency of adverse events between treatment groups.

Neurological Adverse Events

Rare, individual case reports of neurologic adverse events following rabies vaccination have been reported but in none of the cases has causality been established. Five cases of neurologic illness resembling Guillain-Barré syndrome occurring after treatment with HDCV or PCEC have been identified. One case of acute neurologic syndrome involving seizure activity was reported following the administration of HDCV and human RIG. Other central and peripheral nervous system disorders have been temporally associated with HDCV vaccine.

Management of Adverse Reactions

Once initiated, rabies prophylaxis should not be interrupted or discontinued because of local or mild systemic adverse reactions to rabies vaccine. Usually, such reactions can be successfully managed with anti-inflammatory and antipyretic agents, such as ibuprofen or acetaminophen.

When a person with a history of serious hypersensitivity to rabies vaccine must be revaccinated, antihistamines can be administered. Epinephrine should be readily available to counteract anaphylactic reactions, and the person should be observed carefully immediately after vaccination.

Although serious systemic, anaphylactic, or neuroparalytic reactions are rare during and after the administration of rabies vaccines, such reactions pose a serious dilemma for the patient and the attending physician. A patient's risk of acquiring rabies must be carefully considered before deciding to discontinue vaccination. Advice and assistance on the management of serious adverse reactions for persons receiving rabies vaccines may be sought from the Alabama Department of Public Health.

All clinically significant adverse events occurring following administration of rabies biologics should be reported to the Vaccine Adverse Event Reporting System (VAERS), even if causal relation to vaccination is not certain. Although VAERS is subject to limitations common to passive surveillance systems, including underreporting and reporting bias, it is a valuable tool for characterizing the safety profile of vaccines and identifying risk factors for rare serious adverse reactions to vaccines. VAERS reporting forms and information are available electronically at <http://www.vaers.hhs.gov/> or by telephone via a 24-hour toll-free telephone number (1-800-822-7967). Web-based reporting is available at <https://secure.vaers.org/VaersDataEntryintro.htm>* to promote better timeliness and quality of safety data.

Animal Vaccination Protocols

Public Health laws in Alabama (Section 3-7A of the Code of Alabama 1975) mandate that parenteral animal rabies vaccines can be administered only by a licensed veterinarian. This is to ensure accountability and assurance that the animal has been properly vaccinated. An animal is considered currently vaccinated if the primary vaccination was administered by a licensed veterinarian at least 28 days previously. Regardless of the age of the animal at initial vaccination, a second vaccination should be administered 1 year later. Because a rapid anamnestic (memory) response is expected, an animal is considered currently vaccinated immediately after a booster vaccination.

- **Dogs, Cats, and Ferrets**

All dogs, cats and ferrets are required by Alabama Law to be vaccinated against rabies. They should be vaccinated in accordance with the Code of the Alabama, Title 3. If a previously vaccinated animal is overdue for a booster, it should be revaccinated with a single dose of vaccine and placed on an interval in accordance with the vaccine's label.

- **Livestock**

Vaccinating all livestock against rabies is neither economically feasible nor justified from a public health standpoint. However, strong consideration should be given to vaccinating livestock that are particularly valuable or that might have frequent contact with humans, such as show animals or those in petting zoos. (For specific vaccines licensed for use in livestock, please see the Currently FDA Licensed Rabies Vaccines Section on page 43 of this Manual.) It is recommended that horses traveling interstate or with significant public contact (riding stables, etc.) should be currently vaccinated against rabies.

- **Other Animals**

- **Wild Animals**

No parenteral rabies vaccine is licensed for use in wild animals; therefore the ADPH does not recommend any wild animal be immunized against rabies. Additionally, because of the risk of rabies in wild animals (especially raccoons, skunks, coyotes, foxes, and bats), the Alabama Department of Conservation and Natural Resources has rigid regulations which prohibit the ownership of wild and wild/domestic hybrids as pets. For further information, please see www.dcnr.alabama.gov

- **Maintained in Exhibits and in Zoological Parks**

Captive animals that are not completely excluded from all contact with rabies vectors can become infected with rabies. Moreover, wild animals might be incubating rabies when initially captured; therefore, wild-caught animals susceptible to rabies should be placed in strict isolation for a minimum of 6 months before being exhibited. Employees who work with animals at such facilities should consider pre-exposure vaccination prophylaxis. The use of pre- or post-exposure rabies vaccinations for employees who work with animals at such facilities might reduce the need for euthanasia of captive animals. Carnivores and bats should be housed in a manner that precludes direct contact with the public.