

Human Rabies

According to the World Health Organization, worldwide there are over 50,000 cases of human rabies annually, with the majority, approximately 98%, of these cases occurring in Asia, primarily China and India, and approximately 1.5% in the American tropics. The predominance of cases are attributed to dog bites. Before canine rabies was controlled in the United States in the 1940s and 1950s, there were about 50 human rabies cases per year, most from dog bites. The last human rabies case in Kansas City was a 2 year old child in October 1933, and in Missouri, the last human case of rabies occurred in 1952 in Pulaski County. As the number of cases in dogs decreased, the number of human rabies cases also declined to the point that human rabies acquired indigenously in the United States now is rare. In addition to rabies contracted in the United States, there have been a number of persons, both United States citizens and immigrants, who were diagnosed in this country, but who acquired their infection elsewhere. Among the indigenously acquired cases, bats have been the source of infection for 25 (96%) of the 26 human rabies cases between 1990-2000. In none of these cases was medical treatment sought until the individual became symptomatic; monoclonal antibody studies of isolates from the victims revealed that the viruses were bat associated serotypes. The non-bite cases reported in the 1950s and 1970s were infections acquired through aerosols (naturally occurring and from laboratory accidents) and from corneal transplants.

Prevention

Two types of rabies immunizing products are available in the United States:

- ! Rabies vaccines that induce an active immune response including the production of neutralizing antibodies. This antibody response requires approximately 7-10 days to develop and usually persists \geq 2 years.
- ! Rabies immune globulins (RIG) provide a rapid, passive immunity that persists for

only a short time (half-life of approximately 21 days).

In all post-exposure prophylaxis regimens, except for persons previously immunized, both products should be used concurrently.

Table 3.1. Human Rabies Diagnosed in the United States, 1950-2000.

Decade	Source for Cases Acquired in United States				Acquired in Foreign Country
	Domestic Animal	Wild Animal	Unknown	Non-bite	
1950-1959	71	14	23	2	0
1960-1969	5	6	1	0	4
1970-1979	3	6	4	3	7
1980-1989	0	1	2	0	9
1990-1999	1	21	0	0	6
2000	0	4	0	0	1

Table 3.2. Rabies Biologics — United States, 2001.

Preparation	Product Name	Manufacturer
Human diploid cell vaccine (HDCV)	Imovax® Rabies	Aventis Pasteur Inc
Purified chick embryo cell vaccine (PCEC)	RabAvert™	Chiron Corporation
Rabies immune globulin (RIG)	Imogram® Rabies-HT	Aventis Pasteur Inc
	BayRab™	Bayer Corporation

The formulations of inactivated intramuscular rabies vaccines, when used as indicated,

are considered equally safe and efficacious. The potency of one dose is ≥ 2.5 international units (IU) per 1.0 ml of rabies virus antigen, which is the World Health Organization recommended standard. A full 1.0 ml dose can be used for both pre-exposure and post-exposure prophylaxis. Usually, an immunization series is initiated and completed with one vaccine product. No clinical studies have been conducted that document a change in efficacy or the frequency of adverse reactions when the series is completed with a second vaccine product.

The two RIG products are antirabies immunoglobulin preparations concentrated from plasma of hyperimmunized human donors. Rabies neutralizing antibody, standardized at a concentration of 150 IU per ml, is supplied in 2 ml (300 IU) vials for pediatric use and 10 ml (1,500 IU) vials for adult use; the recommended dose is 20 IU/kg body weight. Both RIG preparations are considered equally efficacious.

Pre-Exposure Vaccination

1. Vaccination candidates:

Pre-exposure vaccination should be offered to persons among high-risk groups, such as veterinarians, animal handlers, certain laboratory workers, and persons spending time, e.g., 1 month, in foreign countries where canine rabies is endemic (Table 3.4 and Table 3.5). Other persons whose activities bring them into frequent contact with rabies virus or potentially rabid dogs, cats, skunks, raccoons, bats, or other species at risk of having rabies also should be considered for pre-exposure prophylaxis.

The reason to consider pre-exposure rabies vaccination for travelers to foreign countries with high levels of endemic dog rabies is that surveys of such travelers find that >1% of them are bitten by dogs. Also, globally, there is a potpourri of rabies vaccines employed in post-exposure therapy, including many that have a poor profile of safety and efficacy. Semple-type vaccines that are made in sheep and goat brains remain the only or predominant vaccines used in some areas. The efficacy of Semple-

type vaccines is estimated to be 84%, even less in cases of severe bites. This is in contrast to an efficacy >99% for human diploid cell vaccine plus rabies immunoglobulin. Neuroparalytic events are reported in 1 in 230 to 1 in 6,000 persons receiving Semple-type vaccine, with 15-

Table 3.3. Percentage of Post-exposure Treatment Courses with Tissue Culture Vaccines

Region	%
Western Europe, United States	100
Middle East	70
Southeast Asia	70

25% of events ending in death. Furthermore, many foreign countries employed equine rabies immunoglobulin rather than human rabies immunoglobulin, however, the last remaining international manufacturer of that product discontinued its production in 2001. Also, globally, only 9% of persons undergoing post-exposure therapy receive rabies immunoglobulin of any type.

2. Primary Pre-exposure vaccination:

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

3. Precautions and Contraindications:

Three 1.0 ml injections of HDCV or PCEC should be given intramuscularly (deltoid area), one each on days 0, 7, and 21 or 28. Corticosteroids, other immunosuppressive agents, antimalarials, and immunosuppressive illnesses can interfere with

the development of active immunity after vaccination. For persons with immunosuppression, pre-exposure prophylaxis should be administered with the awareness that the immune response

If there is substantial risk of exposure to rabies, pre-exposure prophylaxis may be indicated during pregnancy.

might be inadequate. Persons who are immunosuppressed by disease or medications should postpone pre-exposure vaccinations and consider avoiding activities for which rabies pre-exposure prophylaxis is indicated. When this course is not possible, immunosuppressed persons who are at risk for rabies should be vaccinated and their antibody titers checked.

4. Pre-exposure Booster Vaccination:

Persons who work with live rabies virus in research laboratories or vaccine production facilities (continuous risk category) are at the highest risk of inapparent exposures. Such persons should have a serum sample tested for rabies antibody every 6 months. Booster doses of vaccine should be given to maintain a serum titer corresponding to at least complete neutralization at a 1:5 serum dilution by the rapid fluorescent focus inhibition test (RFFIT). The frequent risk category includes other laboratory workers, such as those doing rabies diagnostic testing, spelunkers, veterinarians and staff, animal control and wildlife officers in areas where animal rabies is epizootic, and

Table 3.4. Rabies Pre-Exposure Prophylaxis Schedule		
Type of vaccination	Route	Regimen
Primary	IM	HDCV or PCEC, 1.0 ml (deltoid area), one each on days 0, 7, and 21 or 28
Booster*	IM	HDCV or PCEC, 1.0 ml (deltoid area), day 0 only

* Administration of routine booster dose of vaccine depends on exposure risk category as noted in Table 3.5.

Table 3.5. Rabies Pre-Exposure Prophylaxis Guide

Risk category	Nature of risk	Typical populations	Pre-exposure recommendations
Continuous	Virus present continuously, often in high concentrations. Aerosol, mucous membrane, bite, or non-bite exposure. Specific exposures may go unrecognized.	Rabies research laboratory worker; rabies biologic production workers.	Primary course. Serologic testing every 6 months; booster vaccination when antibody level falls below 1:5 by RFFIT.
Frequent	Exposure usually episodic, with source recognized, but exposure also may be unrecognized. Aerosol, bite or nonbite exposure	Rabies diagnostic laboratory workers, spelunkers, veterinarians and staff, and animal control and wildlife workers in rabies enzootic areas.	Primary course. Serologic testing every 2 years; booster vaccination when antibody level falls below 1:5 by RFFIT.
Infrequent (greater than population at large)	Exposure nearly always episodic with source recognized. Bite or nonbite exposure.	Veterinarians and animal control and wildlife workers in areas with low rabies rates. Veterinary students. Travelers visiting foreign areas of enzootic rabies and immediate access to appropriate medical care including biologicals is limited.	Primary course; no serologic testing or booster vaccination.
Rare (population at large)	Exposures always episodic with source recognized. Bite or nonbite exposure.	United States population at large, including persons in rabies epizootic areas.	No vaccination necessary.

international travelers living or visiting, for greater than 30 days, in areas where canine rabies is endemic. Persons among this group should have a serum sample tested for

rabies antibody every 2 years and, if the titer is less than complete neutralization at a 1:5 serum dilution by the RFFIT, should have a booster dose of vaccine. Alternatively, a booster dose can be administered in lieu of a titer determination. Veterinarians and animal control and wildlife officers working in areas with low rabies rates (an infrequent exposure group) do not require routine pre-exposure booster doses of HDCV or PCEC after completion of primary pre-exposure vaccination.

5. Serologic Testing:

It is not necessary to test serum samples from persons completing pre-exposure prophylaxis to document seroconversion unless the person is immunosuppressed. If titers are obtained, specimens collected 2-4 weeks after pre-exposure prophylaxis should completely neutralize challenge virus at a 1:5 serum dilution by RFFIT. Two years after primary pre-exposure vaccination, a 1:5 serum dilution will fail to neutralize challenge virus completely among 2-7% of persons who received the three-dose pre-exposure series intramuscularly and 5%-17% of persons who received the three-dose series intradermally (intradermal rabies vaccine was discontinued in 2001). If the titer falls below 1:5, a pre-exposure booster dose of vaccine is recommended for a person at continuous or frequent risk of exposure to rabies. A person in the continuous risk category should have a serum sample tested for rabies antibody every 6 months. A person in the frequent risk category should have a serum sample tested for rabies antibody every 2 years or receive a booster dose.

Serologic testing is available through the Kansas State University, College of Veterinary Medicine Rabies Laboratory, Manhattan, KS. Two types of RFFIT testing are available — screening test and endpoint test. In the screening test, serum is diluted 1:5 and 1:50 and results reported as <1:5, >1:5, or >1:50. In the endpoint test, serum is initially diluted at 1:5 and then in 5-fold increments until an endpoint is reached. Approximately 2 ml of serum, without preservatives, is required for either test, and the cost varies by the test. Results are available within one week. To order a test, call the

laboratory (785) 532-4455 for instructions for shipping and payment, or visit the laboratory's WEB site at <http://www.vet.ksu.edu/depts/rabies/guideline.htm>.

Post-Exposure Prophylaxis

Administration of rabies post-exposure prophylaxis is a medical urgency, not a medical emergency. Physicians should evaluate each possible exposure to rabies and, if necessary, consult with the Kansas City Health Department (816-513-6152) regarding the need for rabies prophylaxis. The likelihood of rabies infection varies with the nature and extent of exposure. In deciding whether to administer treatment to persons who may have been exposed to rabies, it should be determined whether an exposure occurred and the risk that the animal was rabid. The likelihood of rabies infection varies with the nature and extent of exposure.

An exposure is a bite (penetration of the skin by teeth) by an animal or human, contamination of an open wound or mucous membrane with saliva or infected tissue from a rabid animal or human, or similar contact with live rabies virus in a laboratory. Bites by some animals, such as bats, can inflict minor injury and be undetected. All bites by wild carnivores and bats must be considered possible exposures to rabies. Although exposures that do not involve a bite may allow a sufficient inoculum of rabies virus to come into contact with body tissues or mucous membranes, virtually all patients with rabies who recall contact with an animal report that they have been bitten.

Non-bite exposures rarely cause rabies. The non-bite exposures of highest risk appear to be exposures to large amounts of aerosolized rabies virus, organs (e.g., corneas, transplanted from patients who died of rabies) and, *theoretically*, scratches by rabid animals. Cases of rabies after scratches, abrasions, or the licking of open wounds are extremely rare, if they even occur. In fact, no person in the United States has been reported to have contracted rabies in this manner in at least the last 50 years. With the exception of eight cases of rabies caused by transplantation of corneas from donors

who died of undiagnosed rabies, and two non-laboratory diagnosed cases from Ethiopia, the transmission of rabies between humans has not been documented. Petting a rabid animal, touching a rabid human, or coming into contact with the blood, urine, or feces of a rabid animal does not constitute an exposure and does not require prophylaxis. Because rabies virus is inactivated by desiccation and ultraviolet irradiation, in general, if the material containing the virus is dry, the virus can be considered noninfectious.

A decision to initiate treatment is next based on the likelihood that the exposing animal was rabid (Tables 3.6 to 3.8). However, physicians may be pressured to administer post-exposure prophylaxis even when such treatment is not indicated, particularly when a rabies epizootic is occurring. In these situations, a detailed history of a person's interactions with the animal is important, as well as whether the animal is available for observation or testing before making a decision about treatment.

Laboratory confirmed cases of rabies among wild animals, especially skunks, raccoons, and bats, have become more prevalent since the 1950s, accounting for greater than 85% of all reported cases of animal rabies every year since 1976. Rabies among animals occurs throughout the continental United States; only Hawaii remains consistently rabies free. Wild animals now constitute the most important potential source of infection for both humans and domestic animals in the United States. In much of the rest of the world, including most of Asia, Africa, and Latin America, the dog remains the major species with rabies and the major source of rabies for humans. Post-exposure prophylaxis should be initiated when patients are exposed to wild carnivores unless 1) the exposure occurred in a part of the continental United States known to be free of terrestrial rabies and the results of immunofluorescence antibody testing will be available within 48 hours, or 2) the animal has already been tested and shown not to be rabid. If treatment has been initiated and subsequent immunofluorescence testing shows that the exposing animal was not rabid, treatment

can be discontinued.

Contact with bats, however, presents a deviation from the post-exposure logic used with other animals. This is because of the most recent 26 human rabies deaths resulting from bat-associated strains of rabies, a history of a bat bite was known in only two cases. Consequently, it is recommended that post-exposure prophylaxis be considered when direct contact between a human and a bat has occurred, unless the exposed person can be certain a bite, scratch or mucous membrane exposure did not occur. In instances in which a bat is found indoors and there is no history of bat-human contact, the likely effectiveness of post-exposure prophylaxis must be balanced against the low risk such exposures appear to present. In this setting, post-exposure prophylaxis can be considered for persons who were in the same room as the bat and who might be unaware that a bite or direct contact had occurred, e.g., a sleeping person awakens to find a bat in the room or an adult witnesses a bat in the room with a previously unattended child, mentally disabled person, or intoxicated person, and rabies cannot be ruled out by testing the bat. Post-exposure prophylaxis would not be warranted for other household members. Therefore, it is extremely important that there is prudent evaluation of exposure incidents, as it has been estimated that vaccine costs alone to prevent a single case of rabies from true exposure to a rabid bat in a state with a low prevalence of rabies would be \$180 million if all bat "contacts" resulted in post-exposure treatment.

Signs of rabies among carnivorous wild animals cannot be interpreted reliably; therefore, any such animal that bites or scratches a person should be killed at once, without unnecessary damage to the head, and the brain submitted for rabies testing. If the results of testing are negative by immunofluorescence, the saliva can be assumed to contain no virus, and the person bitten does not require treatment.

Rodents, such as squirrels, hamsters, guinea pigs, gerbils, chipmunks, rats, mice, and

lagomorphs (rabbits and hares), are almost never found to be infected with rabies and have not been known to cause rabies among humans in the United States. Persons bitten when handling or feeding such animals probably do not need rabies prophylaxis, however, highly unusual behavior by the animal and a totally unprovoked attack should warrant consideration of rabies prophylaxis. The Missouri Department of Health will not test rodents or lagomorphs for rabies without the authorization of the State Public

Table 3.6. Rabies Post-Exposure Prophylaxis Guide

Animal type	Evaluation and disposition of animal	Post-exposure prophylaxis recommendation
Dogs, cats and ferrets	Healthy and available for 10 days of observation	Should not begin prophylaxis unless the animal develops signs of rabies.*
	Rabid or suspected rabid	Immediate vaccination
	Unknown (escaped)	Consult Kansas City Health Dept.
Skunks, raccoons, foxes and other carnivores; bats	Regard as rabid unless geographic area is known to be free of rabies or until animal proven negative by laboratory tests.**	Immediate vaccination
Livestock, small rodents, lagomorphs (rabbits and hares), large rodents (woodchucks and beavers), and other mammals	Consider individually.	Consult Kansas City Health Dept. Bites of squirrels, hamsters, guinea pigs, gerbils, chipmunks, mice, rats, other rodents, rabbits, and hares almost never require antirabies treatment.
<p>* During the 10 day holding period, begin treatment with RIG and HDCV or PCEP at first sign of rabies in a dog or cat that has bitten someone. The symptomatic animal should be killed immediately and tested.</p>		
<p>** The animal should be killed and tested as soon as possible. Holding for observation is not recommended. Discontinue vaccine if immunofluorescence test results of the animal are negative.</p>		

Health Veterinarian. Therefore, the Kansas City Health Department (816-513-6152) should be consulted before a decision is made to initiate post-exposure antirabies prophylaxis or request that a rodent or lagomorph be examined for rabies.

Table. 3.7. Algorithm for Rabies Prophylaxis Following Exposure to a Domestic Animal (Dog, Cat, Ferret or Livestock); Crosses Between Domestic and Wild Species are Considered Wild Animals.

Was the animal a dog, cat or ferret?	<u>No</u>	Risk of rabies is very low; prophylaxis probably not warranted; evaluate each situation individually.
Yes		
Was the attack unprovoked?	<u>No</u>	Risk of rabies is very low; prophylaxis probably not warranted; evaluate each situation individually.
Yes		
Was the skin penetrated by the animal's teeth?	<u>No</u>	Risk of rabies is very low; prophylaxis probably not warranted; evaluate each situation individually.
Yes		
Is the animal available for observation?	<u>No</u>	Initiate prophylaxis; stop if the animal can be reliably observed to be healthy 10 days or more after incident (day 1); if the animal is dead base prophylaxis decision on laboratory examination of the brain.
Yes		
Did the animal develop signs of rabies or die during the observation period?	<u>No</u>	Prophylaxis not required; stop if already initiated.
Yes		
Initiate prophylaxis and submit head for rabies examination.		
Was the laboratory test positive for rabies?	<u>No</u>	Stop prophylaxis.
Yes		
Complete prophylactic series.		

Exotic pets and domestic animals crossbred with wild animals are considered wild animals by the National Association of State Public Health Veterinarians and the Conference of State and Territorial Epidemiologists because they may be highly susceptible to rabies and could transmit the disease. Because the period of rabies

Table. 3.8. Algorithm for Rabies Prophylaxis Following Exposure to a Wild Animal or Wild Animal/Domestic Animal Cross, or Small Mammals Sold as Pets.

<p>The animal was not a rodent (other than woodchuck) or lagomorph (rabbit/hare).</p>	<p><u>No</u></p>	<p>Unless highly bizarre circumstances surround the incident, rabies prophylaxis is not warranted for contact with rodents or lagomorphs.</p>
<p> Yes</p>		
<p>Was the attack unprovoked?</p>	<p><u>No</u></p>	<p>Risk of rabies is very low; prophylaxis probably not warranted; evaluate each situation individually.</p>
<p> Yes</p>		
<p>Was the skin penetrated by the animal's teeth?</p>	<p><u>No</u></p>	<p>Risk of rabies is very low; prophylaxis probably not warranted; evaluate each situation individually.</p>
<p> Yes</p>		
<p>Was the animal captured or killed and is the brain available for laboratory examination?</p>	<p><u>No</u></p>	<p>Consider rabid if both conditions are not met; there is no observation period for a wild animal or a wild/domestic cross; initiate and complete rabies prophylaxis.</p>
<p> Yes</p>		
<p>Initiate prophylaxis until laboratory result is back.</p>		
<p> </p>		
<p>Was the laboratory result positive for rabies?</p>	<p><u>No</u></p>	<p>Stop prophylaxis.</p>
<p> Yes</p>		
<p>Complete prophylactic series.</p>		

virus shedding in these animals is unknown, these animals should be killed and tested rather than confined and observed when they bite humans. Wild animals, skunks, raccoons, and bats, and wild animals crossbred with dogs should not be kept as pets. If an exotic pet or

The last rabid dog in Kansas City was prior to 1955. However, six (6) rabid cats have been diagnosed since 1955; the most recent three having been in 1975, 1978 (vaccine-induced case), and 1980. Rabid dogs have been found near Greenwood, Jackson Co., and Platte City, Platte Co., as recently as 1980.

crossbreed has been vaccinated against rabies, the vaccination history should be dismissed and the animal considered as unvaccinated. Failure of vaccines to protect against rabies have been documented in a number of species.

The likelihood that a domestic animal is infected with rabies varies by region, hence, the need for post-exposure prophylaxis also varies. In the continental United States, rabies among dogs is reported most commonly along the United States-Mexico border and sporadically from the areas of the United States with enzootic wildlife rabies, especially the Midwest. During the past 20 years in the United States, more cats than dogs were reported rabid; the majority of these cases were associated with the mid-Atlantic epizootic of rabies among raccoons. The large number of rabies infected cats may be attributed to fewer cat vaccination laws, fewer leash laws, and the roaming habits of cats. Cattle, horses and other livestock tend to be most often exposed to rabies via rabid skunks.

In areas where canine rabies is not enzootic, including virtually all of the United States and its territories, a healthy domestic dog, cat or ferret that bites a person should be confined and observed for 10 days. Any illness in the animal during confinement or before release should be evaluated by a veterinarian and reported immediately to the Kansas City Health Department (816-513-6152). If signs suggestive of rabies develop, the animal should be humanely killed and its head removed and shipped, under

refrigeration, for examination by the Missouri Department of Health. Any stray or unwanted dog, cat or ferret that bites a person should be killed immediately and the head submitted as described for rabies examination.

In most developing countries of Asia, Africa, and Central and South America, dogs are the major vector of rabies; exposures to dogs in such countries represent a special threat. Although dogs are the main reservoir of rabies in these countries, the epizootiology of the disease among animals differs sufficiently by region or country to warrant the evaluation of all animal bites. Exposures to dogs in canine rabies enzootic areas outside the United States carry a high risk; some authorities therefore, recommend that post-exposure rabies treatment be initiated immediately after such exposures.

An unprovoked attack by a domestic animal is more likely than a provoked attack to indicate that the animal is rabid. Bites inflicted on a person attempting to feed or handle an apparently healthy animal should generally be regarded as provoked. A fully vaccinated dog, cat or ferret is unlikely to become infected with rabies, although rare cases have been reported. In a nationwide study of rabies among dogs and cats in 1988, only one dog and two cats that were vaccinated contracted rabies. All three of these animals had received only single doses of vaccine; no documented vaccine failures occurred among dogs or cats that had received two vaccinations.

1. Local Treatment of Wounds

The essential components of rabies post-exposure prophylaxis are local wound treatment and the administration, in most instances, of both RIG and vaccine (Table 3.9). Persons who have been bitten by animals suspected or proven rabid should begin treatment within 24 hours. According to the Centers for Disease Control and Prevention, incubation periods of >1 y have been reported in humans, thus when a documented or likely exposure has occurred, post-exposure prophylaxis is indicated

regardless of the length of the delay, provided clinical signs of rabies are not present. Immediate and thorough washing of all bite wounds and scratches with soap and water and a virucidal agent such as povidone-iodine solution irrigation are important measures for preventing rabies. In studies of animals, simple local wound cleansing has been shown to reduce markedly the likelihood of rabies. Tetanus prophylaxis and measures to control bacterial infection should be given as indicated. The decision to suture large wounds should take into account cosmetic factors and the potential for bacterial infections.

2. Vaccination

Post-exposure antirabies vaccination should always include administration of both passive antibody and vaccine, with the exception of persons who have previously received complete vaccination regimens, pre-exposure or post-exposure, with a cell culture vaccine, or persons who have been vaccinated with other types of vaccines and have had documented rabies antibody titers. The combination of RIG, local and systemic, and vaccine is recommended for both bite and non-bite exposures regardless of the interval between exposure and initiation of treatment.

A regimen of one dose of RIG and five 1 ml doses of HDCV or PCEC over a 28 day period is safe and induces an excellent antibody response in all recipients. The first dose of the five-dose course should be given as soon as possible after exposure. Additional doses should be given on days 3, 7, 14, and 28 after the first vaccination. For adults, the vaccine should always be administered IM in the deltoid area. For children, the anterolateral aspect of the thigh is also acceptable. The gluteal area should never be used for HDCV or PCEC injections, since administration in this area results in lower neutralizing antibody titers.

RIG is administered only once, i.e., at the beginning of antirabies prophylaxis, to provide immediate antibodies until the patient responds to HDCV or PCEC. If RIG was

not given when vaccination was begun, it can be given through the 7th day after administration of the first dose of vaccine. Beyond the 7th day, RIG is not indicated since an antibody response is presumed to have occurred. The recommended dose of RIG is 20 IU/kg. This formula is applicable for all age groups, including children. If anatomically feasible, up to one-half the dose of RIG should be thoroughly infiltrated in the area around the wound and the rest should be administered intramuscularly in the gluteal area. RIG should never be administered in the same syringe or into the same

Table 3.9. Rabies Post-Exposure Prophylaxis Schedule

Vaccination status	Treatment	Regimen (applicable for all age groups, including children)
Not previously vaccinated	Local wound cleansing	All post-exposure treatment should begin with immediate cleansing of all wounds with soap and water. If available, a virucidal agent such as povidone-iodine solution should be used to irrigate wounds.
	RIG	20 IU/kg body weight. If anatomically feasible, the full dose should be infiltrated around the wound(s) and any remaining volume should be administered IM at an anatomical site distant from vaccine administration. Also, RIG should not be administered in the same syringe as vaccine. Because RIG might partially suppress active production of antibody, no more than the recommended dose should be given.
	Vaccine	HDCV or PCEC 1.0 ml, IM (deltoid area*), one each on days 0, 3, 7, 14, and 28.
Previously vaccinated	Local wound cleansing	Same as above.
	RIG	RIG should not be administered.
	Vaccine	HDCV or PCEC, 1.0 ml, IM (deltoid area), one each on days 0 and 3

* The deltoid is the only acceptable site of vaccination for adults and older children. For younger children, the outer aspect of the thigh may be used. Vaccine should never be administered in the gluteal area.

anatomical site as vaccine. Because RIG may partially suppress active production of antibody, no more than the recommended dose should be given.

If exposed to rabies, persons previously vaccinated should receive two IM doses (1.0 ml each) of vaccine, one immediately and one 3 days later. Previously vaccinated refers to persons who have received one of the recommended pre-exposure or post-exposure regimens of HDCV or PCEC, or those who received another vaccine and had a documented rabies antibody titer. RIG is unnecessary and should not be given in these cases because an anamnestic antibody response will follow the administration of a booster regardless of the pre-booster antibody titer.

3. Accidental Injection with Animal Rabies Vaccines

Accidental inoculation of veterinary personnel may occur while administering animal rabies vaccines. All of the commercially available vaccines in the United States are inactivated products. Therefore, accidental inoculation constitutes no rabies hazard. The only “live” rabies vaccines for animals are oral products that are restricted to state and federal rabies control programs and contain rabies glycoprotein with a live vaccinia vector.

4. Adverse Reactions and Contraindications

Because of the potential consequences of inadequately treated rabies exposure, and because there is no indication that fetal abnormalities have been associated with

Once initiated, rabies prophylaxis should not be interrupted or discontinued because of local or mild systemic adverse reactions to rabies vaccine.

rabies vaccination, pregnancy is not considered a contraindication to post-exposure prophylaxis.

Reactions after vaccination with HDCV or PCEC are less serious

and common than with previously available vaccines. Once initiated, rabies prophylaxis

should not be interrupted or discontinued because of local or mild systemic adverse reactions. Usually such reactions can be successfully managed with antiinflammatory and antipyretic agents. 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 physician. A patient's risk of acquiring rabies must be carefully considered before deciding to discontinue vaccination.

Immunosuppressive agents should not be administered during post-exposure therapy unless essential for the treatment of other conditions. When post-exposure prophylaxis is administered to an immunosuppressed person, it is especially important that a serum sample be tested for rabies antibody to ensure that an acceptable antibody response has developed.

5. Serologic Testing

Because the antibody response after the recommended post-exposure vaccination regimen with HDCV or PCEC has been satisfactory, routine post-vaccination serologic testing is not recommended. Serologic testing is only indicated in unusual instances, as when the patient is known to be immunosuppressed.

Incubation, Symptoms and Diagnosis

1. Incubation Period

The incubation period for rabies in humans is usually 2 to 8 weeks, occasionally as short as 5 days or as long as a year or more. However, incubation periods less than 15

days or more than 1 year are highly unusual. In most of the reported cases with long incubation periods, the possibility of a second rabies exposure during the incubation period could

Rabies is a reportable disease. Therefore, suspected or confirmed cases of human rabies should be reported immediately to the Kansas City Health Department at (816) 516-6152.

not be ruled out. The length of the incubation period is dependent upon the severity of the wound, site of the wound in relation to the richness of the nerve supply and its distance from the brain, the amount of virus introduced, protection provided by clothing, and other factors.

2. Symptoms

During the incubation period the person usually is entirely well except for symptoms related to local wound healing or post-exposure treatment. The first symptoms of clinical rabies are usually malaise, anorexia, fatigue, headache and fever. In about half of the individuals neuritic type pain or paresthesias are present at the site of exposure, and these local symptoms often precede the non-specific symptoms by 1-4 days. When the local complaints are absent the prodrome may be entirely non-specific or apprehension, anxiety, agitation, irritability, nervousness, insomnia, or depression may be prominent.

Two to 10 days after onset of the prodromal symptoms, the patient develops objective signs of nervous system involvement usually including hyperactivity, disorientation, hallucinations, seizures, bizarre behavior, nuchal stiffness, or paralysis. In the majority of cases a period of marked hyperactivity develops lasting hours or days (furious rabies). The hyperactivity characteristically is intermittent and consists of periods of agitation, thrashing, running, biting, or other bizarre behavior lasting up to 5 minutes. These hyperactive episodes may occur spontaneously or be precipitated by tactile,

auditory, visual or olfactory stimuli. Between these episodes the patient usually is relatively lucid and cooperative, although often anxious. In more than half of the cases, attempts to drink during this period are followed by severe, painful spasms of the pharynx and larynx producing choking, gagging, and fear. Many of these individuals subsequently will exhibit hydrophobia, a psychic reaction to seeing water or other liquids which precipitates pharyngeal spasms. Other abnormalities which may be noted during this period of hyperactivity include fasciculations, particularly near the site of exposure, hyperventilation, hypersalivation, focal or generalized convulsions, and rarely priapism.

Unless the patient dies abruptly, paralysis gradually becomes the predominant problem and heralds the impending coma phase. The period of hyperactivity is not always dramatic, however, and in about 5-20% of cases paralytic symptoms dominate the entire clinical course. The paralysis may be diffuse and symmetrical, maximal in the bitten extremity, or ascend until there is respiratory paralysis.

During the acute neurologic phase the mental status gradually deteriorates from confusion to disorientation, stupor, and finally coma. There may be nuchal rigidity. The acute neurologic phase may last from 2-10 days, with longer durations in the paralytic forms, and ends with either an abrupt death, or with onset of coma. Throughout this period the clinical status continues to fluctuate, with periods of severe obtundation alternating with periods of relative normalcy.

The period of coma may last for hours or months. In the untreated cases the patient usually develops respiratory arrest shortly after onset of coma and expires. In cases aggressively treated, respiratory arrest may not occur, or the patient may live with assisted ventilation for prolonged periods after respiratory arrest. During the coma phase a variety of potentially fatal complications can develop.

In patients who develop signs of rabies encephalomyelitis, the prognosis remains virtually hopeless. As of this writing, only 3 documented cases of humans recovering from clinical rabies have been reported: a woman bitten by a rabid dog and vaccinated with suckling mouse brain vaccine; a boy bitten by a bat and vaccinated with duck embryo vaccine; and a laboratory worker who had received pre-exposure vaccination with duck embryo vaccine.

Diagnosis

The diagnosis of rabies is not difficult when a history of animal bite is elicited from a patient with clinical disease, but a history of probable exposure to rabies may not be obtained in up to 50% of cases in the United States. Thus, rabies should be considered in the differential diagnosis of any rapidly progressive encephalitic disease of suspected viral etiology regardless of the exposure history. Rabies encephalitis can be confirmed during life by immunofluorescence of skin and brain biopsies, but the corneal impression smear technique is too often falsely negative to be useful. Early in the illness, rabies virus can be isolated from saliva, brain, CSF, and even spun urine, but not from blood. The presence of rabies antibody in the CSF or serum is diagnostic of rabies encephalitis unless the patient has been vaccinated or given rabies immune globulin.

Infection Control Issues

Apart from corneal transplants, bite and non-bite exposures inflicted by infected humans could theoretically transmit rabies, but no such cases have been documented. Adherence to respiratory precautions will minimize the risk of airborne exposure. It is recommended that when rabies is being considered, strict isolation precautions be maintained. There also should be education of the employees about the risks of transmission in this setting, careful documentation of exposures, and adherence to the guidelines for post-exposure prophylaxis.

Anyone having direct contact with the patient should wear a gown, gloves, face mask, and goggles. Laboratorians should be warned that sputum and CSF may be infectious and that appropriate precautions should be taken. When the patient dies, the pathology department and funeral home similarly should be warned. Persons exposed to the patient's potentially infectious tissues or fluids should immediately wash the area with soap and water, which is perhaps the best prophylactic measure available.

If rabies has been proven in the patient, contacts should be asked to report possible exposures, and should be interviewed to determine if, in fact, an exposure occurred. The period of possible risk of transmission is not well defined, but should be assumed to the highest during the first three weeks of illness and to persist to the 5th week. Studies of the dog model suggest that the week before the onset of clinical illness should be considered to be a period of risk as well. Exposures for which prophylaxis might be recommended include: 1) bites, with penetration of the skin by teeth; 2) exposure to patient's saliva or other potentially infectious material in direct contact with mucous membranes or broken skin (cut, scratch, or abrasion); and, 3) scalpel nicks or needle sticks if the treatment was in contact with CSF, nervous tissue, ocular tissue, or internal organs. Exposures for which prophylaxis is unnecessary include those to potentially infectious material in direct contact with unbroken skin and any contact with blood, stool, or unspun urine. When post-exposure prophylaxis is recommended, it should be administered as described above.