

CLINICAL PRACTICE

Prophylaxis against Rabies

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This Journal feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the authors' clinical recommendations.

A six-month-old girl presents for a “well-baby” appointment in New Jersey. The mother is concerned about a dead bat she found in the child’s bedroom.

A Virginia businessman relaxing on his patio after work pulls a toy from his puppy’s mouth. He notices a dead raccoon within his fenced yard, where his puppy has been playing, and telephones you for advice.

You receive e-mail from a South American colleague, who has been bitten by a stray dog while jogging. She solicits your medical opinion.

How would you manage these situations?

THE CLINICAL PROBLEM

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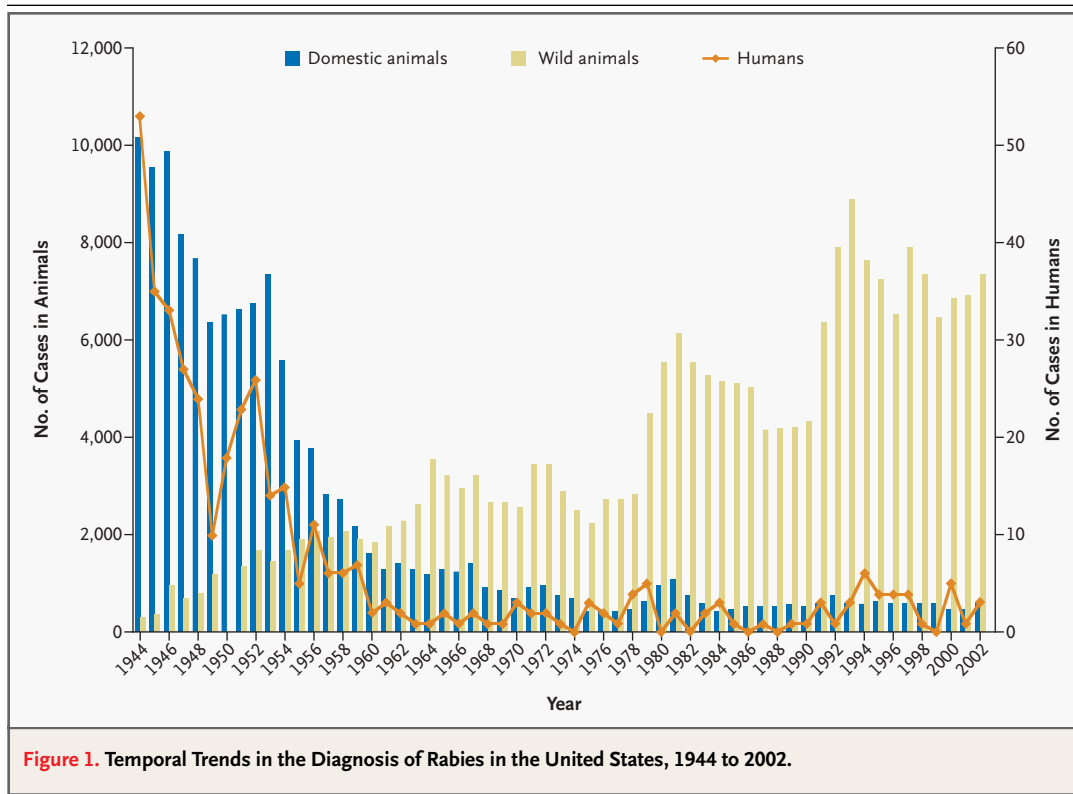
Human rabies is uncommon in developed nations.¹⁻⁵ In the United States, scores of deaths from rabies were documented annually in the early 20th century. Now, fewer than three deaths are reported each year, most without a documented exposure (Fig. 1 and Table 1). Still, this zoonosis exerts a disproportionate influence on health resources because of the necessity for prophylactic measures, including the administration of biologic agents. Continued apprehension is rooted in ancient superstitions, the dramatic manifestation of hydrophobia, and the extreme case fatality ratio. Cases of the disease in humans are preventable, but enzootic foci are plentiful and are not eliminated easily. The public may not appreciate that their surroundings are a veritable sea of rabies, maintained by common animals (Table 2).

Globally, dogs are the major reservoirs. Bites from rabid dogs cause tens of thousands of deaths per year and prompt prophylactic treatment in millions of persons.^{4,5} Recent assessments illustrate that the magnitude of rabies in developing countries is grossly underestimated.⁶ Exposures may occur as single events, or one rabid animal may expose multiple people.⁷ In the United States, 15,000 to 40,000 people receive prophylaxis annually.⁸

Prophylaxis is effective and safe, but it is expensive and is often used inappropriately.^{9,10} As with any pharmaceutical agent, minimal considerations when prophylactic measures are used include proper training, storage, handling, administration, infection-control precautions, and sterile technique.

NATURE OF THE INFECTION

Rabies is an acute progressive encephalitis caused by RNA viruses in the family Rhabdoviridae, genus lyssavirus.¹¹⁻¹⁴ Rabies virus is the only known lyssavirus in the New World. Some locations are considered rabies-free: among them are Hawaii and many islands in the Pacific Ocean and the Caribbean (except Cuba, the Dominican Republic,



Haiti, Grenada, and Puerto Rico).¹⁵ However, their continued freedom from rabies depends on effective methods to prevent introduction of the virus and depends on active laboratory-based surveillance.

All mammals are susceptible and can transmit rabies virus, but true reservoirs, which are responsible for ultimate long-term disease maintenance, persist only among Carnivora (mainly carnivorous mammals) and Chiroptera (bats).¹⁵ Specific viruses are adapted to these hosts and typically perpetuate infection within a species before the hosts die. In North America, raccoons, skunks, bats, and foxes are the primary reservoirs responsible for transmission (Table 2). Unvaccinated domestic animals and humans become rabid after exposure to such reservoirs. By definition, all reservoirs are capable of transmitting infection, but not all potential vectors are reservoirs. For example, livestock die of the disease without effective prolonged transmission. Cats (usually infected by dogs or wild animals) are effective vectors but do not sustain the disease.

In developed countries, the incidence of human exposure to rabid domestic animals has decreased as a result of improved canine vaccination.¹⁶ Whereas more than 9000 rabid dogs were reported in the

United States in 1944, fewer than 100 were reported in 2002.¹⁵ Because cats are popular but less well supervised and less often vaccinated than dogs, rabid cats now outnumber rabid dogs. Rabies in small mammals (such as mice and squirrels) is rare, and transmission from them to humans remains undocumented.¹⁷ Larger rodents, like woodchucks, are more frequently reported to be rabid (Table 2).

TRANSMISSION

In nature, the rabies virus is labile; is inactivated by sunlight, heat, desiccation, and other environmental factors; and is not viable outside the host. Exposure occurs when there is penetration of the skin by teeth or direct transdermal or mucosal contact with infectious material, such as brain tissue or saliva. Almost all cases are caused by bites from infected mammals.

Lyssaviruses are highly neurotropic and travel by retrograde axoplasmic flow from the periphery to the central nervous system.¹⁸ Replication occurs primarily in neurons. There is passive, centrifugal movement from the brain to other organs or glands, such as the salivary glands. The virus is excreted abundantly in saliva. Excretion is concomitant with

Table 1. Sources of Human Exposure to Rabies in the United States.

Year	Domestic Animal*	Wildlife	Other Sources†	Unknown‡	Total No. of Cases
<i>number of cases (percent)</i>					
1946–1955	86 (72)	8 (7)	0	26 (22)	120
1956–1965	21 (55)	7 (18)	0	10 (26)	38
1966–1975	6 (38)	7 (44)	1 (6)	2 (12)	16
1976–1985	6 (30)	1 (5)	2 (10)	11 (55)	20
1986–1995	2 (12)	1 (6)	0	14 (82)	17
1996–2003	4 (19)	2 (10)	0	15 (71)	21

* After 1979, there were no cases involving documented exposure to a domestic animal known to be rabid or probably rabid. Thereafter, all cases originated in countries where canine rabies was endemic.

† Other sources of exposure included laboratory aerosol (in 1972 and 1977) and corneal transplantation (in 1978).

‡ If a definitive source of exposure was not identified in the patient's history, the source of exposure was considered to be unknown, regardless of the source suspected on the basis of antigenic or genetic characterization.

Table 2. Cases of Animal Rabies in the United States.

Animal*	Average No. of Cases, 1998–2002	Geographic Focus†
Raccoon	2962	Eastern United States
Skunk	2257	California, upper and lower Midwest, eastern United States
Bat	1175	Entire United States, except Hawaii
Fox	443	Alaska, Texas, southwestern United States
Cat	276	Entire United States, except Hawaii
Cattle	106	Entire United States, except Hawaii
Dog	105	Entire United States, except Hawaii
Horse or mule	62	Entire United States, except Hawaii
Mongoose	58	Puerto Rico
Woodchuck	50	Eastern United States
Bobcat	30	Entire United States, except Hawaii
Sheep or goat	9	Entire United States, except Hawaii
Other wild animal	24	Entire United States, except Hawaii
Other domestic animal	3	Entire United States, except Hawaii

* All mammals are considered to be susceptible to rabies, and incidental (or spillover) infection from wild-animal reservoirs may occur in any species.

† Rabies may occur in an exposed animal in any location; the geographic foci listed here are based on current epidemiologic trends. No cases of rabies have been reported in Hawaii or in American Samoa, the Commonwealth of the Northern Mariana Islands, Guam, or the U.S. Virgin Islands.

the development of clinical signs but may begin several days beforehand. The virus may be detected in practically any tissue.

According to experimental data and epidemiologic observations, some domestic species may be observed for signs of rabies. A healthy dog, cat, or ferret that exposes a person may be observed for 10 days.¹⁶ If the animal remains healthy, the patient does not need prophylaxis; only wound care is needed. If the animal sickens with signs compatible with rabies, it should be euthanized and the brain should immediately be examined. If infection is confirmed within 24 to 48 hours after the animal is euthanized, there is adequate time to begin prophylaxis. After exposure to wildlife in which rabies is suspected, prophylaxis is warranted in most circumstances. Vaccination is discontinued if tests of the animal's brain tissue are negative for infection.

STRATEGIES AND EVIDENCE

PROPHYLAXIS

Decisions regarding prophylaxis are complex: they depend on local epidemiology, the nature of the animal involved and its behavior, the degree of contact, and (when possible) the results of diagnostic testing. Procedures include treatment of the patient after exposure as well as vaccination of those at risk for exposure. Efficacy data for prophylaxis are generated by experiments in animals as well as clinical trials.¹⁹

Postexposure prophylaxis consists of three primary elements: wound care, infiltration of rabies immune globulin, and vaccine administration.²⁰ Immediate and thorough washing of wounds with a soap solution may considerably reduce the risk of contracting rabies.²¹ Other measures, such as the use of tetanus toxoid or antibiotics, are applied as needed.²² Decisions are urgent, because delays may affect the outcome. Postexposure prophylaxis is highly effective if applied appropriately. In the United States, no failures have been reported since 1979.^{1–3}

VACCINES

Three rabies vaccines are licensed in the United States. Table 3 summarizes their uses and potential adverse effects, which are generally minor.^{20,27–31} Serious reactions are infrequent³² and are less common with current cell-culture vaccines than with products derived from nerve tissue.³³ Although as-

Table 3. Biologic Agents Licensed in the United States for Human Rabies Prevention.*

Product	Dose	Route	Indications
Vaccines†			
RabAvert (Chiron Behring)‡	1 ml	Intramuscular	Preexposure or postexposure§
Rabies vaccine adsorbed (BioPort)¶	1 ml	Intramuscular	Preexposure or postexposure§
Imovax Rabies (Aventis Pasteur)‡	1 ml	Intramuscular	Preexposure or postexposure§
Human rabies immune globulins**			
BayRab (Bayer)	20 IU/kg	Local††	Postexposure only
Imogam Rabies-HT (Aventis Pasteur)	20 IU/kg	Local††	Postexposure only

* Adverse reactions include pain, erythema, swelling, or induration (in 15 to 74 percent of recipients); itching or local lymphadenopathy; headache, malaise, myalgia, or dizziness (10 to 25 percent); gastrointestinal symptoms (in less than 10 percent); allergic reactions during primary vaccination (in 0.1 percent [less than 10 percent of whom have anaphylactic reactions]); type III hypersensitivity reactions (in 6 to 10 percent after booster doses of human diploid cell vaccine and in fewer during primary vaccination).²³⁻²⁶ Precautions should be taken if a serious allergic reaction has been documented after previous administration of a product or component.

† The vaccines are inactivated with beta-propiolactone. Additives (e.g., polygeline) or residual substances used during the manufacturing process (e.g., antibiotics) may be present.

‡ This vaccine is a lyophilized preparation.

§ For postexposure prophylaxis, the vaccine is administered on days 0, 3, 7, 14, and 28 in patients who have not previously been vaccinated and on days 0 and 3 in patients who have been previously vaccinated; for preexposure prophylaxis, the vaccine is administered on days 0, 7, and 21 or 28.

¶ This vaccine is currently not available.

|| Imovax Rabies I.D., given by the intradermal route, is no longer available in the United States.

** Human rabies immune globulins are purified from the serum of vaccinated donors. Historically, licensed human rabies immune globulins in the United States have been safe. No human infection with adventitious agents has been documented.

†† As much of the product as is anatomically feasible is infiltrated into and around the wound, and any remainder is administered intramuscularly, in the deltoid or quadriceps (at a location other than that used for vaccine inoculation, to minimize potential interference).

sociations have been reported between current vaccines and cases of neurologic illness, causality has not been established.³⁴⁻³⁹

When possible, the same product is used for an entire vaccine series. Switching to another product is reasonable if sensitivity to a vaccine or its components develops between doses, although follow-up data are limited.^{20,40} Prophylaxis should not be discontinued after the development of local or mild systemic signs.

Modern cell-culture vaccines are potent, but the immunity they afford eventually wanes. After primary vaccination, additional doses are needed after known exposures or as part of routine maintenance of the antibody titer in persons deemed at risk (as discussed below). When booster doses of vaccine are given, complex anamnestic responses occur: they include the stimulation and deployment of existing memory T cells, the differentiation of memory B cells into antibody-secreting cells, elicitation of additional memory B cells, and replenishment of antigen depots at lymphoid germinal centers.

HUMAN RABIES IMMUNE GLOBULIN

Passive administration of virus-neutralizing antibodies, before a patient mounts an active immune response from vaccination, is an important part of postexposure prophylaxis.²⁰ For patients who have not been vaccinated, human rabies immune globulin is administered only once, concomitantly with vaccine. When there is a visible wound, as much of the dose as is feasible is infiltrated directly into the wound (Table 3). The expense and limited distribution of human rabies immune globulin, however, are problems in the developing world.⁴ Equine rabies immune globulin may be an alternative. Multi-site intradermal vaccination is another possible strategy to accelerate the immune response.

As compared with unpurified or heterologous serum, modern commercial preparations of human rabies immune globulin are highly safe and are not associated with the acquisition of disease. Human blood products can contain antibodies to other agents and may inhibit immune responses to non-inactivated viral vaccines. Interference depends

on the amount of specific antibody. Administration of vaccines such as measles and varicella vaccines should be delayed for at least four months after postexposure prophylaxis to allow the degradation of human rabies immune globulin.^{41,42} If the interval is shorter, additional vaccination may be necessary, unless serologic testing indicates that the immunologic response has been appropriate.

PREEXPOSURE VACCINATION

It is recommended that vaccination be provided to persons at risk (laboratory workers, diagnosticians, veterinarians and their staff, animal-control officers, rabies researchers, and some travelers to areas where rabies is prevalent) before exposure.²⁰ This strategy simplifies the management of a subsequent exposure because fewer doses are needed and because human rabies immune globulin is not required (Table 3). To avoid injury to sciatic nerves and lessen the delivery to adipose depots, it is recommended that the gluteal region not be used for administration.⁴¹ Routine serologic analysis for verification of the presence of virus-neutralizing antibody is unnecessary after primary vaccination, unless major interruptions in the schedule occur or questions arise about immune competence. Thereafter, the need for routine booster vaccination may be monitored by serologic testing performed every six months to two years as long as a person remains at risk. If titers fall below a minimal acceptable level (i.e., complete neutralization at a serum dilution of 1:5), a single vaccine booster is administered. Healthy adults maintain adequate titers for years. No absolute protective level exists, and two booster doses are administered as part of postexposure prophylaxis, regardless of titer. Antibodies are important but are only one means of preventing a productive viral infection. More short-lived immune functions, such as cytokine responses, are reinvigorated in response to vaccination.

AREAS OF UNCERTAINTY

BATS AND RABIES

"Cryptic" human cases, in which there is no history of exposure to a rabid animal, are now the norm in the United States (Table 1). Molecular characterization has determined that the majority of these cases are associated with bat rabies viruses.⁴³ Bat bites are not dramatic and may not be appreciated when they occur or when the patient is examined (Fig. 2). In other cases, people may recognize that a

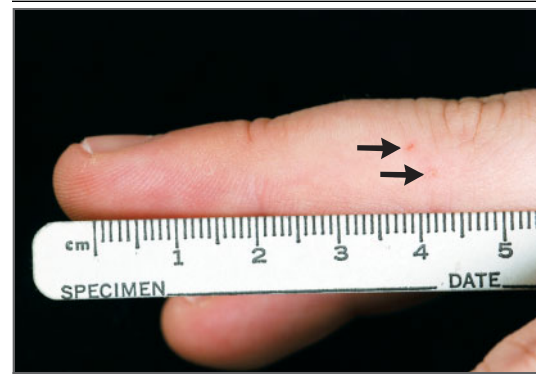


Figure 2. Bat Bite (Arrows) on the Finger.

The bite occurred in a 23-year-old man as he handled a bat.

bite has occurred but may not comprehend its implications⁴⁴ or may believe that the risk of rabies is exceedingly low.⁴⁵ Certain persons, such as young children or persons with disabilities, may be unable to provide an accurate history of a bite. When in doubt, attempts should be made to capture animals safely for submission to a laboratory.

Rabies is not commonly reported in free-ranging bats (estimated frequency, less than 1 percent, according to field surveillance) and is diagnosed in approximately 5 to 15 percent of bats submitted for public health evaluation. If test results are negative, postexposure prophylaxis is unnecessary. As with wild-carnivore bites, prophylaxis should begin if the bat is unavailable for examination.²⁰ Once the risks have been explained, many patients without a definitive exposure (such as healthy adults who are light sleepers or who had body parts covered and would have detected a bat bite) may elect to forgo postexposure prophylaxis.

EXPOSURES OTHER THAN BITES

Since 1960, exposures other than bites have resulted in fewer than 35 well-documented human cases.⁴⁶ Most of the reported cases were due to poorly inactivated vaccine (in 18 instances) or transplantation (in 12). Although extremely uncommon, transplantation of tissue from a donor with rabies will have disastrous consequences for the transplant recipient, as has recently been described.⁴⁷ No cases in humans after indirect, nonbite exposure, such as touching a pet that may have been exposed to a rabid animal, have been reported. Theoretically, human-to-human transmission is possible, but no cases have been documented among health care

workers. Barrier procedures and personal-protection equipment minimize the risk of true exposure.

Many circumstances, though fueled by fear, are not indications for prophylaxis. The medical care of a patient with rabies can cause anxiety on the part of the clinician because of the voluminous production of saliva and the opportunity for unnoticed exposure. Often, postexposure prophylaxis is entertained because the threat of disease is erroneously considered to be greater than unanticipated risks of vaccination. *Primum non nocere*: if the benefits do not outweigh the risks, postexposure prophylaxis should not be performed.

SCHEDULES AND DELAYS

Clinicians should adhere to prophylaxis schedules. Deviations of a few days are unimportant, but the effect of lapses lasting weeks or months is unknown. Most deviations will not require complete reinitiation of vaccination.⁴¹ For example, if a patient who had begun postexposure prophylaxis missed the dose scheduled for day 14 and attended a clinic visit on day 21, vaccination may be continued with administration of doses at intervals as if the patient had been on schedule. When in doubt, the patient's immune status may be monitored by serologic testing 7 to 14 days after the final dose is given.²⁰

Prophylaxis should be instituted whenever exposure is suspected, and it is warranted regardless of the interval between exposure and presentation. Delays in initiating prophylaxis are associated with treatment failure.⁴⁸ Typical incubation periods are between one and three months¹⁻³; in rare cases, incubation periods are less than two weeks or exceed one year.^{49,50} The extent of delay that renders postexposure prophylaxis ineffective is not known.⁵¹

TRAVEL

Rabies vaccination is not warranted for most routine international travel.⁵² Business ventures lasting several days are unlikely to pose a substantive risk. If an exposure does occur, timely access to proper care can be sought on the traveler's return. Concerns related to the rise in ecotourism are minimized by careful planning, tempered with common sense. Minimally, all travelers should receive education about rabies and refrain from contact with animals. Modern biologic agents are not readily available in developing countries. Regardless of the duration of travel, if the location and activity are such that contact with animals is probable but opportunities for intervention are unlikely (especially

in the case of travel to a remote region where rabies is endemic), preexposure vaccination should be encouraged.²⁰ Guidelines related to travel are available from the Centers for Disease Control and Prevention (www.cdc.gov/travel/diseases/rabies.htm).

PREGNANCY

Specific testing of reproductive outcomes has not been performed, but pregnancy is not a contraindication to postexposure prophylaxis against rabies. Vaccination has not been associated with adverse outcomes.⁵³ Prophylaxis is appropriate after exposure to protect the life of the mother and the fetus. Exposure, or the diagnosis of rabies in the mother, is not an indication for termination of the pregnancy.

TREATMENT

Once symptoms begin, treatment is largely futile. Patients usually die within days to weeks after presentation. Historically, five patients who survived represent unusual occurrences and received some form of prophylaxis before onset. Diagnosis by detection of virus, antigen, antibodies, or nucleic acid in the patient's saliva, tissues, serum, or cerebrospinal fluid warrants attempts to treat,⁵⁴ although management is essentially palliative. Experimental trials have included rabies immune globulin, interferon, and ribavirin, without beneficial effect.⁴⁵

GUIDELINES

The Advisory Committee on Immunization Practices (ACIP) publishes routine protocols for prevention of human rabies in the United States (www.cdc.gov/nip/publications/acip-list.htm).²⁰ The information presented in this article is consistent with the ACIP guidelines. The recommendations of the American Academy of Pediatrics are in accord with those of the ACIP; vaccine doses during postexposure prophylaxis are equivalent in adults and children.⁵⁵ The National Association of State Public Health Veterinarians regularly issues a compendium of recommendations for the prevention and control of rabies in animals.¹⁶ As a barrier to human infection, pets and other animals should be vaccinated and receive regular booster doses. Exposed, currently vaccinated animals should receive immediate booster doses, whereas unvaccinated animals should either be euthanized or quarantined. The World Health Organization maintains information on the global distribution of rabies and recommendations for postexposure prophylaxis, includ-

ing alternative vaccines, schedules, and routes, on its Web site (www.who.int/emc-documents/rabies/whocdscsreph200210.html#english%20contents).^{5,56} Booster doses of vaccine are suggested when the antibody titer in a patient at risk falls below 0.5 IU per milliliter.

SUMMARY AND RECOMMENDATIONS

Once symptoms develop, rabies is almost invariably fatal. The overarching public health goals are to educate the public about the disease, prevent exposures, offer vaccination to those at increased risk, and administer postexposure prophylaxis appropriately. Figure 3 provides general guidance for the most common circumstances encountered in the United States.

The child described in the first vignette should be examined thoroughly for any evidence of a small lesion compatible with a bite wound. If the bat is available, the carcass should be sent to a diagnostic facility. Postexposure prophylaxis is unnecessary if test results in the bat are negative. However, prophylaxis is needed if the bat is found to have been rabid. If the bat is unavailable, consultation with the local or state health department is appropriate, and prophylaxis should be considered if it is likely that the child was exposed.

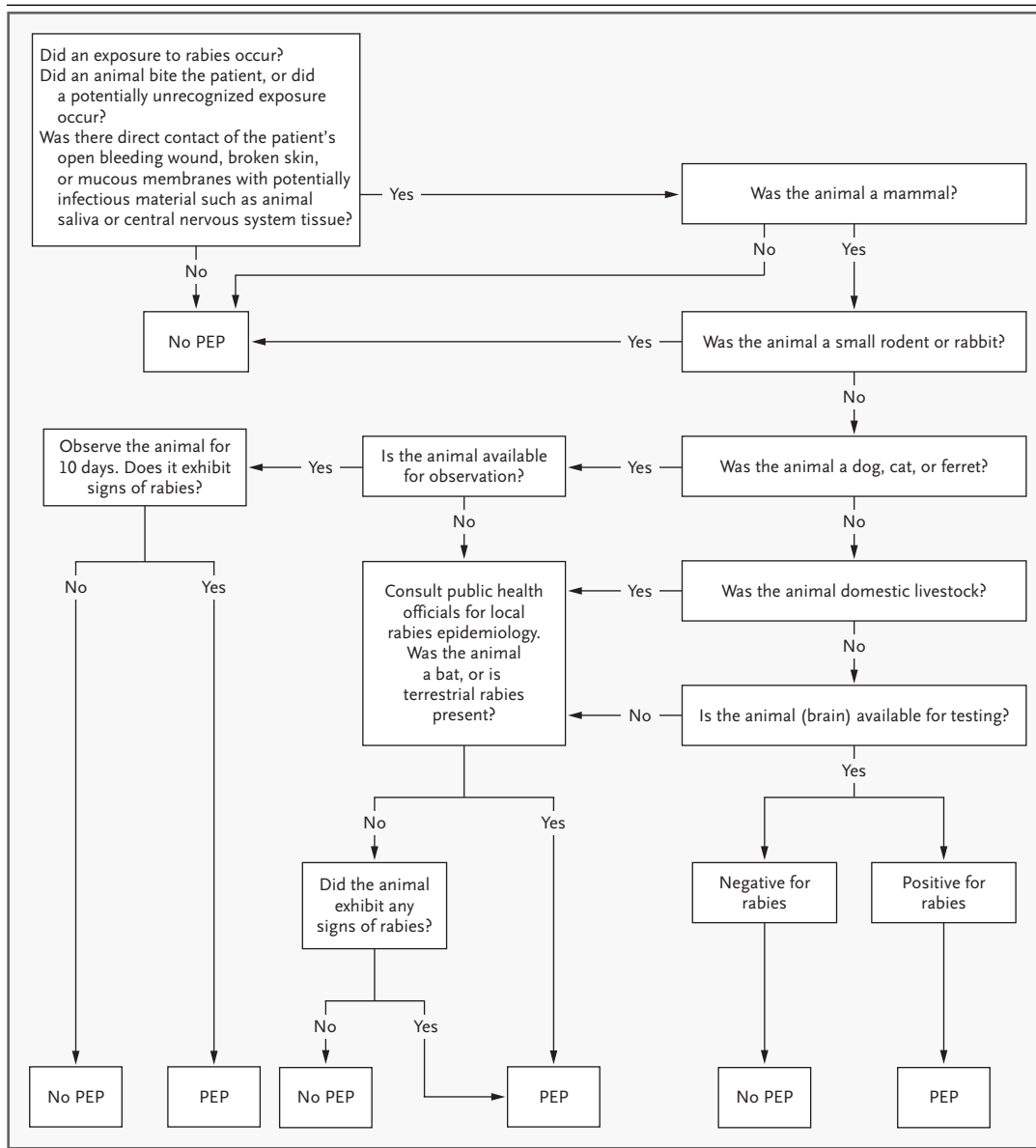
In the second vignette, the owner has not been exposed, even if his puppy had contact with the raccoon sometime that morning. Actions should focus on diagnostic testing of the raccoon and pet management, depending on the results and depending on the immune status of the puppy.

In the last vignette, the action to be taken depends on the specific circumstances. If the suspicion of rabies is low (i.e., the dog appeared healthy; the attack was provoked; the woman was bitten on an ankle through her clothing; there were only minor abrasions, which were washed well; and the episode occurred in a major city free of canine rabies in recent years, such as Rio de Janeiro or Montevideo, Uruguay) or if the dog is found alive, prophylaxis is not indicated. If the bite occurred in an area where canine rabies is endemic, immediate postexposure prophylaxis is warranted, either with locally produced biologic agents or those obtained from the closest major urban area or country.

The views expressed in this article are those of the authors and do not necessarily represent the official policies of the Centers for Dis-

Figure 3 (facing page). General Guidelines for Prophylaxis against Rabies in the United States.

Bites from bats and high-risk wild carnivores such as raccoons, skunks, foxes, bobcats, coyotes, and mongoose are of great concern and warrant consideration of immediate postexposure prophylaxis (PEP). In the case of direct contact between a human and a bat, the possibility of a bite should be considered unless the exposed person can be reasonably certain that a bite did not occur. PEP should be considered for persons who were in the same room as a bat and who might be unaware, or unable to communicate, that a bite had occurred. Rabies has been reported in large rodents (e.g., woodchucks and beavers) in areas where terrestrial rabies is enzootic. Rabies has rarely been diagnosed in small mammals such as rabbits and small rodents (e.g., squirrels, chipmunks, rats, hamsters, gerbils, guinea pigs, and mice). There has never been a documented case of transmission from these small mammals to a human. PEP may be considered for the latter in unusual circumstances (e.g., a bite from a small mammal with a history and clinical signs compatible with rabies), unless the animal is available for testing and is negative. An apparently healthy dog, cat, or ferret that bites a person should be confined and observed daily for 10 days. (The determination of whether a bite was provoked is necessarily subjective. For domestic animals, territorial-defense-related aggression and bites that occur when the animal is surprised, startled, or manipulated are generally viewed as provoked.) The animal should not receive a rabies vaccine during the observation period. A veterinarian should evaluate the animal at the first sign of illness. Management of animals other than dogs, cats, and ferrets depends on the species, the circumstances of the bite, the local rabies epidemiology, and the biting animal's history, current health status, and potential for exposure to rabies. Because prior vaccination of an animal may not be 100 percent effective, current vaccination does not preclude the necessity of a 10-day observation period or, as warranted, euthanasia and testing. State and local authorities should be informed of biting incidents involving cats, dogs, and ferrets. If the animal exhibits signs of rabies during the 10-day observation period, the patient should immediately begin to receive prophylaxis, and the animal should be euthanized and its brain tissue tested for rabies. If the animal is confirmed to have been rabid, PEP should be completed; if test results are negative, PEP can cease. Diagnostic testing of brain tissue should be completed within 24 to 48 hours so that a decision about starting PEP can be made. If the diagnosis cannot be completed within this period, prophylaxis should be started, pending the results of testing. Incubation periods of less than one week have been reported after severe bites on the face, head, and neck. The initiation of PEP should be considered in persons with such exposures before the results of laboratory testing become available.



ease Control and Prevention, the Department of the Army, or the Department of Defense. Use of trade names does not constitute government endorsement.

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ure 2; to the staff in the Viral and Rickettsial Zoonoses Branch, Centers for Disease Control and Prevention, for their valuable insights; and to our many national and international colleagues for their timely devotion to the amelioration of this often ignored disease.

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