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MMWR™
MORBIDITY AND MORTALITY WEEKLY REPORT

Recommendations and Reports

Inside: Continuing Education Examination

Human Rabies Prevention — United States, 1999

Recommendations of the Advisory Committee on Immunization Practices (ACIP)

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Centers for Disease Control and Prevention (CDC)
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Human Rabies Prevention – United States, 1999
Recommendations of the Advisory Committee on Immunization Practices (ACIP)

Summary

These revised recommendations of the Advisory Committee on Immunization Practices update the previous recommendations on rabies prevention (MMWR 1991;40[No.RR-3]:1–14) to reflect the current status of rabies and antirabies biologics in the United States. This report includes new information about a human rabies vaccine approved for U.S. use in 1997, recommendations regarding exposure to bats, recommendations regarding an observation period for domestic ferrets, and changes in the local administration of rabies immune globulin.[*]

INTRODUCTION

Rabies is a viral infection transmitted in the saliva of infected mammals. The virus enters the central nervous system of the host, causing an encephalomyelitis that is almost always fatal. After the marked decrease of rabies cases among domestic animals in the United States in the 1940s and 1950s, indigenously acquired rabies among humans decreased substantially (*1*). In 1950, for example, 4,979 cases of rabies were reported among dogs, and 18 cases were reported among humans. Between 1980 and 1997, 95–247 cases were reported each year among dogs, and on average only two human cases were reported each year in which rabies was attributable to variants of the virus associated with indigenous dogs (*2*). Thus, the likelihood of human exposure to a rabid domestic animal in the United States has decreased greatly. However, during the same period, 12 cases of human rabies were attributed to variants of the rabies virus associated with dogs from outside the United States (*3,4*). Therefore, international travelers to areas where canine rabies is still endemic have an increased risk of exposure to rabies.

Rabies among wildlife — especially raccoons, skunks, and bats — has become more prevalent since the 1950s, accounting for >85% of all reported cases of animal rabies every year since 1976 (*1*). Rabies among wildlife occurs throughout the continental United States; only Hawaii remains consistently rabies-free. Wildlife is the most important potential source of infection for both humans and domestic animals in the United States. Since 1980, a total of 21 (58%) of the 36 human cases of rabies diagnosed in the United States have been associated with bat variants (*2,5,6*). In most other countries — including most of Asia, Africa, and Latin America — dogs remain the major species with rabies and the most common source of rabies among humans. Twelve (33%) of the 36 human rabies deaths reported to the Centers for Disease Control and Prevention (CDC) from 1980 through 1997 appear to have been related to rabid animals outside the United States (*2,6*).

[*] For assistance with problems or questions about rabies prophylaxis, contact your local or state health department. If local or state health department personnel are unavailable, call the Division of Viral and Rickettsial Diseases, National Center for Infectious Diseases, CDC at (404) 639-1050 during working hours or (404) 639-2888 during nights, weekends, and holidays.

Although rabies among humans is rare in the United States, every year approximately 16,000–39,000 persons receive postexposure prophylaxis (*7*). To appropriately manage potential human exposures to rabies, the risk of infection must be accurately assessed. Administration of rabies postexposure prophylaxis is a medical urgency, not a medical emergency, but decisions must not be delayed. Systemic prophylactic treatments occasionally are complicated by adverse reactions, but these reactions are rarely severe (*8–12*).

Data on the safety, immunogenicity, and efficacy of active and passive rabies immunization have come from both human and animal studies. Although controlled human trials have not been performed, extensive field experience from many areas of the world indicates that postexposure prophylaxis combining wound treatment, passive immunization, and vaccination is uniformly effective when appropriately applied (*13–18*). However, rabies has occasionally developed among humans when key elements of the rabies postexposure prophylaxis regimens were omitted or incorrectly administered (see Treatment Outside the United States).

RABIES BIOLOGICS

Two types of rabies immunizing products are available in the United States (Table 1):

- Rabies vaccines induce an active immune response that includes the production of neutralizing antibodies. This antibody response requires approximately 7–10 days to develop and usually persists for ≥2 years.
- Rabies immune globulin (RIG) provides a rapid, passive immunity that persists for only a short time (half-life of approximately 21 days) (*19*).

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

TABLE 1. Rabies biologics — United States, 1999

Human rabies vaccine	Product name	Manufacturer
Human diploid cell vaccine (HDCV) • Intramuscular • Intradermal	Imovax® Rabies Imovax® Rabies I.D.	Pasteur-Merieux Serum et Vaccins, Connaught Laboratories, Inc. Phone: (800) VACCINE *(822-2463)*
Rabies vaccine adsorbed (RVA) • Intramuscular	Rabies Vaccine Adsorbed (RVA)	BioPort Corporation Phone: (517) 335-8120
Purified chick embryo cell vaccine (PCEC) • Intramuscular	RabAvert™	Chiron Corporation Phone: (800) CHIRON8 *(244-7668)*
Rabies immune globulin (RIG)	Imogam® Rabies-HT	Pasteur-Merieux Serum et Vaccins, Connaught Laboratories, Inc. Phone: (800) VACCINE *(822-2463)*
	BayRab™	Bayer Corporation Pharmaceutical Div. Phone: (800) 288-8370

Vaccines Licensed for Use in the United States

Four formulations of three inactivated rabies vaccines are currently licensed for preexposure and postexposure prophylaxis in the United States (Table 1). When used as indicated, all three types of rabies vaccines 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 (*20*). A full 1.0-mL dose can be used for both preexposure and postexposure prophylaxis. However, only the Imovax® Rabies I.D. vaccine (human diploid cell vaccine [HDCV]) has been evaluated and approved by the Food and Drug Administration (FDA) for the intradermal dose and route for preexposure vaccination (*21–24*). Therefore, rabies vaccine adsorbed (RVA) and purified chick embryo cell vaccine (PCEC) should not be used intradermally. 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.

Human Diploid Cell Vaccine (HDCV)

HDCV is prepared from the Pitman-Moore strain of rabies virus grown on MRC-5 human diploid cell culture, concentrated by ultrafiltration, and inactivated with beta-propiolactone (*16*). It is supplied in two forms:

- Intramuscular (IM) administration, a single-dose vial containing lyophilized vaccine that is reconstituted in the vial with the accompanying diluent to a final volume of 1.0 mL just before administration.
- Intradermal (ID) administration, a single-dose syringe containing lyophilized vaccine that is reconstituted in the syringe to a final volume of 0.1 mL just before administration (*25*).

Rabies Vaccine Adsorbed (RVA)

RVA was developed and is currently manufactured and distributed in the state of Michigan by BioPort Corporation. The vaccine is prepared from the Kissling strain of Challenge Virus Standard (CVS) rabies virus adapted to fetal rhesus lung diploid cell culture (*26–31*). The vaccine virus is inactivated with betapropiolactone and concentrated by adsorption to aluminum phosphate. Because RVA is adsorbed to aluminum phosphate, it is liquid rather than lyophilized. It is approved for IM administration only as a 1.0-mL dose.

Purified Chick Embryo Cell Vaccine (PCEC)

PCEC became available in the United States in autumn 1997 (*32*). It is prepared from the fixed rabies virus strain Flury LEP grown in primary cultures of chicken fibroblasts. The virus is inactivated with betapropiolactone and further processed by zonal centrifugation in a sucrose density gradient. It is formulated for IM administration only. PCEC is available in a single-dose vial containing lyophilized vaccine that is reconstituted in the vial with the accompanying diluent to a final volume of 1.0 mL just before administration.

Rabies Immune Globulin Licensed for Use in the United States

The two RIG products, BayRab™ and Imogam® Rabies-HT (Table 1), are an antirabies immunoglobulin (IgG) preparation concentrated by cold ethanol fractionation 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 when used as described in this report (see Treatment of Wounds and Immunization).

PRIMARY OR PREEXPOSURE VACCINATION

Preexposure vaccination should be offered to persons in high-risk groups, such as veterinarians, animal handlers, and certain laboratory workers. Preexposure 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 candidates for preexposure vaccination if they are likely to come in contact with animals in areas where dog rabies is enzootic and immediate access to appropriate medical care, including biologics, might be limited. Routine preexposure prophylaxis for other situations might not be indicated (*33,34*).

Preexposure prophylaxis is administered for several reasons. First, although preexposure 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 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, preexposure prophylaxis might protect persons whose postexposure therapy is delayed. Finally, it might provide protection to persons at risk for inapparent exposures to rabies.

Intramuscular Primary Vaccination

Three 1.0-mL injections of HDCV, RVA, or PCEC should be administered intramuscularly (deltoid area) — one injection per day on days 0, 7, and 21 or 28 (Table 2). In a study in the United States, >1,000 persons received HDCV according to this regimen. Antibody was found in serum samples of all subjects when tested by the rapid fluorescent focus inhibition test (RFFIT). Studies with other products have produced comparable results (*21,35–39*).

Intradermal Primary Vaccination

A regimen of three 0.1-mL ID doses of HDCV, one each on days 0, 7, and 21 or 28, is also used for preexposure vaccination (Table 2) as an alternative to the 1.0-mL IM regimen for rabies preexposure prophylaxis with HDCV (*8,21,22,24,35–37,40*). A single dose of lyophilized HDCV (Imovax® Rabies I.D.) is available prepackaged for reconstitution in the syringe just before administration. The syringe is designed to deliver 0.1 mL of HDCV reliably and has been approved by the FDA since 1986 (*25*).

TABLE 3. Rabies preexposure prophylaxis guide — United States, 1999

Risk category	Nature of risk	Typical populations	Preexposure 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 lab workers,* spelunkers, veterinarians and staff, and animal-control and wildlife workers in rabies-enzootic areas.	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 and wildlife workers in areas with low rabies rates. 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 rabies-epizootic areas.	No vaccination necessary.

* Judgment of relative risk and extra monitoring of vaccination status of laboratory workers is the responsibility of the laboratory supervisor (*43*).
† 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.

with low rabies rates (infrequent exposure group) and at-risk international travelers do not require routine preexposure booster doses of vaccine after completion of primary preexposure vaccination.

Postexposure Therapy for Previously Vaccinated Persons

If exposed to rabies, previously vaccinated persons should receive two IM doses (1.0 mL each) of vaccine, one immediately and one 3 days later. Previously vaccinated persons are those who have received one of the recommended preexposure or postexposure regimens of HDCV, RVA, or PCEC, or those who received another vaccine and had a documented rabies antibody titer. RIG is unnecessary and should not be administered to these persons because an anamnestic response will follow the administration of a booster regardless of the prebooster antibody titer (*44*).

Preexposure Vaccination and Serologic Testing

Because the antibody response has been satisfactory after these recommended preexposure prophylaxis vaccine regimens, routine serologic testing to confirm seroconversion is not necessary except for persons suspected of being immunosuppressed. Patients who are immunosuppressed by disease or medications should postpone preexposure vaccinations and consider avoiding activities for which rabies preexposure prophylaxis is indicated. When that is not possible, immunosuppressed persons who are at risk for exposure to rabies should be vaccinated and their antibody titers checked. In these cases, failures to seroconvert after the third dose should be managed in consultation with appropriate public health officials.

POSTEXPOSURE PROPHYLAXIS

Rationale for Treatment

Administration of rabies postexposure prophylaxis is a medical urgency, not a medical emergency. Physicians should evaluate each possible exposure to rabies and, if necessary, consult with local or state public health officials regarding the need for rabies prophylaxis (Table 4). In the United States, the following factors should be considered before specific antirabies postexposure prophylaxis is initiated.

TABLE 4. Rabies postexposure prophylaxis guide — United States, 1999

Animal type	Evaluation and disposition of animal	Postexposure prophylaxis recommendations
Dogs, cats, and ferrets	Healthy and available for 10 days observation	Persons should not begin prophylaxis unless animal develops clinical signs of rabies.*
	Rabid or suspected rabid	Immediately vaccinate.
	Unknown (e.g., escaped)	Consult public health officials.
Skunks, raccoons, foxes and most other carnivores; bats	Regarded as rabid unless animal proven negative by laboratory tests†	Consider immediate vaccination.
Livestock, small rodents, lagomorphs (rabbits and hares), large rodents (woodchucks and beavers), and other mammals	Consider individually.	Consult public health officials. Bites of squirrels, hamsters, guinea pigs, gerbils, chipmunks, rats, mice, other small rodents, rabbits, and hares almost never require antirabies postexposure prophylaxis.

*During the 10-day observation period, begin postexposure prophylaxis at the first sign of rabies in a dog, cat, or ferret that has bitten someone. If the animal exhibits clinical signs of rabies, it should be euthanized immediately and tested.

†The animal should be euthanized and tested as soon as possible. Holding for observation is not recommended. Discontinue vaccine if immunofluorescence test results of the animal are negative.

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Recommendations and Reports

Continuing Education Activity Sponsored by CDC

Human Rabies Prevention — United States, 1999
Recommendations of the Advisory Committee on Immunization Practices (ACIP)

OBJECTIVE

This *MMWR* provides recommendations for preventing rabies among humans. These recommendations were developed by CDC staff members and the Rabies Working Group of the ACIP. This report is intended to guide clinical practice and policy development related to appropriate management of persons at risk for rabies. Upon completion of this educational activity, the reader should be able to identify groups for whom rabies preexposure prophylaxis is indicated; identify groups for whom rabies serologic testing and booster dosing are indicated; identify some of the common rabies reservoirs in the United States; describe the essential elements of rabies postexposure prophylaxis; and describe appropriate management of persons exposed to bats.

ACCREDITATION

Continuing Medical Education (CME): This activity has been planned and implemented in accordance with the Essentials and Standards of the Accreditation Council for Continuing Medical Education (ACCME) by CDC. CDC is accredited by the ACCME to provide continuing medical education for physicians. CDC designates this educational activity for a maximum of 1 hour in category 1 credit toward the AMA Physician's Recognition Award.

Continuing Education Units (CEU): CDC awards 0.1 hours of CEUs. This activity has been structured following the International Association for Continuing Education and Training (IACET) Criteria and Guidelines and therefore is awarding CEUs. The CEU is a nationally recognized unit designed to provide a record of an individual's continuing education accomplishments.

Continuing Nursing Education (CNE) Credit: This activity for 1.2 contact hours is provided by CDC, which is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center's (ANCC) Commission on Accreditation.

EXPIRATION — January 8, 2000

The response form must be completed and returned electronically, by fax, or by mail, **postmarked no later than one year from the publication date of this report**, for eligibility to receive continuing education credit.

INSTRUCTIONS

1. Read this *MMWR (Vol. 48, RR-1*), which contains the correct answers to the questions beginning on the next page.
2. Complete all registration information on the response form, including your name, mailing address, phone number, and e-mail address, if available.
3. Indicate whether you are registering for Continuing Medical Education (CME), Continuing Education Unit (CEU), *or* Continuing Nursing Education (CNE) credit.
4. Select your answers to the questions, and mark the corresponding letters on the response form. To receive continuing education credit, you must answer *all* of the questions. Questions with more than one answer will instruct you to "indicate all that are true."
5. Sign and date the response form.
6. Return the response form, or a photocopy of the form, no later than **January 8, 2000**, to CDC by one of the following methods:

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If you answer all of the questions, you will receive an award letter for 1 hour of CME credit, 0.1 hour of CEU credit, or 1.2 hours of CNE credit within 90 days. No fees are charged for participating in this continuing education activity.

U.S. DEPARTMENT OF HEALTH & HUMAN SERVICES

1. In which of the following situations would it be appropriate to administer rabies postexposure prophylaxis? *(Indicate all that are true.)*

A. A family discovers a colony of bats in the garage of their home.

B. The family cat brings a dead bat into the yard and the 5-year-old son handles it.

C. A dead bat (which is tested and found to be positive for rabies) is found in the crib of a 6-month-old baby.

D. A troop of Boy Scouts witnesses the emergence of a colony of bats from a cave.

2. Which of the following are not components of postexposure prophylaxis in the United States? *(Indicate all that are false.)*

A. Thorough cleaning of the wound with at least soap and water.

B. Administration of as much rabies immune globulin as possible at the exposure site.

C. Intradermal administration of rabies vaccine.

D. Intramuscular administration of rabies vaccine.

3. Which of the following statements are true about rabies preexposure prophylaxis? *(Indicate all that are true.)*

A. It is indicated for international travelers only if they will be in a country where rabies is enzootic for greater than 30 days.

B. It consists of 3 doses of rabies vaccine administered intramuscularly or intradermally.

C. In the event of an exposure, persons who have received preexposure prophylaxis still require 2 booster doses of rabies vaccine, but no rabies immune globulin.

D. Veterinarians in areas where rabies is enzootic should have titers checked every 2 years.

4. Which of the following would be appropriate responses to concerns about nosocomial transmission of rabies from a hospitalized patient suspected of having rabies? *(Indicate all that are true.)*

A. Contact your local or state health department for assistance.

B. Advise that the patient be placed in a negative pressure isolation room.

C. Advise immediate vaccination of all hospital personnel involved in the care of the patient.

D. Encourage adherence to standard precautions.

5. A person reports an unprovoked bite from a stray dog. The dog was captured by animal control and appears healthy. What are the appropriate actions? *(Indicate all that are true.)*

A. Confine and observe the dog for 10 days for signs suggestive of rabies.

B. Immediately begin postexposure prophylaxis.

C. Consult your local or state health department.

D. Because canine rabies has decreased in the United States, dog bites are no longer indications for postexposure prophylaxis and no further action is needed.

6. Which of the following animals are frequently reported rabid in the United States? *(Indicate all that are true.)*

A. Squirrels

B. Raccoons

C. Rabbits

D. Skunks

E. Bats

7. Which of the following statements about the timing of postexposure prophylaxis are true? *(Indicate all that are true.)*

A. For postexposure prophylaxis to be effective, it must always be administered on the same day the exposure occurred.

B. Postexposure prophylaxis should be administered regardless of any delay after a true exposure.

C. If rabies immune globulin was not administered when vaccination was begun, it can be administered through the seventh day after the administration of the first dose of vaccine.

D. Day 0 refers to the day the first dose of vaccine was administered.

8. Which of the following statements are true? *(Indicate all that are true.)*

A. Human rabies is a fatal disease 50% of the time.

B. In the last 2 decades, most human rabies cases in the United States have been associated with bat variants of the rabies virus.

C. U.S. citizens traveling abroad can be at risk of exposure to canine rabies.

D. Although human rabies cases in the United States are rare, exposure to rabid or potentially rabid animals remains a relatively common event.

9. Indicate your work setting.

A. State/local health department

B. Other public health agency

C. Public hospital

D. Managed care organization/private hospital or practice

E. Academic hospital

F. Other

10. Which best describes your professional activities?

A. Patient care — emergency/urgent care department

B. Patient care — inpatient

C. Patient care — primary care clinic

D. Laboratory/pharmacy

E. Administration/public health

F. Veterinary medicine/animal control

11. Have you ever been involved in the administration of postexposure prophylaxis? *(In this three-part question, indicate all that apply.)*

A. Yes

B. No

Did you refer to the previous Rabies Prevention Guidelines of the ACIP?

C. Yes

D. No

Did you contact public health officials for advice?

E. Yes

F. No

12. Are rabies vaccine and rabies immune globulin available in your work setting or readily available if needed?

A. Yes, available in work setting

B. Yes, available if needed

C. No or unsure

13. I plan to use these guidelines as the basis for: *(Indicate all that apply.)*

A. Health education materials

B. Insurance reimbursement policies

C. Local practice guidelines

D. Public policy

E. Other

14. How much time was required to complete this continuing education activity (both reading the document and completing the test)?

A. ≤1 hour

B. >1 hour but <1½ hours

C. ≥1½ hours

	Strongly agree	Agree	Neither agree nor disagree	Disagree	Strongly disagree
15. Overall, this report met the stated objectives.	**A**	**B**	**C**	**D**	**E**
16. The tables and figures are useful.	**A**	**B**	**C**	**D**	**E**
17. These recommendations will affect my practice.	**A**	**B**	**C**	**D**	**E**

Answer guide for questions 1–8.
1. B, C; 2. C; 3. B, C, D; 4. A, D ; 5. A, C; 6. B, D, E; 7. B, C, D; 8. B, C, D

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MMWR Vol. 48/No. RR-1. January 8, 1999

Human Rabies Prevention — United States, 1999
Recommendations of the Advisory Committee on Immunization Practices (ACIP)

Fill in the appropriate block(s) to indicate your answer(s). T**o receive continuing education credit, you must answer all of the questions.**

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Types of Exposure

Rabies is transmitted only when the virus is introduced into bite wounds or open cuts in skin or onto mucous membranes. If no exposure has occurred (i.e., no bite or nonbite exposure), postexposure prophylaxis is not necessary. The likelihood of rabies infection varies with the nature and extent of exposure. Two categories of exposure — bite and nonbite — should be considered.

Bite

Any penetration of the skin by teeth constitutes a bite exposure. All bites, regardless of location, represent a potential risk of rabies transmission. Bites by some animals, such as bats, can inflict minor injury and thus be undetected (*45*).

Nonbite

Nonbite exposures from terrestrial animals rarely cause rabies. However, occasional reports of transmission by nonbite exposure suggest that such exposures constitute sufficient reason to consider postexposure prophylaxis (*46*). The nonbite exposures of highest risk appear to be among persons exposed to large amounts of aerosolized rabies virus and surgical recipients of corneas transplanted from patients who died of rabies. Two cases of rabies have been attributed to probable aerosol exposures in laboratories, and two cases of rabies have been attributed to possible airborne exposures in caves containing millions of free-tailed bats (*Tadarida brasiliensis*) in the Southwest (*47–51*).

The contamination of open wounds, abrasions, mucous membranes, or theoretically, scratches, with saliva or other potentially infectious material (such as neural tissue) from a rabid animal also constitutes a nonbite exposure. Other contact by itself, such as petting a rabid animal and contact with blood, urine, or feces (e.g., guano) of a rabid animal, does not constitute an exposure and is not an indication for prophylaxis. Because the 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.

Human-to-Human Transmission

Human-to-human transmission has occurred among eight recipients of transplanted corneas. Investigations revealed each of the donors had died of an illness compatible with or proven to be rabies (*52–58*). The eight cases occurred in five countries: Thailand (two cases), India (two cases), Iran (two cases), the United States (one case), and France (one case). Stringent guidelines for acceptance of donor corneas have been implemented to reduce this risk.

Apart from corneal transplants, bite and nonbite exposures inflicted by infected humans could theoretically transmit rabies, but no laboratory-diagnosed cases occurring under such situations have been documented (*59*). Two nonlaboratory-confirmed cases of human-to-human rabies transmission in Ethiopia have been described (*60*). The reported route of exposure in both cases was direct salivary contact from another human (a bite and a kiss). Routine delivery of health care to a patient with rabies is not an indication for postexposure prophylaxis unless exposure of mucous membranes or nonintact skin to potentially infectious body fluids has occurred. Adherence to

standard precautions as outlined by the Hospital Infection Control Practices Advisory Committee will minimize the risk of exposure (*61*).

Animal Rabies Epidemiology and Evaluation of Involved Species

Bats

Rabid bats have been documented in the 49 continental states, and bats are increasingly implicated as important wildlife reservoirs for variants of rabies virus transmitted to humans (*1*). Recent epidemiologic data suggest that transmission of rabies virus can occur from minor, seemingly unimportant, or unrecognized bites from bats (*5,6,62*). The limited injury inflicted by a bat bite (in contrast to lesions caused by terrestrial carnivores) and an often inaccurate recall of the exact exposure history might limit the ability of health-care providers to determine the risk of rabies resulting from an encounter with a bat (*45*). Human and domestic animal contact with bats should be minimized, and bats should never be handled by untrained and unvaccinated persons or be kept as pets (*6,63*).

In all instances of potential human exposures involving bats, the bat in question should be safely collected, if possible, and submitted for rabies diagnosis. Rabies postexposure prophylaxis is recommended for all persons with bite, scratch, or mucous membrane exposure to a bat, unless the bat is available for testing and is negative for evidence of rabies. Postexposure prophylaxis might be appropriate even if a bite, scratch, or mucous membrane exposure is not apparent when there is reasonable probability that such exposure might have occurred.

On the basis of the available but sometimes conflicting information from the 21 bat-associated cases of human rabies reported since 1980, in 1–2 cases, a bite was reported; in 10–12 cases, apparent contact occurred but no bite was detected; and in 7–10 cases, no exposure to bats was reported, but an undetected or unreported bat bite remains the most plausible hypothesis. Clustering of bat-associated human cases within the same household has never been reported.

Consequently, postexposure prophylaxis should 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 postexposure prophylaxis must be balanced against the low risk such exposures appear to present. In this setting, postexposure 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. Postexposure prophylaxis would not be warranted for other household members.

Wild Terrestrial Carnivores

Raccoons, skunks, foxes, and coyotes are the terrestrial animals most often infected with rabies. All bites by such wildlife must be considered possible exposures to the rabies virus. Postexposure prophylaxis should be initiated as soon as possible after patients are exposed to wildlife unless the animal has already been tested and shown not to be rabid. If postexposure prophylaxis has been initiated and subsequent

immunofluorescence testing shows that the exposing animal was not rabid, postexposure prophylaxis can be discontinued.

Signs of rabies among wildlife cannot be interpreted reliably; therefore, any such animal that exposes a person should be euthanized at once (without unnecessary damage to the head) and the brain should be submitted for rabies testing (*64*). 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 postexposure prophylaxis.

Other Wild Animals

Small rodents (e.g., squirrels, hamsters, guinea pigs, gerbils, chipmunks, rats, and mice) and lagomorphs (including rabbits and hares) are almost never found to be infected with rabies and have not been known to transmit rabies to humans. From 1990 through 1996, in areas of the country where raccoon rabies was enzootic, woodchucks accounted for 93% of the 371 cases of rabies among rodents reported to CDC (*1,65,66*). In all cases involving rodents, the state or local health department should be consulted before a decision is made to initiate antirabies postexposure prophylaxis (*67*).

The offspring of wild animals crossbred to domestic dogs and cats (wild animal hybrids) are considered wild animals by the National Association of State and Public Health Veterinarians (NASPHV) and the Council of State and Territorial Epidemiologists (CSTE). Because the period of rabies virus shedding in these animals is unknown, these animals should be euthanized and tested rather than confined and observed when they bite humans. Wild animals and wild animal hybrids should not be kept as pets (*63*). Animals maintained in United States Department of Agriculture-licensed research facilities or accredited zoological parks should be evaluated on a case-by-case basis.

Domestic Dogs, Cats, and Ferrets

The likelihood of rabies in a domestic animal varies by region; hence, the need for postexposure prophylaxis also varies. In the continental United States, rabies among dogs is reported most commonly along the United States-Mexico border and sporadically in areas of the United States with enzootic wildlife rabies. During most of the 1990s, more cats than dogs were reported rabid in the United States. The majority of these cases were associated with the epizootic of rabies among raccoons in the eastern United States. The large number of rabies-infected cats might be attributed to fewer cat vaccination laws, fewer leash laws, and the roaming habits of cats. In many developing countries, dogs are the major vector of rabies; exposures to dogs in such countries represent an increased risk of rabies transmission.

On the basis of new information regarding rabies pathogenesis and viral shedding patterns in ferrets, ferrets are now considered in this category with dogs and cats rather than as wild terrestrial carnivores (*68*). A healthy domestic dog, cat, or ferret that bites a person may 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 local public health department. If signs suggestive of rabies develop, the animal should be euthanized and its head removed and shipped, under refrigeration, for examination by a qualified laboratory. If the biting animal is

stray or unwanted, it should either be observed for 10 days or be euthanized immediately and submitted for rabies examination (*63*).

Circumstances of Biting Incident and Vaccination Status of Exposing Animal

An unprovoked attack by an 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 currently vaccinated dog, cat, or ferret is unlikely to become infected with rabies (*68–71*).

Treatment of Wounds and Immunization

The essential components of rabies postexposure prophylaxis are wound treatment and, for previously unvaccinated persons, the administration of both RIG and vaccine (Table 5 [*72*]). Persons who have been bitten by animals suspected or proven to be rabid should begin postexposure prophylaxis immediately. Incubation periods of >1 year have been reported in humans (*73*). Thus, when a documented or likely exposure has occurred, postexposure prophylaxis is indicated regardless of the length of the delay, provided the clinical signs of rabies are not present.

In 1977, the World Health Organization recommended a regimen of RIG and six doses of HDCV over a 90-day period. This recommendation was based on studies in Germany and Iran (*14,18*). When used this way, the vaccine was found to be safe and effective in protecting persons bitten by animals proven to be rabid and induced an excellent antibody response in all recipients (*14*). Studies conducted in the United States by CDC have documented that a regimen of one dose of RIG and five doses of HDCV over a 28-day period was safe and induced an excellent antibody response in all recipients (*13*). Clinical trials with RVA and PCEC have demonstrated immunogenicity equivalent to that of HDCV (*26,74*).

Treatment of Wounds

Immediate and thorough washing of all bite wounds and scratches with soap and water and a virucidal agent such as a povidone-iodine solution irrigation are important measures for preventing rabies (*72*). In studies of animals, thorough wound cleansing alone without other postexposure prophylaxis has been shown to reduce markedly the likelihood of rabies (*75,76*). Tetanus prophylaxis and measures to control bacterial infection also should be administered as indicated (*77*). The decision to suture large wounds should take into account cosmetic factors and the potential for bacterial infections.

Immunization

Postexposure antirabies vaccination should always include administration of both passive antibody and vaccine, with the exception of persons who have previously received complete vaccination regimens (preexposure or postexposure) with a cell culture vaccine or persons who have been vaccinated with other types of vaccines and have had documented rabies antibody titers. These persons should receive only vaccine (see Postexposure Therapy for Previously Vaccinated Persons). The combination of RIG and vaccine is recommended for both bite and nonbite exposures (see

TABLE 5. Rabies postexposure prophylaxis schedule — United States, 1999

Vaccination status	Treatment	Regimen*
Not previously vaccinated	Wound cleansing	All postexposure treatment should begin with immediate thorough cleansing of all wounds with soap and water. If available, a virucidal agent such as a povidone-iodine solution should be used to irrigate the wounds (*72*).
	RIG	Administer 20 IU/kg body weight. If anatomically feasible, **the full dose** should be infiltrated around the wounds(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, RVA, or PCEC 1.0 mL, IM (deltoid area†), one each on days 0§, 3, 7, 14, and 28.
Previously vaccinated¶	Wound cleansing	All postexposure treatment should begin with immediate thorough cleansing of all wounds with soap and water. If available, a virucidal agent such as a povidone-iodine solution should be used to irrigate the wounds (*72*).
	RIG	RIG should **not** be administered.
	Vaccine	HDCV, RVA, or PCEC 1.0 mL, IM (deltoid area†), one each on days 0§ and 3.

HDCV=human diploid cell vaccine; PCEC=purified chick embryo cell vaccine; RIG=rabies immune globulin; RVA=rabies vaccine adsorbed; IM, intramuscular.
*These regimens are applicable for all age groups, including children.
†The deltoid area 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.
§Day 0 is the day the first dose of vaccine is administered.
¶Any person with a history of preexposure vaccination with HDCV, RVA or PCEC; prior postexposure prophylaxis with HDCV, RVA, or PCEC; or previous vaccination with any other type of rabies vaccine and a documented history of antibody response to the prior vaccination.

Rationale for Treatment), regardless of the interval between exposure and initiation of treatment.

Rabies Immune Globulin Use. RIG is administered only once (i.e., at the beginning of antirabies prophylaxis) to previously unvaccinated persons to provide immediate antibodies until the patient responds to HDCV, RVA, or PCEC by actively producing antibodies. If RIG was not administered when vaccination was begun, it can be administered through the seventh day after the administration of the first dose of vaccine (*78*). Beyond the seventh day, RIG is not indicated since an antibody response to cell culture vaccine is presumed to have occurred. Because RIG can partially suppress active production of antibody, no more than the recommended dose should be administered (*79*). The recommended dose of human RIG is 20 IU/kg body weight. This formula is applicable to all age groups, including children. If anatomically feasible, the

full dose of RIG should be thoroughly infiltrated in the area around and into the wounds. Any remaining volume should be injected intramuscularly at a site distant from vaccine administration. This change in the recommendations for RIG administration is based on reports of rare failures of postexposure prophylaxis when smaller amounts of RIG were infiltrated at the exposure sites (*80*). RIG should never be administered in the same syringe or in the same anatomical site as vaccine.

Vaccine Use. Three rabies vaccines are currently available in the United States (Table 1); any one of the three can be administered in conjunction with RIG at the beginning of postexposure therapy. A regimen of five 1-mL doses of HDCV, RVA, or PCEC should be administered intramuscularly. The first dose of the five-dose course should be administered as soon as possible after exposure. Additional doses should be administered on days 3, 7, 14, and 28 after the first vaccination. For adults, the vaccination 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, RVA, or PCEC injections because administration of HDCV in this area results in lower neutralizing antibody titers (*81*).

Treatment Outside the United States

U.S. citizens who are exposed to rabies while traveling outside the United States in countries where rabies is enzootic might sometimes receive postexposure therapy with regimens or biologics that are not used in the United States (Table 6). This information is provided to familiarize physicians with some of the regimens used more widely abroad. The regimens described in the references in this report have not been submitted for approval by the FDA for use in the United States (*82–93*). If postexposure prophylaxis is begun outside the United States using one of these regimens or biologics of nerve tissue origin, it might be necessary to provide additional therapy when the patient reaches the United States. State or local health departments should be contacted for specific advice in such cases. If titers are obtained, specimens collected 2–4 weeks after preexposure or postexposure prophylaxis should completely neutralize challenge virus at a 1:5 serum dilution by the RFFIT.

Purified equine rabies immune globulin (ERIG) has been used effectively in developing countries where RIG might not have been available. The incidence of adverse reactions has been low (0.8%–6.0%), and most of those that occurred were minor (*94–96*). In addition, unpurified antirabies serum of equine origin might still be used in some countries where neither RIG nor ERIG are available. The use of this antirabies serum is associated with higher rates of serious adverse reactions, including anaphylaxis *(97)*.

TABLE 6. Cell culture rabies vaccines widely available outside the United States

Purified chick embryo cell vaccine (PCEC)	Rabipur®
Purified vero cell rabies vaccine (PVRV)	Verorab™ Imovax – Rabies vero™ TRC Verorab™
Human diploid cell vaccine (HDCV)	Rabivac™
Purified duck embryo vaccine (PDEV)	Lyssavac N™

Although no postexposure vaccine failures have occurred in the United States since cell culture vaccines have been routinely used, failures have occurred abroad when some deviation was made from the recommended postexposure treatment protocol or when less than the currently recommended amount of antirabies sera was administered (*80,98–100*). Specifically, patients who contracted rabies after postexposure prophylaxis did not have their wounds cleansed with soap and water, did not receive their rabies vaccine injections in the deltoid area (i.e., vaccine was administered in the gluteal area), or did not receive RIG around the wound site.

VACCINATION AND SEROLOGIC TESTING

Serologic Response Shortly After Vaccination

All persons tested during several CDC studies 2–4 weeks after completion of preexposure and postexposure rabies prophylaxis in accordance with ACIP guidelines have demonstrated an antibody response to rabies (*13,38,101,102*). Therefore, serum samples from patients completing preexposure or postexposure prophylaxis do not need to be tested to document seroconversion unless the person is immunosuppressed (see Precautions and Contraindications). If titers are obtained, specimens collected 2–4 weeks after preexposure or postexposure prophylaxis should completely neutralize challenge virus at a 1:5 serum dilution by the RFFIT. In animal studies, neutralizing antibody titers have been shown to be imperfect markers of protection. Antibody titers will vary with time since the last vaccination. Differences among laboratories that test blood samples also can influence the results.

Cell culture vaccines have been used effectively with RIG or ERIG worldwide to treat persons bitten by various rabid animals (*13,14*). Worldwide, the World Health Organization estimates that 10–12 million persons are started on postexposure therapy annually (*74*). An estimated 16,000–39,000 persons in the United States receive a full postexposure course with HDCV each year (*7*). When postexposure prophylaxis has been properly administered, no treatment failures have occurred in the United States.

Serologic Response and Preexposure Booster Doses of Vaccine

Although antibody levels do not define a person's immune status, they are a marker of continuing immune response (*103*). To ensure the continuity of an immune response, titers should be checked periodically, with booster doses administered as needed. Two years after primary preexposure vaccination, a 1:5 serum dilution will neutralize challenge virus completely (by the RFFIT) among 93%–98% of persons who received the three-dose preexposure series intramuscularly and 83%–95% of persons who received the three-dose series intradermally (*104*). If the titer falls below the minimum acceptable antibody level, a preexposure booster dose of vaccine is recommended for a person at continuous or frequent risk for exposure to rabies (Table 3). The following guidelines are recommended for determining when serum testing should be performed after primary preexposure vaccination:

- A person in the continuous-risk category (Table 3) should have a serum sample tested for rabies antibody every 6 months (*43*).
- A person in the frequent-risk category (Table 3) should have a serum sample tested for rabies antibody every 2 years (*105*).

State or local health departments can provide the names and addresses of laboratories performing rabies serologic testing.

ADVERSE REACTIONS

HDCV, RVA, and PCEC

Reactions after vaccination with HDCV, RVA, and PCEC are less serious and less common than with previously available vaccines (*74,106,107*). In previous studies with HDCV, local reactions (e.g., pain, erythema, and swelling or itching at the injection site) have been reported among 30%–74% of recipients (*108*). Systemic reactions (e.g., headache, nausea, abdominal pain, muscle aches, and dizziness) have been reported among 5%–40% of recipients. Three cases of neurologic illness resembling Guillain-Barré syndrome that resolved without sequelae in 12 weeks have been reported (*8,109,110*). In addition, other central and peripheral nervous system disorders have been temporally associated with HDCV vaccine, but a causal relationship has not been established in these rare reports (*111*).

An immune complex-like reaction occurred among approximately 6% of persons who received booster doses of HDCV 2–21 days after administration of the booster dose (*9,10*). The patients developed generalized urticaria, sometimes accompanied by arthralgia, arthritis, angioedema, nausea, vomiting, fever, and malaise. In no cases have these reactions been life-threatening. This reaction occurred less frequently among persons receiving primary vaccination. The reactions have been associated with the presence of betapropiolactone-altered human albumin in the HDCV and the development of immunoglobulin E (IgE) antibodies to this allergen (*112–114*).

Rabies Immune Globulin (Human)

Local pain and low-grade fever might follow receipt of RIG. Although not reported specifically for RIG, angioneurotic edema, nephrotic syndrome, and anaphylaxis have been reported after injection of immune globulin (IG), a product similar in biochemical composition but without antirabies activity. These reactions occur so rarely that a causal relationship between IG and these reactions has not been established.

Both formulations of RIG, BayRab™ and Imogam®Rabies-HT, undergo multiple viral clearance procedures during preparation. There is no evidence that any viruses have ever been transmitted by commercially available RIG in the United States.

Vaccines and Immune Globulins Used in Other Countries

Many developing countries use inactivated nerve tissue vaccines made from the brains of adult animals or suckling mice. Nerve tissue vaccine (NTV) is reported to induce neuroparalytic reactions among approximately 1 per 200 to 1 per 2,000 persons

vaccinated; suckling mouse brain vaccine (SMBV) causes reactions in approximately 1 per 8,000 persons vaccinated (*15,115*). The vaccines HDCV, PCEC, PDEV, and purified vero cell rabies vaccine (PVRV) (Table 6) are cell culture-derived and not of nerve tissue origin. In addition, unpurified antirabies serum of equine origin might still be used in some countries where neither RIG nor ERIG are available. The use of this antirabies serum is associated with higher rates of serious adverse reactions, including anaphylaxis.

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 antiinflammatory 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 (*9*). 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 state health department or CDC.

All serious systemic, neuroparalytic, or anaphylactic reactions should be reported to the Vaccine Adverse Event Reporting System (VAERS) via a 24-hour toll-free telephone number ([800] 822-7967).

PRECAUTIONS AND CONTRAINDICATIONS

Immunosuppression

Corticosteroids, other immunosuppressive agents, antimalarials, and immunosuppressive illnesses can interfere with the development of active immunity after vaccination (*41,116*). For persons with immunosuppression, preexposure prophylaxis should be administered with the awareness that the immune response might be inadequate (see Primary or Preexposure Vaccination). Patients who are immunosuppressed by disease or medications should postpone preexposure vaccinations and consider avoiding activities for which rabies preexposure prophylaxis is indicated. When this course is not possible, immunosuppressed persons who are at risk for rabies should be vaccinated by the IM route and their antibody titers checked. Failure to seroconvert after the third dose should be managed in consultation with appropriate public health officials (see Preexposure Vaccination and Serologic Testing).

Immunosuppressive agents should not be administered during postexposure therapy unless essential for the treatment of other conditions. When postexposure 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.

Pregnancy

Because of the potential consequences of inadequately treated rabies exposure, and because there is no indication that fetal abnormalities have been associated with rabies vaccination, pregnancy is not considered a contraindication to postexposure prophylaxis (*117,118*). If the risk of exposure to rabies is substantial, preexposure prophylaxis might also be indicated during pregnancy.

Allergies

Persons who have a history of serious hypersensitivity to rabies vaccine should be revaccinated with caution (see Management of Adverse Reactions).

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