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# Human Rabies Prevention — United States, 2008

## Recommendations of the Advisory Committee on Immunization Practices



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# Human Rabies Prevention — United States, 2008

## Recommendations of the Advisory Committee on Immunization Practices

Prepared by
Susan E. Manning, MD,[1,8] Charles E. Rupprecht, VMD,[2] Daniel Fishbein, MD,[3,8] Cathleen A. Hanlon, VMD,[2]
Boonlert Lumlertdacha, DVM, [2] Marta Guerra, DVM,[2] Martin I. Meltzer, PhD,[4] Praveen Dhankhar, PhD,[4]
Sagar A.Vaidya, MD,[5] Suzanne R. Jenkins, VMD,[6] Benjamin Sun, DVM,[6] Harry F. Hull, MD[7]
[1]*Preventive Medicine Residency, Office of Workforce and Career Development, CDC*
[2]*Division of Viral and Rickettsial Diseases, National Center for Zoonotic, Vector-Borne and Enteric Diseases, CDC*
[3]*Immunization Services Division, National Center for Immunization and Respiratory Diseases, CDC*
[4]*Division of Emerging Infections and Surveillance Services, National Center for Preparedness, Detection, and Control of Infectious Diseases, CDC*
[5]*Combined Internal Medicine/Pediatrics Program, Mount Sinai School of Medicine*
[6]*National Association of State Public Health Veterinarians*
[7]*Minnesota Department of Public Health*
[8]*Commissioned Corps of the United States Public Health Service*

### Summary

*These recommendations of the Advisory Committee on Immunization Practices (ACIP) update the previous recommendations on human rabies prevention* (CDC. Human rabies prevention—United States, 1999: recommendations of the Advisory Committee on Immunization Practices. MMWR 1999;48 [No. RR-1]) *and reflect the status of rabies and antirabies biologics in the United States. This statement 1) provides updated information on human and animal rabies epidemiology; 2) summarizes the evidence regarding the effectiveness/efficacy, immunogenicity, and safety of rabies biologics; 3) presents new information on the cost-effectiveness of rabies postexposure prophylaxis; 4) presents recommendations for rabies postexposure and pre-exposure prophylaxis; and 5) presents information regarding treatment considerations for human rabies patients.*

*These recommendations involve no substantial changes to the recommended approach for rabies postexposure or pre-exposure prophylaxis. ACIP recommends that prophylaxis for the prevention of rabies in humans exposed to rabies virus should include prompt and thorough wound cleansing followed by passive rabies immunization with human rabies immune globulin (HRIG) and vaccination with a cell culture rabies vaccine. For persons who have never been vaccinated against rabies, postexposure antirabies vaccination should always include administration of both passive antibody (HRIG) and vaccine (human diploid cell vaccine [HDCV] or purified chick embryo cell vaccine [PCECV]). Persons who have ever previously received complete vaccination regimens (pre-exposure or postexposure) with a cell culture vaccine or persons who have been vaccinated with other types of vaccines and have previously had a documented rabies virus neutralizing antibody titer should receive only 2 doses of vaccine: one on day 0 (as soon as the exposure is recognized and administration of vaccine can be arranged) and the second on day 3. HRIG is administered only once (i.e., at the beginning of antirabies prophylaxis) to previously unvaccinated persons to provide immediate, passive, rabies virus neutralizing antibody coverage until the patient responds to HDCV or PCECV by actively producing antibodies. A regimen of 5 1-mL doses of HDCV or PCECV should be administered intramuscularly to previously unvaccinated persons. The first dose of the 5-dose course should be administered as soon as possible after exposure (day 0). Additional doses should then be administered on days 3, 7, 14, and 28 after the first vaccination. Rabies pre-exposure vaccination should include three 1.0-mL injections of HDCV or PCECV administered intramuscularly (one injection per day on days 0, 7, and 21 or 28).*

*Modifications were made to the language of the guidelines to clarify the recommendations and better specify the situations in which rabies post- and pre-exposure prophylaxis should be administered. No new rabies biologics are presented, and no changes were made to the vaccination schedules. However, rabies vaccine adsorbed (RVA, Bioport Corporation) is no longer available for rabies postexposure or pre-exposure prophylaxis, and intradermal pre-exposure prophylaxis is no longer recommended because it is not available in the United States.*

The material in this report originated in the National Center for Zoonotic, Vector-Borne and Enteric Diseases, Lonnie King, DVM, Director.
**Corresponding preparer:** Charles E. Rupprecht, VMD, National Center for Zoonotic, Vector-Borne and Enteric Diseases, 1600 Clifton Road, N.E., MS G33, Atlanta, GA 30333. Telephone: 404-639-1050; Fax: 404-639-1564; E-mail: cyr5@cdc.gov.

## Introduction

Rabies is a zoonotic disease caused by RNA viruses in the Family *Rhabdoviridae*, Genus *Lyssavirus* (*1–4*). Virus is typically present in the saliva of clinically ill mammals and is transmitted through a bite. After entering the central nervous system of the next host, the virus causes an acute, progressive encephalomyelitis that is almost always fatal. The incubation period in humans is usually several weeks to months, but ranges from days to years.

As a result of improved canine vaccination programs and stray animal control, a marked decrease in domestic animal rabies cases in the United States occurred after World War II. This decline led to a substantial decrease in indigenously acquired rabies among humans (*5*). In 1946, a total of 8,384 indigenous rabies cases were reported among dogs and 33 cases in humans. In 2006, a total of 79 cases of rabies were reported in domestic dogs, none of which was attributed to enzootic dog-to-dog transmission, and three cases were reported in humans (*6*). The infectious sources of the 79 cases in dogs were wildlife reservoirs or dogs that were translocated from localities where canine rabies virus variants still circulate. None of the 2006 human rabies cases was acquired from indigenous domestic animals (*6*). Thus, the likelihood of human exposure to a rabid domestic animal in the United States has decreased substantially. However, one of the three human rabies cases diagnosed in 2006 was associated with a dog bite that occurred in the Philippines, where canine rabies is enzootic. The risk for reintroduction from abroad remains (*7*). International travelers to areas where canine rabies remains enzootic are at risk for exposure to rabies from domestic and feral dogs.

Unlike the situation in developing countries, wild animals are the most important potential source of infection for both humans and domestic animals in the United States. Most reported cases of rabies occur among carnivores, primarily raccoons, skunks, and foxes and various species of bats. Rabies among insectivorous bats occurs throughout the continental United States. Hawaii remains consistently rabies-free. For the past several decades, the majority of naturally acquired, indigenous human rabies cases in the United States have resulted from variants of rabies viruses associated with insectivorous bats (*5*). The lone human case reported in the United States during 2005 and two of the three human rabies cases in 2006 were attributed to bat exposures (*6,8*). During 2004, two of the eight human rabies cases resulted from bat exposures. One of these rabies patients recovered and remains the only rabies patient to have survived without the administration of rabies vaccination (*9*). Rabies was not immediately recognized as the cause of death in the other 2004 patient, and organs and a vascular graft from this patient were transplanted into four persons, resulting in clinical rabies and death in all of the recipients (*10*).

Approximately 16,000–39,000 persons come in contact with potentially rabid animals and receive rabies postexposure prophylaxis each year (*11*). To appropriately manage potential human exposures to rabies, the risk for infection must be accurately assessed. Administration of rabies postexposure prophylaxis is a medical urgency, not a medical emergency, but decisions must not be delayed. Prophylaxis is occasionally complicated by adverse reactions, but these reactions are rarely severe (*12–16*).

For these recommendations, data on the safety and efficacy of active and passive rabies vaccination were derived from both human and animal studies. Because controlled human trials cannot be performed, studies describing extensive field experience and immunogenicity studies from certain areas of the world were reviewed. These studies indicated that postexposure prophylaxis combining wound treatment, local infiltration of rabies immune globulin (RIG), and vaccination is uniformly effective when appropriately administered (*17–22*). However, rabies has occasionally developed among humans when key elements of the rabies postexposure prophylaxis regimens were omitted or incorrectly administered. Timely and appropriate human pre-exposure and postexposure prophylaxis will prevent human rabies; however, the number of persons receiving prophylaxis can be reduced if other basic public health and veterinary programs are working to prevent and control rabies. Practical and accurate health education about rabies, domestic animal vaccination and responsible pet care, modern stray animal control, and prompt diagnosis can minimize unnecessary animal exposures, alleviate inherent natural risks after exposure, and prevent many circumstances that result in the need for rabies prophylaxis.

## Methods

The Advisory Committee on Immunization Practices (ACIP) Rabies Workgroup first met in July 2005 to review previous ACIP recommendations on the prevention of human rabies (published in 1999) and to outline a plan for updating and revising the recommendations to provide clearer, more specific guidance for the administration of rabies preexposure and postexposure prophylaxis. The workgroup held monthly teleconferences to discuss their review of published and unpublished data on rabies and related biologic products. Data on the effectiveness, efficacy, immunogenicity, and safety of rabies biologics in both human and animal studies were reviewed using a systematic, evidence-based approach.

Randomized trials or well-conducted cohort studies with untreated comparison groups would provide the best evidence of the direct effectiveness of rabies pre-exposure and postexposure prophylaxis to prevent rabies-associated death. However, because of the almost universal fatality among untreated persons infected with rabies virus, no such controlled studies exist. However, studies describing final health outcomes among persons exposed to the rabies virus do exist, including studies using formulations of rabies biologics, timing of vaccine doses, and routes of administration that are not recommended for use in the United States. These and other studies were identified by reviewing the PubMed database and relevant bibliographies and by consulting subject-matter experts. The literature review did not identify any studies of the direct effectiveness of rabies pre-exposure vaccination in preventing human rabies cases. Such studies would be difficult to conduct because rabies pre-exposure vaccination is intended to simplify the postexposure prophylaxis that is required after a recognized rabies exposure. Rabies pre-exposure vaccination also might afford immunity against an unrecognized rabies exposure, an outcome that would be difficult to measure in controlled studies. However, rabies cases have occurred among those who received rabies pre-exposure prophylaxis and did not receive rabies postexposure prophylaxis (*23*), indicating that pre-exposure prophylaxis in humans is not universally effective without postexposure prophylaxis. Because of the paucity of formal studies on the effectiveness of rabies pre-exposure vaccination in humans, the literature was searched for studies that reported clinical outcomes among animals that received pre-exposure rabies prophylaxis with cell culture rabies vaccine and were subsequently challenged with rabies virus. Evaluation of the effectiveness of antirabies biologics in experimental animal models has been essential to developing successful rabies prevention approaches for exposed humans. Animal studies investigating the effectiveness of both pre-exposure and posteexposure rabies prophylaxis were reviewed and were used to make inferences about the direct effectiveness of licensed rabies biologics in preventing human rabies.

Data regarding the immunogenicity of rabies biologics also were reviewed. Assessing protective immunity against rabies is complex. Virus neutralizing antibodies are believed to have a primary role in preventing rabies virus infection. However, antibody titers alone do not always directly correlate with absolute protection because of other important immunologic factors. Nonetheless, the ability of a vaccine to elicit rabies virus neutralizing antibodies in animals and humans and the demonstration of protection in animals is generally viewed as a reasonable surrogate of protection for inferential extension to humans (*24*). Although a definitive "protective" titer cannot be described for all hosts under all exposure scenarios, two working definitions of adequate rabies virus neutralizing antibody reference values have been developed to define an appropriate, intact adaptive host response to vaccination. The literature review included studies in humans that measured rabies virus neutralizing antibody in response to rabies postexposure prophylaxis consisting of human rabies immune globulin (HRIG) and 5 intramuscular (IM) doses of cell culture rabies vaccine and the recommended pre-exposure prophylaxis regimen of 3 IM doses of cell culture vaccine. The outcomes of interest for these studies were antibody titers of 0.5 IU/mL (used by the World Health Organization [WHO] as an indicator of an adequate adaptive immune response) (*25*) or complete virus neutralization at a 1:5 serum dilution by the rapid fluorescent focus inhibition test (RFFIT) (used by ACIP as an indicator of an adequate adaptive immune response) (*26*). The literature also was searched for evidence regarding the safety of the licensed rabies biologics available for use in the United States in both pre-exposure and postexposure situations.

ACIP's charter requires the committee to consider the costs and benefits of potential recommendations when they are deliberating recommendations for vaccine use in the United States. Few studies exist on the cost-effectiveness of rabies prophylaxis in various potential exposure scenarios. A challenge in conducting such studies is the lack of data on the probability of rabies transmission under different exposure scenarios, except when the involved animal tests positive for rabies. To provide information on the cost-effectiveness of rabies postexposure prophylaxis, a new analysis was conducted to estimate the cost-effectiveness of rabies postexposure prophylaxis in various potential exposure scenarios. A Delphi methodology was used to estimate the risk for transmission of rabies to a human in each of the scenarios, and this information was used in the cost-effectiveness calculations.

The rabies workgroup reviewed the previous ACIP recommendations on the prevention of human rabies and deliberated on the available evidence. When definitive research evidence was lacking, the recommendations incorporated expert opinion of the workgroup members. The workgroup sought input from members of the National Association of State Public Health Veterinarians, the Council of State and Territorial Epidemiologists (CSTE), and state and local public health officials. The proposed revised recommendations and a draft statement were presented to ACIP in October 2006. After deliberations, the recommendations were unanimously approved with minor modifications. Further modifications to the draft statement were made following the CDC

and external review process to update and clarify wording in the document.

## Rabies Biologics

Three cell culture rabies vaccines are licensed in the United States: human diploid cell vaccine (HDCV, Imovax® Rabies, sanofi pasteur), purified chick embryo cell vaccine (PCECV, RabAvert®, Novartis Vaccines and Diagnostics), and rabies vaccine adsorbed (RVA, Bioport Corporation). Only HDCV and PCECV are available for use in the United States (Table 1). For each of the available vaccines, the potency of 1 dose is greater than or equal to the WHO-recommended standard of 2.5 international units (IU) per 1.0 mL of vaccine (*27*). A full 1.0-mL IM dose is used for both pre-exposure and postexposure prophylaxis regimens. Rabies vaccines induce an active immune response that includes the production of virus neutralizing antibodies. The active antibody response requires approximately 7–10 days to develop, and detectable rabies virus neutralizing antibodies generally persist for several years. A vaccination series is initiated and completed usually with one vaccine product. No clinical trials were identified that document a change in efficacy or the frequency of adverse reactions when the series is initiated with one vaccine product and completed with another.

The passive administration of RIG is intended to provide an immediate supply of virus neutralizing antibodies to bridge the gap until the production of active immunity in response to vaccine administration. Use of RIG provides a rapid, passive immunity that persists for a short time (half-life of approximately 21 days) (*28*). Two antirabies immune globulin (IgG) formulations prepared from hyperimmunized human donors are licensed and available for use in the United States: HyperRab™ S/D (Talecris Biotherapeutics) and Imogam® Rabies-HT (sanofi pasteur). In all postexposure prophylaxis regimens, except for persons previously vaccinated, HRIG should be administered concurrently with the first dose of vaccine.

## Vaccines Licensed for Use in the United States

### Human Diploid Cell Vaccine

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 (*22*). HDCV is formulated for IM administration in a single-dose vial containing lyophilized vaccine that is reconstituted in the vial with the accompanying sterile diluent to a final volume of 1.0 mL just before administration. One dose of reconstituted vaccine contains <150 μg neomycin sulfate, <100 mg albumin, and 20 μg of phenol red indicator. It contains no preservative or stabilizer.

### Purified Chick Embryo Cell Vaccine

PCECV became available in the United States in 1997. The vaccine is prepared from the fixed rabies virus strain Flury LEP grown in primary cultures of chicken fibroblasts (*29*). The virus is inactivated with betapropiolactone and further processed by zonal centrifugation in a sucrose density gradient. It is formulated for IM administration in a single-dose vial containing lyophilized vaccine that is reconstituted in the vial with the accompanying sterile diluent to a final volume of 1.0 mL just before administration. One dose of reconsti-

**TABLE 1. Currently available rabies biologics — United States, 2008**

| Human rabies vaccine | Product name | Manufacturer | Dose | Route | Indications |
|---|---|---|---|---|---|
| Human diploid cell vaccine | Imovax® Rabies* | sanofi Pasteur<br>Phone: 800-822-2463<br>Website: http://www.vaccineplace.com/products/ | 1 mL | Intramuscular | Pre-exposure or postexposure† |
| Purified chick embryo cell vaccine | RabAvert® | Novartis Vaccines and Diagnostics<br>Phone: 800-244-7668<br>Website: http://www.rabavert.com | 1 mL | Intramuscular | Pre-exposure or postexposure† |
| **Rabies immune globulin** | Imogam® Rabies-HT | sanofi pasteur<br>Phone: 800-822-2463<br>Website: http://www.vaccineplace.com/products/ | 20 IU/kg | Local§ | Postexposure only |
| | HyperRab™ S/D | Talecris Biotherapeutics<br>Bayer Biological Products<br>Phone: 800-243-4153<br>Website: http://www.talecris-pi.info | 20 IU/kg | Local§ | Posteexposure only |

* Imovax rabies I.D., administered intradermally, is no longer available in the United States.
† For postexposure prophylaxis, the vaccine is administered on days 0, 3, 7, 14 and 28 in patients who have not been previously vaccinated and on days 0 and 3 in patients who have been previously vaccinated. For pre-exposure prophylaxis, the vaccine is administered on days 0, 7 and 21 or 28.
§ As much of the product as is anatomically feasible should be infiltrated into and around the wound. Any remaining product should be administered intramuscularly in the deltoid or quadriceps (at a location other than that used for vaccine inoculation to minimize potential interference).

tuted vaccine contains <12 mg polygeline, <0.3 mg human serum albumin, 1 mg potassium glutamate, and 0.3 mg sodium EDTA. No preservatives are added.

## Rabies Immune Globulins Licensed for Use in the United States

The two HRIG products, HyperRab™ S/D and Imogam® Rabies-HT, are IgG preparations concentrated by cold ethanol fractionation from plasma of hyperimmunized human donors. The HyperRab™ S/D is formulated through the treatment of the immune globulin fraction with 0.3% tri-n-butyl phosphate (a solvent to inactivate potential adventitious viruses) and 0.2% sodium cholate (a detergent to inactivate potential adventitious viruses) and the application of heat (30°C [86°F] for 6 hours). After ultrafiltration, the final product is a 15%–18% protein solution in glycine. The Imogam® Rabies-HT is prepared from the cold ethanol fraction of pooled venous plasma of donors, stabilized with glycine, and subjected to a heat-treatment process (58°C–60°C [136°F–140°F] for 10 hours) to inactivate potential adventitious viruses, with the final formulation consisting of 10%–18% protein. Both HRIGs are standardized at an average potency value of 150 IU per mL, and 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 (0.133 mL/kg) body weight. Both HRIG preparations are considered equally efficacious when used as described in these recommendations.

These products are made from the plasma of hyperimmunized human donors that, in theory, might contain infectious agents. Nevertheless, the risk that such products will transmit an infectious agent has been reduced substantially by screening plasma donors for previous exposure to certain viruses, by testing for the presence of certain current virus infections, and by inactivating and/or removing certain viruses. No transmission of adventitious agents has been documented after administration of HRIGs licensed in the United States.

## Effectiveness and Immunogenicity of Rabies Biologics

### Effectiveness of Rabies Postexposure Prophylaxis: Human Studies

A literature search identified 11 studies regarding the direct effectiveness of varying regimens of rabies postexposure prophylaxis in preventing rabies-associated deaths (*18,30–39*). An additional eight studies were identified from reviews of bibliographies or consultations with subject matter experts (*19,40–46*).

Three large retrospective cohort studies were identified that describe differences in rabies mortality between rabies-exposed persons (persons who were exposed to proven or suspected rabid animals) who were vaccinated with older formulations of rabies vaccine compared with similarly exposed persons who were not administered prophylaxis (*41,44,46*). In one 1923 study of 2,174 persons bitten by "presumably rabid" dogs in India, 2.9% of persons vaccinated with 1% Semple nerve tissue rabies vaccine (NTV) subcutaneously for 14 days died from rabies compared with 6.2% of unvaccinated persons (*41*). Another study of persons bitten by assumed infective rabid animals (i.e., one or more other persons bitten by the same animal died from rabies) during 1946–1951 indicated that 8.3% of persons "completely treated" with 5% Semple rabies vaccine, 23.1% of "incompletely treated", and 43.2% of unvaccinated persons died from rabies (*46*). A third study in Thailand in 1987 documented no deaths among 723 persons bitten by dogs (661 of these persons were bitten by confirmed rabid dogs) who received one of three rabies vaccines: Semple vaccine (n = 427), HDCV (n = 257), or duck embryo vaccine (n = 39) (*44*). However, 45% (nine of 20) of unvaccinated persons who were bitten by confirmed rabid dogs died from rabies. All of the persons who died were severely bitten on the face, neck, or arms. All unvaccinated persons who survived after having been bitten by confirmed rabid dogs were bitten either on the legs or feet. Although these studies describe outcomes of persons receiving older formulations of rabies vaccines that are not used in the United States, they demonstrate that a majority of persons bitten by known rabid dogs did not acquire rabies and provide historical evidence of a substantial protective effect of rabies vaccination after rabies exposure.

The effectiveness of cell culture rabies vaccine plus rabies IgG in preventing human deaths after rabies exposure has been demonstrated in certain studies (*18,19,30–32,39,45*). One prospective study described 10 children (aged <12 years) and 32 adults who had been administered HRIG (Hyperrab®, Cutter Laboratories, Berkeley, CA, USA) and 5 IM doses of HDCV (L'Institut Merieux, Lyons, France) after exposure to suspected or confirmed rabid animals (brain-tissue positive by fluorescent antibody testing) (*30*). All exposed persons remained rabies-free during 5 years of observation. Another study investigated outcomes for 90 persons with high-risk exposures (bites or direct exposure to saliva from animals shown to be rabid by fluorescent antibody tests or bites from wild carnivores or bats that were not available for testing) who were treated with HRIG and 5 IM doses of HDCV (Wyeth Laboratories, Radnor, PA) (*18*). All patients, including 21 who were bitten by proven rabid animals (brain tissue

fluorescent antibody positive), were rabies-free after 10–18 months of follow-up. A third study documented 45 persons severely bitten by confirmed rabid animals (brain tissue fluorescent antibody positive) who were administered RIG of mule origin and 5 IM doses of HDCV (L'Institut Merieux) (*19*). No rabies-related deaths were documented 6–12 months after exposure. A fourth study indicated no human rabies cases in 12 months of follow-up among 45 patients receiving HRIG (Berirab®) and 6 IM doses of PCECV (Behringwerke Research Laboratories, Marburg, West Germany) after contact with proven rabid animals (brain tissue fluorescent antibody positive) (*32*). Other studies examining outcomes for persons with varying degrees of exposure to confirmed rabid animals who were administered 6 doses of PCECV IM with or without HRIG also reported no rabies deaths in 12–15 months of follow-up (*39,45*). Several studies also have demonstrated the effectiveness of intradermal (ID) administration of cell culture rabies vaccine with or without RIG (of human or equine origin) in preventing rabies among exposed humans (*33–35,37*).

Two studies demonstrated the role of RIG administration in conjunction with vaccine in rabies postexposure prophylaxis (*42,43*). The first described quantitative serologic outcomes in 29 persons severely bitten by a rabid wolf and demonstrated the importance of rabies antiserum administration in the establishment of an early, passive, rabies virus neutralizing antibody level in patients and protection against rabies (*40,43*). Among five patients treated with 2 doses of rabies antiserum and NTV for 21 days, all had detectable levels of rabies virus neutralizing antibody during the first 5 days and all survived. Among seven patients treated with 1 dose of antiserum in addition to NTV, all had detectable antibody during the first 5 days, but four of six had low antibody titers by day 21. One of the seven failed to develop more than a very low antibody level beyond day 7 and eventually died from rabies. Among the five persons treated with NTV without antiserum, none had detectable antibody levels before day 19, and three died from rabies. In the second study, none of 27 persons severely wounded by rabid animals in China who were treated with purified hamster kidney cell (PHKC) rabies vaccine plus horse-origin rabies immune serum died from rabies (*42*). In contrast, all three severely wounded persons treated with PHKC alone died.

## Effectiveness of Rabies Postexposure Prophylaxis: Animal Studies

During the preceding four decades, results of experimental studies using various animal species have supported the use of cell culture-based vaccines for protection against rabies after infections. For example, a postexposure prophylaxis experiment conducted in 1971 in rhesus monkeys using an experimental purified, concentrated tissue-culture vaccine alone, or in combination with homologous antirabies serum, demonstrated that a single administration of tissue-culture vaccine after exposure to rabies virus provided substantial (seven of eight animals) protection against the development of rabies. In addition to demonstrating that homologous or heterologous antirabies serum alone resulted in poor protection from rabies (63%–88% mortality), the experimental data suggested that highly concentrated, purified tissue-culture vaccine might be effective for postexposure prophylaxis in humans (*47*). A study in 1981 documented limited protection against a lethal rabies virus challenge in goats who received ERA vaccine with or without antirabies goat serum (*48*). In cattle, another livestock species, the superiority of tissue culture vaccine over brain-origin vaccine was demonstrated (*49*). Similarly, in sheep, vaccine alone provided limited protection, but vaccine in combination with polyclonal IgG provided the best outcome (*50*). A 1989 evaluation of postexposure prophylaxis administered to dogs demonstrated similar findings. The combination of serum and vaccine provided nearly complete protection compared with animals receiving vaccine only and nontreated controls (*51*).

Previous animal postexposure research focused primarily on interventions against traditional rabies viruses. However, new causative agents of rabies continue to emerge, as demonstrated by the recent description of four novel lyssaviruses from bats in Eurasia, Aravan (ARAV), Khujand (KHUV), Irkut (IRKV), and West Caucasian bat virus (WCBV) (*52,53*). The combined effect of RIG and vaccine after exposure to these four new isolates was investigated in a Syrian hamster model, using commercially available human products or an experimental mAb (*54*). Conventional rabies postexposure prophylaxis provided little or no protection against all four new bat viruses. In general, protection was inversely related to the genetic distance between the new isolates and traditional rabies viruses, which demonstrated the usefulness of this animal model in estimating the potential impact of these new lyssaviruses on human and domestic animal health.

## Immunogenicity of Rabies Postexposure Prophylaxis

To assess the ability of rabies postexposure prophylaxis to elicit rabies virus neutralizing antibodies in humans, studies were reviewed that documented antibody responses to rabies postexposure prophylaxis. Four studies of antibody responses to rabies postexposure prophylaxis with 5 IM doses of HDCV with or without HRIG were identified (*30,55–57*). Because no studies were identified that examined antibody responses to postexposure or simulated postexposure prophylaxis with

5 IM doses of the licensed PCECV vaccine (RabAvert®) plus HRIG, a study reporting antibody responses to 6 IM doses of another PCECV formulation (Rabipur®, Novartis Vaccines and Diagnostics) administered with or without HRIG was reviewed (*36*). In a randomized trial, all persons receiving HRIG and 5 IM doses of HDCV (Imovax® Rabies) developed rabies virus antibody titers ≥0.5 IU/mL lasting up to 42 days after prophylaxis initiation (*56*). In a 1999 case-series, among 40 persons with diverse histories of exposure to animals suspected of having rabies, all persons who received 5 IM doses of HDCV with or without HRIG seroconverted or had increases in baseline serum antibody titers after the fifth vaccine dose (geometric mean titer [GMT] = 6.22 IU/mL) (*57*). Furthermore, a significantly higher mean antibody titer was observed in the group that received HDCV and HRIG (GMT = 12.3 IU/mL; standard error [SE] = 2.9) than in the group that received HDCV alone (GMT = 8.5 IU/mL; SE = 1.6; p=0.0043). In a randomized, modified double-blind, multicenter, simulated postexposure trial, 242 healthy adult volunteers were administered HRIG (Imogam® Rabies-HT) and 5 IM doses of either HDCV (Imovax® Rabies) or a chromatographically purified Vero-cell rabies vaccine (CPRV) (*55*). All participants had rabies virus neutralizing antibody titers ≥0.5 IU/mL by day 14 and maintained this level through day 42. Participants receiving HDCV had higher GMTs on days 14 and 42 than did participants receiving CPRV. In the prospective study comparing rabies neutralizing antibodies in the serum of children compared with adults following postexposure prophylaxis, all 25 adults and eight children tested on day 14 had rabies virus neutralizing antibody concentrations ≥0.5 IU/mL (*30*). In addition, no differences in antibody titer were observed between adults and children, and all persons remained alive during the 5 years of follow-up.

## Effectiveness of Rabies Pre-Exposure Prophylaxis: Animal Studies

Because no studies exist on the effectiveness of rabies pre-exposure prophylaxis in preventing rabies deaths in humans, literature was reviewed on the effectiveness of pre-exposure vaccination in animal models. The effectiveness of rabies vaccine has been appreciated for most of the 20th century on the basis of animal experiments. Commercial rabies vaccines are licensed for certain domestic species, all of which entail the direct demonstration of efficacy after the administration of a single pre-exposure dose, and observed protection from rabies virus challenge for a minimum duration of 1–4 years after vaccination of captive animals. In addition, rabies pre-exposure vaccine research varies typically either by modification of standard regimens of vaccination or the relative antigenic value or potency of vaccine administration to animals. For example, at least five studies involved animals challenged with rabies viruses (challenge standard virus [CVS] or street rabies virus isolates) and other lyssaviruses (European bat lyssavirus [EBL] 1, EBL2, Australian bat lyssavirus [ABL], and WCBV, IRKV, ARAV, KHUV) after primary vaccination with PCECV (*58*) or HDCV (*54,58–62*). Two of seven studies reported seroconversion in mice and humans. Complete protection of animals from rabies virus infection was observed in all experiments that used PCECV or HDCV IM for primary vaccination except in one group that had been challenged by CVS through the intracranial route and experienced 5% mortality (*59*). Evaluation of crossprotection of HDCV against WCBV, ARAV, IRKV, KHUV, and ABL through IM challenge showed 44%, 55%, 67%, 89% and 79% survival, respectively (*54*). These studies demonstrated the usefulness of commercial human vaccines when administered to animals, with resulting protection dependent on the relative degree of phylogenetic relatedness between the rabies vaccine strain and the particular lyssavirus isolate.

## Immunogenicity of Rabies Pre-Exposure Prophylaxis: Human Studies

Thirteen studies were identified that provide evidence of the effectiveness of pre-exposure rabies vaccination in eliciting an adaptive host immune response in humans. The outcomes of interest for these studies (*29,63–74*) include the two working definitions of adequate rabies virus neutralizing antibody reference values that have been developed to define an appropriate, intact adaptive host response to vaccination: antibody titers of 0.5 IU/mL or complete virus neutralization at a 1:5 serum dilution by RFFIT (*26*).

Multiple studies comparing different pre-exposure prophylaxis regimens provide evidence that vaccination with 3 IM doses of cell culture rabies vaccine (the recommended pre-exposure regimen) result in neutralizing antibody titers ≥0.5 IU/mL by days 14 (*70,71*), 21 (*63,74*), 28 (*64,69,72*), or 49 (*67,68,75*) after primary vaccination. One study in 1987 documented antibody responses in 177 healthy student volunteers aged 18–24 years following primary vaccination with either PCECV (Behringwerke) or HDCV (Behringwerke) (*71*). On day 14 after vaccination (first dose administered on day 0), no significant difference in GMT was observed between participants who received 3 IM doses of PCECV on days 0, 7, and 21 (GMT = 5.9 IU/mL) compared with persons who received 3 IM doses of HDCV (GMT = 4.4 IU/mL). On day 42, the GMT of the HDCV group was significantly higher than that of the PCECV group (13.7 IU/mL versus 8.4 IU/mL; p<0.025). Another study documented similar antibody responses to primary vaccination with HDCV in healthy veterinary students (*64*). The GMT of persons

receiving 3 IM doses of HDCV on days 0, 7, and 28 was 10.2 IU/mL (range: 0.7–51.4) on day 28 and 37.7 IU/mL (range: 5.4–278.0) on day 42. Another study documented even higher GMTs among 78 volunteers in a randomized trial studying differences between primary vaccination with PCECV (Behringwerke) and HDCV (L'Institut Merieux) administered IM or ID on days 0, 7, and 28 (*29*). The day 28 GMT among persons receiving HDCV IM (GMT = 239 RFFIT titer/mL; range: 56–800) was significantly higher than the GMT among persons receiving PCECV IM (GMT = 138 RFFIT titer/mL; range: 45–280). On days 50 and 92, no significant difference in GMT was observed between the two groups in which vaccine was administered IM, and the GMTs of the IM groups were significantly higher than the ID groups. Another study also observed higher antibody titers on days 49 and 90 and 26 months after primary vaccination with HDCV (Imovax® Rabies) when the vaccine was administered IM compared with ID on days 0, 7, and 28 (*68*). A randomized trial was conducted to determine the equivalence and interchangeability of PCECV (RabAvert®) and HDCV (Imovax® Rabies) administered IM on days 0, 7, and 28 for rabies pre-exposure prophylaxis to 165 healthy, rabies vaccine naïve veterinary students (*66*). No significant difference in GMT was observed among the HDCV and PCECV groups on days 28 and 42.

Although the 3-dose rabies pre-exposure prophylaxis series has been the standard regimen recommended by WHO (*17*) and ACIP (*26*), a 2-dose pre-exposure series has been used previously in some countries (*76*). One study compared antibody responses in persons receiving 2 (days 0 and 28) versus 3 (days 0, 7, and 28) IM doses of either HDCV (Pasteur Merieux Connaught, Lyon, France) or purified Vero cell rabies vaccine (PVRV) (Pasteur Merieux Connaught) and indicated that the cohort seroconversion rate decreased more rapidly among persons receiving 2 doses compared with those receiving 3 doses ($p<0.001$), indicating superior longer term immunogenicity when 3 vaccine doses were administered (*73*).

In addition to the rapidity of the immune response resulting from rabies pre-exposure vaccination, another important consideration is the length of duration or persistence of the immune response. One study reported rapid declines in GMT at 4 months after initial vaccination among persons receiving 3-dose primary vaccination with HDCV (L'Institut Merieux) or PVRV (L'Institut Merieux) on days 0, 7, and 21 followed by stabilization of the antibody level through 21 months (*63*). Another study observed persistent GMTs among persons receiving 3-dose (days 0, 7, and 28) primary vaccination with PCECV (Behringwerke) and HDCV (L'Institut Merieux) IM on day 365 (PCECV GMT = 189 RFFIT titer/mL; range: 53–1400; HDCV GMT = 101 RFFIT titer/mL; range: 11–1400) and day 756 (PCECV GMT = 168 RFFIT titer/mL; range: 50–3600; HDCV GMT = 92 RFFIT titer/mL; range: 11–480) after initial vaccination (*29*). On day 387 post vaccination, another study indicated that the GMT among persons receiving PCECV (RabAvert®) IM on days 0, 7, and 28 (GMT = 2.9 IU/mL) was significantly higher than the GMT in the HDCV (Imovax® Rabies) group (GMT = 1.5 IU/mL; $p<0.05$) (*66*). All persons vaccinated with PCECV had antibody titers >0.5 IU/mL on days 387, as did 95.7% of persons vaccinated with HDCV. Another study indicated that all persons receiving PCECV (Behringwerke) IM on days 0, 7, and 21 maintained antibody titers >0.5 IU/mL 2 years after primary vaccination (*71*). In summary, rabies virus neutralizing antibody titers >0.5 IU/mL were observed in all persons at 180 days and 96.8% at 365 days after initial vaccination (*72*), 94% of persons at 21 months after initial vaccination (*63*), and all persons tested at 26 months after primary vaccination (*77*).

An important use of rabies pre-exposure prophylaxis is to prime the immune response to enable a rapid anamnestic response to postexposure booster vaccination and simplify the postexposure prophylaxis requirements for previously vaccinated persons. One study observed antibody responses to 1- or 2-dose (days 0 and 3) IM booster vaccinations with PCECV (RabAvert®) in persons who had received primary vaccination with either PCECV IM or HDCV IM 1 year earlier (*66*). All participants who had initially received PCECV primary vaccination and 66 of 69 (96%) who had initially received HDCV primary vaccination had titers >0.5 IU/mL before booster vaccination. No significant differences in GMT were observed between 1- and 2-dose booster groups on days 3 (2-dose GMT = 2.07 IU/mL; 1-dose GMT = 2.87 IU/mL), seven (2-dose GMT = 51.67 IU/mL; 1-dose GMT = 51.23 IU/mL) and 365 (2-dose GMT = 30.60 IU/mL; 1-dose GMT = 26.10 IU/mL) (*66*). However, a significantly higher GMT was observed on day 21 for persons receiving 2-dose boosters (GMT = 151.63 IU/mL) compared with 1-dose boosters (GMT = 120.91 IU/mL). All persons tested at day 365 post-booster dose in both 1- and 2-dose booster groups had rabies virus neutralizing antibody titers >0.5 IU/mL regardless of whether PCECV or HDCV was used for primary vaccination. Another study documented rapid antibody responses to a single booster dose of HDCV (Imovax® Rabies) or CPRV (Pasteur Merieux Connaught), with all persons in both groups exhibiting antibody titers >0.5 IU/mL on days 7 and 14 post-booster dose (*72*).

## Safety of Rabies Biologics

Eight studies regarding the safety of rabies biologics used in postexposure or simulated postexposure settings (*36,55–57,78–81*) and eight studies of safety in pre-exposure settings were identified (*63–65,68,71,72,82*). Three identified studies investigated reports of adverse events in both postexposure and pre-exposure settings (*14,83,84*). Reviews of relevant bibliographies identified one additional study examining the safety of PCECV when used without HRIG for postexposure prophylaxis in children (*85*).

### HDCV

Studies of the use of HDCV reported local reactions (e.g., pain at the injection site, redness, swelling, and induration) among 60.0%–89.5% of recipients (*63–65,68,72*). Local reactions were more common than systemic reactions. Most local reactions were mild and resolved spontaneously within a few days. Local pain at the injection site was the most frequently reported adverse reaction occurring in 21%–77% of vaccinees (*24,63,68,71,72,80*). Mild systemic reactions (e.g., fever, headache, dizziness, and gastrointestinal symptoms) were reported in 6.8%–55.6% of recipients (*63,64,68,72*).

Systemic hypersensitivity reactions have been reported in up to 6% of persons receiving booster vaccination with HDCV following primary rabies prophylaxis, 3% occurring within 1 day of receiving boosters, and 3% occurring 6–14 days after boosters (*82*). In one study, hypersensitivity reactions (e.g., urticaria, pruritic rash, and angioedema) were reported in 5.6% (11 of 99) of schoolchildren aged 5–13 years following pre-exposure prophylaxis with IM HDCV (*72*). Angioedema was observed in 1.2% of these school children after booster doses of HDCV 1 year after primary vaccination with HDCV. In 46 months of surveillance for adverse events following HDCV administration during 1980–1984, CDC received reports of 108 systemic allergic reactions (ranging from hives to anaphylaxis) following HDCV (11 per 10,000 vaccinees) (*14*). These included nine cases of presumed Type I immediate hypersensitivity (one of 10,000), 87 cases of presumed Type III hypersensitivity (nine of 10,000), and 12 cases of hypersensitivity of indeterminate type. All nine of the presumed immediate hypersensitivity reactions occurred during either primary pre-exposure or postexposure vaccination. Most (93%) of the Type III hypersensitivity reactions were observed following booster vaccination. Systemic allergic reactions have been associated with the presence of betapropiolactone-altered human albumin in HDCV and the development of immunoglobulin E (IgE) antibodies to this allergen (*82,86*). No deaths resulting from these reactions were reported.

In four studies investigating the safety of rabies postexposure prophylaxis with both HRIG and HDCV, no serious adverse events were observed (*55–57,78*). Local reactions were common, and pain at the injection site was reported by 7%–92% of participants (*55–57*). Studies of the frequency of systemic adverse reactions following rabies vaccination are limited by small sample sizes. Systemic adverse reactions were not observed in any of the participants in one study with a relatively small sample size (*78*). In two other studies in which adverse events were collected using patient self-monitoring forms and investigator interviews at each visit, systemic reactions were reported by 76%–100% of participants (*55,56*). However, none of these reported systemic adverse events was considered to be serious.

Rare, individual case reports of neurologic adverse events following rabies vaccination have been reported, but in none of the cases has causality been established. Four cases of neurologic illness resembling Guillain-Barré syndrome occurring after treatment with HDCV were identified (*13,87–89*). One case of acute neurologic syndrome involving seizure activity was reported following the administration of HDCV and HRIG (*90*). Other central and peripheral nervous system disorders have been temporally associated with HDCV vaccine (*91*).

### PCECV

In studies of PCECV use, local reactions (e.g., pain at the injection site, redness, swelling, and induration) were reported among 11%–57% of recipients (*29,79,84*). Local pain at the injection site, the most common local reaction, was reported in 2%–23% of vaccinees (*29,71,79,81,83,85*). Systemic reactions were less common and have been reported in 0–31% of vaccine recipients (*79,83,84*). One study investigated adverse events among 271 children in India who received rabies postexposure prophylaxis with PCECV IM without HRIG following bites from suspected or confirmed rabid dogs (*85*). Overall, 7% of the children experienced mild to moderate clinical reactions. The most frequently reported reaction was local pain after the first or second dose (4%). Another study documented clinical reactions in 29 persons administered 6 IM doses of PCECV with (n = four) or without HRIG following bites by suspected rabid stray dogs. No serious adverse events were observed during the course of or after prophylaxis (*36*). Another case report documented one case of neurologic illness resembling Guillain-Barré syndrome after vaccination with PCECV in India (*92*).

A retrospective review of adverse events following administration of PCECV was conducted using data from the United

States Vaccine Adverse Events Reporting System (VAERS) (*93*). During 1997–2005, approximately 1.1 million doses of PCECV were distributed in the United States and 336 reports describing adverse events following PCECV administration were received by VAERS (30 events per 100,000 doses distributed and three serious events per 100,000 doses distributed). A total of 199 reported adverse events (4% serious [i.e., adverse events that involve hospitalization, life-threatening illness, disability, or death]) occurred following administration of PCECV alone, and 137 (12% serious) occurred following PCECV administered concomitantly with another vaccine or following postexposure prophylaxis (PCECV co-administered with HRIG). Among the 312 nonserious adverse events, the most frequently reported were headache, fever, myalgia, nausea, and weakness. A limitation of VAERS is that causality between vaccine administration and reported adverse events cannot be established (*94*). No deaths or rabies cases were reported following administration of PCECV.

### HRIG

In a clinical trial involving 16 volunteers in each group, participants receiving HRIG plus placebo (administered to mimic vaccine) commonly reported local reactions (100% in conventionally produced HRIG group, 75% in heat-treated HRIG group), including pain/tenderness (100% conventional HRIG, 50% heat-treated HRIG), erythema (63% conventional, 25% heat-treated), and induration (50% conventional, 31% heat-treated) (*56*). Systemic reactions were reported in 75% of participants in the conventional HRIG group and 81% in the heat-treated group. Headache was the most commonly reported systemic reaction (50% conventional, 69% heat-treated). The majority of the reported local and systemic reactions were mild, and no significant differences were observed in the frequency of adverse events between treatment groups. No serious adverse events, including immediate hypersensitivity reactions or immune-complex-like disease, were reported.

## Cost-Effectiveness of Rabies Postexposure Prophylaxis

ACIP's charter requires the committee, when deliberating recommendations for vaccine use in the United States, to consider the cost and benefits of potential recommendations. Cost-effectiveness studies combine different types of data (e.g., epidemiologic, clinical, cost, and vaccine effectiveness), and the results from such studies allow public health officials, medical practitioners, and the public to make more informed decisions when evaluating the risk for disease against the cost of the vaccine, including vaccine-related side effects.

CDC analyzed the cost-effectiveness of rabies postexposure prophylaxis for each of eight contact (risk of transmission) scenarios, with the outcome being the net cost (in dollars) per life saved (in 2004 dollars). The perspective was societal, which means that all costs and all benefits were included, regardless of who pays and who benefits. For each risk-of-transmission scenario, three cost-effectiveness ratios were calculated: average, most, and least cost-effective. Average cost-effective ratios were calculated using median transmission risk values (Table 2) and average cost of postexposure prophylaxis. Most cost-effective ratios were calculated using greatest (largest) transmission risk values and least cost of postexposure prophylaxis. Least cost-effective ratios were calculated using lowest transmission risk and greatest cost of postexposure prophylaxis. The analysis assumed that the direct medical costs associated with postexposure prophylaxis included 1 dose of HRIG ($326–$1,434), 5 doses of HDCV ($113–$679 each), hospital charges ($289–$624), and physician charges ($295–$641) (*95*). Indirect costs included travel, lost wages, alternative medicine, and other costs ($161–$2,161) (*96*). A societal perspective requires the valuation of the loss of productivity to society caused by premature death. Therefore, human life lost was valued using the average present value, in 2004 dollars, of expected future lifetime earnings and housekeeping services ($1,109,920) (*97*). All costs were adjusted to 2004 dollars using the medical care price index. The study also assumed that rabies postexposure prophylaxis, when administered according to these recommendations, was essentially 100% effective in preventing a clinical case of human rabies. The probabilities of rabies transmission to a human following possible contact with different species of potentially rabid animals was assessed by a panel of experts using the Delphi methodology, except for "animal tests positive for rabies" when probabilities were obtained from a previous study (*98*) (Table 2).

Under all three cost-effectiveness scenarios, the analysis determined that it is always cost saving to administer postexposure prophylaxis if a patient is bitten by a rabid animal that has tested positive for rabies or if a patient is bitten by a reservoir or vector species (e.g. skunk, raccoon, bat, or fox bite in the United States or dog bite in countries with dog variant rabies), even if the animal is not available for testing. For all other transmission risk situations, the average net cost effectiveness ratio was always a net cost per life saved (range: $2.9 million per life saved following a bite from an untested cat to $4 billion per life saved following a lick from an untested dog). The wide range of probabilities of risk for trans-

**TABLE 2. Cost-effectiveness ratios (cost/life saved) for rabies postexposure prophylaxis, by different scenarios of potential exposure* — United States**

| Contact scenario | Probability of rabies† Median (minimum–maximum) | Baseline cost scenario§ Average cost effectiveness (most cost-effective–least cost-effective) |
|---|---|---|
| Animal tests positive for rabies | (0.01–0.7) | Cost Saving |
| Skunk bite¶ | 0.05 (0.01–0.1) | Cost Saving |
| Possible bat bite¶** | 0.001 (0.000001–0.01) | $2.9 million (Cost saving–$8.4 billion) |
| Dog bite¶ | 0.00001 (0.00001–0.001) | $403 million ($524,080–$840 million) |
| Dog lick¶ | 0.000001 (0.000001–0.00001) | $4 billion ($162 million–$8.4 billion) |
| Cat bite¶ | 0.001 (0.00001–0.01) | $2.9 million (Cost saving–$840 million) |
| Cat lick¶ | 0.000001 (0.000001–0.0001) | $4 billion ($15 million–$8.4 billion) |
| Contact with rabid human in clinical setting** | 0.000001 (0.000001–0.00001) | $4 billion ($162 million–$8.4 billion) |

* Contact with a potentially rabid animal does not necessarily constitute an exposure. A bite exposure is defined as "any penetration of the skin by teeth." A nonbite exposure is defined as "contamination of open wounds, abrasions (including scratches) or mucous membranes with saliva or other potentially infectious material (e.g., neural tissue)."
† Probabilities of rabies transmission to a human were obtained from a panel of experts, except for "animal tests positive for rabies" when probabilities obtained from a previous study.
§ Estimates of the direct medical costs of rabies postexposure prophylaxis (PEP) were converted into 2004 dollars using the medical care price index. The cost-effectiveness of PEP under each contact scenario is calculated using the median probability of becoming clinically ill with rabies and the average cost of PEP. The most cost-effective ratio is calculated using the minimum cost of PEP and the maximum probability of becoming clinically ill with rabies. The least cost-effective ratio is calculated using the maximum cost of PEP and the minimum probability of becoming clinically ill with rabies.
¶ Animals not available for testing. The skunk bite data are considered applicable to bites from other rabies reservoir species (e.g., bats, raccoons, and foxes in the United States and dog bites occurring in countries with dog variant rabies).
** No recognized bite or saliva exposure.

mission for the bat bite scenario resulted in the widest range of cost-effectiveness ratios (Table 2). Until more precise estimates of risk for transmission are obtained, these estimates illustrate the difficulty clinicians and public health officials will continue to encounter in unequivocally determining the cost-effectiveness of providing PEP.

# Rabies Postexposure Prophylaxis

## Rationale for Prophylaxis

ACIP (*26*) and WHO (*25*) recommend that prophylaxis for the prevention of rabies in humans exposed to rabies virus should include prompt and thorough wound cleansing followed by passive vaccination with HRIG and vaccination with cell culture rabies vaccines. Administration of rabies postexposure prophylaxis is a medical urgency, not a medical emergency. Because rabies biologics are valuable resources that are periodically in short supply, a risk assessment weighing potential adverse consequences associated with administering postexposure prophylaxis along with their severity and likelihood versus the actual risk for the person acquiring rabies should be conducted in each situation involving a possible rabies exposure. Because the balance of benefit and harm will differ among exposed persons on the basis of the risk for infection, recommendations regarding rabies postexposure prophylaxis are dependent upon associated risks including 1) type of exposure, 2) epidemiology of animal rabies in the area where the contact occurred and species of animal involved, and 3) circumstances of the exposure incident. The reliability of this information should be assessed for each incident. The decision of whether to initiate rabies postexposure prophylaxis also depends on the availability of the exposing animal for observation or rabies testing (Table 3). Because the epidemiology and pathogenesis of rabies are complex, these recommendations cannot be specific for every possible circumstance. Clinicians should seek assistance from local or state public health officials for evaluating exposures or determining the need for postexposure management in situations that are not routine. State and local officials have access to CDC rabies experts for particularly rare situations or difficult decisions.

**TABLE 3. Rabies postexposure prophylaxis guide — United States, 2008**

| 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 begin prophylaxis. |
| | 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 prophylaxis. |
| Livestock, small rodents (rabbits and hares), large rodents (woodchucks and beavers), and other mammals | Consider individually | Consult public health officials. Bites from squirrels, hamsters, guinea pigs, gerbils, chipmunks, rats, mice, other small rodents, rabbits, and hares almost never require 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.
† Postexposure prophylaxis should be initiated as soon as possible following exposure to such wildlife unless the animal is available for testing and public health authorities are facilitating expeditious laboratory testing or it is already known that brain material from the animal has tested negative. Other factors that might influence the urgency of decision-making regarding initiation of postexposure prophylaxis before diagnostic results are known include the species of the animal, the general appearance and behavior of the animal, whether the encounter was provoked by the presence of a human, and the severity and location of bites. Discontinue vaccine if appropriate laboratory diagnostic test (i.e., the direct fluorescent antibody test) is negative.
§ The animal should be euthanized and tested as soon as possible. Holding for observation is not recommended.

## Types of Exposure

When an exposure has occurred, the likelihood of rabies infection varies with the nature and extent of that exposure. Under most circumstances, two categories of exposure (bite and nonbite) should be considered. The most dangerous and common route of rabies exposure is from the bite of a rabid mammal. An exposure to rabies also might occur when the virus, from saliva or other potentially infectious material (e.g., neural tissue), is introduced into fresh, open cuts in skin or onto mucous membranes (nonbite exposure). Indirect contact and activities (e.g., petting or handling an animal, contact with blood, urine or feces, and contact of saliva with intact skin) do not constitute exposures; therefore, postexposure prophylaxis should not be administered in these situations. Exposures to bats deserve special assessment because bats can pose a greater risk for infecting humans under certain circumstances that might be considered inconsequential from a human perspective (i.e., a minor bite or lesion). Human-to-human transmission occurs almost exclusively as a result of organ or tissue transplantation. Clinicians should contact local or state public health officials for assistance in determining the likelihood of a rabies exposure in a specific situation.

**Bite exposures.** Any penetration of the skin by teeth constitutes a bite exposure. All bites, regardless of body site or evidence of gross trauma, represent a potential risk. The risk for transmission varies in part with the species of biting animal, the anatomic site of the bite, and the severity of the wound (*98*). Although risk for transmission might increase with wound severity, rabies transmission also occurs from bites by some animals (e.g., bats) that inflict rather minor injury compared with larger-bodied carnivores, resulting in lesions that are difficult to detect under certain circumstances (*8,99–103*).

**Nonbite exposures.** Nonbite exposures from animals very rarely cause rabies. However, occasional reports of nonbite transmission suggest that such exposures require assessment to determine if sufficient reasons exist to consider postexposure prophylaxis (*104*). The nonbite exposures of highest risk appear to be among surgical recipients of corneas, solid organs, and vascular tissue transplanted from patients who died of rabies and persons exposed to large amounts of aerosolized rabies virus. 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. However, alternative infection routes can not be discounted (*105–109*). Similar airborne incidents have not occurred in approximately 25 years, probably because of elevated awareness of such risks resulting in increased use of appropriate preventive measures.

The contamination of open wounds or abrasions (including scratches) or mucous membranes with saliva or other potentially infectious material (e.g., neural tissue) from a rabid animal also constitutes a nonbite exposure. Rabies virus is inactivated by desiccation, ultraviolet irradiation, and other factors and does not persist in the environment. In general, if the suspect material is dry, the virus can be considered noninfectious. Nonbite exposures other than organ or tissue trans-

plants have almost never been proven to cause rabies, and postexposure prophylaxis is not indicated unless the nonbite exposure met the definition of saliva or other potentially infectious material being introduced into fresh, open cuts in skin or onto mucous membranes.

**Bat Exposures.** The most common rabies virus variants responsible for human rabies in the United States are bat-related; therefore, any potential exposure to a bat requires a thorough evaluation. If possible, bats involved in potential human exposures should be safely collected and submitted for rabies diagnosis. Most submitted bats (approximately 94%) (*110*) will not be rabid and such timely diagnostic assessments rule out the need for large investments in risk assessments and unnecessary prophylaxis.

The risk for rabies resulting from an encounter with a bat might be difficult to determine because of the limited injury inflicted by a bat bite (compared with more obvious wounds caused by the bite of terrestrial carnivores), an inaccurate recall of a bat encounter that might have occurred several weeks or months earlier, and evidence that some bat-related rabies viruses might be more likely to result in infection after inoculation into superficial epidermal layers (*111*). For these reasons, any direct contact between a human and a bat should be evaluated for an exposure. If the person can be reasonably certain a bite, scratch, or mucous membrane exposure did not occur, or if the bat is available for testing and is negative for presence of rabies virus, postexposure prophylaxis is not necessary. Other situations that might qualify as exposures include finding a bat in the same room as a person who might be unaware that a bite or direct contact had occurred (e.g., a deeply 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). These situations should not be considered exposures if rabies is ruled out by diagnostic testing of the bat, or circumstances suggest it is unlikely that an exposure took place. Other household members who did not have direct contact with the bat or were awake and aware when in the same room as the bat should not be considered as having been exposed to rabies. Circumstances that make it less likely that an undetected exposure occurred include the observation of bats roosting or flying in a room open to the outdoors, the observation of bats outdoors or in a setting where bats might normally be present, or situations in which the use of protective covers (e.g., mosquito netting) would reasonably be expected to preclude unnoticed contact. Because of the complexity of some of these situations, consultation with state and local health departments should always be sought. If necessary, further guidance can be sought from CDC and experts in bat ecology.

During 1990–2007, a total of 34 naturally acquired bat-associated human cases of rabies was reported in the United States. In six cases, a bite was reported; in two cases, contact with a bat and a probable bite were reported; in 15 cases, physical contact was reported (e.g., the removal of a bat from the home or workplace or the presence of a bat in the room where the person had been sleeping), but no bite was documented; and in 11 cases, no bat encounter was reported. In these cases, an unreported or undetected bat bite remains the most plausible hypothesis because the genetic sequences of the human rabies viruses closely matched those of specific species of bats. Clustering of human cases associated with bat exposures has never been reported in the United States (e.g., within the same household or among a group of campers where bats were observed during their activities) (*8,101,110*).

**Human-to-Human Exposures.** Human-to-human transmission can occur in the same way as animal-to-human transmission (i.e., the virus is introduced into fresh open cuts in skin or onto mucous membranes from saliva or other potentially infectious material such as neural tissue). Organ and tissue transplantation resulting in rabies transmission has occurred among 16 transplant recipients from corneas (n = eight), solid organs (n = seven), and vascular tissue (n = one). Each of the donors died of an illness compatible with or proven to be rabies (*10,112–123*). The 16 cases occurred in five countries: the United States (five cases: one corneal transplant transmission, three solid organ transmissions, and one vascular graft transmission), Germany (four cases), Thailand (two cases), India (two cases), Iran (two cases), and France (one case).

No documented laboratory-diagnosed cases of human-to-human rabies transmission have been documented from a bite or nonbite exposure other than the transplant cases (*124*). At least two cases of human-to-human rabies transmission in Ethiopia have been suggested, but rabies as the cause of death was not confirmed by laboratory testing (*125*). The reported route of exposure in both cases was direct salivary contact from another human (i.e., a bite and a kiss). Routine delivery of health care to a patient with rabies is not an indication for postexposure prophylaxis unless the health-care worker is reasonably certain that he or she was bitten by the patient or that his or her mucous membranes or nonintact skin was exposed directly to potentially infectious saliva or neural tissue. Adherence to standard precautions for all hospitalized patients as outlined by the Hospital Infection Control Practices Advisory Committee will minimize the need for postexposure prophylaxis in such situations (*126*). Staff should wear gowns, goggles, masks, and gloves, particularly during intubation and suctioning (*25*).

## Animal Rabies Epidemiology

**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 (*5,101,102,110*). Transmission of rabies virus can occur from minor, seemingly underappreciated or unrecognized bites from bats (*8,99–103*). Laboratory data support a hypothesis that bat rabies virus variants associated with silver-haired bats (*Lasionycteris noctivagans*) and eastern pipistrelles (*Pipistrellus subflavus*) have biologic characteristics that might allow a higher likelihood of infection after superficial inoculation, such as into cells of epidermal origin (*127*). 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 (*128*).

**Wild Terrestrial Carnivores.** Raccoons, skunks, and foxes are the terrestrial carnivores most often infected with rabies in the United States (*5*). Suggestive clinical signs of rabies among wildlife cannot be interpreted reliably. All bites by such wildlife should be considered possible exposures to rabies virus. Postexposure prophylaxis should be initiated as soon as possible following exposure to such wildlife, unless the animal is available for diagnosis and public health authorities are facilitating expeditious laboratory testing, or if the brain tissue from the animal has already tested negative. Wild terrestrial carnivores that are available for diagnostic testing should be euthanized as soon as possible (without unnecessary damage to the head), and the brain should be submitted for rabies diagnosis (*129,130*). If the results of testing are negative by immunofluorescence, human rabies postexposure prophylaxis is not necessary. Other factors that might influence the urgency of decision-making regarding the initiation of postexposure prophylaxis before diagnostic results are known include the species of the animal, the general appearance and behavior of the animal, whether the encounter was provoked by the presence of a human, and the severity and location of bites.

**Other Wild Animals.** Rodents are not reservoirs of rabies virus. Small rodents (e.g., squirrels, chipmunks, rats, mice, hamsters, guinea pigs, and gerbils) and lagomorphs (including rabbits and hares) are rarely infected with rabies and have not been known to transmit rabies to humans (*131,132*). During 1990–1996, 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 (*5,133,134*). In all cases involving rodents, the state or local health department should be consulted before a decision is made to initiate postexposure prophylaxis (*135*).

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 and CSTE. Because the period of rabies virus shedding in wild animal hybrids is unknown, when such animals bite humans euthanasia and rabies testing of the hybrid animal is the safest course of action. Vaccination should be discontinued if diagnostic tests of the involved animal are negative for rabies infection. However, because wolves and dogs have very similar genetic makeup and many animals that are advertised as "wolf-dogs" might actually be dogs, each wolf hybrid bite situation should be evaluated individually, taking into account the likelihood that it is a hybrid, the severity of the wound, and the assessment by the bite victim and his or her health-care provider. State or local health departments should be consulted before a decision is made to euthanize and test an animal. Wild animals and wild animal hybrids should not be kept as pets (*128*) or be publicly accessible. Humans who work with wild animals maintained in United States Department of Agriculture-licensed research facilities or accredited zoological parks should be educated on preventing bites and should receive rabies pre-exposure vaccinations. Rabies exposures of these animal handlers might require booster postexposure vaccinations in lieu of euthanasia and testing of the animal depending on employment requirements.

**Domestic Dogs, Cats, and Ferrets.** The likelihood of rabies in a domestic animal varies regionally, and the need for postexposure prophylaxis also varies on the basis of regional epidemiology. The number of reported cases of rabies in domestic dogs has decreased substantially in the United States, primarily because of improved canine vaccination and stray animal control programs (*5*). In the continental United States, rabies among dogs has been reported sporadically along the United States-Mexico border and in areas of the United States with enzootic wildlife rabies (*5*). During 2000–2006, more cats than dogs were reported rabid in the United States (*6*). The majority of these cases were associated with the epizootic of rabies among raccoons in the eastern United States. The large number of rabid cats compared with other domestic animals might be attributed to a lower vaccination rate among cats because of less stringent cat vaccination laws; fewer confinement or leash laws; and the nocturnal activity patterns of cats placing them at greater risk for exposure to infected raccoons, skunks, foxes, and bats. In certain developing countries, dogs remain the major reservoir and vector of rabies and represent an increased risk for rabies exposure in such countries (*136*).

A healthy domestic dog, cat, or ferret that bites a person should be confined and observed for 10 days (*128,137,138*).

Those that remain alive and healthy 10 days after a bite would not have been shedding rabies virus in their saliva and would not have been infectious at the time of the bite (*25*). All domestic dogs, cats, and ferrets kept as pets should be vaccinated against rabies. Even if they are not, such animals might still be confined and observed for 10 days after a bite to reliably determine the risk for rabies exposure for the person who was bitten. Any illness in the animal during the confinement period before release should be evaluated by a veterinarian and reported immediately to the local public health department. If signs suggestive of rabies develop, postexposure prophylaxis of the bite victim should be initiated. 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 confined and observed for 10 days or euthanized immediately and submitted for rabies diagnosis (*128*).

**Other Domestic Animals.** In all instances of exposure to other domestic animal species, local or state health department should be consulted before a decision is made to euthanize and test the animal or initiate postexposure prophylaxis (*128*).

### Circumstances of Biting Incident and Vaccination Status of Exposing Animal

An unprovoked attack by an animal might be 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. Other factors to consider when evaluating a potential rabies exposure include the epidemiology of rabies in the area, the biting animal's history and health status (e.g., abnormal behavior and signs of illness), and the potential for the animal to be exposed to rabies (e.g., presence of an unexplained wound or history of exposure to a rabid animal). A dog, cat, or ferret with a history of continuously current vaccination (i.e., no substantial gaps in vaccination coverage) is unlikely to become infected with rabies (*128,137,139–141*). Even after an initial rabies vaccination, young or naïve animals remain at risk for rabies because of the potential exposures preceding vaccination or before adequate induction of immunity during the 28 days after primary vaccination (*128*).

## Treatment of Wounds and Vaccination

The essential components of rabies postexposure prophylaxis are wound treatment and, for previously unvaccinated persons, the administration of both HRIG and vaccine (Table 4) (*142*). Administration of rabies postexposure prophylaxis is a medical urgency, not a medical emergency, but decisions must not be delayed. Incubation periods of more than 1 year have been reported in humans (*143*). Therefore, when a documented or likely exposure has occurred, postexposure prophylaxis should be administered regardless

**TABLE 4. Rabies postexposure prophylaxis schedule — United States, 2008**

| Vaccination status | Treatment | Regimen* |
|---|---|---|
| Not previously vaccinated | Wound cleansing | All postexposure prophylaxis should begin with immediate thorough cleansing of all wounds with soap and water. If available, a virucidal agent such as povidine-iodine solution should be used to irrigate the wounds. |
| | Rabies immune globulin (RIG) | Administer 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 intramuscularly (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 | Human diploid cell vaccine (HDCV) or purified chick embryo cell vaccine (PCECV) 1.0 mL, IM (deltoid area§), one each on days 0¶, 3, 7, 14, and 28. |
| Previously vaccinated† | Wound cleansing | All postexposure prophylaxis should begin with immediate thorough cleansing of all wounds with soap and water. If available, a virucidal agent such as povidine-iodine solution should be used to irrigate the wounds. |
| | RIG | RIG should not be administered. |
| | Vaccine | HDCV or PCECV 1.0 mL, IM (deltoid area§), one each on days 0¶ and 3. |

* These regimens are applicable for all age groups, including children.
† Any person with a history of a complete pre-exposure or postexposure vaccination regimen with HDCV, PCECV, or rabies vaccine adsorbed, or previous vaccination with any other type of rabies vaccine and a documented history of antibody response to the prior vaccination.
§ The deltoid area is the only acceptable site of vaccination for adults and older children. For younger children, the outer aspect of the thigh can be used. Vaccine should never be administered in the gluteal area.
¶ Day 0 is the day the first dose of vaccine is administered.

of the length of the delay, provided that compatible clinical signs of rabies are not present in the exposed person. The administration of postexposure prophylaxis to a clinically rabid human patient has demonstrated consistent ineffectiveness (*25*).

In 1977, WHO recommended a regimen of RIG and 6 doses of HDCV over a 90-day period. This recommendation was based on studies in Germany and Iran (*19,21*). When used in this manner, the vaccine was safe and effective in persons bitten by animals proven to be rabid and induced an adequate antibody response in all recipients (*19*). Studies conducted in the United States by CDC have documented that a regimen of 1 dose of HRIG and 5 doses of HDCV over a 28-day period was safe and induced an adequate antibody response in all recipients (*18*). Clinical trials with PCECV have demonstrated immunogenicity equivalent to that of HDCV (*144*).

Cell culture vaccines have been used effectively with HRIG or RIG of equine origin (ERIG) worldwide to prevent rabies in persons bitten by various rabid animals (*18,19*). Worldwide, WHO estimates that postexposure prophylaxis is initiated on 10–12 million persons annually (*144*). An estimated 16,000–39,000 persons in the United States receive a full postexposure course each year (*11*). Although postexposure prophylaxis has not always been properly administered in the United States, no failures have been documented since current biologics have been licensed.

## Treatment of Wounds

Regardless of the risk for rabies, the optimal medical treatment of animal bite wounds includes the recognition and treatment of serious injury (e.g., nerve or tendon laceration), avoidance or management of infection (both local and systemic), and approaches that will yield the best possible cosmetic results (*145*). For many types of bite wounds, immediate gentle irrigation with water or a dilute water povidone-iodine solution markedly decrease the risk for bacterial infection (*146*). Care should be taken not to damage skin or tissues. Wound cleansing is especially important in rabies prevention because thorough wound cleansing alone without other postexposure prophylaxis markedly reduce the likelihood of rabies in animal studies (*147,148*). Consideration should be given to the need for a booster dose of tetanus vaccine (*149,150*). Decisions regarding the use of antibiotic prophylaxis (*151*) and primary wound closure (*152*) should be individualized on the basis of the exposing animal species, size and location of the wound(s), and time interval since the bite. Suturing should be avoided, when possible.

## Vaccination

Postexposure antirabies vaccination should always include administration of both passive antibody and vaccine, with the exception of persons who have ever previously received complete vaccination regimens (pre-exposure or postexposure) with a cell culture vaccine or persons who have been vaccinated with other types of vaccines and have previously had a documented rabies virus neutralizing antibody titer. These persons should receive only vaccine (i.e., postexposure for a person previously vaccinated). The combination of HRIG and vaccine is recommended for both bite and nonbite exposures reported by persons who have never been previously vaccinated for rabies, regardless of the interval between exposure and initiation of prophylaxis. If postexposure prophylaxis has been initiated and appropriate laboratory diagnostic testing (i.e., the direct fluorescent antibody test) indicates that the exposing animal was not rabid, postexposure prophylaxis can be discontinued.

**Rabies IgG Use.** HRIG is administered only once (i.e., at the beginning of antirabies prophylaxis) to previously unvaccinated persons to provide immediate, passive, rabies virus-neutralizing antibody coverage until the patient responds to HDCV or PCECV by actively producing antibodies. If HRIG was not administered when vaccination was begun (i.e., day 0), it can be administered up to and including day 7 of the postexposure prophylaxis series (*153*). Beyond the seventh day, HRIG is not indicated because an antibody response to cell culture vaccine is presumed to have occurred. Because HRIG can partially suppress active production of antibody, the dose administered should not exceed the recommended dose (*154*). The recommended dose of HRIG is 20 IU/kg (0.133 mL/kg) body weight. This formula is applicable to all age groups, including children. If anatomically feasible, the full dose of HRIG should be thoroughly infiltrated in the area around and into the wounds. Any remaining volume should be injected IM at a site distant from vaccine administration. This recommendation for HRIG administration is based on reports of rare failures of postexposure prophylaxis when less than the full amount of HRIG was infiltrated at the exposure sites (*155*). HRIG should never be administered in the same syringe or in the same anatomical site as the first vaccine dose. However, subsequent doses of vaccine in the 5-dose series can be administered in the same anatomic location where the HRIG dose was administered, if this is the preferable site for vaccine administration (i.e., deltoid for adults or anterolateral thigh for infants and small children).

**Vaccine Use.** Two rabies vaccines are available for use in the United States (Table 1); either can be administered in conjunction with HRIG at the beginning of postexposure pro-

phylaxis. A regimen of 5 one-mL doses of HDCV or PCECV should be administered IM to previously unvaccinated persons. The first dose of the 5-dose course should be administered as soon as possible after exposure. This date is then considered day 0 of the postexposure prophylaxis series. Additional doses should then 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 or PCECV injections because administration of HDCV in this area results in lower neutralizing antibody titers (*156*).

### Deviations from Recommended Postexposure Vaccination Schedules

Every attempt should be made to adhere to the recommended vaccination schedules. Once vaccination is initiated, delays of a few days for individual doses are unimportant, but the effect of longer lapses of weeks or more is unknown (*157*). Most interruptions in the vaccine schedule do not require reinitiation of the entire series (*158*). For most minor deviations from the schedule, vaccination can be resumed as though the patient were on schedule. For example, if a patient misses the dose scheduled for day 7 and presents for vaccination on day 10, the day 7 dose should be administered that day and the schedule resumed, maintaining the same interval between doses. In this scenario, the remaining doses would be administered on days 17 and 31. When substantial deviations from the schedule occur, immune status should be assessed by performing serologic testing 7–14 days after administration of the final dose in the series.

## Postexposure Prophylaxis Outside the United States

Persons exposed to rabies outside the United States in countries where rabies is enzootic might receive postexposure prophylaxis with regimens or biologics that are not used in the United States, including purified vero cell rabies vaccine (Verorab™, Imovax – Rabies vero™, TRC Verorab™), purified duck embryo vaccine (Lyssavac N™), and different formulations of PCECV (Rabipur®) or HDCV (Rabivac™). This information is provided to familiarize physicians with some of the regimens used more widely abroad. These regimens have not been submitted for approval by the U.S. Food and Drug Administration (FDA) for use in the United States (*37,74,159–168*). If postexposure prophylaxis is initiated outside the United States using one of these regimens or vaccines of nerve tissue origin, additional prophylaxis might be necessary when the patient presents for care in the United States. State or local health departments should be contacted for specific advice in such cases. Rabies virus neutralizing antibody titers from specimens collected 1–2 weeks after preexposure or postexposure prophylaxis would be considered adequate if complete neutralization of challenge virus at a 1:5 serum dilution by RFFIT occurs.

Purified ERIG or fractions of ERIG have been used in developing countries where HRIG might not have been available. The incidence of adverse reactions after ERIG administration has been low (0.8%–6.0%), and most of those that occurred were minor (*169–171*). In addition, unpurified antirabies serum of equine origin might still be used in some countries where neither HRIG nor ERIG are available. The use of this antirabies serum is associated with higher rates of serious adverse reactions, including anaphylaxis (*172*).

Although no postexposure prophylaxis failures have occurred in the United States since cell culture vaccines and HRIG have been routinely used, failures have occurred abroad when less than potent biologics were used, if some deviation was made from the recommended postexposure prophylaxis protocol, or when less than the recommended amount of RIG was administered (*155,173–175*). Specifically, patients who contracted rabies after postexposure prophylaxis might not have had adequate local wound cleansing, might not have received rabies vaccine injections in the deltoid area (i.e., vaccine was administered in the gluteal area), or might not have received appropriate infiltration of RIG around the wound site. Substantial delays between exposure and initiation of prophylaxis are of concern, especially with severe wounds to the face and head, which might provide access to the central nervous system through rapid viral neurotropism.

# Rabies Pre-Exposure Prophylaxis

Pre-exposure rabies prophylaxis is administered for several reasons. First, although pre-exposure vaccination does not eliminate the need for additional medical evaluation after a rabies exposure, it simplifies management by eliminating the need for RIG and decreasing the number of doses of vaccine needed. This is particularly important for persons at high risk for being exposed to rabies in areas where modern immunizing products might not be available or where cruder, less safe biologics might be used, placing the exposed person at increased risk for adverse events. Second, pre-exposure prophylaxis might offer partial immunity to persons whose postexposure prophylaxis is delayed. Finally, pre-exposure prophylaxis might provide some protection to persons at risk for unrecognized exposures to rabies.

Pre-exposure vaccination should be offered to persons in high-risk groups, such as veterinarians and their staff, animal handlers, rabies researchers, and certain laboratory workers. Pre-exposure vaccination also should be considered for 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, some international travelers might be candidates for pre-exposure vaccination if they are likely to come in contact with animals in areas where dog or other animal rabies is enzootic and immediate access to appropriate medical care, including rabies vaccine and immune globulin, might be limited. Routine pre-exposure prophylaxis for the general U.S. population or routine travelers to areas where rabies is not enzootic is not recommended (*176,177*).

## Primary Vaccination

Three 1.0-mL injections of HDCV or PCECV should be administered IM (deltoid area), one injection per day on days 0, 7, and 21 or 28 (Table 5). The immunogenicity of IM primary vaccination with PCECV and HDCV has been reviewed. Vaccine preparations for ID administration are no longer available in the United States.

## Pre-Exposure Booster Doses of Vaccine

Persons who work with rabies virus in research laboratories or vaccine production facilities (continuous risk category [Table 6]) (*178*) are at the highest risk for inapparent exposures. Such persons should have a serum sample tested for rabies virus neutralizing antibody every 6 months. An IM booster dose (Table 5) of vaccine should be administered if the serum titer falls to maintain a serum titer corresponding to a value of at least complete neutralization at a 1:5 serum dilution by the RFFIT. The frequent-risk category includes other laboratory workers (e.g., those performing rabies diagnostic testing), cavers, veterinarians and staff, and animal-control and wildlife officers in areas where animal rabies is enzootic. The frequent-risk category also includes persons who frequently handle bats, regardless of location in the United States or throughout the world, because of the existence of lyssaviruses on all continents except Antarctica. Persons in the frequent-risk group should have a serum sample tested for rabies virus neutralizing antibody every 2 years. If the titer is less than complete neutralization at a 1:5 serum dilution by the RFFIT, the person also should receive a single booster dose of vaccine. Veterinarians, veterinary students, and terrestrial animal-control and wildlife officers working in areas where rabies is uncommon to rare (infrequent exposure group) and certain at-risk international travelers who have completed a full pre-exposure vaccination series with licensed vaccines and according to schedule do not require routine serologic verification of detectable antibody titers or routine pre-exposure booster doses of vaccine. If they are exposed to rabies in the future, they are considered immunologically primed against rabies and simply require postexposure prophylaxis for a person previously vaccinated (i.e., days 0 and 3 vaccination).

## Postexposure Prophylaxis for Previously Vaccinated Persons

If a person is exposed to rabies, local wound care remains an important part of postexposure prophylaxis, even for previously vaccinated persons. Previously vaccinated persons are those who have received one of the recommended pre-exposure or postexposure regimens of HDCV, PCECV, or RVA or those who received another vaccine and had a documented rabies virus neutralizing antibody titer. These persons should receive 2 IM doses (1.0 mL each in the deltoid) of vaccine, one immediately and one 3 days later. Administration of RIG is unnecessary and should not be administered to previously vaccinated persons because the administration of passive antibody might inhibit the relative strength or rapidity of an expected anamnestic response (*77*). For previously vaccinated persons who are exposed to rabies, determining the rabies virus neutralizing antibody titer for decision-making about prophylaxis is inappropriate for at least three reasons. First, several days will be required to collect the serum and determine the test result. Second, no "protective" titer is known. Finally, although rabies virus neutralizing antibodies are important

**TABLE 5. Rabies pre-exposure prophylaxis schedule — United States, 2008**

| Type of vaccination | Route | Regimen |
|---|---|---|
| Primary | Intramuscular | Human diploid cell vaccine (HDCV) or purified chick embryo cell vaccine (PCECV); 1.0 mL (deltoid area), one each on days 0,* 7, and 21 or 28 |
| Booster† | Intramuscular | HDCV or PCECV; 1.0 mL (deltoid area), day 0 only |

*Day 0 is the day the first dose of vaccine is administered.
† Persons in the continuous-risk category should have a serum sample tested for rabies virus neutralizing antibody every 6 months, and persons in the frequent-risk category should be tested every 2 years. An intramuscular booster dose of vaccine should be administered if the serum titer falls to maintain a value of at least complete neutralization at a 1:5 serum dilution by rapid fluorescent focus inhibition test.

**TABLE 6. Rabies pre-exposure prophylaxis guide — United States, 2008**

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

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

components, other immune effectors also are operative in disease prevention.

# Vaccination and Serologic Testing

## Post-Vaccination Serologic Testing

In CDC studies, all healthy persons tested 2–4 weeks after completion of pre-exposure and postexposure rabies prophylaxis in accordance with ACIP guidelines demonstrated an adequate antibody response to rabies (*18,73,179,180*). Therefore, no testing of patients completing pre-exposure or postexposure prophylaxis is necessary to document seroconversion unless the person is immunosuppressed. Patients 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 that is not possible, immunosuppressed persons who are at risk for exposure to rabies should be vaccinated and their virus neutralizing antibody titers checked. In these cases, failures to seroconvert after the third dose should be managed in consultation with appropriate public health officials. When titers are obtained, specimens collected 1–2 weeks after pre-exposure or postexposure prophylaxis should completely neutralize challenge virus at a 1:5 serum dilution by the RFFIT. Antibody titers might decline over time since the last vaccination. Small differences (i.e., within one dilution of sera) in the reported values of rabies virus neutralizing antibody titer (most properly reported according to a standard as IU/mL) might occur among laboratories that provide antibody determination using the recommended RFFIT. Rabies antibody titer determination tests that are not approved by FDA are not appropriate for use as a substitute for RFFIT in suspect human rabies antemortem testing because discrepant results between such tests and measures of actual virus neutralizing activity by RFFIT have been observed (*181*).

## Serologic Response and Pre-Exposure Booster Doses of Vaccine

Although virus neutralizing antibody levels might not definitively determine a person's susceptibility or protection from a rabies virus exposure, titers in persons at risk for exposure are used to monitor the relative rabies immune status over time (*182*). To ensure the presence of a primed immune response over time among persons at higher than normal risk for exposure, titers should be checked periodically, with booster doses administered only as needed. Two years after primary pre-exposure vaccination, a complete neutralization of challenge virus at a dilution of 1:5 (by the RFFIT) was observed among 93%–98% of persons who received the 3-dose pre-exposure series intramuscularly and 83%–95% of persons who received the 3-dose series intradermally (*68*). If

the titer falls below the minimum acceptable antibody level of complete neutralization at a serum dilution of 1:5, a single pre-exposure booster dose of vaccine is recommended for persons at continuous or frequent risk for exposure to rabies (Table 6). The following guidelines are recommended for determining when serum testing should be performed after primary pre-exposure vaccination:

- A person in the continuous-risk category should have a serum sample tested for rabies virus neutralizing antibody every 6 months (*178*).
- A person in the frequent-risk category should have a serum sample tested for rabies virus neutralizing antibody every 2 years (*183*).

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

## Management and Reporting of Adverse Reactions to Rabies Biologics

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

When a person with a history of hypersensitivity to rabies vaccine must be revaccinated, empiric intervention such as pretreatment with antihistamines might be considered. Epinephrine should be readily available to counteract anaphylactic reactions, and the person should be observed carefully immediately after vaccination (*184*).

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 (*14*). A patient's risk for 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 can be sought from the state or local health department or CDC.

All clinically significant adverse events occurring following administration of rabies vaccine should be reported to VAERS, even if causal relation to vaccination is not certain. Although VAERS is subject to limitations common to passive surveillance systems, including underreporting and reporting bias, it is a valuable tool for characterizing the safety profile of vaccines and identifying risk factors for rare serious adverse reactions to vaccines (*94*). VAERS reporting forms and information are available at http://www.vaers.hhs.gov or by telephone (800-822-7967). Web-based reporting is available and health-care providers are encouraged to report electronically at https://secure.vaers.org/VaersData Entryintro.htm. Clinically significant adverse events following HRIG administration should be reported to the Food and Drug Administration's MedWatch. Reports can be submitted electronically to http://www.fda.gov/MedWatch.

## Precautions and Contraindications

### Immunosuppression

Corticosteroids, other immunosuppressive agents, antimalarials, and immunosuppressive illnesses can interfere with the development of active immunity after vaccination (*185,186*). For persons with immunosuppression, pre-exposure prophylaxis should be administered with the awareness that the immune response might be inadequate. Patients 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 have their virus neutralizing antibody titers checked after completing the pre-exposure series. A patient who fails to seroconvert after the third dose should be managed in consultation with their physician and appropriate public health officials. No cases of rabies postexposure prophylaxis failure have been documented among persons immunosuppressed because of human immunodeficiency virus infection.

Immunosuppressive agents should not be administered during postexposure prophylaxis unless essential for the treatment of other conditions. When postexposure prophylaxis is administered to an immunosuppressed person, one or more serum samples should be tested for rabies virus neutralizing antibody to ensure that an acceptable antibody response has developed. If no acceptable antibody response is detected, the patient should be managed in consultation with their physician and appropriate public health officials.

### Pregnancy

Because of the potential consequences of inadequately managed rabies exposure, pregnancy is not considered a contraindication to postexposure prophylaxis. Certain studies have indicated no increased incidence of abortion, premature births, or fetal abnormalities associated with rabies vaccination (*187–189*). If the risk for exposure to rabies is substantial, pre-exposure prophylaxis also might be indicated during pregnancy. Rabies exposure or the diagnosis of rabies in the mother

should not be regarded as reasons to terminate the pregnancy (*157*).

### Allergies

Persons who have a history of serious hypersensitivity to components of rabies vaccine or to other vaccines with components that are also present in rabies vaccine should be revaccinated with caution (*184*).

## Indigent Patient Programs

Both rabies vaccine manufacturers have patient assistant programs that provide medications to uninsured or underinsured patients. Sanofi pasteur's Indigent Patient Program (providing Imogam® Rabies-HT and Imovax® Rabies) is administered through the National Organization for Rare Disorders. Information is available by telephone (877-798-8716) or e-mail (nnadiq@rarediseases.org). Information on Novartis Pharmaceuticals Patient Assistance Program for RabAvert® is available at http://www.corporatecitizenship.novartis.com/patients/drug-pricing/assistance-programs.shtml.

## Treatment of Human Rabies

Rabies is associated with the highest case fatality rate of any infectious disease. No proven effective medical treatment is recognized after the development of clinical signs. Combined with intensive care, experimental measures have included administration of vidarabine, multisite ID vaccination with cell-culture vaccines, human leukocyte interferon, RIG by the intravenous and intrathecal routes, antithymocyte globulin, inosine pranobex, ribavirin, ketamine, and high doses of steroids (*190–197*). Initiation of rabies vaccination after onset of clinical symptoms in patients with confirmed rabies diagnoses is not recommended and might be detrimental.

Survival has been well documented for only six patients. In five of these cases, the persons had received rabies vaccination before the onset of disease (*198–202*). Only one patient has recovered from rabies without the institution of rabies vaccination (*9,203*). Despite these successes, rabies is not considered curable. Treatment of clinical rabies remains an extreme challenge. Rapid antemortem diagnosis is a priority. When a definitive diagnosis is obtained, primary health considerations should focus, at a minimum, on comfort care and adequate sedation of the patient in an appropriate medical facility. Sedation is often necessary because patients might become extremely agitated, especially in the presence of stimuli such as loud noises, air currents, and the sight or sound of running water, particularly during the acute neurologic phase of the disease (*25*). Beyond the overt clinical situation associated with progressive encephalitis, during fluctuating periods of lucidity, patient stress might be compounded by the psychological trauma resulting from a sense of personal isolation and hopelessness from the prognosis. As new potential treatments become available, medical staff at specialized tertiary care hospitals might consider institution of an aggressive approach to experimental therapies, especially in confirmed cases in young healthy persons at an early stage of clinical disease, after in depth discussions and informed consent by the patient, family or legal representatives (http://www.mcw.edu/display/router.asp?DocID=11655). Parties authorized to give permission for such treatment also should be aware of the high probability for treatment failure, the anticipated expenses, and that in the rare instances of patient survival, the recovery might be associated with a variety of neurologic deficits requiring a lengthy period of rehabilitation (*204*). Continued efforts focusing on the elimination of exposure to sources of virus and the institution of appropriate and timely prophylaxis after exposure occurs remain the most effective public health measures to prevent human rabies.

## Precautions for Safe Clinical Management of Human Rabies Patients

Human rabies patients do not pose any greater infection risk to health-care personnel than do patients with more common bacterial and viral infections (*25*). Medical staff should adhere to standard precautions as outlined by the Hospital Infection Control Practices Advisory Committee (*126*). Staff should wear gowns, goggles, masks, and gloves, particularly during intubation and suctioning (*25*). Postexposure prophylaxis is indicated only when the patient has bitten another person or when the patient's saliva or other potentially infectious material such as neural tissue has contaminated an open wound or mucous membrane.

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# Appendix

## Abbreviations Used in This Report

| | |
|---|---|
| ABL | Australian bat lyssavirus |
| ACIP | Advisory Committee on Immunization Practices |
| ARAV | Aravan bat virus |
| CPRV | Chromatographically purified Vero-cell rabies vaccine |
| CSTE | Council of State and Territorial Epidemiologists |
| CVS | Challenge standard virus |
| EBL | European bat lyssavirus |
| FDA | Food and Drug Administration |
| GMT | Geometric mean titer |
| HDCV | Human diploid cell vaccine |
| HRIG | Human rabies immune globulin |
| IgG | Immune globulin |
| IM | Intramuscular |
| IRKV | Irkut bat virus |
| KHUV | Khujand bat virus |
| NTV | Nerve tissue rabies vaccine |
| PCECV | Purified chick embryo cell vaccine |
| PHKC | Purified hamster kidney cell |
| RFFIT | Rapid fluorescent focus inhibition test |
| RIG | Rabies immune globulin |
| RVA | Rabies vaccine adsorbed |
| VAERS | Vaccine Adverse Events Reporting System |
| WCBV | West Caucasian bat virus |
| WHO | World Health Organization |

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Recommendations and Reports
May 23, 2008 / Vol. 57 / RR-3

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## Human Rabies Prevention — United States, 2008
## Recommendations of the Advisory Committee on Immunization Practices

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You must complete and return the response form electronically or by mail by **May 23, 2010,** to receive continuing education credit. If you answer all of the questions, you will receive an award letter for 2.0 hours Continuing Medical Education (CME) credit; 0.2 Continuing Education Units (CEUs); 2.0 contact hours Continuing Nursing Education (CNE) credit; 2.0 contact hours Certified Health Education Specialist (CHES) credit; or 2.0 hours Continuing Veterinary Education (CVE) credit. If you return the form electronically, you will receive educational credit immediately. If you mail the form, you will receive educational credit in approximately 30 days. No fees are charged for participating in this continuing education activity.

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2. Go to the *MMWR* Continuing Education Internet site at http://www.cdc.gov/mmwr/cme/conted.html.
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DEPARTMENT OF HEALTH AND HUMAN SERVICES
CENTERS FOR DISEASE CONTROL AND PREVENTION

## Goal and Objectives

This report provides recommendations for preventing rabies among humans. These recommendations were developed by CDC staff members and the Rabies Working Group of the Advisory Committee on Immunization Practices. The goal of this report is 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 to1) describe groups for whom rabies pre-exposure prophylaxis are indicated, 2) describe groups for whom rabies serologic testing are indicated, 3) describe groups for whom booster dosing are indicated, 4) describe some of the common rabies reservoirs in the United States, and 5) describe the essential elements of rabies postexposure prophylaxis.

**To receive continuing education credits, please answer all of the following questions.**

1. **Evidence from controlled, double-blinded clinical studies among humans indicates that the administration of postexposure prophylaxis after an exposure to a virulent dose of rabies virus is an effective means of preventing a productive infection.**
   A. True.
   B. False.

2. **On the basis of available evidence from field observations or animal studies, postexposure prophylaxis is most likely to be beneficial when initiated as soon as possible after exposure, and in the majority of cases, should not be initiated if >____ days have elapsed since the exposure.**
   A. 2.
   B. 3.
   C. 7.
   D. 10.
   E. None of the above.

3. **Contact of which of the following body sites with rabies virus-infected materials constitutes a legitimate exposure?**
   A. Facial lesion.
   B. Eye.
   C. Intact skin.
   D. Hand scratch.
   E. A, B, and D.

4. **In a rabid animal, potentially infectious material include...**
   A. Brain.
   B. Saliva.
   C. Salivary glands.
   D. All of the above.
   E. None of the above.

5. **Which of the following lists of potential exposure types by animals are correctly ordered from the likely greatest risk for rabies virus infection to the least risk for infection?**
   A. Raccoon scratches are greater than licks to the skin, which are greater than bites.
   B. Dog licks to the skin are greater than scratches, which are greater than bites.
   C. Skunk scratches are greater than bites, which are greater than licks to the skin.
   D. Bat licks to the skin are greater than scratches, which are greater than bites.
   E. None of the above.

6. **The recommended duration of routine rabies postexposure prophylaxis in the naïve person is over a period of...**
   A. 3 days.
   B. 7 days.
   C. 14 days.
   D. 28 days.
   E. None of the above.

7. **A runner reports an 'unprovoked bite' from a neighborhood dog. The dog was captured by local animal control authorities, and it 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. Begin postexposure prophylaxis of the bitten person.
   C. Immediately euthanize the dog.
   D. Because canine rabies has been eliminated in the United States, dog bites are no longer an indication for postexposure prophylaxis, and no further action is needed.
   E. None of the above.

8. **Which of the following statements are true about rabies pre-exposure prophylaxis in the United States? (*Indicate all that are true.*)**
   A. It is indicated for all international visitors if they will be in this country for >30 days.
   B. It consists of 5 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 10 years.
   E. None of the above.

9. **Which of the following animals are commonly reported rabid in the United States? (*Indicate all that are true.*)**
   A. Squirrels.
   B. Raccoons.
   C. Rabbits.
   D. Swine.
   E. Rats.

10. **Which of the following statements about rabies are true? (*Indicate all that are true.*)**
    A. Human rabies is a fatal disease <50% of the time.
    B. During the previous 2 decades, the majority of indigenous human rabies cases in the United States have been associated with canine variants of the rabies virus.
    C. U.S. citizens traveling abroad can be at serious risk for exposure to avian rabies.
    D. Although human rabies cases in the United States are rare, exposure to rabid or potentially rabid animals remains a relatively common event.
    E. Postexposure prophylaxis is effective after the onset of clinical illness in the majority of cases.

11. **Which best describes your professional activities?**
    A. Physician.
    B. Nurse.
    C. Health educator.
    D. Veterinarian.
    E. Other.

**12. I plan to use these recommendations 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.

**13. Overall, the length of the journal report was…**

A. Much too long.
B. A little too long.
C. Just right.
D. A little too short.
E. Much too short.

**14. After reading this report, I am confident I can describe groups for whom rabies preexposure prophylaxis is indicated.**

A. Strongly agree.
B. Agree.
C. Neither agree nor disagree.
D. Disagree.
E. Strongly disagree.

**15. After reading this report, I am confident I can describe groups for whom rabies serologic testing and booster dosing are indicated.**

A. Strongly agree.
B. Agree.
C. Neither agree nor disagree.
D. Disagree.
E. Strongly disagree.

**16. After reading this report, I am confident I can describe groups for whom booster dosing are indicated.**

A. Strongly agree.
B. Agree.
C. Neither agree nor disagree.
D. Disagree.
E. Strongly disagree.

**17. After reading this report, I am confident I can describe some of the common rabies reservoirs in the United States.**

A. Strongly agree.
B. Agree.
C. Neither agree nor disagree.
D. Disagree.
E. Strongly disagree.

**18. After reading this report, I am confident I can describe the essential elements of rabies postexposure prophylaxis.**

A. Strongly agree.
B. Agree.
C. Neither agree nor disagree.
D. Disagree.
E. Strongly disagree.

**19. The learning outcomes (objectives) were relevant to the goal of this report.**

A. Strongly agree.
B. Agree.
C. Neither agree nor disagree.
D. Disagree.
E. Strongly disagree.

*(Continued on pg CE-4)*

Detach or photocopy.

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| 1. | [ ]A | [ ]B | | | 15. | [ ]A | [ ]B | [ ]C | [ ]D | [ ]E | | | | |
| 2. | [ ]A | [ ]B | [ ]C | [ ]D | [ ]E | 16. | [ ]A | [ ]B | [ ]C | [ ]D | [ ]E | | | |
| 3. | [ ]A | [ ]B | [ ]C | [ ]D | [ ]E | 17. | [ ]A | [ ]B | [ ]C | [ ]D | [ ]E | | | |
| 4. | [ ]A | [ ]B | [ ]C | [ ]D | [ ]E | 18. | [ ]A | [ ]B | [ ]C | [ ]D | [ ]E | | | |
| 5. | [ ]A | [ ]B | [ ]C | [ ]D | [ ]E | 19. | [ ]A | [ ]B | [ ]C | [ ]D | [ ]E | | | |
| 6. | [ ]A | [ ]B | [ ]C | [ ]D | [ ]E | 20. | [ ]A | [ ]B | [ ]C | [ ]D | [ ]E | | | |
| 7. | [ ]A | [ ]B | [ ]C | [ ]D | [ ]E | 21. | [ ]A | [ ]B | [ ]C | [ ]D | [ ]E | | | |
| 8. | [ ]A | [ ]B | [ ]C | [ ]D | [ ]E | 22. | [ ]A | [ ]B | [ ]C | [ ]D | [ ]E | | | |
| 9. | [ ]A | [ ]B | [ ]C | [ ]D | [ ]E | 23. | [ ]A | [ ]B | [ ]C | [ ]D | [ ]E | | | |
| 10. | [ ]A | [ ]B | [ ]C | [ ]D | [ ]E | 24. | [ ]A | [ ]B | [ ]C | [ ]D | [ ]E | | | |
| 11. | [ ]A | [ ]B | [ ]C | [ ]D | [ ]E | 25. | [ ]A | [ ]B | [ ]C | [ ]D | [ ]E | | | |
| 12. | [ ]A | [ ]B | [ ]C | [ ]D | [ ]E | 26. | [ ]A | [ ]B | [ ]C | [ ]D | [ ]E | | | |
| 13. | [ ]A | [ ]B | [ ]C | [ ]D | [ ]E | 27. | [ ]A | [ ]B | | | | | | |
| 14. | [ ]A | [ ]B | [ ]C | [ ]D | [ ]E | 28. | [ ]A | [ ]B | [ ]C | [ ]D | [ ]E | [ ]F | | |

***Signature*** ***Date I Completed Exam***

**20. The instructional strategies used in this report (text, tables, and references) helped me learn the material.**

A. Strongly agree.
B. Agree.
C. Neither agree nor disagree.
D. Disagree.
E. Strongly disagree.

**21. The content is appropriate given the stated objectives of the report.**

A. Strongly agree.
B. Agree.
C. Neither agree nor disagree.
D. Disagree.
E. Strongly disagree.

**22. The content expert(s) demonstrated expertise in the subject matter.**

A. Strongly agree.
B. Agree.
C. Neither agree nor disagree.
D. Disagree.
E. Strongly disagree.

**23. Overall, the quality of the journal report was excellent.**

A. Strongly agree.
B. Agree.
C. Neither agree nor disagree.
D. Disagree.
E. Strongly disagree.

**24. These recommendations will improve the quality of my practice.**

A. Strongly agree.
B. Agree.
C. Neither agree nor disagree.
D. Disagree.
E. Strongly disagree.

**25. The availability of continuing education credit influenced my decision to read this report.**

A. Strongly agree.
B. Agree.
C. Neither agree nor disagree.
D. Disagree.
E. Strongly disagree.

**26. The *MMWR* format was conductive to learning the content.**

A. Strongly agree.
B. Agree.
C. Neither agree nor disagree.
D. Disagree.
E. Strongly disagree.

**27. Do you feel this course was commercially biased? (*indicate yes or no; if yes, please explain in the space provided*)**

A. Yes
B. No

**28. How did you learn about this continuing education activity?**

A. Internet.
B. Advertisement (e.g., fact sheet, *MMWR* cover, newsletter, or journal).
C. Coworker/supervisor.
D. Conference presentation.
E. *MMWR* subscription.
F. Other.

**Correct answers for questions 1–10.**
1B; 2E; 3E; 4D; 5E; 6D; 7A; 8C; 9B; 10D.

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