U.S. Army Public Health Command

Public Health Notice

# Rabies Prevention and Post-Deployment Assessments: Information for Providers and Public Health Personnel

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**Rabies Prevention and Deployment: Information for Providers and Public Health Personnel**

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Note: This version supersedes previous editions.


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This information is intended to assist providers to appropriately screen, risk assess and provide treatment for persons who report potential rabies risk exposures after a delay. All providers who conduct post-deployment health assessments must understand and apply the training and guidance contained in this document.

**BACKGROUND**

A U.S. Army Soldier died of rabies on 31 August 2011. Laboratory results indicate the Soldier was infected from contact with a dog while deployed in Afghanistan.

During the public health investigation of this case, members of the Soldier's unit reported they had also received dog bites in Afghanistan, had not reported the bites to medical providers, and had not received rabies post-exposure prophylaxis (PEP). Medical record reviews in Afghanistan identified other individuals who presented for care but did not receive the recommended PEP. As a result of these discoveries, the Army Surgeon General ordered a public health response to identify, notify, and treat all Service Members, civilians, contractors and other personnel who had sustained rabies risk exposures during deployment.

Between 22 August 2011 and 20 April 2012, 8899 individuals from all Services, as well as deployed civilians and contractor personnel, were contacted. Twenty-nine individuals were provided post-exposure prophylaxis (PEP) as a result of contact with Soldier who died. Between 1 March 2010 and 1 September 2011, a total of 8577 individuals either had theater medical encounters for a potential rabies-risk encounter or indicated concern about an animal bite on a post-deployment health assessment. Over 300 additional individuals were contacted as a result of hotline calls, unit recalls, and Soldier redeployment medical processing referrals. Overall, 262 (3%) individuals had exposures that required rabies prevention treatment that was not provided at the time of the event.

Supplemental actions in support of the public health investigation included reinforcing General Order #1B, which forbids the adoption of (whether as pet or mascot), caring for, or feeding of any type of domestic or wild animal during deployment; education campaigns targeting Service members and leaders on the risk of rabies outside the United States; and revisions to the post-deployment health assessment forms to specifically assess rabies-risk exposures. The entire Army post-deployment health assessment process was assessed and improvements were made to ensure all reported concerns and exposures are addressed and documented during the encounter.

Despite these efforts, Service members who have sustained otherwise unreported and untreated potential rabies risk exposures during deployment continue to be identified on post-deployment health assessments.

## KEY FACTS FOR PROVIDERS

- Rabies is a viral infection that can be transmitted to humans through the saliva of infected animals, either through bites or if the saliva of an infected animal contacts broken skin, eyes or mouth.

- Although rabies is not transmitted through touching, petting, or contact that does not involve saliva to broken skin, eyes or mouth, it is still important to stress to patients that all potential risk contact should be evaluated by a provider.

- Animals present in deployment settings are not vaccinated against rabies as pets are in the United States. Dogs are the most common source of human infections in developing countries.

- A person cannot tell if an animal has rabies. Despite the common belief that rabid animals are easily identified by foaming at the mouth and aggressive behavior, infected animals may appear calm and not look sick or act strange.

- The incubation period for rabies depends on the time it takes the virus to reach the central nervous system (CNS) and consequently varies with virus inoculum, the distance of exposure site to CNS and other factors that are not yet well understood.

- Rabies is preventable. Yet once the signs and symptoms of rabies develop, the disease is almost always fatal. Early treatment of exposures prevents nearly all disease, but even late treatment prior to symptom onset may increase survival.

- Macaque monkeys can transmit Simian Herpes B virus (SHBV). Although rare, SHBV causes a highly fatal encephalomyelitis in humans. Consequently, bites from these monkeys require additional preventive treatment measures.

- For more information on rabies, deployment and prevention, see the training slides in Appendix C of this document. They are also available at: http://phc.amedd.army.mil/topics/discond/aid/Pages/Rabies.aspx.

## GUIDELINES FOR EVALUATION AND TREATMENT

A potential rabies risk exposure is a bite that broke the skin, a scratch that bled or wet animal saliva contact with mucous membranes or broken skin as a result of contact with warm-blooded animals, such as dogs, cats, bats, foxes, skunks, raccoons, mongooses, and jackals. Rats and mice very rarely transmit rabies and do not typically require rabies prophylaxis. Bats

in sleeping quarters also present risk exposures even if the person is not sure if they were bitten (i.e., while sleeping, as bat teeth are very small, very sharp, and may not leave noticeable injuries).

Persons who had no medical evaluation or incomplete/undocumented evaluation or postexposure prophylaxis (PEP) following the exposure incident should be evaluated, *regardless of the time interval since exposure*. In addition, individuals who are not completely confident they received appropriate and completely documented care should also be evaluated. There is no prescribed time period after an exposure where prophylaxis should not be considered. The decision to treat should be based on the circumstances of the exposure, consideration of the patient's situation and risk of future exposures as well as provider judgment. An algorithm is provided below to assist with decision-making.

Although the vast majority(>99%) of persons who develop rabies disease will do so within a year after a risk exposure, there have been reports of individuals presenting with rabies disease up to six years or more after their last known risk exposure. Persons presenting for care for risk exposures that occurred over 18 months prior to presentation should still be evaluated. The decision to treat should be based on an assessment of the exposure and the patient's situation, including their risk of future exposures, and will require provider judgment. For instance, for a Soldier with a clear history of a high-risk exposure (e.g., feral dog bite) while downrange, it would be prudent to provide PEP regardless of time since the exposure, while lower risk exposures (e.g., licks, scratches) require additional information and discussion with the patient to inform a treatment decision.

Detailed reviews of rabies exposure evaluations and PEP are provided in guidance from the US Centers for Disease Control and Prevention, but these guidelines are intended to be applied to exposures in the United States. Providers must be cautious in applying these guidelines too strictly to Soldiers who sustain exposures in higher risk countries. Although bats are the most common source of human rabies in the US today, dogs are responsible for over 90% of the estimated 55,000 rabies deaths that occur annually around the world.

The following algorithm provides guidance for determining what exposures should be considered for treatment with PEP. It is not intended for treatment of acute exposures. The algorithm is primarily intended to apply to deployments to countries with Intermediate or High Rabies Risk as assessed by NCMI. For the latest country-specific rabies risk assessment by NCMI, go to the NCMI Homepage at the following link: https://www.intelink.gov/ncmi/index.php. The rabies risk assessment is found in the Infectious Disease Risk Assessment, which can be linked to from each country's NCMI page.

## Evaluation & Treatment of Potential Deployment-Related Rabies Exposures (SEP2012.v2)

**NOTE: Applies to deployments to countries with Intermediate or High Rabies Risk as assessed by NCMI**

**IMPORTANT: THIS ALGORITHM SHOULD NOT BE USED TO EVALUATE ACUTE BITES OR EXPOSURES[1]**

**Did the patient have contact with a mammal capable of spreading rabies?[2]**

**NOTE: Providers who have questions or concerns regarding application of this algorithm should contact their local Rabies Advisory Board for assistance.**

**YES**

**Did the patient sustain a bite that broke the skin, a scratch that bled, or have wet animal saliva contact mucous membranes or broken skin or have a bat in sleeping quarters?**

**NO** → **NO Rabies PEP Indicated**
Document the incident and clinical assessment in AHLTA.

**YES/UNSURE**

**Was the animal a US/NATO military working dog?**

**YES** → **NO Rabies PEP Indicated**
Document the incident and assessment in AHLTA. Code exposure[3] and use supplemental codes E906 for dog bite, or E906.5 for injuries due to monkey or other animal as appropriate.

**NO/UNSURE**

**Was the animal directly observed for 10 days following the exposure and appeared healthy at day 10?**

**YES** → **NO Rabies PEP Indicated**
Document the incident and assessment in AHLTA. Code exposure[3] and use supplemental E codes as appropriate.

**NO/UNSURE**

**Is appropriate Rabies Post Exposure Prophylaxis (PEP) for this exposure documented in the medical record?[4]**

**YES** → **NO Rabies PEP Indicated**
Document the incident and assessment in AHLTA. Code exposure[3] and use supplemental E codes as appropriate.

**NO**

**Rabies PEP MAY Be Indicated**

- **Administer both Human Rabies Immunoglobulin (HRIG) and rabies vaccine regardless of time since incident unless patient has previously received rabies vaccine series. HRIG should not be given more than 7 days after first vaccine dose if the patient already received some rabies vaccine.**
- **Document exposure incident, assessment, and treatment in AHLTA. Use appropriate wound code and supplemental E codes, as well as code V04.5.[3] Document HRIG and rabies vaccines in Service immunization tracking system.**

→ **PEP Regimens[5]** (also see next page)

**Not previously vaccinated:**
**RIG**: 20 IU/kg body wt at site of wound and any remaining volume distal to rabies vaccine site
**Rabies Vaccine[6]**: 1ml IM days 0, 3, 7, and 14 (Also day 28 if immunosuppressed or on antimalarials)

**Previous vaccine series or titer documented:**
**HRIG should not be used.**
**Rabies vaccine only**: 1ml IM days 0 and 3

1. For acute bites and exposures, refer to http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5703a1.htm and http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5902a1.htm . These guidelines apply to the US. Do not apply them too strictly to persons who sustain exposures in countries with higher rabies risk.
2. Dogs, cats, bats, raccoons, skunks, ferrets, and wild terrestrial carnivores. 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.
3. Use codes 870.0-897.7 (wound, open) or 910-919 (superficial injury codes) with the appropriate supplemental code: E906 for dog bite or E906.5 for injuries due to monkey or other animal. Include code V04.5 for animal bite requiring rabies vaccination.
4. See protocols on next page.
5. If the vaccine series was interrupted for more than a few days or not completed, providers should complete the series and then assess immune status by performing serologic testing 7–14 days after administration of the final dose in the series. If drawing a titer is not practical or feasible, restart the vaccine series (but do NOT administer HRIG).
6. Purified Chick Embryo Cell Vaccine (PCECV) should not be given to individuals with egg allergies. Human Diploid Cell Vaccine (HDCV) is safe in egg-allergic individuals.

**Rabies postexposure prophylaxis (PEP) schedule — United States, 2010**

| Vaccination status | Intervention | Regimen* |
|---|---|---|
| Not previously vaccinated | Wound cleansing | All PEP should begin with immediate thorough cleansing of all wounds v available, a virucidal agent (e.g., povidine-iodine solution) should be use wounds. |
| | Human rabies immune globulin (HRIG) | Administer 20 IU/kg body weight. If anatomically feasible, the full dose should be infiltrated around and into the wound(s), and any remaining volume should be administered at an anatomical site (intramuscular [IM]) distant from vaccine administration. Also, HRIG should not be administered in the same syringe as vaccine. Because RIG might partially suppress active production of rabies virus antibody, no more than the recommended dose should be administered. |
| | Vaccine | Human diploid cell vaccine (HDCV) or purified chick embryo cell vaccine (PCECV) 1.0 mL, IM (deltoid area†), 1 each on days 0,§ 3, 7 and 14. A fifth dose on Day 28 is required if patient is immunosuppressed or on antimalarials |
| Previously vaccinated** | Wound cleansing | All PEP 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. |
| | HRIG | HRIG should not be administered. |
| | Vaccine | HDCV or PCECV 1.0 mL, IM (deltoid area†), 1 each on days 0§ and 3. |

* These regimens are applicable for persons in all age groups, including children.
† The deltoid area is the only acceptable site of vaccination for adults and older children. For younger children, the outer aspect of the thigh may be used. Vaccine should never be administered in the gluteal area.
§ Day 0 is the day dose 1 of vaccine is administered.
** Any person with a history of pre-exposure vaccination with HDCV, PCECV, or rabies vaccine adsorbed (RVA); prior PEP with HDCV, PCECV or RVA; or previous vaccination with any other type of rabies vaccine and a documented history of antibody response to the prior vaccination.

Source: http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5902a1.htm

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**ADDITIONAL CONSIDERATIONS FOR MONKEY BITES**

Rhesus macaque monkeys are native to eastern Afghanistan and throughout central and Southeast Asia. They are often kept as pets or mascots by local nationals. In addition to rabies, monkeys in the macaque group can carry Simian Herpes B virus (SHBV). Although rare, SHBV causes an encephalomyelitis in humans that is fatal in up to 80% of cases. A monkey infected with rabies or SHBV may not have clinical signs even though it can transmit the disease. Most of what is known about SHBV comes from occupational exposures in research labs that use macaque monkeys, and not travel-related exposures, which may differ. However, given that SHBV is a highly fatal disease in humans, and preventive treatment is generally well-tolerated, the risk of treatment generally outweighs the risk of possible disease.

Disease risk appears to vary with type of exposure. The riskiest exposures appear to include deep puncture wounds that are difficult to clean, inadequately cleansed wounds, and wounds sustained on the face (especially wounds to the eye), neck, or thorax-that is, like rabies, sites nearer the CNS. Ocular splashes with infected fluids, such as saliva, may also transmit SHBV.

The human incubation period after an identified exposure ranges from 2 days to 5 weeks. Most persons develop their disease within 5–21 days of an exposure. Symptoms associated with disease onset vary, and may involve symptoms at the site of exposure, the onset of peripheral or central nervous system (CNS) signs, or simply a flu-like illness followed by the rapid onset of CNS symptoms.

Treatment to Service Members bitten by a monkey should include the following:

- Immediate wound/mucous membrane cleansing for at least 15 minutes
- Antiviral medication within 24 hrs to 5 days of the bite (see below)
- Baseline testing for antibodies against SHBV
- Rabies post-exposure prophylaxis (PEP)
- Ensure SM's tetanus status is current
- Consider antibiotic prophylaxis for other bacterial infections
- Follow-up testing for SHBV seroconversion should be done at 2, 4 and 6 weeks and finally 3 months after exposure.

Infectious disease or preventive medicine physicians should be consulted for any questions.

Either Valacyclovir or Acyclovir can be used for preventive treatment. Neither is contraindicated with RIG or rabies vaccine.

•Valacylovir—1g by mouth every 8 hours for 14 days, or
•Acyclovir—800 mg by mouth 5 times daily for 14 days

Additional information is available at: http://www.cdc.gov/herpesbvirus/index.html and http://cid.oxfordjournals.org/content/35/10/1191.full.pdf+html. See also http://wwwnc.cdc.gov/eid/article/18/10/12-0419_article.htm

**DOCUMENTATION OF CLINIC VISIT**

A record of the exposure event should be created in Armed Forces Health Longitudinal Technology Application (AHLTA) and coded as directed below. An AHLTA template, titled "**RB_BITE_LATE,**" has been developed to simplify the documentation of circumstances surrounding delayed presentations for rabies risk exposures. This template includes all questions from the questionnaire/interview form provided in Appendix B.

NOTE: Another template, "**RB_BITE_ACUTE**," is available for documenting circumstances of acute rabies risk exposures. Directions for accessing and using each of the templates is available at: http://phc.amedd.army.mil/topics/discond/aid/Pages/Rabies.aspx

For each exposure event, the note should include the following:

- Date of the incident
- Country and installation (do not include classified information, use descriptors like remote FOB)
- Animal type (dog, bat, etc) and if the animal was previously vaccinated (Military Working Dog, etc). Unofficial animal vaccinations (not done by U.S. military veterinarian) should be noted but the animal should not be considered vaccinated.
- Circumstances around the exposure (provoked, unprovoked, etc)
- Health of the animal after 10 days (if known)
- If the animal was euthanized and tested for rabies
- Type and location of wound(s) or mucous membrane exposures
- If the patient had received a rabies pre-exposure vaccine series or not
- If the patient presented for care following the exposure. If so, where was care performed (unit medic, aid station, military treatment facility, etc) and by what level of provider.
- What post-exposure care was given and when (wound cleaning, HRIG, vaccine doses). Include the timing of the Human Rabies Immune Globulin (HRIG) and vaccine and how they were administered.

If the questionnaire/interview form provided in Appendix B is used, ensure the form is scanned into AHLTA as part of the encounter note.

## DIAGNOSTIC CODING

The primary diagnosis code used for the initial evaluation of an animal bite could be 870.0–897.7 (wound, open) or 910–919 (superficial injury codes). The specific code reported is based on the anatomical location of the wound. For example, 891.0 would be the appropriate code for an open wound on the lower leg.

The secondary diagnosis code (required) is an E code. (Without the proper E code, there is no way to determine from medical data systems that the injury was the result of an animal bite.) E codes are not stand-alone codes; they must accompany a primary diagnosis code as described above. For dog bites, the correct E code is E906.0, which would be reported only on the initial treatment of the dog bite. For bites from other animals, use E906.5.

To document administration of RIG and/or vaccine at the initial or subsequent visits, use V04.5. (Unlike E codes, V codes can be used as stand-alone codes for patient visits.)

Unless the patient has signs or symptoms of clinical rabies, do not use 071, the International Classification of Diseases, Version 9 (or ICD-9) code for the actual disease.

Summary of Diagnosis Codes

| | |
|---|---|
| 870-897 | Open wounds (code depends on anatomical location) |
| 910-919 | Superficial wounds (code depends on anatomical location) |
| E906.0 | Dog bite |
| E906.5 | Bite by unspecified animal: use for injuries due to bats, monkeys or other animal not a dog |
| V04.5 | Need for prophylactic vaccination and inoculation against rabies |
| 071.0 | Rabies. Only use if patient has developed signs or symptoms of clinical rabies |

## DOCUMENTATION OF PEP IN MEDPROS

In addition to documentation in AHLTA, all doses of Rabies Immune Globulin (RIG) and rabies vaccine will be entered into for Active Duty, Reserve, National Guard and other individuals who are deployable in their current jobs.

**RESOURCES**

U.S. Army Public Health Command Rabies Webpage
http://phc.amedd.army.mil/rabies

US Army Public Health Command AKO Site (medical threat briefings)
https://www.us.army.mil/suite/page/583959

National Center for Medical Intelligence (NCMI) (country-specific rabies risk assessments): https://www.intelink.gov/ncmi/index.php

U.S. Centers for Disease Control and Prevention (CDC) Rabies Website
http://www.cdc.gov/rabies/

MMWR: March 19, 2010 / 59(RR02); 1-9: Use of a Reduced (4-Dose) Vaccine Schedule for Postexposure Prophylaxis to Prevent Human Rabies
http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5902a1.htm

MMWR: May 23, 2008 / 57(RR03); 1-26,28: Human Rabies Prevention --- United States, 2008
http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5703a1.htm

Rabies Fact Sheet: US Army Public Health Command
http://phc.amedd.army.mil/PHC%20Resource%20Library/Rabies%20Fact%20Sheet%2013-001-0911.pdf

Vaccine Healthcare Centers Network-Rabies Vaccine Course
http://www.vhcpir.org/hsi/m_ourcourses.asp

Rabies Postexposure Prophylaxis (PEP) Basics: Case Illustrations of the 2010 Advisory Committee on Immunization Practices (ACIP) Guidelines
http://ideha.dhmh.maryland.gov/training/SitePages/rabies.aspx

Centers for Disease Control and Prevention. B Virus Information Page:
http://www.cdc.gov/herpesbvirus/index.html

Cohen, et al. Recommendations for Prevention of and Therapy for Exposure to B Virus (Cercopithecine Herpesvirus 1). Clin Infect Dis. (2002) 35 (10): 1191-1203. Available at: http://cid.oxfordjournals.org/content/35/10/1191.full.pdf+html

Mease LE & KA Baker. 2012. Monkey Bites among US Military Members, Afghanistan, 2011. Emerging Infectious Diseases. 18:9. Available at:
http://wwwnc.cdc.gov/eid/article/18/10/12-0419_article.htm

# INFORMATION ABOUT RABIES FOR HEALTH CARE PROVIDERS

FACT SHEET 13-002-0911

Rabies is a zoonotic disease caused by RNA viruses in the family Rhabdoviridae, genus Lyssavirus. Virus is transmitted through contact with the saliva of infected, or rabid, warm-blooded animals, such as dogs, cats, bats, foxes, skunks, raccoons, mongooses and jackals. Mice, rats and other small rodents are almost never found to be infected with rabies. It is not always possible to tell if an animal has rabies. Not all animals infected with rabies appear sick or display abnormal behavior, such as foaming at the mouth or aggressive behavior. After entry to the central nervous system, these viruses cause an acute, progressive encephalomyelitis. The incubation period usually ranges from 1 to 3 months after exposure, but can range from days to years. Rarely does rabies develop more than one year after exposure. The incubation period varies depending on the amount of virus introduced into the body and the distance the virus has to travel from the site of exposure to the central nervous system (CNS). The closer the bite is to the CNS, the shorter the incubation period. Bites to the head and neck are usually associated with shorter incubation periods.

## *POST-EXPOSURE PROPHYLAXIS (PEP)*

For unvaccinated persons, the combination of Human Rabies Immune Globulin (HRIG) and vaccine is recommended for both bite and nonbite exposures, regardless of the time interval between exposure and initiation. For previously vaccinated persons, only vaccine is recommended, again regardless of the time interval between exposure and initiation. Observational studies indicate that PEP is universally effective in preventing human rabies when administered promptly and appropriately. Of the >55,000 persons who die annually of rabies worldwide, the majority either did not receive any PEP, received some form of PEP (usually without RIG) after substantial delays, or were administered PEP according to schedules that deviated substantially from current ACIP or WHO recommendations.

## *SIGNS AND SYMPTOMS OF CLINICAL RABIES*

The first symptoms of rabies may be very similar to those of the flu, including general weakness or discomfort, fever, or headache. These symptoms may last for days. There may be discomfort or a prickling or itching sensation at the site of bite, progressing within days to symptoms of cerebral dysfunction, anxiety, confusion, and agitation. As the disease progresses, the person may experience delirium, abnormal behavior, hallucinations, and insomnia. The acute period of disease typically ends after 2 to 10 days. Once clinical signs of rabies appear, the disease is nearly always fatal, and treatment is typically supportive. To date less than 10 documented cases of human survival from clinical rabies have been reported and only 2 have not had a history of pre- or post-exposure prophylaxis.

Several tests are necessary to diagnose rabies ante-mortem (before death) in humans; no single test is sufficient. Tests are performed on samples of saliva, serum, spinal fluid, and skin biopsies of hair follicles at the nape of the neck. Saliva can be tested by virus isolation or reverse transcription followed by polymerase chain reaction (RT-PCR). Serum and spinal fluid are tested for antibodies to rabies virus. Skin biopsy specimens are examined for rabies antigen in the cutaneous nerves at the base of hair follicles.

Refer to the following sources for more detailed information:
http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5703a1.htm
http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5902a1.htm

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## Rabies Risk Assessment: Animal Exposure Questionnaire

This questionnaire can be used by medical providers to determine treatment needs of individuals who sustained potential exposure to rabies and either **did not seek treatment in a timely manner** or **may not have completed a full course** of preventive treatment. The content of this questionnaire is also available as an AHLTA template, titled "RB_BITE_LATE." If this template cannot be accessed, this questionnaire should be scanned into the individual's AHLTA record. [NOTE: Another template, "RB_BITE_ACUTE," is available for documenting circumstances of acute rabies risk exposures. This questionnaire should **NOT** be used to assess acute rabies risk exposures. Directions for accessing and using each of the templates are available at: http://phc.amedd.army.mil/topics/discond/aid/Pages/Rabies.aspx.]

## SECTION-1: Personal Information

**Last Name** _____ **First Name**_____
**Middle Initial**_____ **SSN** _____ **DOB**_____
**Rank**_____ **Sex:** ___**Male** ___**Female**

**Service**
__**Army** __**Navy** __ **Air Force** __**Marines** __**Coast Guard**
__**Civilian** __**Contractor** __**Other (specify)**_____

**MOS/AFSC** _____ **Unit** _____

**Current Address:** _____
_____
_____
**Email** _____
**Cell phone** _____
**Work phone** _____
**Other phone** _____

**How many separate animal exposures–bites, scratches, broken skin that may have been contaminated with animal saliva, or exposures of animal saliva to mucous membranes (eyes, mouth, nose)–have you had during this deployment ?***(Do not include those from vaccinated pets in CONUS)*

__ **One** __**Two** __**Three** __**Other (specify)**_____

**NOTE: Complete a new copy of Section-2 below for EACH exposure incident**

**Name (Last, First)_____SSN_____**

**Exposure #__of__total exposures during deployment**

## Section-2: Exposure Information

***Complete a new copy of this section for EACH exposure incident during deployment***

**Date of exposure _____**
**MM/DD/YYYY**

**Country where exposure occurred**
**__ Afghanistan __ Iraq __ Other (specify)**

**Type of exposure (check all that apply)**
**__ Bite**
**__ Scratch**
**__ Animal saliva in eye, nose, mouth or broken skin**
**__ Other (specify) _____**

**Type of animal**
**__ Dog __ Cat __ Other (specify)**

| | | | |
|---|---|---|---|
| **US/NATO Military Working Dog** | **__ Yes** | **__ No** | **__ Unknown** |
| **Adopted local animal (mascot, pet)** | **__ Yes** | **__ No** | **__ Unknown** |
| **Feral (Stray) Animal** | **__ Yes** | **__ No** | **__ Unknown** |
| | **__ Other (specify)** | | |

**Vaccination status of animal**
**__ Current (US/NATO Military Working Dog) __ Unknown**

**Location of the exposure**
**__ On the FOB __ On patrol __ Other (specify)**

**Describe the circumstances of the exposure (i.e., what happened):**

**Name (Last, First)_____ Last 4: _____ Exposure #__of__**

**What was done to the animal after the exposure? (check all that apply)**

**__ Animal was confined and observed for at least 10 days**
**__ Animal was euthanized (put to sleep)**
**__ Nothing**
**__ Don't know**
**__ Other (specify) _____**

**If the animal was put to sleep, were parts of it sent for rabies testing?**

**__ Yes**
**__ No**
**__ Don't know**

**Did the same animal appear perfectly healthy 10 or more days after the exposure?**

**__ Yes, I am positive I saw the same animal and it appeared healthy on or after day 10 (alert, not lethargic or overly aggressive; walking normally; not drooling)**
**__ I did not see the animal 10 or more days after the exposure**
**__ Don't know or couldn't say for certain**
**__ Other (specify)_____**

**Result of rabies test on the animal (if done):**

**__ Positive __ Negative __ Don't know**

**Who told you the rabies test results?_____**

**Describe the injury/injuries (bite, scratch) and the locations(s) on your body**

**Did the bite or scratch break the skin?**

**__ Yes __ No __ Don't know __ N/A**

**Did you bleed from the bite or scratch?**

**__ Yes __ No __ Don't know __ N/A**

**Did you see a medical care provider for this exposure?**

**__ Yes __ No __ Don't know __ N/A**

**If not, why not?**

**Name (Last, First)_____ Last 4: _____ Exposure #___of___**

**If you received medical care, answer the following:**

**Location where treatment was provided (name of FOB, etc)?**

**Type of medical provider?**
**__ Physician __ PA __ Medic __ Don't Know __ Other_____**

**Name of provider_____ Unit of provider_____**

**Date of treatment _____**
**MM/DD/YYYY**

**Did you ever have a previous rabies vaccination series (at least three shots) before this exposure occurred?**
**__ Yes __ No __ Don't Know**

**Did the provider say you needed a rabies vaccination after this exposure?**
**__ Yes __ No __ Don't Know**

**Treatment already provided (check all that apply)**

**__ None**
**__ Wound cleaning with soap and water**
**__ Tetanus shot**
**__ Antibiotics**
**__ Rabies immunoglobulin (RIG)(on Day 07)**
**__ Other (specify)**
**__ Rabies vaccine dose #1 (on Day 0)**
**__ Rabies vaccine dose #2 (on Day 3)**
**__ Rabies vaccine dose #3 (on Day 7)**
**__ Rabies vaccine dose #4 (on Day 14)**
**__ Rabies vaccine dose #5 (on Day 28)**

**Were you taking malaria pills when you received any vaccine doses?**
**__ Yes __ No __ Don't Know**

**Do you have a paper copy of the treatment record for this exposure?**
**__ Yes __ No __ Don't Know**
***NOTE: If yes, obtain copy, adapt treatment plan accordingly, and scan into AHLTA.***

**Was an electronic treatment record created for this exposure?**
**__ Yes __ No __ Don't know**

**Is there anything else your provider should know about your animal exposure?**

# Evaluating Rabies Risk Exposures

Presenter:

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# Goals

- Ensure appropriate treatment of individuals who may have sustained unreported or incompletely treated rabies risk exposures
  - Ensure assessment is routine part of post-deployment evaluations
  - Ensure appropriate care for persons identified with risk (theater encounter, PDHA/PDHRA responses, self report)
- Ensure all persons presenting with rabies risk exposures receive appropriate care

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The goals of today's presentation is to ensure you are familiar with the appropriate treatment of all persons presenting with rabies risk exposures, whether acute or delayed. Assessment of rabies risk exposures should be a routine part of post-deployment evaluations as well.

# Agenda

- Review of rabies epidemiology, disease and treatment
- Approach to preventive care for risk exposures
  - Acute presentations
  - Delayed presentations
- Resources

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Here is the agenda

## Human Rabies Update

- A US Soldier died from rabies in AUG 2011
  - Acquired from a dog bite while deployed in Afghanistan
  - First case in DoD in over 30 years
  - Symptoms began 3 months after redeployment
  - AR 15-6 investigation currently ongoing
- Public health investigation into case revealed 11 other Soldiers in unit had sustained unreported and untreated rabies risk exposures
  - Mostly dog bites
  - Several persons had more than one exposure
  - 10 required post-exposure prophylaxis

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So why all the sudden concern about rabies? In August 2011, a US Soldier died from rabies acquired from a dog bite while deployed in Afghanistan. This represents the first case in DoD in over 30 years. His symptoms began 3 months after redeployment. However, the bigger concern: Public health investigation into case revealed 11 other Soldiers in unit had sustained **unreported** and **untreated** rabies risk exposures. Most of these were dog bites, but some reported cat or monkey bites, too. Several persons had more than one exposure. 10 of these persons sustain exposures that were deemed to require post-exposure prophylaxis.

## Rabies Outside United States

- 55,000 people die of rabies world-wide every year
  - US typically reports only 1-2 human cases per year
  - Dogs are the most common vector in developing countries
    - Lack of vaccination programs
    - US travelers may not realize risk
  - Fewer than 10 survivors known
- Once symptoms develop, almost uniformly fatal
  - Early treatment prevents nearly 100% disease
  - Treatment before symptoms begin can still be effective
    - Most survivors had some history of vaccination
    - Only three survivors with no prior history of preventive care
- CDC guidance is written primarily for risk in US, not other countries and not for military deployments!

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Rabies is a bigger problem abroad than in the US. World-wide, 55,000 people die of rabies year, but in the US there are usually only 1-2 human cases per year. Dogs are the most common vector in developing countries, but bats are the most common source of rabies disease in the US. Developing countries typically cannot support routine rabies vaccination programs for dogs and cats. There may be cultural differences in the concept of pets. And US travelers may not realize how different the risk is.

Of all human rabies cases, fewer than 10 survivors have been documented. Once symptoms develop, rabies is almost uniformly fatal. However, early treatment prevents nearly 100% of disease. And although delays in treatment are not ideal, treatment before symptoms begin can still be effective. Most survivors had some history of vaccination. There have been only three survivors with no prior history of preventive care. It is important to understand that **CDC guidance is written primarily for risk in US, not other countries and not for military deployments!**

# Rabid Animals

PHOTO: CDC PHIL

PHOTO: U.S. ARMY

You cannot tell whether an animal has rabies by observing its actions.

*Both of these dogs have rabies.*

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Despite common lore, you cannot tell whether an animal has rabies by observing its actions. Both of these animals are rabid. The puppy on the right was a "fob dog." More than 20 people were exposed and required post-exposure treatment, costing over $22,000 in HRIG and vaccine alone.

## Rabies Disease

- Caused by RNA viruses in the family Rhabdoviridae, genus Lyssavirus
- Virus is transmitted through contact with the saliva of infected, or rabid mammals, such as dogs, cats, bats, skunks, raccoons, foxes, mongooses and jackals
  - Mice, rats and other small rodents are almost never found to be infected with rabies.
  - Larger rodents, such as groundhogs or beavers, can be infected
  - Herd animals, such as horses, cows, etc., can be infected
- In CNS, virus causes acute, progressive encephalomyelitis
- Incubation period: Average 1 to 3 months after untreated exposure
  - Most people who develop rabies do so in 12 months
  - Can be only days; rarely longer than one year after exposure
  - Depends on virus inoculum, distance from CNS and other factors
  - Bites to the head or neck usually have the shortest incubation periods

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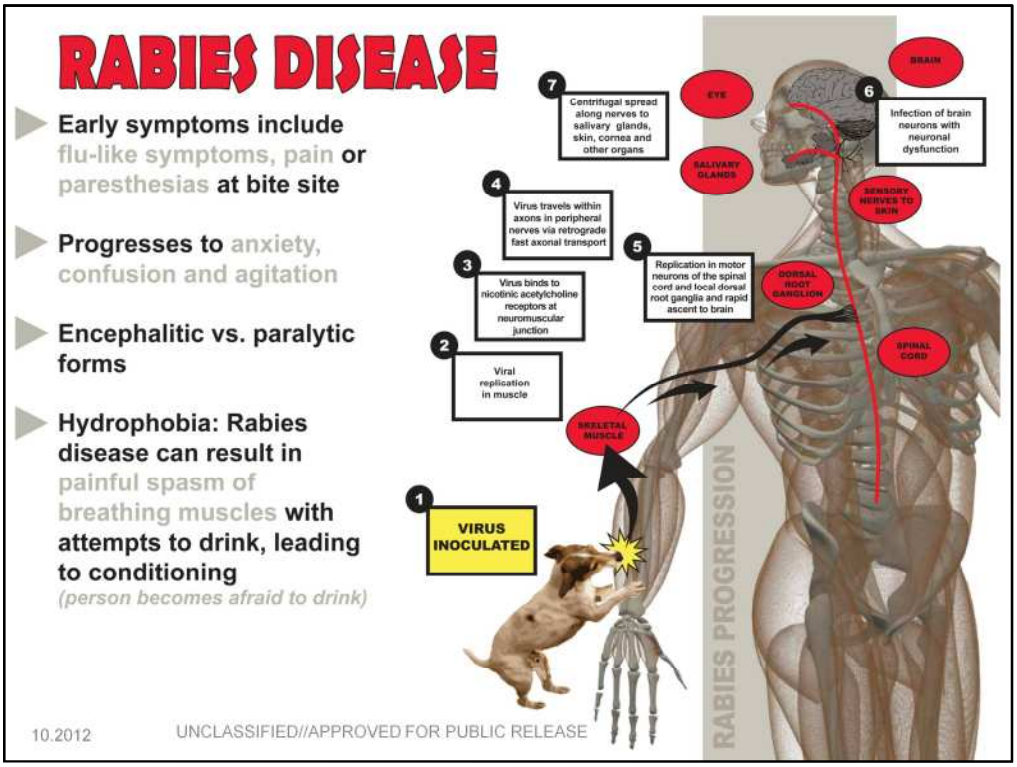
Rabies is caused by an RNA virus in the family Rhabdoviridae, genus Lyssavirus. The virus is transmitted through contact with the saliva of infected, or rabid, warm-blooded animals, such as dogs, cats, bats, skunks, raccoons, foxes, jackals *and even mongooses*. Mice, rats and other small rodents are almost never found to be infected with rabies, but larger rodents, such as groundhogs or beavers, can be infected. Larger animals are more likely to survive an encounter with another rabid animal and thus develop the disease themselves. Similarly, herd or farm animals, such as horses, cows, etc., can be infected. In March 2010, a horse in Michigan was found to have rabies. 6 people required post-exposure prophylaxis, including the owner, trainer, and veterinarian. The horse had never been vaccinated. (ProMed mail)

Once the rabies virus is introduced into the body, it replicates in muscle, then finds its way to nerves. From distal nerves the virus travels to the central nervous system, where it causes an acute, progressive encephalomyelitis. Because of variability in bite location and virus inoculum, the incubation period of rabies can vary from a few days to over a year. The average is 1 to 3 months after an untreated exposure. Most people who develop rabies do so within 12 months of an untreated exposure; only rarely does it develop more than one year after exposure. Because bites to the head or neck allow the virus a shorter trip to the CNS, such bites usually have the shortest incubation periods.


RABIES DISEASE
Early symptoms include flu-like symptoms, pain or paresthesias at bite site
Progresses to anxiety, confusion and agitation
Encephalitic vs. paralytic forms
Hydrophobia: Rabies disease can result in painful spasm of breathing muscles with attempts to drink, leading to conditioning
(person becomes afraid to drink)
1 VIRUS INOCULATED
2 Viral replication in muscle
3 Virus binds to nicotinic acetylcholine receptors at neuromuscular junction
4 Virus travels within axons in peripheral nerves via retrograde fast axonal transport
5 Replication in motor neurons of the spinal cord and local dorsal root ganglia and rapid ascent to brain
6 Infection of brain neurons with neuronal dysfunction
7 Centrifugal spread along nerves to salivary glands, skin, cornea and other organs
SKELETAL MUSCLE
DORSAL ROOT GANGLION
SPINAL CORD
SENSORY NERVES TO SKIN
BRAIN
EYE
SALIVARY GLANDS
RABIES PROGRESSION
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## Rabies Diagnosis & Treatment

- Combination of tests needed to confirm diagnosis ante-mortem
  - No single test is sufficient
  - Saliva: Virus isolation or RNA detection with RT-PCR
  - Serum & spinal fluid: Antibodies to rabies virus
  - Punch skin biopsy of neck: Detect rabies antigen in cutaneous nerves of hair follicles
- Once symptoms begin, no known effective treatment
  - Care is primarily supportive; ICU care required
  - Experimental administration of anti-viral drugs
  - Suppression of brain activity with sedatives may help reduce inflammatory effects of virus
- **The best treatment is PREVENTION**
  - Thorough cleansing of wounds as soon as possible
  - Timely completion of vaccine series and administration of human rabies immunoglobulin as appropriate

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Rabies in live persons is diagnosed with a combination of tests, as no single test is sufficient (usually a brain biopsy is not performed). Tests include virus isolation or RNA detection in saliva; detection of rabies antibodies in serum and CSF; and detection of rabies antigen in the cutaneous nerves of hair follicles (from a punch biopsy of skin at the back of the neck).

Once symptoms begin, there is no known effective treatment. Care is primarily supportive, and ICU care is usually required. Suppression of brain activity with sedatives may help reduce inflammatory effects of virus, *as may experimental uses of antiviral drugs.* A treatment protocol known as the "Milwaukee protocol" has been credited with enabling two persons to survive. However, the protocol or variations of it have been tried on a number of other persons without success, giving it about an 8% survival rate. Consequently, the best treatment is **PREVENTION:** Thorough cleansing of wounds as soon as possible, along with the timely completion of vaccine series and administration of human rabies immunoglobulin as appropriate.

# Rabies Post-Exposure Prophylaxis (PEP), United States, 2010

| Vaccination status | Intervention | Regimen* |
|---|---|---|
| Not previously vaccinated | Wound cleansing | All PEP should begin with immediate thorough cleansing of all wounds with soap and water. If available, a virucidal agent (e.g., povidine-iodine solution) should be used to irrigate the wounds. |
| | Human rabies immune globulin (HRIG) | Administer 20 IU/kg body weight. If anatomically feasible, the full dose should be infiltrated around and into the wound(s), and any remaining volume should be administered at an anatomical site (intramuscular [IM]) distant from vaccine administration. Also, HRIG should not be administered in the same syringe as vaccine. Because RIG might partially suppress active production of rabies virus antibody, no more than the recommended dose should be administered. |
| | Vaccine | Human diploid cell vaccine (HDCV) or purified chick embryo cell vaccine (PCECV) 1.0 mL, IM (deltoid area†), 1 each on days 0,§ 3, 7 and 14.¶ |
| Previously vaccinated** | Wound cleansing | All PEP 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. |
| | HRIG | HRIG should not be administered. |
| | Vaccine | HDCV or PCECV 1.0 mL, IM (deltoid area†), 1 each on days 0§ and 3. |

* These regimens are applicable for persons in all age groups, including children.
† The deltoid area is the only acceptable site of vaccination for adults and older children. For younger children, the outer aspect of the thigh may be used. Vaccine should never be administered in the gluteal area.
§ Day 0 is the day dose 1 of vaccine is administered.
¶ For persons with immunosuppression, rabies PEP should be administered using all 5 doses of vaccine on days 0, 3, 7, 14, and 28.
** Any person with a history of pre-exposure vaccination with HDCV, PCECV, or rabies vaccine adsorbed (RVA); prior PEP with HDCV, PCECV or RVA; or previous vaccination with any other type of rabies vaccine and a documented history of antibody response to the prior vaccination.

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This table from March 2010 MMWR summarizes post-exposure treatment protocols.

# Rabies and Deployment

- Although rabies can infect any mammal, mice, rats and other small rodents are almost never found to be infected with rabies. These bites do not require rabies prophylaxis.
- Other than military working dogs, there are no "safe" dogs or cats when deployed.
  - **~10% of animals tested from Afghanistan were positive**
- Vets in theater do not routinely vaccinate feral animals

PHOTO: CDC PHIL

A rabid dog, cat, or monkey can look and **behave** normally —even during a veterinary exam. The rabid dog above is calm with advanced disease.

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Although rabies can infect any mammal, mice, rats and other small rodents are almost never found to be infected with rabies. These bites do not require rabies prophylaxis. Other than military working dogs, there are no "safe" dogs or cats when deployed. Between January 2010 and August 2011, the Veterinary Lab Europe tested 44 animals from Afghanistan. 4 tested positive; each of these positive animals had bitten at least one military member. Keep in mind that veterinarians in theater do not routinely vaccinate feral animals.

## Rabies and Deployment

- General Order #1 prohibits the keeping of stray animals as pets or mascots by US Service members.
- Poor camp sanitation and actively providing food/water to feral animals increases the threat.
- Although well-meaning family members may send vaccine, lack of temperature control during transport renders it impotent.
- Take all reports of bites, nips or contact with the saliva of warm-blooded animals, such as dogs, cats, bats, monkeys, & jackals seriously and treat accordingly.
- The act of biting increases the pre-test probability the animal is rabid.

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General Order #1 prohibits the keeping of stray animals as pets or mascots by US Service members. Poor camp sanitation and actively providing food/water to feral animals increases the threat. And while well-meaning family members may send vaccine, lack of temperature control during transport renders it impotent. Therefore, healthcare providers at all levels—from medic on up—must take all reports of bites, nips or contact with the saliva of warm-blooded animals, such as dogs, cats, bats, monkeys, & jackals seriously and treat accordingly. After all, simply the act of biting increases the pre-test probability the animal is rabid.

## Overview: Evaluating Acute Exposures

**-Patient presents with obvious bite or shortly after event-**

- All bites MUST be appropriately documented in AHLTA
  - A template is being developed to ensure complete history is captured and appropriate ICD9 and CPT codes are captured
- All suspected rabies exposures MUST be treated with Human Rabies Immunoglobulin (HRIG) and Rabies Vaccine as appropriate
  - CDC algorithm is appropriate for evaluating exposures sustained in US, Australia, Western Europe, Japan, Korea, Bahrain and Singapore
  - A more conservative approach is appropriate for exposures sustained elsewhere; start PEP if animal anything other than MWD
  - PEP may be discontinued if animal remains healthy after 10-day period of quarantine or lab testing of animal is negative
  - Contact Preventive Medicine if there are questions about animal exposures or procedures to prevent rabies

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All bites MUST be appropriately documented in AHLTA. A template is being developed to ensure complete history is captured and appropriate ICD9 and CPT codes are captured

All suspected rabies exposures MUST be treated with Human Rabies Immunoglobulin (HRIG) and Rabies Vaccine as appropriate. A more conservative approach is appropriate for exposures sustained elsewhere; start PEP if animal anything other than MWD. If PEP is started, it may be discontinued ONLY if animal remains healthy after 10-day period of quarantine or lab testing of animal is negative. Reasons for discontinuation must also be documented in AHLTA. Always contact Preventive Medicine if there are questions about animal exposures or procedures to prevent rabies.

## Overview: Evaluating Acute Exposures

**-Patient presents with obvious bite or shortly after event-**

- Animal Bite Report (DD 2341) MUST be completed and sent to veterinarian
  - Ensure patient information, especially contact information, is correct in case person needs to be contacted later
  - Get as much information as possible regarding the biting animal. Veterinarians must try to locate the animal for quarantine.
  - Copy should also be scanned into AHLTA
- Preventive Medicine will coordinate with veterinarians to convene a Rabies Advisory Board to review all cases.

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Whenever an acute rabies risk exposure presents for care, an Animal Bite Report Form (DD 2341) MUST be completed and sent to veterinarians. It is VITAL that you ensure patient information, especially contact information, is correct in case person needs to be contacted later. Get as much information as possible regarding the biting animal. Veterinarians must try to locate the animal for quarantine. A copy should also be scanned into the patient record. Preventive Medicine will coordinate with veterinarians to convene a Rabies Advisory Board to review all cases.

# Treatment of Animal Bite or Other Rabies Risk Exposure

- Copiously wash out wound for at least 15 minutes
- If **not immunized previously:**
  - Give human rabies immunoglobulin (**HRIG**), 20 IU/kg
  - Infiltrate wound with as much HRIG as possible - give excess IM in **deltoid** or **anterior-lateral aspect of the quadriceps (thigh)**
  - Give **1.0 ml rabies vaccine IM** in **other deltoid**—be sure site is distal from HRIG injections!
  - **Series requires minimum of 4 vaccinations on days 0, 3, 7, and 14**
    - 5th dose on day 28 recommended for immunosuppressed persons or those on anti-malarials (standard for US forces in Afghanistan)
- If patient reports **previous rabies immunization:**
  - HRIG should NOT be given—may interfere with natural antibody production
  - Give 2 vaccinations on **days 0 and 3**; 1.0 ml IM in **deltoid**

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When treating a rabies risk exposure, first wash out the wound for at least 15 minutes. Additional cleansing with alcohol, iodine or other virucidal agent can be beneficial. If the patient has **not been immunized previously:** give human rabies immunoglobulin (**HRIG)**, 20 IU/kg by infiltrating the wound with as much HRIG as possible - give the remainder IM in **other deltoid** or **anterior-lateral aspect of the quadriceps (thigh)** region. Also give **1.0 ml rabies vaccine IM** in the other **deltoid**—be sure site is distal from HRIG injections. The s**eries requires minimum of 4 vaccinations on days 0, 3, 7, and 14.** A 5th dose on day 28 is recommended for immunosuppressed persons or those on anti-malarials (standard for US forces in Afghanistan). If the patient reports **previous rabies immunization:** HRIG should NOT be given—may interfere with natural antibody production. The person should only receive 2 vaccinations on **days 0 and 3**; 1.0 ml IM in **deltoid.**

## Monkey Bites: Special Considerations

- Macaque monkeys are native to central and Southeast Asia, including eastern Afghanistan, and are often kept as pets.
- Monkeys in the macaque group can carry Simian Herpes B virus (SHBV).
  - A rare but highly fatal encephalomyelitis in humans (up to 80% of cases)
  - Infected monkeys may be able to transmit SHBV but not show clinical signs

http://wwwnc.cdc.gov/eid/article/18/10/12-0419-f1.htm

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Rhesus macaque monkeys are native to eastern Afghanistan and throughout central and Southeast Asia. They are often kept as pets or mascots by local nationals. In addition to rabies, monkeys in the macaque group can carry Simian Herpes B virus (SHBV). Although rare, SHBV causes an encephalomyelitis in humans that is fatal in up to 80% of cases. A monkey infected with rabies or SHBV may not have clinical signs even though it can transmit the disease.

Disease risk appears to vary with type of exposure. The riskiest exposures appear to include deep puncture wounds that are difficult to clean, inadequately cleansed wounds, and wounds sustained on the face (especially wounds to the eye), neck, or thorax-that is, like rabies, sites nearer the CNS. Ocular splashes with infected fluids, such as saliva, may also transmit SHBV.

## Monkey Bites: Special Considerations

- Treatment for bites by macaque monkeys should include:
  - Immediate wound/mucous membrane cleansing for at least 15 minutes
  - Antiviral medication within 24 hrs to 5 days of the bite (see below)
  - Baseline testing for antibodies against SHBV
  - Rabies post-exposure prophylaxis (PEP)
  - Ensure SM's tetanus status is current
  - Consider antibiotic prophylaxis for prophylaxis of skin infections with oral flora
  - Follow-up testing for SHBV seroconversion should be done at 2, 4 and 6 weeks and finally 3 months after exposure.
- Consult infectious disease physicians for questions.
- Use either Valacyclovir or Acyclovir for prophylaxis.
  - Valacylovir—1g by mouth every 8 hours for 14 days, or
  - Acyclovir—800 mg by mouth 5 times daily for 14 days
- Neither is contraindicated with RIG or rabies vaccine.

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Additional information is available at: http://www.cdc.gov/herpesbvirus/index.html and http://cid.oxfordjournals.org/content/35/10/1191.full.pdf+html. See also http://wwwnc.cdc.gov/eid/article/18/10/12-0419_article.htm

## AHLTA Documentation

- Document **circumstances** of exposure, including date, location and activities leading to exposure
  - Enables Rabies Advisory Board to evaluate exposure risk
  - Helps to corroborate veterinary reports and lab results
- Document any **wounds**, including location
- Document **prior rabies vaccinations**, **current medications** and **medical conditions**
  - Prior rabies vaccinations and/or HRIG immunization
  - High-dose steroid or other immunosuppressive therapies or medical conditions require 5 vaccine doses instead of 4 (e.g., taking malaria pills)

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In the patient encounter note, be certain to document the **circumstances** of exposure, including date, location and activities leading to exposure. Doing so enables the local Rabies Advisory Board to evaluate exposure risk, and helps to corroborate veterinary reports and lab results. Document any **wounds**, including location. Also document **prior rabies vaccinations**, **current medications** and **medical conditions.** This includes prior rabies vaccinations and/or HRIG immunization, high-dose steroid or other immunosuppresive therapies or medical conditions require 5 vaccine doses instead of 4 (e.g., taking malaria pills).

# AHLTA Documentation

- Record treatment provided
  - **Copious washing** of wound for **> 15 minutes**
  - Administration of **HRIG**
  - Vaccine inoculation site
  - **Lot number** and **expiration date**
- Document plan for subsequent vaccination
  - If providing vials for administration at forward location, document **cold chain plan** (between 36 and 46 °F)
  - Provide **contact number** to track case to completion
  - Public health nurses can assist with ensuring follow-up
- Document any reasons for discontinuing vaccination series

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Additionally, record treatment provided

**Copious washing** of wound for **> 15 minutes**
Administration of **HRIG**
Vaccine inoculation site
**Lot number** and **expiration date**

And document the plan for subsequent vaccination. If providing vials for administration at forward location, document **cold chain plan** (between 36 and 46 °F). Provide patient's **contact number** to track case to completion. Public health nurses can assist with ensuring follow-up. Lastly, document any reasons for discontinuing vaccination series. This prevents confusion later.

## MEDPROS Documentation

- All HRIG and rabies vaccine doses must be entered into MEDPROS or other Service-specific immunization tracking program
  - Active duty, Reserve or National Guard
  - DA civilians who are deployable
  - DoD contractors eligible for care in theater

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All HRIG and rabies vaccine doses must be entered into MEDPROS or service-specific immunization tracking program.

Active duty, Reserve or National Guard
DA civilians who are deployable
DoD contractors eligible for care in theater

# Evaluating Past Exposures

**-Patient presents for care well after event-**

- All risk events MUST be appropriately documented in AHLTA
- All suspected rabies exposures MUST be treated with HRIG and Rabies Vaccine as appropriate
  - There is **no time limit** for treatment with HRIG and vaccine
    - Infiltrate site of wound or exposure with HRIG, even if injury is healed
    - Remainder of HRIG should be administered in other deltoid or anterior-lateral aspect of the quadriceps (thigh) region, distal from vaccination site
  - Only persons who have received previous rabies vaccinations should not receive HRIG
  - See algorithm for additional details
- Report case to Preventive Medicine/Public Health at military treatment facility to ensure patient receives appropriate follow-up
- Preventive Medicine will coordinate with veterinarians to convene a Rabies Advisory Board to review all cases

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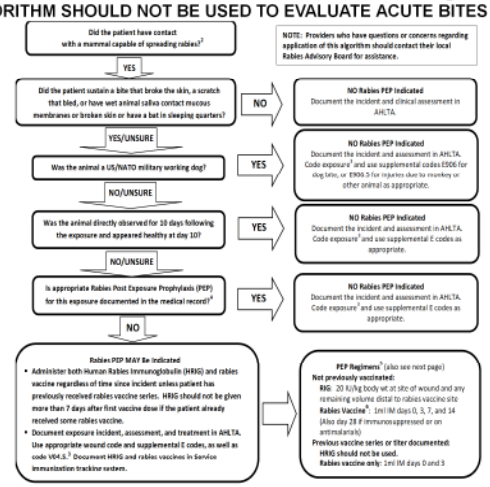
When evaluating persons who report a past exposure, be certain to document all risk events appropriately in AHLTA. A template is being developed to ensure complete history is captured and appropriate ICD9 and CPT codes are captured. All suspected rabies exposures MUST be treated with HRIG and Rabies Vaccine as appropriate. There is no time limit for treatment with HRIG or vaccine. Infiltrate site of wound or exposure with HRIG, even if injury is healed. Remainder of HRIG should be administered in **other deltoid** or **anterior-lateral aspect of the quadriceps (thigh)** region, distal from vaccination siteOnly persons who have received previous vaccinations should not receive HRIG. The algorithm on the next slide has additional details.
Report case to Preventive Medicine to ensure patient receives appropriate follow-up. Preventive Medicine will coordinate with veterinarians to convene a Rabies Advisory Board to review all cases.

# Evaluation and Treatment of Potential Deployment-Related Rabies Exposures

**IMPORTANT: THIS ALGORITHM SHOULD NOT BE USED TO EVALUATE ACUTE BITES OR EXPOSURES[1]**

**Note:** This algorithm is primarily intended to apply to risk exposures reported after a delay and associated with deployments to countries with Intermediate or High Rabies Risk as assessed by NCMI.




1. For acute bites and exposures, refer to http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5703a1.htm and http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5902a1.htm. These guidelines apply to the U.S. Do not apply them too strictly to persons who sustain exposures in countries with higher rabies risk.
2. Dogs, cats, bats, raccoons, skunks, ferrets, and wild terrestrial carnivores. 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.
3. Use codes 870.0-897.7 (wound, open) or 910-929 (superficial injury codes) with the appropriate supplemental code: E906 for dog bite or E906.5 for injuries due to monkey or other animal. Include code V04.5 for animal bite requiring rabies vaccination. 4.See protocols on next page.
5. If the vaccine series was interrupted for more than a few days or not completed, providers should complete the series and then assess immune status by performing serologic testing 7-14 days after administration of the final dose in the series. If drawing a titer is not practical or feasible, [illegible]
6. Purified Chick Embryo Cell Vaccine (PCECV) should not be given to individuals with egg allergies. Human Diploid Cell Vaccine (HDCV) is safe in egg-allergic individuals.

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This algorithm provides guidance for determining what exposures should be considered for treatment with PEP The algorithm is primarily intended to apply to deployments to countries with Intermediate or High Rabies Risk as assessed by NCMI. Keep in mind it is NOT intended to be used for assessing acute rabies risk exposures.

# Resources

## Local Preventive Medicine/Public Health/Veterinary Officers

- Phone:
- Email:

## US Army Public Health Command Rabies Response Team

- Phone: (800) 984-8523 OR DSN 312-421-3700
- Email: PHCRabiesInfo@amedd.army.mil
- http://phc.amedd.army.mil/topics/discond/aid/Pages/Rabies.aspx

## References


- US Centers for Disease Control and Prevention (CDC) Rabies Website http://www.cdc.gov/rabies/
- MMWR: March 19, 2010 / 59(RR02); 1-9: Use of a Reduced (4-Dose) Vaccine Schedule for Postexposure Prophylaxis to Prevent Human Rabies http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5902a1.htm
- MMWR: May 23, 2008 / 57(RR03); 1-26,28: Human Rabies Prevention --- United States, 2008 http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5703a1.htm
- USAPHC Rabies Fact Sheet available at Rabies Response Team webpage above




Here is a list of additional resources

Appendix C

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Questions?

MMWR™
Morbidity and Mortality Weekly Report
www.cdc.gov/mmwr

Recommendations and Reports May 23, 2008 / Vol. 57 / No. RR-3

# Human Rabies Prevention — United States, 2008

## Recommendations of the Advisory Committee on Immunization Practices

INSIDE: Continuing Education Examination

DEPARTMENT OF HEALTH AND HUMAN SERVICES
CENTERS FOR DISEASE CONTROL AND PREVENTION

The *MMWR* series of publications is published by the Coordinating Center for Health Information and Service, Centers for Disease Control and Prevention (CDC), U.S. Department of Health and Human Services, Atlanta, GA 30333.

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# Human Rabies Prevention — United States, 2008

## Recommendations of the Advisory Committee on Immunization Practices

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## 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.
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## 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 pre-exposure 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 $\mu$g neomycin sulfate, <100 mg albumin, and 20 $\mu$g 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 pre-exposure 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

**EXPIRATION — May 23, 2010**

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.

## *MMWR* Response Form for Continuing Education Credit
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### Human Rabies Prevention — United States, 2008
### Recommendations of the Advisory Committee on Immunization Practices

To receive continuing education credit, you must
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1. [ ] A [ ] B
2. [ ] A [ ] B [ ] C [ ] D [ ] E
3. [ ] A [ ] B [ ] C [ ] D [ ] E
4. [ ] A [ ] B [ ] C [ ] D [ ] E
5. [ ] A [ ] B [ ] C [ ] D [ ] E
6. [ ] A [ ] B [ ] C [ ] D [ ] E
7. [ ] A [ ] B [ ] C [ ] D [ ] E
8. [ ] A [ ] B [ ] C [ ] D [ ] E
9. [ ] A [ ] B [ ] C [ ] D [ ] E
10. [ ] A [ ] B [ ] C [ ] D [ ] E
11. [ ] A [ ] B [ ] C [ ] D [ ] E
12. [ ] A [ ] B [ ] C [ ] D [ ] E
13. [ ] A [ ] B [ ] C [ ] D [ ] E
14. [ ] A [ ] B [ ] C [ ] D [ ] E
15. [ ] A [ ] B [ ] C [ ] D [ ] E
16. [ ] A [ ] B [ ] C [ ] D [ ] E
17. [ ] A [ ] B [ ] C [ ] D [ ] E
18. [ ] A [ ] B [ ] C [ ] D [ ] E
19. [ ] A [ ] B [ ] C [ ] D [ ] E
20. [ ] A [ ] B [ ] C [ ] D [ ] E
21. [ ] A [ ] B [ ] C [ ] D [ ] E
22. [ ] A [ ] B [ ] C [ ] D [ ] E
23. [ ] A [ ] B [ ] C [ ] D [ ] E
24. [ ] A [ ] B [ ] C [ ] D [ ] E
25. [ ] A [ ] B [ ] C [ ] D [ ] E
26. [ ] A [ ] B [ ] C [ ] D [ ] E
27. [ ] A [ ] B
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

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

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# Use of a Reduced (4-Dose) Vaccine Schedule for Postexposure Prophylaxis to Prevent Human Rabies

## Recommendations of the Advisory Committee on Immunization Practices

DEPARTMENT OF HEALTH AND HUMAN SERVICES
CENTERS FOR DISEASE CONTROL AND PREVENTION

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# Use of a Reduced (4-Dose) Vaccine Schedule for Postexposure Prophylaxis to Prevent Human Rabies

## Recommendations of the Advisory Committee on Immunization Practices

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## Summary

*This report summarizes new recommendation and updates previous recommendations of the Advisory Committee on Immunization Practices (ACIP) for postexposure prophylaxis (PEP) to prevent human rabies (CDC. Human rabies prevention—United States, 2008: recommendations of the Advisory Committee on Immunization Practices. MMWR 2008;57[No. RR-3]). Previously, ACIP recommended a 5-dose rabies vaccination regimen with human diploid cell vaccine (HDCV) or purified chick embryo cell vaccine (PCECV). These new recommendations reduce the number of vaccine doses to four. The reduction in doses recommended for PEP was based in part on evidence from rabies virus pathogenesis data, experimental animal work, clinical studies, and epidemiologic surveillance. These studies indicated that 4 vaccine doses in combination with rabies immune globulin (RIG) elicited adequate immune responses and that a fifth dose of vaccine did not contribute to more favorable outcomes. For persons previously unvaccinated with rabies vaccine, the reduced regimen of 4 1-mL doses of HDCV or PCECV should be administered intramuscularly. The first dose of the 4-dose course should be administered as soon as possible after exposure (day 0). Additional doses then should be administered on days 3, 7, and 14 after the first vaccination. ACIP recommendations for the use of RIG remain unchanged. For persons who previously received a complete vaccination series (pre- or postexposure prophylaxis) with a cell-culture vaccine or who previously had a documented adequate rabies virus-neutralizing antibody titer following vaccination with noncell-culture vaccine, the recommendation for a 2-dose PEP vaccination series has not changed. Similarly, the number of doses recommended for persons with altered immunocompetence has not changed; for such persons, PEP should continue to comprise a 5-dose vaccination regimen with 1 dose of RIG. Recommendations for pre-exposure prophylaxis also remain unchanged, with 3 doses of vaccine administered on days 0, 7, and 21 or 28. Prompt rabies PEP combining wound care, infiltration of RIG into and around the wound, and multiple doses of rabies cell-culture vaccine continue to be highly effective in preventing human rabies.*

The material in this report originated in the National Center for Emerging and Zoonotic Infectious Diseases (proposed), Lonnie King, DVM, Director.
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## Introduction

Rabies is a zoonotic disease caused by RNA viruses in the family *Rhabdoviridae*, genus *Lyssavirus* (*1*). Virus is transmitted in the saliva of rabid mammals via a bite. After entry to the central nervous system, these viruses cause an acute, progressive encephalomyelitis. The incubation period usually ranges from 1 to 3 months after exposure, but can range from days to

years. Rabies can be prevented by avoidance of viral exposure and initiation of prompt medical intervention when exposure does occur. In the United States, animal rabies is common. In a recent study, approximately 23,000 persons per year were estimated to have been exposed to potentially rabid animals and received rabies postexposure prophylaxis (PEP) (*2*). With the elimination of canine rabies virus variants and enzootic transmission among dogs, human rabies is now rare in the United States, with an average of one or two cases occurring annually since 1960 (*3*).

Prompt wound care and the administration of rabies immune globulin (RIG) and vaccine are highly effective in preventing human rabies following exposure. A variety of empirical schedules and vaccine doses have been recommended over time, based in part on immunogenicity and clinical experience in areas of the world with enzootic canine or wildlife rabies (*4*). As more potent vaccines were developed, the number of vaccine doses recommended for PEP has decreased, and studies aimed at further revision and reduction of PEP schedules and doses in humans have been encouraged. By the latter half of the 20th century, a 4- to 6-dose, intramuscular regimen using human diploid cell vaccine (HDCV) or purified chick embryo cell vaccine (PCECV) was being recommended (*5–8*). In the United States, a 5-dose PEP vaccine regimen was adopted during the 1980s (*9–12*). In 2007, when human rabies vaccine was in limited supply, an ad hoc National Rabies Working Group was formed to reassess the recommendations for rabies prevention and control in humans and other animals. In 2008, a smaller Advisory Committee on Immunization Practices (ACIP) Rabies Workgroup was formed to review rabies vaccine regimen options. This report provides updated ACIP recommendations regarding the use of a 4-dose vaccination regimen, replacing the previously recommended 5-dose regimen, for rabies PEP in previously unvaccinated persons.

## Methods

The ACIP Rabies Workgroup* was formed in October 2008 to review 1) previous recommendations; 2) published and unpublished data from both national and global sources regarding rabies PEP; and 3) the immunogenicity, effectiveness, and safety of a 4-dose PEP rabies vaccination regimen. The ACIP Rabies Workgroup used an evidence-based process for consideration of a reduced vaccination regimen in human rabies PEP. This approach consisted of a review of information available from basic and applied studies of rabies prevention. Because rabies is almost always fatal among immunologically naïve persons once clinical symptoms of rabies occur, randomized, placebo-controlled efficacy studies of vaccine in humans cannot be conducted. The ACIP Rabies Workgroup reviewed six areas: 1) rabies virus pathogenesis, 2) experimental animal models, 3) human immunogenicity studies, 4) prophylaxis effectiveness in humans, 5) documented failures of prophylaxis in humans, and 6) vaccine safety. Studies for review were identified by searching the PubMed database and other relevant references and by consulting subject-matter experts. When definitive research evidence was lacking, the recommendations incorporated the expert opinion of the ACIP Rabies Workgroup members. The ACIP Rabies Workgroup also sought advice and comment from representatives of the vaccine industry, the National Association of State Public Health Veterinarians, the Council of State and Territorial Epidemiologists, state and local public health officials, additional national stakeholder groups, and other national and international experts. The proposed revised recommendations and a draft statement from the ACIP Rabies Workgroup were presented to the full ACIP during February 2009. After review and comment by ACIP, a revised draft, recommending a reduced regimen of 4 1-mL doses of rabies vaccine for PEP in previously unvaccinated persons, was prepared for consideration. These recommendations were discussed and accepted by ACIP at the June 2009 meeting (*13*).

## Rationale for Reduced Doses of Human Rabies Vaccine

A detailed review of the evidence in support of a reduced, 4-dose schedule for human PEP has been published (*14*). The totality of the evidence, obtained from the available peer-reviewed literature, unpublished data sources, epidemiologic reviews, and expert opinion strongly supports a reduced vaccination schedule (Table 1). Since the 19th century, prophylactic interventions against rabies have recognized the highly neurotropic characteristics of lyssaviruses and have aimed at neutralizing the virus at the site of infection before it can enter the human central nervous system (Figure 1) (*4,15,16*). To accomplish this, immunologic interventions must be prompt and must be directed toward local virus neutralization, such as local infiltration with RIG and vaccination. Modern recommended rabies PEP regimens emphasize early wound care and passive immunization (i.e., infiltration of RIG in and around the wound) combined with active immunization (i.e., serial doses of rabies vaccine). Accumulated scientific evidence indicates that, following rabies virus exposure, successful neutralization and clearance of rabies virus mediated via appropriate PEP generally ensures patient survival (*8*).

*A list of the membership appears on page 9 of this report.

**TABLE 1. Summary of evidence in support of a 4-dose postexposure prophylaxis regimen — United States, 2010**

| Evidence | Conclusion | Sources |
|---|---|---|
| Rabies virus pathogenesis | High neurotropism of rabies virus requires immediate immunization (local infiltration with human rabies immune globulin [HRIG] and vaccination) to neutralize virus at the site of infection and prevent viral entry into the central nervous system. | Published literature,* expert national and international opinion, and historic observations |
| Experimental animal models | Protection in animal models was elicited without regard to the absolute number of vaccine doses used. | Published literature,† expert national and international opinion, and unpublished data |
| Human clinical studies | All patients develop adequate levels of virus-neutralizing antibodies by day 14, without any additive value of a 5th dose of vaccine administered at day 28 (in regards to any substantive increase in measured virus-neutralizing antibody levels). | Published literature,§ expert national and international opinion, and unpublished data |
| Epidemiologic surveillance | No human rabies cases were identified in patients who received appropriate wound care, HRIG, and 4 doses of vaccine. | Published literature,¶ expert national and international opinion, and unpublished data |
| Health economics | Expected positive national benefits are related to omission of a 5th dose (e.g., minimized travel expenses, reduced time out of work, health-care workers have more time for other patients, and fewer adverse reactions). | Published literature** and expert national opinion |

* **SOURCES:** Lyles DS, Rupprecht CE. *Rhabdoviridae*. In: Knipe D, Howley P, eds. Fields virology. 5th ed. Philadelphia, PA: Lippincott, Williams, & Wilkins; 2007:1363–408. Plotkin SA, Koprowski H, Rupprecht CE. Rabies vaccines. In: Plotkin SA, Orenstein WA, Offit PA, eds. Vaccines. 5th ed. Philadelphia, PA: Saunders; 2008:687–714. World Health Organization. WHO Expert Consultation on Rabies. 1st report. WHO Technical Report Series, No. 931. Geneva, Switzerland: World Health Organization; 2005. Rupprecht CE, Briggs D, Brown C, et al. Evidence for a 4-dose vaccine schedule for human rabies post-exposure prophylaxis in previously non-vaccinated individuals. Vaccine 2009;27:7141–8. Charlton KM, Nadin-Davis S, Casey GA, Wandeler AI. The long incubation period in rabies: delayed progression of infection in muscle at the site of exposure. Acta Neuropathol 1997;94:73–7. Dietzschold B, Schnell M, Koprowski H. Pathogenesis of rabies. Curr Top Microbiol Immunol 2005;292:45–56.

† **SOURCES:** Lyles DS, Rupprecht CE. *Rhabdoviridae*. In: Knipe D, Howley P, eds. Fields Virology. 5th Ed. Philadelphia, PA: Lippincott, Williams, & Wilkins; 2007:1363–408. World Health Organization. WHO Expert Consultation on Rabies. 1st Report. WHO Technical Report Series, No. 931. Geneva, Switzerland: World Health Organization; 2005. Rupprecht CE, Briggs D, Brown C, et al. Evidence for a 4-dose vaccine schedule for human rabies post-exposure prophylaxis in previously non-vaccinated individuals. Vaccine 2009;27:7141–8. Baer GM. Animal models in the pathogenesis and treatment of rabies. Rev Infect Dis 1988;10(Suppl 4):S739–50. Franka R, Wu X, Jackson RF, et al. Rabies virus pathogenesis in relationship to intervention with inactivated and attenuated rabies vaccines. Vaccine 2009;27:7149–55. Sikes RK, Cleary WF, Koprowski H, Wiktor TJ, Kaplan MM. Effective protection of monkeys against death from street virus by post-exposure administration of tissue-culture rabies vaccine. Bull World Health Organ 1971;45:1–11. Manickama R, Basheer MD, Jayakumar R. Post-exposure prophylaxis (PEP) of rabies-infected Indian street dogs. Vaccine 2008;26:6564–8.

§ **SOURCES:** Plotkin SA, Koprowski H, Rupprecht CE. Rabies vaccines. In: Plotkin SA, Orenstein WA, Offit PA, eds. Vaccines. 5th ed. Philadelphia, PA: Saunders; 2008:687–714. World Health Organization. WHO Expert Consultation on Rabies. 1st Report. WHO Technical Report Series, No. 931. Geneva, Switzerland: World Health Organization; 2005. Rupprecht CE, Briggs D, Brown C, et al. Evidence for a 4-dose vaccine schedule for human rabies post-exposure prophylaxis in previously non-vaccinated individuals. Vaccine 2009;27:7141–8.

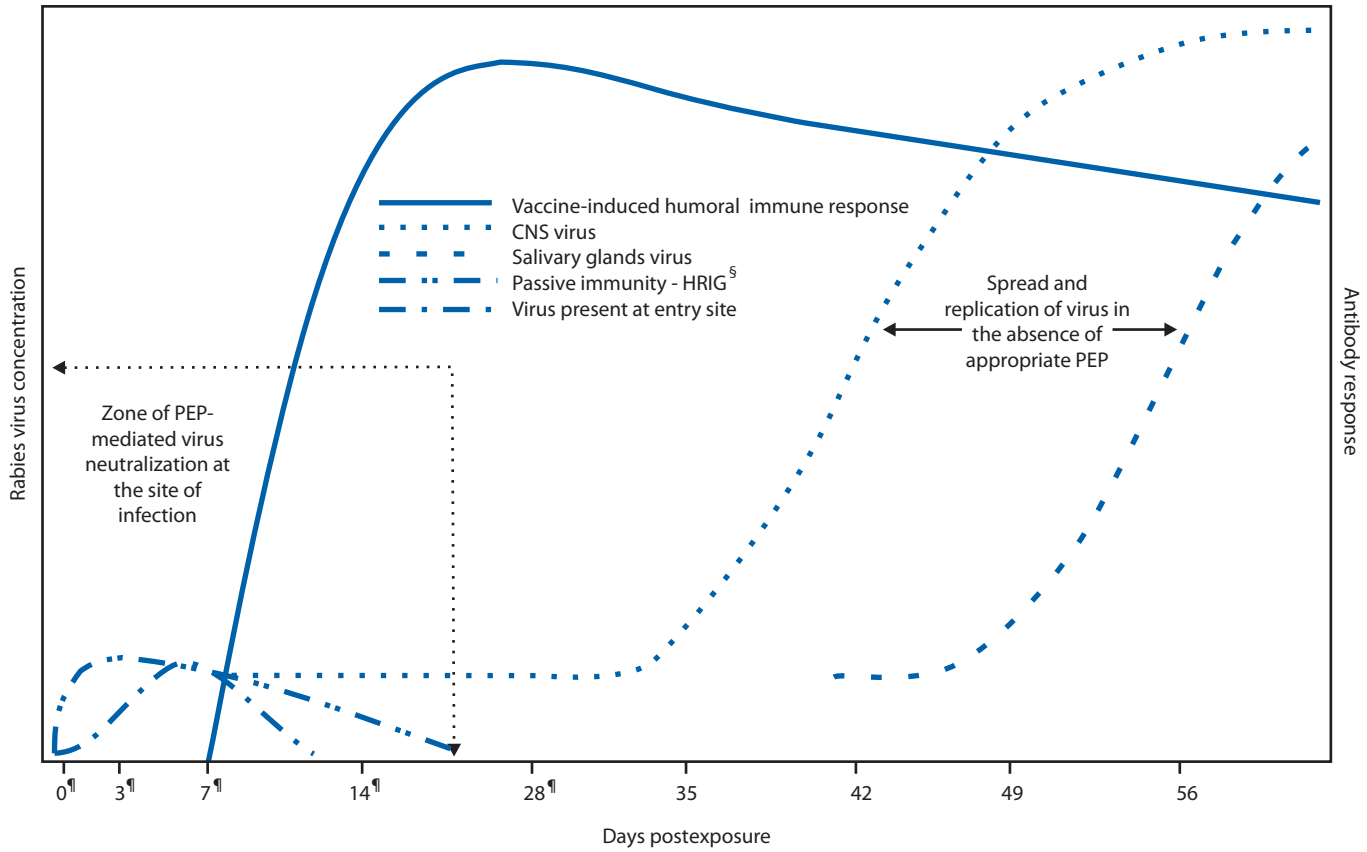
¶ **SOURCES:** Plotkin SA, Koprowski H, Rupprecht CE. Rabies vaccines. In: Plotkin SA, Orenstein WA, Offit PA, eds. Vaccines. 5th ed. Philadelphia, PA: Saunders; 2008:687–714. Rupprecht CE, Briggs D, Brown C, et al. Evidence for a 4-dose vaccine schedule for human rabies post-exposure prophylaxis in previously non-vaccinated individuals. Vaccine 2009; 27:7141–8. Wilde H. Failures of post-exposure rabies prophylaxis. Vaccine 2007;25:7605–9.

** **SOURCES:** Meltzer MI, Rupprecht CE. A review of the economics of the prevention and control of rabies: I: global impact and rabies in humans. PharmacoEconomics 1998:14:365–83. Dhankhar P, Vaidya SA, Fishbien DB, Meltzer MI. Cost effectiveness of rabies post exposure prophylaxis in the United States. Vaccine 2008;26:4251–5.

The induction of a rabies virus-specific antibody response is one important immunologic component of response to vaccination (*4*). Development of detectable rabies virus-specific neutralizing antibodies is a surrogate for an adequate immune response to vaccination. Clinical trials of human rabies vaccination indicate that all healthy persons develop detectable rabies virus-neutralizing antibody titer rapidly after initiation of PEP. For example, in a literature review conducted by the ACIP Rabies Workgroup of at least 12 published rabies vaccination studies during 1976–2008 representing approximately1,000 human subjects, all subjects developed rabies virus-neutralizing antibodies by day 14 (*14*).

Observational studies indicate that PEP is universally effective in preventing human rabies when administered promptly and appropriately. Of the >55,000 persons who die annually of rabies worldwide, the majority either did not receive any PEP, received some form of PEP (usually without RIG) after substantial delays, or were administered PEP according to schedules that deviated substantially from current ACIP or World Health Organization recommendations (*17*). For example, a review of a series of 21 fatal human cases in which patients received some form of PEP indicated that 20 patients developed signs of illness, and most died before day 28 (Figure 2). In such cases, in which widespread infection of the central

**FIGURE 1. Schematic of dynamics of rabies virus pathogenesis* in the presence and absence of postexposure prophylaxis (PEP)–mediated immune responses†**




* Rabies can progress through five stages: incubation period (5 days to >2 years: U.S. median ~35 days), prodrome state (0–10 days), acute neurologic period (2–7 days), coma (5–14 days), and death.

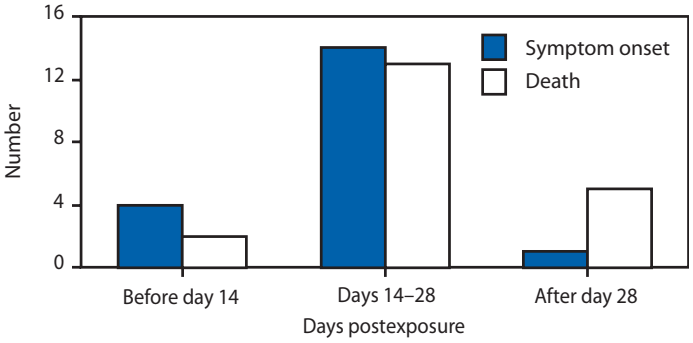
† Once in tissues at the entry site, rabies virus can be neutralized by passively administered rabies immune globulin (RIG). Active immunization (vaccine) stimulates the host immune system, and, as a result, virus-neutralizing antibodies (VNA) are produced approximately 7–10 days after initiation of vaccination. By approximately day 14–28 (after administration of 4 vaccine doses), VNAs peak. In the absence of early and adequate PEP, virus enters host neurons, spreads to the central nervous system (CNS), and causes disease, with inevitably fatal consequence.

§ Human rabies immune globulin.

¶ Day vaccine administered.

nervous system occurs before the due date (i.e., day 28) of the fifth vaccine dose, the utility of that dose must be nil. In the United States, of the 27 human rabies cases reported during 2000–2008, none of the patients had a history of receiving any PEP before illness, and this is the most common situation for human rabies deaths in both developed and developing countries (*3,8*). In India, an analysis from two animal bite centers during 2001–2002 demonstrated that in 192 human rabies cases, all deaths could be attributed to failure to seek timely and appropriate PEP, and none of them could be attributed to a failure to receive the fifth (day 28) vaccine dose (*18*). Even when PEP is administered imperfectly or not according to established scheduled dose recommendations, it might be generally effective. Several studies have reported cases involving persons who were exposed to potentially rabid animals and who received less than 5, 4, or even 3 doses of rabies vaccine but who nevertheless did not acquire rabies (Table 2). For example, in one series from New York, 147 (13%) of 1,132 patients had no report of receiving the complete 5-dose vaccine regimen. Of these patients, 26 (18%) received only 4 doses of vaccine, and two of these patients were exposed to animals with laboratory-confirmed rabies. However, no documented cases of human rabies occurred (CDC, unpublished data, 2003). The ACIP Rabies Working Group estimates that >1,000 persons in the United States receive rabies prophylaxis annually of only 3 or 4 doses, with no resulting documented cases of human rabies, even though >30% of these persons likely have exposure to confirmed rabid animals (*14*). In addition, no case of human rabies in the United States has been reported in which failure of PEP was attributable to receiving less than the 5-dose vaccine course. Worldwide, although human PEP failures have been reported very rarely, even in cases in which intervention

**FIGURE 2. Number of documented rabies postexposure prophylaxis (PEP) failures — Burma, India, the Philippines, South Africa, Sri Lanka, and Thailand, 1984–2007***




**SOURCES:** Wilde H. Failures of post-exposure rabies prophylaxis. Vaccine 2007;25:7605–9; Wilde H, Sirikawin S, Sabcharoen A, et al. Failure of postexposure treatment of rabies in children. Clin Infect Dis 1996;22:228–32; Matha IS, Salunke SR. Immunogenicity of purified vero cell rabies vaccine used in the treatment of fox-bite victims in India. Clin Infect Dis 2005;40:611–3.

* Of 21 reported PEP failures described, 20 patients had symptoms and 15 died before day 28.

appeared both prompt and appropriate (*8*), no cases have been attributed to the lack of receipt of the fifth human rabies vaccine dose on day 28 (*4,17*).

In vivo laboratory animal studies using multiple animal models from rodents to nonhuman primates have underscored the importance of timely PEP using RIG and vaccine, regardless of the absolute number of vaccine doses used or the schedule (*14,19*). For example, in a study in which 1, 2, 3, 4, or 5 doses of rabies vaccine were used in a Syrian hamster model in combination with human rabies immune globulin (HRIG), no statistically significant differences in elicited protection and consequent survivorship were observed among groups receiving different doses (*20*). In the same study, using a murine model, no differences were detected in immunogenicity and efficacy of PEP with 2, 3, or 4 vaccine doses. In another study using a nonhuman primate model, 1 dose of cell-culture vaccine, in combination with RIG administered 6 hours postexposure, provided substantial protection (*21*). In another study, a 3-dose regime was evaluated in a canine model and determined to be effective in preventing rabies (*22*).

Compared with older, nerve tissue-based products, adverse reactions associated with modern human rabies vaccination are uncommon (*4*). A review by the Workgroup of published and unpublished human rabies vaccine clinical trials and Vaccine Adverse Event Reporting System data identified no adverse events that were correlated to a failure to receive the fifth vaccine dose. As some adverse reactions might be independent clinical events with each vaccine administration, the omission of the vaccine dose on day 28 might have some positive health benefits. Otherwise, the overall safety of human rabies PEP is expected to be unchanged from the evidence provided in the 2008 ACIP report (*12*).

Preliminary economic assessments support the cost savings associated with a reduced schedule of vaccination (*23,24*). The ACIP Rabies Workgroup has estimated that, assuming 100% compliance with a recommended vaccine regimen, a change in recommendation from a 5-dose schedule to a 4-dose schedule would save approximately $16.6 million in costs to the U.S. health-care system. Persons who receive rabies vaccination might see some savings related to deletion of the fifth recommended dose of vaccine, measured in both the cost of the vaccine and the costs associated with the additional medical visit.

## Revised Rabies Postexposure Prophylaxis Recommendations

This report presents revised recommendations for human rabies PEP (Table 3). Rabies PEP includes wound care and administration of both RIG and vaccine.

### Postexposure Prophylaxis for Unvaccinated Persons

For unvaccinated persons, the combination of RIG and vaccine is recommended for both bite and nonbite exposures, regardless of the time interval between exposure and initiation

**TABLE 2. Number and percentage of patients with suspected rabies exposures who received <5 doses of vaccine — India, 2003; New York, 1998–2000; and Puerto Rico, 2008***

| Location (year) | No. of persons exposed | Persons who received <5 doses of vaccine | | No. of documented rabies deaths |
|---|---|---|---|---|
| | | No. | (%) | |
| New York (1998–2000)† | 1,132 | 147 | (13) | 0 |
| India (2003)§ | 439 | 261 | (59) | 0 |
| Puerto Rico (2008)¶ | 191 | 30 | (16) | 0 |

* No cases of human rabies were recorded that were attributable to receipt of only 4 doses of vaccine.

† **SOURCE:** CDC, unpublished data, 2003.

§ **SOURCE:** Association for the Prevention and Control of Rabies (APCRI) in India. Assessing the burden of rabies in India: WHO sponsored national multi-centric rabies survey 2003. Final report May 2004. Available at http://rabies.org.in. Accessed March 8, 2010. Sudarshan MK, Madhusudana SN, Mahendra BJ, et al. Assessing the burden of human rabies in India: results of a national multi-center epidemiological survey. Intl J Infect Dis 2007;11:29–35.

¶ **SOURCE:** CDC, unpublished data, 2008.

**TABLE 3. Rabies postexposure prophylaxis (PEP) schedule — United States, 2010**

| Vaccination status | Intervention | Regimen* |
|---|---|---|
| Not previously vaccinated | Wound cleansing | All PEP should begin with immediate thorough cleansing of all wounds with soap and water. If available, a virucidal agent (e.g., povidine-iodine solution) should be used to irrigate the wounds. |
| | Human rabies immune globulin (HRIG) | Administer 20 IU/kg body weight. If anatomically feasible, the full dose should be infiltrated around and into the wound(s), and any remaining volume should be administered at an anatomical site (intramuscular [IM]) distant from vaccine administration. Also, HRIG should not be administered in the same syringe as vaccine. Because RIG might partially suppress active production of rabies virus antibody, no more than the recommended dose should be administered. |
| | Vaccine | Human diploid cell vaccine (HDCV) or purified chick embryo cell vaccine (PCECV) 1.0 mL, IM (deltoid area†), 1 each on days 0,§ 3, 7 and 14.¶ |
| Previously vaccinated** | Wound cleansing | All PEP 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. |
| | HRIG | HRIG should not be administered. |
| | Vaccine | HDCV or PCECV 1.0 mL, IM (deltoid area†), 1 each on days 0§ and 3. |

* These regimens are applicable for persons in all age groups, including children.
† The deltoid area is the only acceptable site of vaccination for adults and older children. For younger children, the outer aspect of the thigh may be used. Vaccine should never be administered in the gluteal area.
§ Day 0 is the day dose 1 of vaccine is administered.
¶ For persons with immunosuppression, rabies PEP should be administered using all 5 doses of vaccine on days 0, 3, 7, 14, and 28.
** Any person with a history of pre-exposure vaccination with HDCV, PCECV, or rabies vaccine adsorbed (RVA); prior PEP with HDCV, PCECV or RVA; or previous vaccination with any other type of rabies vaccine and a documented history of antibody response to the prior vaccination.

of PEP. If PEP has been initiated and appropriate laboratory diagnostic testing (i.e., the direct fluorescent antibody test) indicates that the animal that caused the exposure was not rabid, PEP may be discontinued.

### Vaccine Use

A regimen of 4 1-mL vaccine doses of HDCV or PCECV should be administered intramuscularly to previously unvaccinated persons (Table 3). The first dose of the 4-dose regimen should be administered as soon as possible after exposure. The date of the first dose is considered to be day 0 of the PEP series. Additional doses then should be administered on days 3, 7, and 14 after the first vaccination. Recommendations for the site of the intramuscular vaccination remain unchanged (e.g., for adults, the deltoid area; for children, the anterolateral aspect of the thigh also is acceptable). The gluteal area should not be used because administration of vaccine in this area might result in a diminished immunologic response. Children should receive the same vaccine dose (i.e., vaccine volume) as recommended for adults.

### HRIG Use

The recommendations for use of immune globulin in rabies prophylaxis remain unchanged by the revised recommendation of a reduced rabies vaccine schedule. HRIG is administered once to previously unvaccinated persons to provide rabies virus-neutralizing antibody coverage until the patient responds to vaccination by actively producing virus-neutralizing antibodies. HRIG is administered once on day 0 at the time PEP is initiated, in conjunction with human rabies vaccines available for use in the United States. If HRIG was not administered when vaccination was begun on day 0, it can be administered up to and including day 7 of the PEP series (*12,25*). If anatomically feasible, the full dose of HRIG is infiltrated around and into any wounds. Any remaining volume is injected intramuscularly at a site distant from vaccine administration. HRIG is not administered in the same syringe or at the same anatomic site as the first vaccine dose. However, subsequent doses (i.e., on days 3, 7, and 14) of vaccine in the 4-dose vaccine series can be administered in the same anatomic location in which HRIG was administered.

## Postexposure Prophylaxis for Previously Vaccinated Persons

Recommendations for PEP have not changed for persons who were vaccinated previously. Previously vaccinated persons are those who have received one of the ACIP-recommended pre- or postexposure prophylaxis regimens (with cell-culture vaccines) or those who received another vaccine regimen (or vaccines other than cell-culture vaccine) and had a documented adequate rabies virus-neutralizing antibody response. Previously vaccinated persons, as defined above, should receive 2 vaccine doses (1.0 mL each in the deltoid), the first dose

immediately and the second dose 3 days later. Administration of HRIG is unnecessary, and HRIG should not be administered to previously vaccinated persons to avoid possible inhibition of the relative strength or rapidity of an expected anamnestic response (*26*). Local wound care remains an important part of rabies PEP for any previously vaccinated persons.

## Vaccination and Serologic Testing

### Postvaccination Serologic Testing

All healthy persons tested in accordance with ACIP guidelines after completion of at least a 4-dose regimen of rabies PEP should demonstrate an adequate antibody response against rabies virus (*14*). Therefore, no routine testing of healthy patients completing PEP is necessary to document seroconversion (*12*). When titers are obtained, serum specimens collected 1–2 weeks after prophylaxis (after last dose of vaccine) should completely neutralize challenge virus at least at a 1:5 serum dilution by the rapid fluorescent focus inhibition test (RFFIT). The rabies virus-neutralizing antibody titers will decline gradually since the last vaccination. Minimal differences (i.e., within one dilution of sera) in the reported values of rabies virus-neutralizing antibody results might occur between laboratories that provide antibody determination using the recommended RFFIT. Commercial rabies virus antibody titer determination kits that are not approved by the Food and Drug Administration are not appropriate for use as a substitute for the RFFIT. Discrepant results might occur after the use of such tests, and actual virus-neutralizing activity in clinical specimens cannot be measured.

## Management of Adverse Reactions, Precautions, and Contraindications

### Management of Adverse Reactions

Recommendations for management and reporting of vaccine adverse events have not changed. These recommendations have been described in detail previously (*12*).

### Immunosuppression

Recommendations for rabies pre- and postexposure prophylaxis for persons with immunosuppression have not changed. General recommendations for active and passive immunization in persons with altered immunocompetence have been summarized previously (*27,28*). This updated report discusses specific recommendations for patients with altered immunocompetence who require rabies pre- and postexposure prophylaxis. All rabies vaccines licensed in the United States are inactivated cell-culture vaccines that can be administered safely to persons with altered immunocompetence. Because corticosteroids, other immunosuppressive agents, antimalarials, and immunosuppressive illnesses might reduce immune responses to rabies vaccines substantially, for persons with immunosuppression, rabies PEP should be administered using a 5-dose vaccine regimen (i.e., 1 dose of vaccine on days 0, 3, 7, 14, and 28), with the understanding that the immune response still might be inadequate. Immunosuppressive agents should not be administered during rabies PEP unless essential for the treatment of other conditions. If possible, immunosuppressed patients should postpone rabies preexposure prophylaxis until the immunocompromising condition is resolved. When postponement is not possible, immunosuppressed persons who are at risk for rabies should have their virus-neutralizing antibody responses checked after completing the preexposure series. Postvaccination rabies virus-neutralizing antibody values might be less than adequate among immunosuppressed persons with HIV or other infections (*29,30*). When rabies pre- or postexposure prophylaxis is administered to an immunosuppressed person, one or more serum samples should be tested for rabies virus-neutralizing antibody by the RFFIT to ensure that an acceptable antibody response has developed after completing the series. If no acceptable antibody response is detected after the final dose in the pre- or postexposure prophylaxis series, the patient should be managed in consultation with their physician and appropriate public health officials.

## Variation from Human Rabies Vaccine Package Inserts

These new ACIP recommendations differ from current rabies vaccine label instructions, which still list the 5-dose series for PEP. Historically, ACIP review and subsequent public health recommendations for the use of various biologics has occurred after vaccine licensure and generally are in agreement with product labels. However, differences between ACIP recommendations and product labels are not unprecedented. For example, during the early 1980s, ACIP review and recommendations concerning the intradermal use of rabies vaccines occurred well in advance of actual label claims and licensing (*9*). On the basis of discussions with industry representatives, alterations of current product labels for HDCV and PCEC are not anticipated by the producers of human rabies vaccines licensed for use in the United States.

Please note: An erratum has been published for this issue. To view the erratum, please click here.



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