Rabies Prevention

The Clinical Management of Animal Bites

West Virginia Bureau for Public Health
Division of Surveillance & Disease Control
March 1999

Cecil H. Underwood
Governor

Joan E. Ohl
Secretary

Document Prepared By:

West Virginia Bureau for Public Health
Office of Epidemiology and Health Promotion
Division of Surveillance and Disease Control
Loretta Haddy, MA, MS, Division Director

Catherine Slemp, MD, MPH, Director
Infectious Disease Epidemiology Program

Carl Berryman, DVM, MPH, Public Health Veterinarian
Infectious Disease Epidemiology Program

Myra Fernatt, Data Analyst, Layout and Design
Infectious Disease Epidemiology Program

AN INTRODUCTION TO RABIES

Animal bites and scratches nationally continue to cause around 2 percent of emergency department visits. The physician is often faced with the question of whether or not these patients have been exposed to the rabies virus, for which post-exposure treatment (PET) is indicated. This question is often perplexing, and in many cases there are no clear-cut answers.

The enclosed information is intended to assist in the management of animal bite cases and the decision to initiate post-exposure treatment for rabies. One of the most important documents contained in this packet is a bite report form, much of which can be completed by the patient. Each local health department may have its own form in lieu of the form included here. Initiation of a bite report form will greatly assist the animal control officer/sheriff and public health sanitarian in securing the offending animal in a timely manner, and thus will aid in the decision-making process of when, or if, to initiate PET.

There are many factors to consider in deciding the need for PET. The following are important items to note. More detailed information is provided in the subsequent pages of this packet.

- Since 1980, the cat has been the domestic animal most involved in human exposure to rabies in the United States.
- Unprovoked attacks by most wildlife species, with the exception of small rodents, is sufficient indication to initiate PET. Species-specific information is available from your local health department or the Division of Surveillance and Disease Control.
- Potential exposure to a bat bite (many bat bites are cryptic) is sufficient to initiate PET.
- Important factors to consider in initiating PET are the location of the bite wound, its nature (i.e., whether it is a puncture or superficial lesion), the species of animal involved, history of rabies in the area, and the circumstances of the attack.
- Immediate cleansing of the wound is considered by many authorities to be the most important single factor in preventing rabies. Puncture wounds are more difficult to clean. Immediate and thorough cleansing prevents the rabies virus from attaching to nerve fiber endings or muscle cells at the area of the bite.
- As a generalization, the less severe the bite and the more distal from the central nervous system (CNS), then the more time one has before initiating PET.
- Bites of the neck and head are considered more serious because of the proximity to the CNS.
- As a generalization for domestic animal bites on distal extremities, waiting 10 days while the animal is in quarantine is not unreasonable.

Division of Surveillance and Disease Control, West Virginia Bureau for Public Health, March 1999

OBTAINING ASSISTANCE

Information on animal rabies in your area and assistance in evaluating individual cases are available from your local health department or the Division of Surveillance and Disease Control, West Virginia Bureau for Public Health. Please complete the information below pertaining to your local health department, and keep this information in a convenient place in the event that you are faced with managing a potential rabies exposure.

Your Local Health Department:

Address:

Contact Person:

Daytime Phone: **Emergency Phone:**

Fax:

West Virginia Bureau for Public Health, Division of Surveillance and Disease Control
Primary Contact: Carl Berryman, DVM, MPH
Secondary Contact: Catherine Slemp, MD, MPH
Tertiary Contact: Loretta Haddy, MA, MS, State Epidemiologist
(304) 558-5358 or (800) 423-1271 (normal business hours)
(304) 558-4117 (emergency contact information after normal business hours)

West Virginia Poison Control Center
(304) 348-4211 (Charleston area)
(800) 642-3625 (outside Charleston area)

COMMONLY ASKED QUESTIONS ON RABIES POST-EXPOSURE TREATMENT (PET)

How Is Post-Exposure Treatment For Rabies Administered?

Post-exposure treatment (PET) for rabies involves administration of both Human Rabies Immune Globulin (HRIG) and rabies vaccine.

HRIG dosage is based on patient weight (20 IU/kg). It is given only once, on day 0 of the series. As much as is anatomically feasible is infiltrated into and around the wound(s) in an effort to bind rabies virus locally. Any remaining HRIG is given intramuscularly in the gluteal muscle. (NOTE: In years past, only half of the HRIG dose was infiltrated locally. Current recommendations are for all of the HRIG, or as much as is anatomically feasible, to be infiltrated into and around the wound.) HRIG provides passive immunization against the rabies virus.

Rabies vaccine is administered as a 1 ml dose given intramuscularly into the deltoid muscle. It is administered on days 0, 3, 7, 14, and 28 of the series (1 ml each time, regardless of patient weight). Rabies vaccine provides active immunization against the rabies virus.

How Can Rabies Vaccines Be Obtained?

Both HRIG and rabies vaccines may be obtained through your usual pharmaceutical distributor or directly from the manufacturer. Overnight delivery is usually available. In rare instances, immunization is available from the Bureau for Public Health, Office of Laboratory Services through consultation with the Division of Surveillance and Disease Control (see contact numbers at the end of this sheet).

Is Vaccine Ever Administered Without HRIG For Post-Exposure Treatment?

Unless an individual has previously been immunized against rabies, vaccine is never administered without HRIG. If the decision is made to administer post-exposure prophylaxis, then both HRIG and rabies vaccine are always used.

Is There A Time Frame Following The Bite In Which Post-Exposure Treatment Must Be Given To Be Effective?

No. Post-exposure treatment should be initiated as soon as possible once adequate information is obtained identifying a bite as a potential rabies exposure. Depending on the circumstances of the situation, it may be appropriate to initiate PET immediately, or it may be appropriate to wait several days until lab testing or animal observation has been completed. There is no specific time frame immediately post-bite after which PET is no longer effective in preventing rabies.

(continued)

Is It Ever Too Late To Begin Rabies Post-Exposure Treatment?

The incubation period for rabies in humans is generally weeks to months, but has been as long as 5 years (this depends on the amount of virus injected, the type of exposure, and the location of the wound). Thus, if a true potential exposure to rabies has been identified, it is appropriate to initiate PET, even if weeks to months have passed since the incident.

Once Begun, Can Post-Exposure Treatment Be Stopped?

If, given a high-risk exposure, the decision was made to initiate PET immediately, and subsequent testing of the animal's head shows it to be negative for rabies, or if a domestic dog, cat, or ferret under observation is healthy 10 days post-exposure, then the series can be stopped.

Is Post-Exposure Treatment Still Needed If An Individual Has Received Pre-Exposure Rabies Vaccine Or If They Have Previously Undertaken PET?

Previous vaccination against rabies simplifies, but does not preclude, the need for post-exposure treatment. In the event of a potential rabies exposure, individuals who have had pre-exposure vaccine or who have received the full course of PET using one of the currently available vaccines do not need HRIG but should receive 2 doses of rabies vaccine, 1 dose on day 0 and 1 dose on day 3.

How Does The Rabies Virus Cause Clinical Illness?

Once injected into a bite, open wound, or mucous membrane, the rabies virus multiplies locally in muscle tissue (thus, the importance of local cleaning of the wound and why HRIG is infiltrated at the site of the bite). Eventually, the virus reaches adequate concentrations to work its way into sensory and motor nerve cells, where it begins a slow migration by retrograde axoplasmic flow up the neuronal axon, traveling only a few millimeters a day. Clinical illness begins to appear only after the virus reaches the spinal cord. (This slow migration up the neuronal axon explains why the incubation period for a distal extremity bite is much longer than the incubation period for a bite closer to the central nervous system, such as a bite to the head or neck.) Once the virus reaches the central nervous system, it rapidly disseminates and spreads systemically through peripheral nerves, causing further signs and symptoms of clinical disease. Once clinical illness begins, little can be done in terms of treatment, and the disease is usually fatal.

Where Can I Ask Further Questions Or Get Assistance In Assessing The Need For Post-Exposure Treatment?

Your local health department should be able to assist you with rabies questions as well as management of suspect animals involved in human exposures. In addition, rabies consultation is available from the West Virginia Bureau for Public Health, Division of Surveillance and Disease Control by calling 1-800-423-1271 (in Charleston, 558-5358) during business hours. After-hours emergency contact information is available either by calling 1-304-558-4117 or through the West Virginia Poison Control Center at 1-800-642-3625.

CLINICAL MANAGEMENT OF ANIMAL BITES REGARDING RABIES

1. IMMEDIATELY AND THOROUGHLY CLEANSE THE WOUND. Many authorities believe that this is the most important single factor in preventing rabies in the patient. The concept is to eliminate the virus prior to its attachment to the muscle cells or nerve endings at the site of the bite. This involves deep flushing of any penetrating bite wounds as well as scratches and abrasions. Any soap will do, but quarternary ammoniacals are most effective.

2. AVOID SUTURING IF POSSIBLE. As a generalization, suturing is not recommended unless absolutely necessary for cosmetic or other reasons. This is due to concern for infection by a variety of pathogens as well as the rabies virus (over 60 pathogens have been isolated from the oral cavities of both dogs and cats).

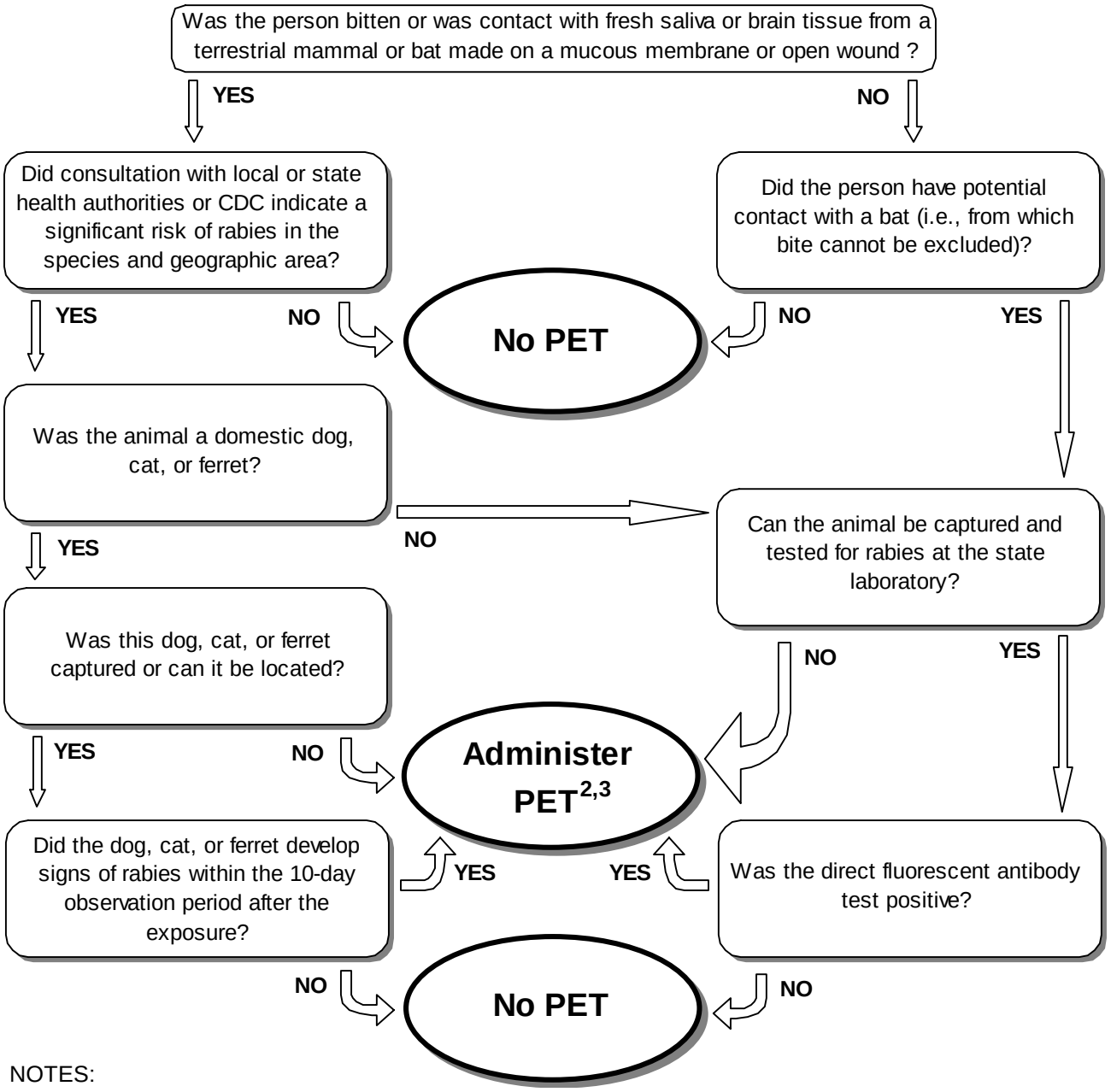
3. CONSIDER ANTIBIOTIC THERAPY. Appropriate antibiotic therapy is a consideration. Both alpha and beta hemolytic streptococci, pasteurella spp., and staphylococci are part of the normal flora of the oral cavities of both dogs and cats. Since it is a virus, antibiotics do nothing to prevent rabies.

4. CONSIDER TETANUS. If the individual has not had a tetanus immunization in at least 5 years, a booster immunization should be considered.

5. CONSIDER POST-EXPOSURE TREATMENT (PET) FOR RABIES. As a generalization, and there are many factors, PET is not immediately initiated unless a wild animal is involved, or other factors are paramount. Among these factors are the circumstances surrounding the attack, the location of the bite, incidence of rabies in the area, and the history of the offending animal. The emergency department (ED) staff and the public health sanitarian can greatly assist each other in case management. The ED staff can take a good history from the victim, which will save a great deal of time for the sanitarian, often days, in the location and quarantine of the offending animal. The sanitarian can assist the medical staff by prompt efforts in locating the offending animal, ascertaining its history, and, in conjunction with the animal control officer or sheriff's department, placing the dog, cat, or ferret in quarantine for 10 days or arranging for laboratory testing. With domestic dogs, cats, or ferrets, waiting through the 10-day quarantine period is generally indicated. If the offending dog, cat, or ferret can be located and is healthy 10 DAYS POST-BITE, there is no indication for PET, as the animal would not have been shedding rabies virus at the time of the bite. In some high-risk circumstances (e.g., severe head and neck wounds, bites by wild animals with highly unusual behavior, etc.), it is not appropriate to wait to initiate PET. Consultation should be obtained in these situations.

6. OBTAIN PUBLIC HEALTH CONSULTATION. Your local health department should be able to assist you with rabies questions as well as management of suspect animals involved in human exposures. In addition, rabies consultation is available from the West Virginia Bureau for Public Health, Division of Surveillance and Disease Control by calling 1-800-423-1271 (in Charleston, 558-5358) during business hours. After-hours emergency contact information is available either by calling 1-304-558-4117 or through the West Virginia Poison Control Center at 1-800-642-3625.

RABIES POST-EXPOSURE TREATMENT (PET) ALGORITHM[1]



NOTES:

1. This algorithm only addresses rabies immunization. Obviously, other treatments such as wound care, antibiotics, and tetanus immunization may be indicated.

2. Unless the person previously received rabies immunoprophylaxis, PET consists of 5 doses of vaccine (1.0 ml each administered IM in the deltoid region) on days 0, 3, 7, 14, and 28, and 1 dose of HRIG administered on day 0 (infiltrated into and around the bite wound as much as anatomically feasible, the remainder IM in the gluteal region). HRIG dosage is based on patient weight (20 IU/kg).

3. In the event that the biting animal is captured and tests negative for rabies after PET has begun, PET may be discontinued.

Algorithm modified from Fishbein, 1999

Division of Surveillance and Disease Control, West Virginia Bureau for Public Health, March 1999

OBTAINING RABIES IMMUNIZATIONS

Medical wholesalers and distributors now routinely stock both rabies vaccine and Human Rabies Immune Globulin (HRIG). Physicians can call their regular distributors with whom they have accounts to receive these products. This may be less expensive and more timely than going to the manufacturer, since wholesalers are usually within the region. The vaccine and the HRIG do not have to be from the same company. If wholesalers do not routinely stock these products, they should be requested to do so. If needed, these products are available to the provider directly from the manufacturer, usually by overnight delivery.

Most products have descriptions, dosage schedules, adverse reactions, etc., listed in the *Physicians' Desk Reference* and on the package insert.

RABIES VACCINES

Manufacturer: Chiron Corporation, 1564 McDaniel Drive, West Chester, PA 19380
Contact: Customer Service (800) 244-7668 or (800) 745-2388 ext. 5123 or (610) 429-4054
Product: RabAvert™ - 1.0 ml per dose intramuscularly for either pre- or post-exposure treatment

Manufacturer: Connaught Laboratories, Swiftwater, PA 18370
Contact: Customer Service (800) 822-2463
Product: Imovax® - 1.0 ml per dose intramuscularly for either pre- or post-exposure treatment
Product: Imovax® I.D. - 0.1 ml per dose intradermally for pre-exposure prophylaxis only

HUMAN RABIES IMMUNE GLOBULIN (HRIG)

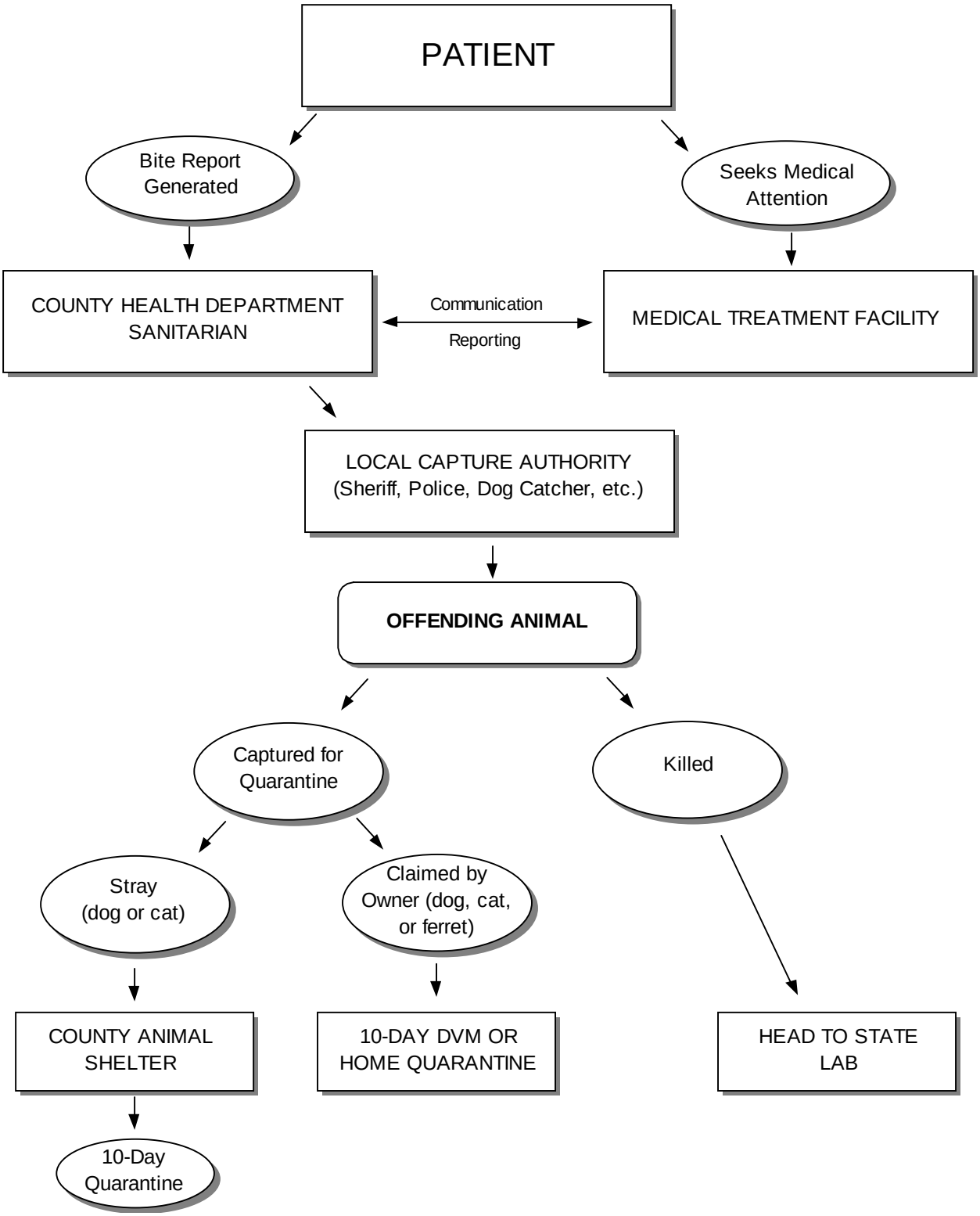
Manufacturer: Bayer Corporation Pharmaceutical Division
Contact: (800) 288-8370
Product: BayRab™ - available in 2.0 ml and 10.0 ml vials, given at the dose of 20 IU/kg (1.0 ml per 16 pounds body weight)

Manufacturer: Connaught Laboratories, Swiftwater, PA 18370
Contact: Customer Service (800) 822-2463
Product: Imogam® - available in 2.0 ml and 10.0 ml vials, given at the dose of 20 IU/kg (1.0 ml per 16 pounds body weight)

The average wholesale cost of biologicals for post-exposure treatment of a 165-pound patient was approximately $1,500.00 as of September 1998.

When ordering these products, keep in mind that for post-exposure prophylaxis, both rabies vaccine (5 doses) *and* HRIG (1 dose based on body weight) are necessary.

SUGGESTED ALGORITHM FOR HANDLING A SUSPECT ANIMAL FOLLOWING HUMAN EXPOSURE



Division of Surveillance and Disease Control, West Virginia Bureau for Public Health, March 1999

BITE REPORT FORM

MEDICAL FACILITY: FACILITY PHONE:
FACILITY ADDRESS: FACILITY FAX:

DATE: _____

I. PATIENT

NAME _____

ADDRESS _____

PHONE _____ AGE _____ SEX _____ WEIGHT _____

DATE AND TIME OF BITE _____

CIRCUMSTANCES OF BITE _____

_____

LOCATION OF BITE (HAND, FOOT, FACE, ETC.) _____

_____

SEVERITY OF WOUND (SCRATCH, MULTIPLE PUNCTURES, ETC.) _____

_____

HOW LONG BEFORE WOUND(S) WERE CLEANSED WITH SOAP AND WATER? _____

II. OFFENDING ANIMAL

SPECIES _____ SEX (IF KNOWN) _____

COLOR/ PATTERNS (BLACK ON WHITE, SOLID, SPOTTED, SADDLE, ETC.) _____

_____

HAIR: LONG _____ SHORT _____ CURLY _____ STRAIGHT _____

SIZE: HEIGHT (AT SHOULDER) _____ WEIGHT _____

OWNER AND ADDRESS/PHONE (IF KNOWN) _____

_____

RABIES VACCINATION HISTORY (INCLUDING DATE AND TYPE OF LAST RABIES VACCINATION) _____

_____

III. TREATMENT

TREATMENT UNDERTAKEN _____

DATE AND TIME OF TREATMENT _____

NAME OF ATTENDING PHYSICIAN/HEALTH CARE PROVIDER _____

FOLLOW-UP PLANS _____

IV. PERSON WHO NOTIFIED LOCAL HEALTH DEPARTMENT

NAME _____ DATE _____ TIME _____

V. COMMENTS _____

_____

_____

Human Rabies Prevention — United States, 1999

Recommendations of the Advisory Committee on Immunization Practices (ACIP)

Contents

Human Rabies Prevention — United States, 1999

Recommendations of the Advisory Committee on Immunization Practices (ACIP)

Summary

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

INTRODUCTION

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

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

---

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

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

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

RABIES BIOLOGICS

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

- Rabies vaccines induce an active immune response that includes the production of neutralizing antibodies. This antibody response requires approximately 7-10 days to develop and usually persists for greater than or equal to 2 years.

- Rabies immune globulin (RIG) provides a rapid, passive immunity that persists for only a short time (half-life of approximately 21 days) (*19*).

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

Table 1. Rabies biologics — United States, 1999

Human rabies vaccine	Product name	Manufacturer
Human diploid cell vaccine (HDCV) • Intramuscular • Intradermal	 Imovax® Rabies Imovax® Rabies I.D.	Pasteur-Merieux Serum et Vaccins, Connaught Laboratories, Inc. Phone: (800) VACCINE *(822-2463)*
~~Rabies vaccine adsorbed (RVA)~~ • ~~Intramuscular~~	~~Rabies Vaccine Adsorbed (RVA)~~ *BioPort no longer produces RVA*	~~BioPort Corporation~~ ~~Phone: (517) 335-8120~~
Purified chick embryo cell vaccine (PCEC) • Intramuscular	RabAvert™	Chiron Corporation Phone: (800) CHIRON8 *(244-7668)*
Rabies immune globulin (RIG)	Imogam® Rabies-HT	Pasteur-Merieux Serum et Vaccins, Connaught Laboratories, Inc. Phone: (800) VACCINE *(822-2463)*
	BayRab™	Bayer Corp. Pharmaceutical Div. Phone: (800) 288-8370

Vaccines Licensed for Use in the United States

Four formulations of three inactivated rabies vaccines are currently licensed for preexposure and postexposure prophylaxis in the United States (Table 1). When used as indicated, all three types of rabies vaccines are considered equally safe and efficacious. The potency of one dose is greater than or equal to 2.5 international units (IU) per 1.0 mL of rabies virus antigen, which is the World Health Organization recommended standard (*20*). A full 1.0-mL dose can be used for both preexposure and postexposure prophylaxis. However, only the Imovax® Rabies I.D. vaccine (human diploid cell vaccine (HDCV)) has been evaluated and approved by the Food and Drug Administration (FDA) for the intradermal dose and route for preexposure vaccination (*21-24*). Therefore, rabies vaccine adsorbed (RVA) and purified chick embryo cell vaccine (PCEC) should not be used intradermally. Usually, an immunization series is initiated and completed with one vaccine product. No clinical studies have been conducted that document a change in efficacy or the frequency of adverse reactions when the series is completed with a second vaccine product.

Human Diploid Cell Vaccine (HDCV)

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

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

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

~~*Rabies Vaccine Adsorbed (RVA) Note: BioPort no longer produces RVA*~~

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

Purified Chick Embryo Cell Vaccine (PCEC)

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

Rabies Immune Globulin Licensed for Use in the United States

The two RIG products, BayRab™ and Imogam® Rabies-HT (Table 1), are an antirabies immunoglobulin (IgG) preparation concentrated by cold ethanol fractionation from plasma of hyperimmunized human donors. Rabies neutralizing antibody, standardized at a concentration of 150 IU per mL, is supplied in 2-mL (300 IU) vials for pediatric use and 10-mL (1,500 IU) vials for adult use; the recommended dose is 20 IU/kg body weight. Both RIG preparations are considered equally efficacious when used as described in this report (see Treatment of Wounds and Immunization).

PRIMARY OR PREEXPOSURE VACCINATION

Preexposure vaccination should be offered to persons in high-risk groups, such as veterinarians, animal handlers, and certain laboratory workers. Preexposure vaccination also should be considered for other persons whose activities bring them into frequent contact with rabies virus or potentially rabid bats, raccoons, skunks, cats, dogs, or other species at risk for having rabies. In addition, international travelers might be candidates for preexposure vaccination if they are likely to come in contact with animals in areas where dog rabies is enzootic and immediate access to appropriate medical care, including biologics, might be limited. Routine preexposure prophylaxis for other situations might not be indicated (*33, 34*).

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

Intramuscular Primary Vaccination

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

Intradermal Primary Vaccination

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

Table 2. Rabies preexposure prophylaxis schedule — United States, 1999

Type of vaccination	Route	Regimen
Primary	Intramuscular	HDCV, PCEC or RVA; 1.0 mL (deltoid area), one each on days 0*, 7, and 21 or 28
	Intradermal	HDCV; 0.1 mL, one each on days 0*, 7, and 21 or 28
Booster	Intramuscular	HDCV, PCEC or RVA; 1.0 mL (deltoid area), day 0* only
	Intradermal	HDCV; 0.1 mL, day 0* only

HDCV=human diploid cell vaccine; PCEC=purified chick embryo cell vaccine; RVA=rabies vaccine adsorbed.
* Day 0 is the day the first dose of vaccine is administered.

and has been approved by the FDA since 1986 (*25*). The 0.1-mL ID doses, administered in the area over the deltoid (lateral aspect of the upper arm) on days 0, 7, and 21 or 28, are used for primary preexposure vaccination. One 0.1-mL ID dose is used for routine preexposure booster vaccination (Table 2). The 1.0-mL vial is not approved for multidose ID use. RVA and PCEC are not approved for and should not be administered intradermally (*26*).

When chloroquine phosphate was used routinely for malaria prophylaxis, investigators discovered that the drug decreased the antibody response to concomitantly administered HDCV (*41*). Although interference with the immune response to rabies vaccine by other antimalarials structurally related to chloroquine (e.g., mefloquine) has not been evaluated, precautions for persons receiving these drugs should be followed. Accordingly, HDCV should not be administered intradermally to a person traveling to malaria-endemic countries while the person is receiving one of these antimalarials (*42*). The IM administration of three doses of 1.0 mL of vaccine for preexposure prophylaxis provides a sufficient margin of safety in this situation (*42*). For persons who will be receiving both rabies preexposure prophylaxis and antimalarial chemoprophylaxis in preparation for travel to a rabies-enzootic area, the ID regimen should be initiated at least 1 month before travel to allow for completion of the full three-dose vaccine series before antimalarial prophylaxis begins. If this schedule is not possible, the IM regimen should be used.

Preexposure Booster Doses of Vaccine

Persons who work with rabies virus in research laboratories or vaccine production facilities (continuous risk category (Table 3) (*43*)) are at the highest risk for inapparent exposures. Such persons should have a serum sample tested for rabies antibody every 6 months. Booster doses (IM or ID (Table 2)) of vaccine should be administered to maintain a serum titer corresponding to 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), spelunkers, veterinarians and staff, and animal-control and wildlife officers in areas where animal rabies is enzootic. Persons in this group should have a serum sample tested for rabies 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 animal-control and wildlife officers

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

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

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

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

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

Postexposure Therapy for Previously Vaccinated Persons

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

Preexposure Vaccination and Serologic Testing

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

POSTEXPOSURE PROPHYLAXIS

Rationale for Treatment

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

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

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

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

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

Types of Exposure

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

Bite

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

Nonbite

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

The contamination of open wounds, abrasions, mucous membranes, or theoretically, scratches, with saliva or other potentially infectious material (such as neural tissue) from a rabid animal also constitutes a nonbite exposure. Other contact by itself, such as petting a rabid animal and contact with blood, urine, or feces (e.g., guano) of a rabid animal, does not constitute an exposure and is not an indication for prophylaxis. Because the rabies virus is inactivated by desiccation and ultraviolet irradiation, in general, if the material containing the virus is dry, the virus can be considered noninfectious.

Human-to-Human Transmission

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

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

body fluids has occurred. Adherence to standard precautions as outlined by the Hospital Infection Control Practices Advisory Committee will minimize the risk of exposure (*61*).

Animal Rabies Epidemiology and Evaluation of Involved Species

Bats

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

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

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

Consequently, postexposure prophylaxis should be considered when direct contact between a human and a bat has occurred, unless the exposed person can be certain a bite, scratch, or mucous membrane exposure did not occur. In instances in which a bat is found indoors and there is no history of bat-human contact, the likely effectiveness of postexposure prophylaxis must be balanced against the low risk such exposures appear to present. In this setting, postexposure prophylaxis can be considered for persons who were in the same room as the bat and who might be unaware that a bite or direct contact had occurred (e.g., a sleeping person awakens to find a bat in the room or an adult witnesses a bat in the room with a previously unattended child, mentally disabled person, or intoxicated person) and rabies cannot be ruled out by testing the bat. Postexposure prophylaxis would not be warranted for other household members.

Wild Terrestrial Carnivores

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

postexposure prophylaxis has been initiated and subsequent immunofluorescence testing shows that the exposing animal was not rabid, postexposure prophylaxis can be discontinued.

Signs of rabies among wildlife cannot be interpreted reliably; therefore, any such animal that exposes a person should be euthanized at once (without unnecessary damage to the head) and the brain should be submitted for rabies testing (*64*). If the results of testing are negative by immunofluorescence, the saliva can be assumed to contain no virus, and the person bitten does not require postexposure prophylaxis.

Other Wild Animals

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

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

Domestic Dogs, Cats, and Ferrets

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

On the basis of new information regarding rabies pathogenesis and viral shedding patterns in ferrets, ferrets are now considered in this category with dogs and cats rather than as wild terrestrial carnivores (*68*). A healthy domestic dog, cat, or ferret that bites a person may be confined and observed for 10 days. Any illness in the animal during confinement or before release should be evaluated by a veterinarian and reported immediately to the local public health department. If signs suggestive of rabies develop, the animal should be euthanized and its head removed and shipped, under refrigeration, for examination by a qualified laboratory. If the biting animal is stray or unwanted, it should either be observed for 10 days or be euthanized immediately and submitted for rabies examination (*63*).

Circumstances of Biting Incident and Vaccination Status of Exposing Animal

An unprovoked attack by an animal is more likely than a provoked attack to indicate that the animal is rabid. Bites inflicted on a person attempting to feed or handle an apparently healthy animal should generally be regarded as provoked. A currently vaccinated dog, cat, or ferret is unlikely to become infected with rabies (*68-71*).

Treatment of Wounds and Immunization

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

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

Treatment of Wounds

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

Immunization

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

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

Vaccination status	Treatment	Regimen*
Not previously vaccinated	Wound cleansing	All postexposure treatment should begin with immediate thorough cleansing of all wounds with soap and water. If available, a virucidal agent such as a povidone-iodine solution should be used to irrigate the wounds (*72*).
	RIG	Administer 20 IU/kg body weight. If anatomically feasible, **the full dose** should be infiltrated around the wound(s) and any remaining volume should be administered IM at an anatomical site distant from vaccine administration. Also, RIG should not be administered in the same syringe as vaccine. Because RIG might partially suppress active production of antibody, no more than the recommended dose should be given.
	Vaccine	HDCV, RVA, or PCEC 1.0 mL, IM (deltoid area†), one each on days 0⁴, 3, 7, 14, and 28.
Previously vaccinated^	Wound cleansing	All postexposure treatment should begin with immediate thorough cleansing of all wounds with soap and water. If available, a virucidal agent such as a povidone-iodine solution should be used to irrigate the wounds (*72*).
	RIG	HRIG should **not** be administered.
	Vaccine	HDCV, RVA, or PCEC 1.0 mL, IM (deltoid area†), one each on days 0⁴ and 3.

HDCV=human diploid cell vaccine; PCEC=purified chck embryo cell vaccine; RIG=rabies immune globulin; RVA=rabies vaccine adsorbed; IM=intramuscular.

* These regimens are applicable for all age groups, including children.

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

⁴ Day 0 is the day the first dose of vaccine is administered.

^ Any person with a history of preexposure vaccination with HDCV, RVA or PCEC; prior postexposure prophylaxis with HDCV, RVA or PCEC; or previous vaccination with any other type of rabies vaccine and a documented history of antibody response to the prior vaccination.

Rabies Immune Globulin Use. RIG is administered only once (i.e., at the beginning of antirabies prophylaxis) to previously unvaccinated persons to provide immediate antibodies until the patient responds to HDCV, RVA, or PCEC by actively producing antibodies. If RIG was not administered when vaccination was begun, it can be administered through the seventh day after the administration of the first dose of vaccine (*78*). Beyond the seventh day, RIG is not indicated since an antibody response to cell culture vaccine is presumed to have occurred. Because RIG can partially suppress active production of antibody, no more than the recommended dose should be administered (*79*). The recommended dose of human RIG is 20 IU/kg body weight. This formula is applicable to all age groups, including children. If anatomically feasible, the full dose of RIG should be thoroughly infiltrated in the area around and into the wounds. Any remaining volume should be injected intramuscularly at a site distant from vaccine administration. This change in the recommendations for RIG administration is based on reports of rare failures of postexposure prophylaxis when smaller amounts of

RIG were infiltrated at the exposure sites (*80*). RIG should never be administered in the same syringe or in the same anatomical site as vaccine.

Vaccine Use. Three rabies vaccines are currently available in the United States (Table 1); any one of the three can be administered in conjunction with RIG at the beginning of postexposure therapy. A regimen of five 1-mL doses of HDCV, RVA, or PCEC should be administered intramuscularly. The first dose of the five-dose course should be administered as soon as possible after exposure. Additional doses should be administered on days 3, 7, 14, and 28 after the first vaccination. For adults, the vaccination should always be administered IM in the deltoid area. For children, the anterolateral aspect of the thigh is also acceptable. The gluteal area should never be used for HDCV, RVA, or PCEC injections because administration of HDCV in this area results in lower neutralizing antibody titers (*81*).

Treatment Outside the United States

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

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

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

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

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

VACCINATION AND SEROLOGIC TESTING

Serologic Response Shortly After Vaccination

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

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

Serologic Response and Preexposure Booster Doses of Vaccine

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

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

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

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

ADVERSE REACTIONS

HDCV, RVA, and PCEC

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

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

Rabies Immune Globulin (Human)

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

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

Vaccines and Immune Globulins Used in Other Countries

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

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

Management of Adverse Reactions

Once initiated, rabies prophylaxis should not be interrupted or discontinued because of local or mild systemic adverse reactions to rabies vaccine. Usually, such reactions can be successfully managed with antiinflammatory and antipyretic agents, such as ibuprofen or acetaminophen.

When a person with a history of serious hypersensitivity to rabies vaccine must be revaccinated, antihistamines can be administered. Epinephrine should be readily available to counteract anaphylactic reactions, and the person should be observed carefully immediately after vaccination.

Although serious systemic, anaphylactic, or neuroparalytic reactions are rare during and after the administration of rabies vaccines, such reactions pose a serious dilemma for the patient and the attending physician (*9*). A patient's risk of acquiring rabies must be carefully considered before deciding to discontinue vaccination. Advice and assistance on the management of serious adverse reactions for persons receiving rabies vaccines may be sought from the state health department or CDC.

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

PRECAUTIONS AND CONTRAINDICATIONS

Immunosuppression

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

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

Pregnancy

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

Allergies

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

References

1. Krebs JW, Smith JS, Rupprecht CE, Childs JE. Rabies surveillance in the United States during 1996. J Am Vet Med Assoc 1997;211:1525-39.
2. Noah DL, Drenzek CL, Smith JS, et al. Epidemiology of human rabies in the United States, 1980 to 1996. Ann Intern Med 1998;128:922-30.
3. CDC. Human rabies — New Hampshire, 1996. MMWR 1997;46:267-70.
4. Mitmoonpitak C, Wilde H, Tepsumetanon W. Current status of animal rabies in Thailand. J Vet Med Sci 1997;59:457-60.
5. CDC. Human rabies — Montana and Washington, 1997. MMWR 1997;46:770-4.
6. CDC. Human rabies — Texas and New Jersey, 1997. MMWR 1998;47:1-5.
7. Krebs JW, Long-Marin SC, Childs JE. Causes, costs and estimates of rabies postexposure prophylaxis treatments in the United States. J Public Health Manage Pract 1998;4:57-63.
8. Bernard KW, Smith PW, Kader FJ, Moran MJ. Neuroparalytic illness and human diploid cell rabies vaccine. JAMA 1982;248:3136-8.
9. CDC. Systemic allergic reactions following immunization with human diploid cell rabies vaccine. MMWR 1984;33:185-7.
10. Dreesen DW, Bernard KW, Parker RA, Deutsch AJ, Brown J. Immune complex-like disease in 23 persons following a booster dose of rabies human diploid cell vaccine. Vaccine 1986;4:45-9.
11. Aoki FY, Tyrrell DAJ, Hill LE, Turner GS. Immunogenicity and acceptability of a human diploid-cell culture rabies vaccine in volunteers. Lancet 1975;1:660-2.
12. Cox JH, Schneider LG. Prophylactic immunization of humans against rabies by intradermal inoculation of human diploid cell culture vaccine. J Clin Microbiol 1976;3:96-101.
13. Anderson LJ, Sikes RK, Langkop CW, et al. Postexposure trial of a human diploid cell strain rabies vaccine. J Infect Dis 1980;142:133-8.
14. Bahmanyar M, Fayaz A, Nour-Salehi S, Mohammadi M, Koprowski H. Successful protection of humans exposed to rabies infection. Postexposure treatment with the new human diploid cell rabies vaccine and antirabies serum. JAMA 1976;236:2751-4.
15. Hattwick MAW. Human rabies. Public Health Rev 1974;3:229-74.
16. Wiktor TJ, Plotkin SA, Koprowski H. Development and clincal trials of the new human rabies vaccine of tissue culture (human diploid cell) origin. Dev Biol Stand 1978;40:3-9.
17. WHO Expert Committee on Rabies, 7th report. Geneva: World Health Organization, 1984:1-104.
18. Kuwert EK, Werner J, Marcus I, Cabasso VJ. Immunization against rabies with rabies immune globulin, human (RIGH) and a human diploid cell strain (HDCS) rabies vaccine. J Biol Stand 1978;6:211-9.
19. Cabasso VJ, Loofbourow JC, Roby RE, Anuskiewicz W. Rabies immune globulin of human origin: preparation and dosage determination in non-exposed volunteer subjects. Bull World Health Organ 1971;45:303-315.
20. WHO Expert Committee on Rabies, 8th report. Geneva: World Health Organization, 1992;TRS 824.
21. Nicholson KG, Turner GS, Aoki FY. Immunization with a human diploid cell strain of rabies virus vaccine: Two year results. J Infect Dis 1978;137:783-8.
22. Bernard KW, Roberts MA, Sumner J, et al. Human diploid cell rabies vaccine: effectiveness of immunization with small intradermal or subcutaneous doses. JAMA 1982;247:1138-42.
23. Bernard KW, Mallonee J, Wright JC, et al. Preexposure immunization with intradermal human diploid cell rabies vaccine. Risks and benefits of primary and booster vaccination. JAMA 1987;257:1059-63.
24. Fishbein DB, Pacer RE, Holmes DF, Ley AB, Yager P, Tong TC. Rabies preexposure prophylaxis with human diploid cell rabies vaccine: a dose-response study. J Infect Dis 1987;156:50-5.

25. CDC. Rabies prevention: supplementary statement on the preexposure use of human diploid cell rabies vaccine by the intradermal route. MMWR 1986;35:767-8.
26. CDC. Rabies vaccine, adsorbed: a new rabies vaccine for use in humans. MMWR 1988;37:217-8, 223.
27. Burgoyne GH, Kajiya KD, Brown DW, Mitchell JR. Rhesus diploid rabies vaccine (adsorbed): a new rabies vaccine using FRhL-2 cells. J Infect Dis 1985;152:204-10.
28. Levenbook IS, Elisberg BL, Driscoll BF. Rhesus diploid rabies vaccine (adsorbed): neurological safety in guinea pigs and Lewis rats. Vaccine 1986;4:225-7.
29. Berlin BS, Goswick C. Rapidity of booster response to rabies vaccine produced in cell culture. J Infect Dis 1984;150:785.
30. Berlin BS, Mitchell JR, Burgoyne GH, Brown WE, Goswick C. Rhesus diploid rabies vaccine (adsorbed), a new rabies vaccine. II. Results of clinical studies simulating prophylactic therapy for rabies exposure. JAMA 1983;249:2663-5.
31. Berlin BS. Rabies vaccine adsorbed: neutralizing antibody titers after three-dose pre-exposure vaccination. Am J Pub Health 1990;80:476-8.
32. Dreesen DW, Fishbein DB, Kemp DT, Brown J. Two-year comparative trial on the immunogenicity and adverse effects of purified chick embryo cell rabies vaccine for pre-exposure immunization. Vaccine 1989;7:397-400.
33. Fishbein DB, Arcangeli S. Rabies prevention in primary care. A four-step approach. Postgrad Med 1987;82:83-90, 93-5.
34. LeGuerrier P, Pilon PA, Deshaies D, Allard R. Pre-exposure rabies prophylaxis for the international traveler: a decision analysis. Vaccine 1996;14:167-76.
35. Turner GS, Nicholson KG, Tyrrell DAJ, Aoki FY. Evaluation of a human diploid cell strain rabies vaccine: final report of a three year study of pre-exposure immunization. J Hyg Camb 1982;89:101-10.
36. Burridge MJ, Baer GM, Sumner JW, Sussman O. Intradermal immunization with human diploid cell rabies vaccine. JAMA 1982;248:1611-4.
37. Cabasso VJ, Dobkin MB, Roby RE, Hammar AH. Antibody response to a human diploid cell rabies vaccine. Appl Microbiol 1974;27:553-61.
38. CDC. Recommendation of the Immunization Practices Advisory Committee (ACIP). Supplemantary statement on preexposure rabies prophylaxis by the intradermal route. MMWR 1982;31:279-85.
39. Sehgal S, Bhattacharya D, Bhardwaj M. Ten year longitudinal study of efficacy and safety of purified chick embryo cell vaccine for pre- and post-exposure prophylaxis of rabies in Indian population. J Commun Dis 1995;27:36-43.
40. CDC. Rabies prevention—United States, 1984. MMWR 1984;33:393-402, 407-8.
41. Pappaioanou M, Fishbein DB, Dreesen DW, et al. Antibody response to preexposure human diploid-cell rabies vaccine given concurrently with chloroquine. N Engl J Med 1986;314:280-4.
42. Bernard KW, Fishbein DB, Miller KD, et al. Pre-exposure rabies immunization with human diploid cell vaccine: decreased antibody responses in persons immunized in developing countries. Am J Trop Med Hyg 1985;34:633-47.
43. CDC and NIH. Biosafety in microbiological and biomedical laboratories. 3rd ed. Washington, D.C. HHS Publication No. (CDC) 93-8395, Washington, DC: U.S. Department of Health and Human Services, 1993.
44. Fishbein DB, Bernard KW, Miller KD, et al. The early kinetics of the neutralizing antibody response after booster immunizations with human diploid cell rabies vaccine. Am J Trop Med Hyg 1986;35:663-670.
45. Feder HM, Nelson R, Reiher HW. Bat bite? Lancet 1997;350:1300.
46. Afshar A. A review of non-bite transmission of rabies virus infection. Br Vet J 1979;135:142-8.
47. Winkler WG, Fashinell TR, Leffingwell L, Howard P, Conomy P. Airborne rabies transmission in a laboratory worker. JAMA 1973;226:1219-21.
48. Conomy JP, Leibovitz A, McCombs W, Stinson J. Airborne rabies encephalitis: demonstration of rabies virus in the human central nervous system. Neurology 1977;27:67-9.
49. Constantine DG. Rabies transmission by nonbite route. Pub Health Rep 1962;77:287-9.
50. Winkler WG, Baker EF, Hopkins CC. An outbreak of non-bite transmitted rabies in a laboratory animal colony. Am J Epidemiol 1972;95:267-77.
51. CDC. Rabies in a laboratory worker — New York. MMWR 1977;26:183-4.
52. CDC. Human-to-human transmission of rabies via corneal transplant —Thailand. MMWR 1981;30:473-4.
53. Gode GR, Bhide NK. Two rabies deaths after corneal grafts from one donor. Lancet 1988;2:791.
54. CDC. Human-to-human transmission of rabies via a corneal transplant — France. MMWR 1980;29:25-6.
55. Houff SA, Burton RC, Wilson RW, et al. Human-to-human transmission of rabies virus by corneal transplant. N Engl J Med 1979;300:603-4.
56. WHO. Two rabies cases following corneal transplantation. Weekly Epidemiol Rec 1994;69:330.
57. Baer GM, Shaddock JH, Houff SA, Harrison AK, Gardner JJ. Human rabies transmitted by corneal transplant. Arch Neurol 1982;39:103-7.
58. Javadi MA, Fayaz A, Mirdehghan SA, Ainollahi B. Transmission of rabies by corneal graft. Cornea 1996;15:431-3.
59. Helmick CG, Tauxe RV, Vernon AA. Is there a risk to contacts of patients with rabies? Rev Infect Dis 1987;9:511-8.
60. Fekadu M, Endeshaw T, Wondimagegnehu A, Bogale Y, Teshager T, Olson JG. Possible human-to-human transmission of rabies in Ethiopia. Ethiop Med J 1996;34:123-7.
61. Garner JS, The Hospital Infection Control Practices Advisory Committee. Guideline for isolation precautions in hospitals. Infect Contr Hosp Epidemiol 1996;17:54-80.
62. Smith JS, Orciari LA, Yager PA, Seidel HD, Warner CK. Epidemiologic and historical relationships among 87 rabies virus isolates as determined by limited sequence analysis. J Infect Dis 1992;166:296-307.

63. National Association of State Public Health Veterinarians. Compendium of animal rabies control, 1998. J Am Vet Med Assoc 1998;212:213-7.
64. CDC. Rabies learning series: the removal of animal brains for rabies diagnosis {video tape}. Atlanta, GA: Centers for Disease Control and Prevention, 1997.
65. Childs JE, Colby L, Krebs JW, et al. Surveillance and spatiotemporal associations of rabies in rodents and lagomorphs in the United States, 1985-1994. J Wildl Dis 1997;33:20-7.
66. Krebs JW, Strine TW, Smith JS, Noah DL, Rupprecht CE, Childs JE. Rabies surveillance in the United States during 1995. J Am Vet Med Assoc 1996;209:2031-44.
67. Fishbein DB, Belotto AJ, Pacer RE, et al. Rabies in rodents and lagomorphs in the United States, 1971-1984: increased cases in the woodchuck (Marmota monax) in mid-Atlantic states. J Wildl Dis 1986;22:151-5.
68. Niezgoda M, Briggs DJ, Shaddock J, Dreesen DW, Rupprecht CE. Pathogenesis of experimentally induced rabies in domestic ferrets. Am J Vet Res 1997;58:1327-31.
69. CDC. Imported dog and cat rabies — New Hampshire, California. MMWR 1988;37:559-60.
70. Eng TR, Fishbein DB, National Study Group on Rabies. Epidemiologic factors, clinical findings, and vaccination status of rabies in cats and dogs in the United States in 1988. J Am Vet Med Assoc 1990;197:201-9.
71. Clark KA, Neill SU, Smith JS, Wilson PJ, Whadford VW, McKirahan GW. Epizootic canine rabies transmitted by coyotes in south Texas. J Am Vet Med Assoc 1994;204:536-40.
72. Griego RD, Rosen T, Orengo IF, Wolf JE. Dog, cat, and human bites: a review. J Am Acad Dermatol 1995;33:1019-29.
73. Smith JS, Fishbein DB, Rupprecht CE, Clark K. Unexplained rabies in three immigrants in the United States. A virologic investigation. N Engl J Med 1991;324:205-11.
74. Dreesen DW. A global review of rabies vaccines for human use. Vaccine 1997;15(Suppl):S2-6.
75. Dean DJ, Baer GM, Thompson WR. Studies on the local treatment of rabies-infected wounds. Bull World Health Organ 1963;28:477-86.
76. Kaplan MM, Cohen D, Koprowski H, Dean D, Ferrigan L. Studies on the local treatment of wounds for the prevention of rabies. Bull World Health Organ 1962;26:765-75.
77. CDC. Diphtheria, tetanus, and pertussis: recommendations for vaccine use and other preventive measures. Recommendations of the Immunization Practices Advisory Committee (ACIP). MMWR 1991;40(No. RR-10):1-29.
78. Khawplod P, Wilde H, Chomchey P, et al. What is an acceptable delay in rabies immune globulin administration when vaccine alone had been given previously? Vaccine 1996;14:389-91.
79. Helmick CG, Johnstone C, Sumner J, Winkler WG, Fager S. A clinical study of Merieux human rabies immune globulin. J Biol Stand 1982;10:357-67.
80. Wilde H, Sirikawin S, Sabcharoen A, et al. Failure of postexposure treatment of rabies in children. Clin Infect Dis 1996;22:228-32.
81. Fishbein DB, Sawyer LA, Reid Sanden FL, Weir EH. Administration of human diploid-cell rabies vaccine in the gluteal area. N Engl J Med 1988;318:124-5.
82. Nicholson KG. Rabies. Lancet 1990;335:1201-5.
83. Warrell MJ, Nicholson KG, Warrell DA, et al. Economical multiple-site intradermal immunisation with human diploid-cell-strain vaccine is effective for post-exposure rabies prophylaxis. Lancet 1985;1:1059-62.
84. Chutivongse S, Wilde H, Supich C, Baer GM, Fishbein DB. Postexposure prophylaxis for rabies with antiserum and intradermal vaccination. Lancet 1990;335:896-8.
85. Anderson LJ, Baer GM, Smith JS, Winkler WG, Holman RC. Rapid antibody response to human diploid rabies vaccine. Am J Epidemiol 1981;113:270-5.
86. Vodopija I, Sureau P, Lafon M, et al. An evaluation of second generation tissue culture rabies vaccines for use in man: a four-vaccine comparative immunogenicity study using a pre-exposure vaccination schedule and an abbreviated 2-1-1 postexposure schedule. Vaccine 1986;4:245-8.
87. Vodopija I, Sureau P, Smerdel S, et al. Comparative study of two human diploid rabies vaccines administered with antirabies globulin. Vaccine 1988;6:489-90.
88. Vodopija I, Sureau P, Smerdel S, et al. Interaction of rabies vaccine with human rabies immunoglobulin and reliability of a 2-1-1 schedule application for postexposure treatment. Vaccine 1988;6:283-6.
89. Seghal S, Bhattacharya D, Bhardwaj M. Five-year longitudinal study of efficacy and safety of purified Vero cell rabies vaccine for post-exposure prophylaxis of rabies in Indian population. J Commun Dis 1997;29:23-8.
90. Charanasri U, Meesomboon V, Kingnate D, Samuthananont P, Chaeychomsri W. Intradermal simulated rabies postexposure prophylaxis using purified chick embryo rabies vaccine. J Med Assoc Thai 1994;77:157-60.
91. Khawplod P, Glueck R, Wilde H, et al. Immunogenicity of purified duck embryo rabies vaccine (Lyssavac-N) with use of the WHO-approved intradermal postexposure regimen. Clin Infect Dis 1995;20:646-51.
92. Kositprapa C, Limsuwun K, Wilde H, Jaijaroensup W, et al. Immune response to simulated postexposure rabies booster vaccinations in volunteers who received preexposure vaccinations. Clin Infect Dis 1997;25:614-6.
93. Suntharasamai P, Chaiprasithikul P, Wasi C, et al. A simplified and economical intradermal regimen of purified chick embryo cell rabies vaccine for postexposure prophylaxis. Vaccine 1994;12:508-12.
94. Wilde H, Chutivongse S. Equine rabies immune globulin: a product with an undeserved poor reputation. Am J Trop Med Hyg 1990;42:175-8.
95. Wilde H, Chomchey P, Prakongsri S, Puyaratabandhu P, Chutivongse S. Adverse effects of equine rabies immune gobulin. Vaccine 1989;7:10-1.

96. Wilde H, Chomchey P, Punyaratabandhu P, Phanupak P, Chutivongse S. Purified equine rabies immune globulin: a safe and affordable alternative to human rabies immune globulin. Bull World Health Organ 1989;67:731-6.
97. Karliner JS, Belaval GS. Incidence of reactions following administration of antirabies serum. JAMA 1965;193:109-12.
98. CDC. Human rabies despite treatment with rabies immune globulin and human diploid cell rabies vaccine — Thailand. MMWR 1987;36:759-60, 765.
99. Shill M, Baynes RD, Miller SD. Fatal rabies encephalitis despite appropriate post-exposure prophylaxis. A case report. N Engl J Med 1987;316:1257-8.
100. Wilde H, Choomkasien P, Hemachudha T, Supich C, Chutivongse S. Failure of rabies post-exposure treatment in Thailand. Vaccine 1989;7:49-52.
101. Kuwert EK, Marcus I, Werner J, et al. Post-exposure use of human diploid cell culture rabies vaccine. Devel Biol Stand 1977;37:273-86.
102. Strady A, Lang J, Lienard M, Blondeau C, Jaussaud R, Plotkin S. Antibody persistence following preexposure regimens of cell-culture rabies vaccines: 10-year follow-up and proposal for a new booster policy. J Infect Dis 1998;177:1290-5.
103. Thraenhart O, Kreuzfelder E, Hillebrandt M, et al. Long-term humoral and cellular immunity after vaccination with cell culture rabies vaccines in man. Clin Immunol Immunopath 1994;71:287-92.
104. Fishbein DB, Dreesen DW, Holmes DF, et al. Human diploid cell rabies vaccine purified by zonal centrifugation: a controlled study of antibody response and side effects following primary and booster pre-exposure immunizations. Vaccine 1989;7:437-42.
105. Briggs DJ, Schwenke JR. Longevity of rabies antibody titre in recipients of human diploid cell rabies vaccine. Vaccine 1992;10:125-9.
106. Corey L, Hattwick MAW, Baer GM, Smith JS. Serum neutralizing antibody after rabies post-exposure prophylaxis. Ann Intern Med 1976;85:170-6.
107. Rubin RH, Hattwick MAW, Jones S, Gregg MB, Schwartz VD. Adverse reactions to duck embryo rabies vaccine: range and incidence. Ann Intern Med 1973;78:643-9.
108. Noah DL, Smith MG, Gotthardt JC, Krebs JW, Green D, Childs JE. Mass human exposure to rabies in New Hampshire: exposures, treatment, and cost. Am J Pub Health 1996;86:1149-51.
109. Knittel T, Ramadori G, Mayet WJ, Lohr H, Meyer zum Buschenfelde KH. Guillain-Barre syndrome and human diploid cell rabies vaccine. Lancet 1989;1:1334-5.
110. Boe E, Nylan H. Guillain-Barre syndrome after vaccination with human diploid cell rabies vaccine. Scand J Infect Dis 1980;12:231-2.
111. Tornatore CS, Richert JR. CNS demyelination associated with diploid cell rabies vaccine. Lancet 1990;335:1346-7.
112. Anderson MC, Baer H, Frazier DJ, Quinnan GV. The role of specific IgE and beta-propiolactone in reactions resulting from booster doses of human diploid cell rabies vaccine. J Allergy Clin Immunol 1987;80:861-8.
113. Swanson MC, Rosanoff E, Gurwith M, Deitch M, Schnurrenberger P, Reed CE. IgE and IgG antibodies to beta-propiolactone and human serum albumin associated with urticarial reactions to rabies vaccine. J Infect Dis 1987;155:909-13.
114. Fishbein DB, Yenne KM, Dreesen DW, Teplis CF, Mehta N, Briggs DJ. Risk factors for systemic hypersensitivity reactions after booster vaccinations with human diploid cell rabies vaccine: a nationwide prospective study. Vaccine 1993;11:1390-4.
115. Held JR, Lopez Adaros H. Neurological disease in man following administration of suckling mouse brain antirabies vaccine. Bull World Health Org 1972;46:321-7.
116. Enright JB, Franti CE, Frye FL, Behymer DE. The effects of corticosteroids on rabies in mice. Can J Microbiol 1970;16:667-75.
117. Chutivongse S, Wilde H, Benjavongkulchai M, Chomchey P, Punthawong S. Postexposure rabies vaccination during pregnancy: effect on 202 women and their infants. Clin Infect Dis 1995;20:818-20.
118. Varner MW, McGuinness GA, Galask RP. Rabies vaccination in pregnancy. Am J Obstet Gynecol 1982;143:717-8.