

CALIFORNIA COMPENDIUM OF RABIES CONTROL AND PREVENTION



California Department of Public Health
Veterinary Public Health Section, 2012



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2012**

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Introduction

This publication of the California Department of Public Health (CDPH) provides information on rabies to California's public health officials, medical professionals, practicing veterinarians, animal control officers, and other parties concerned with rabies control in the State. The recommendations contained herein are reviewed and updated on a periodic basis to reflect the current status of rabies and rabies prevention activities in California. Updates are based on current rabies research and scientific literature, rabies prevention guidelines published by the federal Advisory Committee on Immunization Practices (ACIP)^{1,2} and by the National Association of State Public Health Veterinarians³, California state statute and regulations, and established rabies control practices and procedures.

Recommendations by state and federal experts and existing standards of practice outlined in this document are intended to provide guidance to individuals and agencies involved with rabies prevention and control in California. Except for statutes and regulations specifically cited, the information contained in this document are recommendations provided for informational purposes only and are not intended to be regulatory in effect.

Part I.

Animal Rabies Control

A. Principles of rabies control

1. Human rabies prevention

Human rabies can be prevented by a) eliminating exposure to rabies virus, b) providing appropriate rabies pre-exposure prophylaxis, and c) prompt local treatment of bite wounds combined with appropriate rabies post-exposure prophylaxis. Human rabies pre- and post-exposure prophylaxis are addressed in Part II of the Compendium.

2. Domestic animal rabies control

The California Health and Safety Code (HSC), §121690, mandates that the governing body of each city, city and county, or county maintain or provide a rabies control shelter system and a rabies control program. The primary components of a rabies control program for companion animals are: immunization and licensing; stray animal control; reporting, investigation, and isolation of animals involved in bite incidents; and public education.

3. Wild animal rabies control

Rabies virus is maintained in populations of wild animals and occasionally spills over into domestic animals and humans. In California, skunks and bats comprise over 90 percent of animal rabies cases reported each year. Prevention and control of rabies in bats and terrestrial mammals pose considerable challenges. It is generally not possible or desirable to control rabies by reducing the size of wild carnivore or bat populations. Selective population reduction may be attempted in terrestrial rabies outbreaks of limited geographic scope, but these efforts can be labor and resource intensive and provide effective control only until immigration or reintroduction of the incriminated species. Immunization of wildlife by widespread distribution of vaccine-impregnated oral baits has shown variable success toward arresting the propagation of rabies in raccoons and coyotes in other states. The effectiveness of oral rabies vaccination programs has not been demonstrated for skunks and such programs would be infeasible for bats. Principles of rabies prevention should focus on excluding wild animals from areas of human and domestic animal habitation and activity, and avoidance of contact with possibly rabid wild animals. Public education on the risks of rabies transmission from wild animals is paramount to effective disease prevention.

B. Rabies control methods for domestic and confined animals

1. Animal bite reporting (Title 17, California Code of Regulations [CCR], §2606)

The local health officer or designee shall be immediately notified of any person or animal bitten

by or potentially exposed to a rabid or suspected rabid animal. In addition, the local health officer or designee shall be notified when any person is bitten by a mammal. Potential human rabies exposures are then evaluated and rabies post-exposure prophylaxis (PEP) recommendations made.

2. Isolation of biting animals (17 CCR §2606)

(a) General considerations

Dogs, cats, and ferrets that bite a human or another dog, cat, or ferret are subject to isolation and observation, or euthanasia and testing. If the bite is judged by the local health officer to be unusual or to represent an increased risk for rabies (e.g., unprovoked attacks, bites to the face, or considerable deep tissue damage), the animal should be euthanized and tested immediately. The National Association of State Public Health Veterinarians recommends that if an animal under isolation develops clinical signs suggestive of rabies, the animal should be humanely euthanized and the head submitted for rabies testing through the local public health laboratory.³ Any unclaimed or stray animal that bites a human may be euthanized and the head promptly submitted to the local public health laboratory for rabies testing. Protocols for submitting samples for rabies testing are available from the local public health laboratory. Rabies or other immunizations should not be administered to a dog, cat, or ferret during isolation because adverse reactions may be misinterpreted as clinical signs of rabies.³

(b) Dogs and cats (17 CCR §2606(b)(2))

Domestic dogs and cats that bite or otherwise expose humans must be isolated in strict confinement and in compliance with the local health officer's isolation order. The biting dog or cat must be either a) observed daily for signs of rabies for ten (10) days following the exposure date, regardless of the animal's vaccination status, or b) euthanized immediately and tested for rabies in a public health laboratory. If an isolated dog or cat is healthy at the end of the ten-day period, there is no risk of a rabies exposure from the original bite wound.

(c) Ferrets

It is illegal in California to possess a ferret as a pet (California Fish and Game Code [FGC] §2118). Nevertheless, bites from these animals occur. If a ferret bites a human in California, it should be isolated in strict confinement and in compliance with the local health officer's isolation order. The biting ferret should be either a) observed daily for signs of rabies for ten (10) days following the exposure date, regardless of the animal's vaccination status, or b) euthanized immediately and tested for rabies in a public health laboratory. Biting ferrets should be confiscated by the animal control agency and isolations conducted under the direction of the local health officer in an animal control shelter or veterinary hospital. If an isolated ferret is healthy at the end of the ten-day period, there is no risk of a rabies exposure from the original bite wound. Because pet ferrets are illegal in California, any ferret isolated for a human bite should be reported to the California Department of Fish and Game for disposition following the isolation.

(d) Other domestic and nondomestic species

The incubation period, clinical presentation, and pre-clinical period of rabies virus shedding are well described only for dogs, cats, and ferrets. The period in which other domestic, non-domestic, and wild animals shed rabies virus prior to showing clinical

signs of rabies is generally not known. Biting wild, nondomestic, or domestic animals other than dogs, cats, and ferrets should not be isolated for observation but should be euthanized and tested for rabies immediately.

While isolation of biting animals other than dogs, cats, and ferrets is not recommended for the reasons given above, local health officers have the prerogative to forego euthanasia and testing in rare special circumstances. If the biting animal has a comprehensive and reliable history that precludes opportunity for exposure to rabies virus, and the risk of rabies in the biting animal is judged by the health officer to be acceptably low, the health officer may institute a prolonged (30-day) isolation of the biting animal. Under the care of a physician, the bite victim could be started immediately on rabies PEP. This special allowance can be considered due to the low risk for exposure, the reliable efficacy of rabies PEP, and the low incidence of serious adverse reactions with that treatment.

3. Isolation of animals exposed to rabies (17 CCR §2606)

Any animal bitten by, scratched by, or having direct contact with a wild mammal (especially bats and skunks) that is not available for rabies testing should be regarded as having been exposed to rabies.

(a) Dogs, cats, and ferrets

Dogs, cats, and ferrets that are currently vaccinated should be revaccinated immediately and placed in strict isolation for 30 days. While isolation provisions are at the discretion of the local health officer, “strict isolation” must preclude contact between the isolated animal and other animals and the public. Any other dogs, cats, or ferrets for which contact with the bitten animal cannot be absolutely prevented during the isolation period should be held to the same restrictions for the entire isolation period. Ferrets must be confiscated by the animal control agency and isolation conducted under the direction of the health officer in an animal control shelter or veterinary hospital. Because ferrets are illegal to possess as pets in California, any ferret must be reported to the California Department of Fish and Game for disposition following the isolation. Unvaccinated dogs, cats, and ferrets exposed to a rabid or suspect rabid animal should be euthanized immediately.³ An alternative to euthanasia is immediate vaccination of the animal and placement in strict isolation for six months (180 days). Euthanasia is strongly recommended for unvaccinated juvenile animals due to their higher susceptibility to rabies infection. Protocols for the post-exposure vaccination of previously unvaccinated animals have not been validated, and there is evidence that the use of vaccine alone in a post-exposure setting may not prevent the disease.

(b) Livestock

All livestock species--horses, cattle, sheep, goats, llamas/alpacas, swine--are susceptible to rabies infection. Cattle and horses are the livestock species most frequently diagnosed with rabies. Unvaccinated livestock bitten by or exposed to a rabid or suspect rabid animal should be euthanized.³ If the animal is slaughtered within seven days after being exposed, the tissues may be consumed without risk of infection, provided liberal portions of the exposed area are discarded. However, the slaughtered animal cannot be sold commercially as a source of food; federal (United States Department of Agriculture [USDA]) meat inspectors are required to reject for slaughter any animal known to have been exposed to rabies within the past eight months.³ Neither tissue nor milk from a

rabid animal should be used for human or animal consumption.³ However, because heat inactivates rabies virus, persons who inadvertently drink pasteurized milk or eat fully cooked meat from an animal subsequently identified as rabid are not considered to have been exposed to rabies.

An alternative to euthanizing exposed livestock is to vaccinate the animal immediately with an approved vaccine and to place it in strict isolation for six months during which time the animal may not be transported, sold, or slaughtered unless approved by the local health officer and the California Department of Food and Agriculture. Livestock that are currently vaccinated should receive a rabies booster immediately and be placed in strict isolation for 30 days.³ In general, an isolation order for the entire herd is not indicated unless the animals have been held in close confinement that would allow for multiple animals exposed to the same rabies source (e.g., a wild animal). It is unusual to have more than one rabid animal in a herd. In such cases, it is more likely that multiple animals were exposed by a single rabid wild animal or dog than that rabies virus was transmitted from herbivore to herbivore. Animals in a herd where a rabies death has occurred should be examined immediately for evidence of bite exposures.

(c) Wild, nondomestic, and other mammals

Wild, nondomestic, and other mammals bitten by or exposed to a rabid or suspect rabid animal should be euthanized immediately.³

4. Animal rabies vaccination

(a) Rabies vaccine administration (HSC §121690, §121700)

Animal rabies vaccines are restricted for sale to licensed veterinarians, biological supply companies, and government agencies that conduct rabies control programs. All animal rabies vaccines are restricted to use by, or under the supervision of, a California-licensed veterinarian. The level of supervision shall be consistent with Title 16, CCR, §2034-2036.5 of the California Veterinary Medicine Practice Act. The veterinarian whose signature is on the rabies certificate retains legal responsibility that the person administering the vaccine is appropriately trained in vaccine storage, handling, administration, and management of adverse events.³ Rabies vaccines should be administered in accordance with the specifications of the vaccine product label or package insert. Rabies vaccine should be administered in a new, sterile needle and syringe. The re-use of cleaned and sterilized needles and syringes is strongly discouraged. Single use of the needle and syringe is consistent with vaccine manufacturers' recommendations.

(b) Accidental human exposure to rabies vaccine

Accidental human inoculation may occur during administration of an animal rabies vaccine. Such exposure to inactivated rabies vaccine does not constitute a risk for rabies infection.

(c) Contraindications and adverse events

There are no absolute contraindications to administration of rabies vaccine to appropriate species. Veterinarians should, if possible, postpone vaccinating animals that are ill or immunocompromised to ensure a robust immune response. There is no epidemiologic association between a particular licensed vaccine product and adverse events, including

vaccine failure. Adverse reactions to vaccination should be reported to the USDA, Center for Veterinary Biologics (http://www.aphis.usda.gov/animal_health/vet_biologics/vb_adverse_event.shtml, Tel: 800-752-6255, e-mail: CVB@usda.gov).

Beginning in the 1990s, an association between the administration of certain vaccines, including rabies, and the development of cancer (sarcoma) in some cats was identified. However, this risk appears to be extremely low (1-2 cases per 10,000 vaccinated cats). The public health implications of rabies in domestic cats outweigh the low risk of a sarcoma developing at a vaccination site. To facilitate management of vaccine-associated sarcomas, to avoid injection of multiple vaccines at a single site (a putative risk factor for sarcoma formation), and to aid in documenting vaccine placement, the American Association of Feline Practitioners recommends that rabies vaccine be administered subcutaneously on the right hind limb distal to the stifle joint.

(d) Canine rabies vaccination (HSC §121690; 17 CCR §2606.4, §2606.6)

The owner of every dog over the age of four months shall ensure that the dog is vaccinated for rabies by a licensed veterinarian and will secure a license for the pet as provided by local city or county ordinance. A current rabies vaccination certificate must accompany dogs over four months of age entering the state. Dogs less than four months of age must be confined at home or kept under close leash supervision by the owner when off property.

Twenty-eight days after primary vaccination peak rabies antibody level is reached and a dog is considered currently vaccinated for one year.³

Regardless of the age of the dog at primary vaccination, a booster vaccination should be given one year later. All vaccines approved for use in dogs in California follow a three-year booster schedule thereafter. There are no laboratory or epidemiologic data to support the annual or biennial administration of three-year vaccines following the initial immunization series. Because a rapid anamnestic response is expected, a dog is considered currently vaccinated immediately after receiving a booster vaccination. An animal that is overdue for a rabies booster should be vaccinated as soon as possible and the three-year booster schedule re-established.³

Only canine rabies vaccines licensed by USDA and approved by the California Department of Public Health (CDPH) can be used in the California Rabies Control Program (17 CCR §2651). The rabies vaccines currently approved for use in California are listed in Part III of the Compendium.

(e) Feline rabies vaccination

Vaccination of domestic cats for rabies is not mandated by California statute. However, because cats are the domestic species that is most frequently reported as rabid in the United States, feline rabies vaccination is required by some local ordinances and is strongly recommended for all cats. A USDA-licensed feline rabies vaccine should be administered according to the vaccine label instructions (see Part III of the Compendium). Cats are considered currently vaccinated from 28 days to one year following primary vaccination, and 1, 3, or 4 years following booster vaccinations, depending on the vaccine used.³

(f) Ferret rabies vaccination

It is illegal in California to possess a ferret as a pet (FGC §2118). Nevertheless, owners of illegally kept ferrets may occasionally seek veterinary care (California Business and Professional Code §4826.2). As a public health measure, veterinarians should vaccinate ferrets against rabies using a USDA-licensed rabies vaccine administered according to vaccine label instructions (see Part III of the Compendium). Ferrets are considered currently vaccinated from 28 days to one year following primary vaccination, and for one year following each booster.³

(g) Livestock rabies vaccination

Routine vaccination of all livestock against rabies is economically inpractical. However, vaccination of horses and livestock with a USDA-licensed vaccine (see Part III of the Compendium) should be considered in areas where wildlife rabies is highly endemic, for valuable individual animals, for horses kept in boarding stables or racetracks or traveling interstate, and for animals having frequent contact with humans (e.g., petting zoos).³

(h) Wildlife and non-domestic rabies vaccination

No rabies vaccines are licensed for use in animal species other than dogs, cats, cattle, horses, sheep, and ferrets in the U.S. The effectiveness of rabies vaccination in other species is unknown. Because of their susceptibility to rabies, wild carnivores and bats should not be kept as pets.³ Bats and certain species of carnivores may not enter California without an importation permit from CDPH (17 CCR §30070-86) and are subject to a 90-day rabies quarantine upon importation into California. Carnivores and bats must be housed in a manner that precludes direct contact with the public.³ Due to the special rabies risk, the trapping, transport, sale, and exchange of skunks in California is prohibited (17 CCR §2606.8). Zoos and research institutions may establish vaccination programs intended to protect valuable animals, but these programs do not substitute for appropriate preventive measures to protect humans.

The effectiveness of rabies vaccination in the progeny of domestic dogs or cats bred to wild animals (e.g., wolf-dog hybrids, civet-cat hybrids) is unknown. Complete rabies vaccine challenge and viral shedding studies have not been conducted for these animals. There is no definitive evidence that the vaccine is protective in these animals. Vaccination may afford some rabies protection to the animal; however, there are no rabies vaccines currently licensed for use in wild animals or in domestic-wild animal hybrids. Vaccination of these animals is considered an extra-label use of a biologic.

State law does not prohibit the use of rabies vaccines in domestic-wild animal hybrids. However, it is illegal to license domestic-wild canine hybrids as “dogs” under the California Rabies Control Program because they are considered wild animals (14 CCR §671(c)(2)(K)). A rabies vaccine certificate issued for a vaccinated hybrid must identify the animal as a "domestic-wild animal hybrid." Local jurisdictions may institute domestic dog-wolf hybrid permitting programs and issue such permits in order to identify these animals in the community (HSC §121695). Canine or feline hybrids previously vaccinated are nonetheless considered “unvaccinated” for purposes of isolation/ observation in the event of a bite incident or contact with a rabid or suspect rabid animal. All hybrids are considered "wild animals" under these circumstances and managed according to sections 2(d) and 3(c) in this Compendium.³

(i) Canine licensing and vaccination procedure (17 CCR §2606.4)

The vaccination of all dogs four months of age or older is required for licensure. Completion of the licensing procedure consists of issuing a license tag or vaccination tag bearing the license data only after presentation of a current valid official rabies vaccination certificate. Official rabies vaccination certificates must contain the following information:

- (a) name, address, and telephone number of the dog's owner;
- (b) description of the dog, including breed, color, age, and sex;
- (c) date of immunization;
- (d) type of rabies vaccine administered;
- (e) name of the manufacturer, product, and lot number of the rabies vaccine used.

Each certificate must bear the signature of the veterinarian administering the vaccination or a signature authorized by him or her. The certificate must be stamped, printed, or typed with the vaccinating veterinarian's name, address, and telephone number.

(j) Rabies immunization exemptions (HSC §121690)

A veterinarian may request from the local health officer an exemption from rabies vaccination for a dog for which the veterinarian determines that vaccination would endanger the dog's life because of disease or other considerations. If approved by the local health officer, the exempted dog may be issued a license but is considered unvaccinated and confined to the premises of the owner. Licensure of an exempted dog may not extend beyond one year; at or before the end of the one-year license period, the dog must be vaccinated for rabies or a request for vaccination exemption must be resubmitted to and reapproved by the local health officer.

(k) Rabies serologic testing

Serologic evidence of rabies neutralizing antibodies in an animal is not a substitute for current rabies vaccination in managing rabies exposures or determining the need for booster vaccinations.³ Serum antibody titer is a measure of the animal's response to vaccine or infection and not a reliable indicator of protection. Elevated serologic titers do not necessarily indicate protection from rabies, nor do low or undetectable serologic titers reflect absence of protection. An ability to measure and interpret all the immunologic factors that play a role in protecting against rabies is not well developed.

6. "Actual cost" rabies vaccination clinics (HSC §121690)

Each city, city and county, or county shall provide or arrange for canine rabies vaccination clinics in the community. No charge in excess of the actual cost may be made for vaccination administration. The CDPH establishes the actual cost that vaccination clinics may charge. Fees in excess of the CDPH-established actual cost require cost documentation and prior approval by CDPH. Procedures and forms to request approval are available in the California Rabies Control Program Public Vaccination Clinic Manual (<http://www.cdph.ca.gov/HealthInfo/discond/Pages/rabies.aspx>).

Part II.

Human Rabies Prevention

A. Rabies post-exposure prevention

Prevention of rabies following a possible exposure to rabies virus consists of two fundamental components: immediate cleaning and medical attention of the site of virus deposition, and post-exposure prophylaxis (PEP)--administration of human rabies immune globulin (HRIG) and rabies vaccine. Persons who have transdermal or mucous membrane contact with saliva or nervous tissue from a confirmed rabid animal, whether by bite or other means, should begin rabies PEP immediately. Persons exposed to a suspected rabid animal should begin PEP if rabies testing of the animal is not immediately available. To appropriately manage potential human exposure to rabies, the risk of infection must be accurately assessed. It is important to remember that rabies PEP is a medical urgency, not a medical emergency. With the exception of direct inoculation of rabies virus into the central nervous system (e.g., severe bite to the head that penetrates the neurocranium), there is time for information to be assembled and the risk to be rationally assessed. Nevertheless, decisions regarding PEP should not be delayed.

Extensive field experience from many parts of the world indicates that prompt wound treatment, passive immunization, and vaccination are uniformly effective in preventing development of clinical rabies when administered appropriately. However, rabies has developed in humans when recommended preventive protocols were not performed completely or correctly. Rabies PEP can be effective when initiated any time prior to onset of clinical disease. There have been many instances in which rabies PEP was not initiated until months after exposure due to delays in recognition of the exposure. Although onset of clinical rabies typically occurs between 60 and 90 days following exposure, incubation periods of one year or more have been reported. PEP should not be denied solely because a prolonged period of time has elapsed since the exposure event.

1. Rabies exposure

Rabies exposure is defined as transdermal or mucous membrane contact with saliva--or, rarely, nervous tissue--from a rabid animal. A break in the cutaneous barrier that permits virus access to subdermal tissue may be created concomitant with (e.g., classic animal bite) or prior to (e.g., open wounds, abrasions, or scratches) deposition of saliva or contact with nervous tissue. Contact with other tissues (e.g. skin, hair, blood), secretions (e.g., skunk spray), or excretions (e.g., urine, feces) of a rabid animal does not constitute an exposure. Rabies virus is inactivated by exposure to ultraviolet radiation and by desiccation, though the exact time required to render the virus inactive varies according to environmental conditions. Dried saliva or neurologic tissue is generally considered noninfectious. Scenarios for secondary exposure or "contact-transfer" of

rabies virus (e.g., dog bites a skunk and then licks a human) are hypothetical and very unlikely to transmit rabies.

2. Assessment of rabies exposure

Anti-rabies biologics are generally safe and in ready supply. Nevertheless, PEP should be allocated judiciously and reserved for individuals for whom exposure to rabies virus is likely. Decisions on PEP are ultimately made by the exposed individual and his/her health care provider, following a thorough assessment of the exposure incident and consultation with public health officials. No single set of criteria can determine the appropriateness of PEP for all situations. PEP decisions should be based on as much information about the exposure incident as can be assembled in a timely fashion. Factors that should be considered in PEP decisions include: species of biting animal, the physical and mental health of the biting animal, whether the bite was provoked, the severity of the bite, whether immediate wound care was implemented, the availability of the biting animal for isolation/observation or euthanasia/testing, and the bite victim's personal anxiety about rabies. Concerns about the bite victim's pre-existing medical conditions or ability to pay should never preclude initiation of PEP for an exposure incident in which PEP would be otherwise indicated (See Sections D and E).

Bats represent an important reservoir for rabies that deserves special consideration. Epidemiologic data suggest that transmission of rabies virus from bats can occur from very minor or even unrecognized bites. The limited injury inflicted by a bat bite (in contrast to wounds caused by carnivores) and equivocal recall of recognized exposure can hinder a health-care provider's ability to assess the risk of rabies resulting from an encounter with a bat.

Between 2000 and 2009, 18 human cases of rabies were identified in the U.S. with natural exposure to a bat variant virus. For only seven of these patients was a definite bat bite known; eight had known bat contact but no apparent bite, and for three no known contact with a bat was identified during the case investigation.

In all instances where a human is possibly exposed to a bat, the bat in question should be safely collected, if possible, and tested for rabies. Rabies PEP is recommended for all persons who experience a bite, scratch, or mucous membrane contact with a bat, unless the bat is available for testing and is negative for evidence of rabies. Rabies PEP may be appropriate even when a bite, scratch, or mucous membrane contact is not apparent if there is reasonable probability that such exposure might have occurred.

Rabies PEP should be considered when direct contact between a bat and a human has occurred, unless the exposed person can be certain that a bite, scratch, or mucous membrane exposure did not occur. In instances in which an apparently healthy bat is found indoors and there is no history of bat-human contact, the likely effectiveness of rabies PEP must be balanced against the low risk that such exposures appear to present. In this setting, rabies PEP can be considered for persons who were in the same room as the bat and are uncertain whether a bite or direct contact 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. Rabies PEP would not be warranted for other household members.

3. Local treatment of wounds

Immediate and thorough washing of any bite or scratch wound with soap and water is an

indispensable measure in preventing rabies. Animal experiments have shown that simple local wound cleaning and irrigation can markedly reduce the likelihood of rabies. Victims of animal bites should consult with their health care provider; medical or surgical attention, a tetanus toxoid booster, and antibiotic prophylaxis may be indicated independent of the assessed risk of rabies transmission.

4. Passive immunization

Human Rabies Immune Globulin (HRIG) is administered only once, at the beginning of rabies PEP, to previously unvaccinated persons to provide immediate antibodies until the patient responds to rabies vaccination by actively producing antibodies. If HRIG is not given with the first dose of vaccine, it can be given up to Day 7 of the vaccine series. After Day 7, HRIG should be avoided due to possible interference with the developing vaccine immune response. HRIG is administered at a dose of 20 IU/kg body weight for all age groups. No more than the recommended dose of HRIG should be used due its potential to partially suppress active immunization. As much as possible of the calculated dose of HRIG should be infiltrated into the subcutaneous tissue and/or muscle around the wound site(s). Any remaining amount of HRIG should be administered intramuscularly at an anatomic site distant from vaccine administration. HRIG should never be administered in the same syringe or at the same anatomical site as vaccine and should never be administered in the gluteal area unless that is the site of exposure. In the absence of a bite or other known site of virus introduction, the full dose of HRIG should be administered at a site distant from vaccine administration (e.g., contralateral deltoid). Regardless of the interval between exposure and initiation of PEP, both HRIG and vaccine should be administered for both bite and nonbite exposures in persons not previously rabies immunized.

5. Active immunization

Human Diploid Cell Vaccine (HDCV) or Purified Chick Embryo Cell Vaccine (PCEC) is administered in conjunction with HRIG at the beginning of postexposure treatment. A regimen of four 1-ml doses of HDCV or PCEC is given intramuscularly. The first dose should be given as soon as possible following an exposure (Day 0), with subsequent doses given on Days 3, 7, and 14. Vaccine should always be administered intramuscularly in the deltoid (lateral aspect of the upper arm). For pediatric patients, vaccine may be administered intramuscularly in the anterolateral aspect of the thigh. Rabies vaccine should never be administered in the gluteal region, as this may result in lower, possibly inadequate neutralizing antibody levels.

Rabies PEP should always include both vaccine and HRIG except in persons who have previously received complete immunization regimens (pre- or post-exposure prophylaxis) with a cell culture vaccine, or persons previously vaccinated with another type of vaccine who have documentation of adequate rabies virus neutralization antibody titers. These persons should immediately receive two 1-ml booster doses of HDCV or PCEC vaccine administered intramuscularly on Days 0 and 3.

Because antibody response has been universally satisfactory in persons receiving the currently recommended rabies PEP schedule, routine post-treatment serologic testing is not recommended. Verification of adequate neutralizing antibody levels by serologic testing may be indicated in unusual circumstances, such as when the patient is known to be immunosuppressed. Immunosuppressive agents should not be administered during rabies PEP unless they are essential for the treatment of other conditions.

B. Pre-exposure prophylaxis

Persons at frequent risk of exposure to rabies virus should consider pre-exposure prophylaxis (PreEP). Occupations considered to be in the "frequent risk" category include veterinarians, animal handlers, animal control officers, laboratory workers potentially exposed to rabies virus, and others who have frequent contact with mammals likely to have rabies. PreEP might be considered for other persons who are likely to come into contact with potentially rabid animals, such as wild mammal rehabilitators and persons traveling to foreign countries where canine rabies is endemic.

1. Primary or pre-exposure vaccination

Three 1.0 ml injections of HDCV or PCEC are administered intramuscularly in the deltoid (lateral aspect of the upper arm) on days 0, 7, and 21 or 28. Multiple studies have documented development of rabies antibodies that meet or exceed recommended neutralizing titers (>0.5 IU/ml) in all persons vaccinated according to this regimen. Persons who are immunosuppressed due to medication or illness should postpone PreEP if possible. Immunosuppressed persons who are at risk of rabies exposure can be vaccinated and should have their antibody titers measured following completion of the regimen.

2. Booster vaccination

Routine rabies booster vaccination is not indicated for any pre-immunized group. The need for booster vaccination should be individually assessed based on current rabies antibody levels and the person's risk of exposure to rabies virus. Persons classified as having "frequent risk" (see B above) should have a serum sample tested for rabies antibody every two years--or every six months for persons working with rabies virus in a laboratory setting--following PreEP. If the titer is less than complete neutralization at 1:5 by the Rapid Fluorescent Focus Inhibition Test (RFFIT), the person should receive a single booster dose of rabies vaccine.

Several laboratories offer RFFIT testing at a cost of approximately \$35-\$45 per sample. Instructions for submission of samples and pricing are available by calling the numbers below. (RFFIT testing may also be available through other laboratories.)

The Rabies Laboratory
Kansas State University
Manhattan, KS 66502
(785) 532-4483 Phone
(785) 532-4474 Fax
<http://www.vet.ksu.edu/depts/dmp/service/rabies/index.htm>

Maryland State Rabies Laboratory
Maryland Department of Health
201 W. Preston Street
Baltimore, MD 21201
(410) 767-6177 Phone
<http://www.dhmh.state.md.us/labs>

Atlanta Health Associates, Inc.
309 Pirkle Ferry Road, Suite D300
Cumming, GA 30040
(770) 205-9091, (800) 717-5612 Phone

C. Rabies immunizing products available in the United States

1. Human rabies vaccine stimulates an active immune response including production of neutralizing antibodies. These antibodies develop in approximately 7-10 days and usually persist for at least 2 years. The two vaccines currently available in the U.S. are considered equally efficacious and safe when used as indicated. The 1.0 ml dose of either HDCV or PCEC can be used for PEP or PreEP.

(a) **Human Diploid Cell Vaccine (HDCV) - Imovax® Rabies**

HDCV is prepared from the Pitman-Moore rabies virus strain grown in MRC-5 human diploid cell culture. The vaccine is concentrated by ultrafiltration and inactivated with beta-propiolactone. A single-dose vial containing lyophilized vaccine is reconstituted with diluent to a volume of 1.0 ml just before administration. Imovax® Rabies is manufactured and distributed by Sanofi Pasteur, Inc. (phone 800-VAC-CINE [800-822-2463], <http://www.vaccineplace.com/products>).

(b) **Purified Chick Embryo Cell Culture (PCEC) - RabAvert®**

PCEC is prepared by growing the Flury LEP fixed-virus strain in primary culture of chicken embryonic fibroblasts. The virus is inactivated with beta-propiolactone, and further processed with zonal centrifugation in a sucrose density-gradient to separate the final product from media and cell culture antigens. The vaccine is then lyophilized after addition of a stabilizer solution. RabAvert® is manufactured and distributed by Chiron Vaccines (phone 800-CHI-RON8 [800-244-7668], <http://www.rabavert.com/>).

2. **Rabies Immune Globulin - Human (HRIG)** provides immediate passive immunity that endures for only a limited time (half-life of approximately 21 days).

Imogam® Rabies-HT, HyperRab™ S/D

Human rabies immune globulin (HRIG) is available from Sanofi Pasteur, Inc., (Imogam® Rabies-HT; phone 800- VAC-CINE [800-822-2463], <http://www.vaccineplace.com/products>), and Talecris Biotherapeutics, Inc., (HyperRab™ S/D; phone 800-243-4153, <http://www.talecris-pi.info/>). HRIG is an antirabies gamma globulin concentrated by cold ethanol fractionation from plasma of hyperimmunized human donors. Rabies neutralizing antibody content is standardized to 150 international units (IU) per ml. HRIG is supplied in 2 ml and 10 ml vials for pediatric and adult use, respectively. Imogam® Rabies-HT is heat treated but has no preservatives. It must be administered within an hour once the seal is broken. Both HRIG preparations are considered equally efficacious and safe when used as indicated.

D. Adverse reactions to rabies immunizing products

1. Vaccine

Local reactions such as pain, erythema, and swelling or itching at the injection site were reported in approximately 30-75 percent of patients receiving HDCV or PCEC. Mild systemic reactions such as headache, malaise, dizziness, muscle aches, nausea, and abdominal pain have been reported in 5-50 percent of recipients. Anaphylactic, encephalitic, or neuromuscular events have been rarely reported.

2. **HRIG**

Local pain and tenderness at the injection site commonly occur following receipt of HRIG. A majority of recipients also experience mild systemic symptoms such as low grade fever and headache. No serious adverse events such as hypersensitivity or immune complex disease have been associated with HRIG.

HyperRab™ and Imogam® Rabies-HT undergo multiple viral clearance procedures during preparation. There is no evidence that hepatitis B virus, human immunodeficiency virus, or other bloodborne pathogens have ever been transmitted by commercially available HRIG in the U.S.

3. **Management of adverse reactions**

Once initiated, rabies PEP 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 non-steroidal anti-inflammatory and antipyretic agents (e.g., ibuprofen or acetaminophen). For more severe reactions, consideration should be given to switching to another product. When a person with a history of hypersensitivity must be given rabies vaccines, pre-medication with antihistamines may be considered; epinephrine should be readily available to counteract anaphylactic reactions, and the person should be carefully observed immediately after administration.

Systemic anaphylactic or neuroparalytic reactions occurring during the administration of rabies vaccines, though rare, pose a serious dilemma for the attending physician. A patient's risk of developing rabies must be carefully considered before deciding to discontinue vaccination. The use of corticosteroids in the treatment of life-threatening neuroparalytic reactions carries the risk of inhibiting the development of active immunity to rabies. It is especially important in these cases that the patient's serum be tested for rabies antibodies following vaccination.

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

4. **Precautions and contraindications**

a. **Immunosuppression**

Persons with compromised immune function—whether by pre-existing medical condition (e.g., neoplasia) or exogenous immunosuppressives (e.g., corticosteroids)—may fail to develop complete and protective immunity after vaccination. Patients who are immunosuppressed should postpone PreEP if possible and consider avoiding activities for which rabies PreEP is indicated. Immunosuppressed persons for whom PreEP is critical should have their antibody titers checked following completion of the vaccine series. Failure to seroconvert after the third dose should be managed in consultation with appropriate public health officials. Immunosuppressive agents should not be administered during rabies PEP unless essential for the treatment of other conditions.

b. **Pregnancy**

Because of the potential consequences of inadequate treatment of a rabies exposure, pregnancy is not considered a contraindication to rabies PEP. No increased incidence of abortion, premature births, or fetal abnormalities has been associated with rabies vaccination. If the risk of exposure to rabies is substantial, PreEP might also be indicated

during pregnancy. Rabies vaccine given to a nursing mother does not affect the safety of breastfeeding for either mother or infant, and breastfeeding is not a contraindication to rabies vaccine.

c. Antimalarials

Concurrent use of antimalarial drugs may interfere with the immune response to rabies vaccination. In one study of persons undergoing PreEP with an intradermal rabies vaccine, individuals who were concurrently taking chloroquine had a lower geometric mean titer of anti-rabies antibodies at all test points compared to persons who were not taking antimalarials.⁴ Nevertheless, all study subjects had serum antibody titers that exceeded the threshold that is considered adequate for protection (complete neutralization at 1:5 on RFFIT). Data are not available as to whether this same immunosuppressive effect occurs with other antimalarial drugs or with rabies PreEP using an intramuscular vaccine.

d. Allergies

Persons who have a history of serious hypersensitivity to rabies vaccine should be revaccinated with caution.

5. Cost

Coverage for rabies immunization, for both PreEP and PEP, varies among health insurance plans. Options are available to persons in need of PEP who are uninsured or otherwise cannot afford treatment.

- a. Rabies vaccine (CPT Codes 90675/90676, and 90460/90461 or 90471/90472) and HRIG (CPT Codes 90375/90376 and 96372) are covered for Medi-Cal eligible persons. Eligibility may need to be determined by emergency certification request at the county welfare office.
- b. For individuals who are ineligible for Medi-Cal, have annual income at or below 200 percent of the federal poverty level, and reside in participating counties, the cost of rabies PEP may be covered through the California County Medical Services Program.
- c. Both rabies vaccine manufacturers have patient assistant programs that provide medications to uninsured or underinsured patients. To be eligible, patients must be indigent, uninsured, ineligible for Medicare or Medi-Cal, have household income below federal poverty level, and the attending physician must waive all fees associated with treatment. Eligibility requirements differ between companies and they should be contacted directly to discuss whether a patient is eligible for their program. 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 800-277-2254 or <http://www.patientassistancenow.com/info/programstoaccessmedicines/patientassistanceinformation.jsp>.

References

¹ Human Rabies Prevention - United States, 2008, Recommendations of the Advisory Committee on Immunization Practices. MMWR 2008; 57(RR-1):1-28. <http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5703a1.htm>

² Use of a Reduced (4-Dose) Vaccine Schedule for Postexposure Prophylaxis to Prevent Human Rabies Recommendations of the Advisory Committee on Immunization Practices. MMWR 2010; 59(RR-2):1-9. <http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5902a1.htm>

³ Compendium of Animal Rabies Prevention and Control, 2011, National Association of State Public Health Veterinarians. <http://www.nasphv.org/documentsCompendia.html>

⁴ Pappaioanou M, Fishbein DB, Dreesen DW, et al. Antibody response to pre-exposure human diploid cell rabies vaccine given concurrently with chloroquine. N Engl J Med 1986; 314:280–4.

Part III.
California Department of Public Health
Compendium of U. S. Licensed Animal Rabies Vaccines - 2012,
and Their Application in Animals Under the California Rabies Control Program

Product Name	Produced By	Marketed By	For Use In	Dosage/Route*	Age at Primary Vaccination [†]	Booster Recommendation
A) MONOVALENT – INACTIVATED						
CONTINUUM RABIES	Intervet, Incorporated License No. 165A	Intervet, Incorporated	Dogs Cats	1 ml SC 1 ml SC	4 months 3 months	1 year later & triennially 1 year later & quadrennially
DEFENSOR 1	Pfizer, Incorporated License No. 189	Pfizer, Incorporated	Dogs Cats	NOT APPROVED FOR USE IN CALIFORNIA		
DEFENSOR 3	Pfizer, Incorporated License No. 189	Pfizer, Incorporated	Dogs Cats Sheep Cattle	1 ml IM or SC 1 ml SC 2 ml IM 2 ml IM	4 months 3 months 3 months 3 months	1 year later & triennially 1 year later & triennially Annually Annually
NOBIVAC 1	Pfizer, Incorporated License No. 189	Pfizer, Incorporated	Dogs Cats	NOT APPROVED FOR USE IN CALIFORNIA		
NOBIVAC 3	Pfizer, Incorporated License No. 189	Pfizer, Incorporated	Dogs Cats Sheep Cattle	1 ml IM or SC 1 ml SC 2 ml IM 2 ml IM	4 months 3 months 3 months 3 months	1 year later & triennially 1 year later & triennially Annually Annually
EQUI-RAB	Intervet, Incorporated License No. 165A	Intervet, Incorporated	Horses	1 ml IM	4 months	Annually
RABVAC 1	Boehringer Ingelheim Vetmedica, Inc. License No. 112	Boehringer Ingelheim Vetmedica, Inc.	Dogs Cats	NOT APPROVED FOR USE IN CALIFORNIA		
RABVAC 3	Boehringer Ingelheim Vetmedica, Inc. License No. 112	Boehringer Ingelheim Vetmedica, Inc.	Dogs Cats Horses	1 ml IM or SC 1 ml IM or SC 2 ml IM	4 months 3 months 3 months	1 year later & triennially 1 year later & triennially Annually
RABVAC 3 TF	Boehringer Ingelheim Vetmedica, Inc. License No. 112	Boehringer Ingelheim Vetmedica, Inc.	Dogs Cats Horses	1 ml IM or SC 1 ml IM or SC 2 ml IM	4 months 3 months 3 months	1 year later & triennially 1 year later & triennially Annually
PRORAB-1	Intervet, Incorporated License No. 165A	Intervet, Incorporated	Dogs Cats Sheep	1 ml IM or SC 2 ml IM	3 months 3 months	Annually Annually
IMRAB 3	Merial, Incorporated License No. 298	Merial, Incorporated	Dogs Cats Sheep Cattle Horses Ferrets	1 ml IM or SC 1 ml IM or SC 2 ml IM or SC 2 ml IM or SC 2 ml IM or SC 1 ml SC	4 months 3 months 3 months 3 months 3 months 3 months	1 year later & triennially 1 year later & triennially 1 year later & triennially Annually Annually Annually
IMRAB 3 TF	Merial, Incorporated License No. 298	Merial, Incorporated	Dogs Cats Ferrets	1 ml IM or SC 1 ml IM or SC 1 ml SC	4 months 3 months 3 months	1 year later & triennially 1 year later & triennially Annually
IMRAB Large Animal	Merial, Incorporated License No. 298	Merial, Incorporated	Cattle Horses Sheep	2 ml IM or SC 2 ml IM or SC 2 ml IM or SC	3 months 3 months 3 months	Annually Annually 1 year later & triennially
IMRAB 1	Merial, Incorporated License No. 298	Merial, Incorporated	Dogs Cats	NOT APPROVED FOR USE IN CALIFORNIA		
IMRAB 1 TF	Merial, Incorporated License No. 298	Merial, Incorporated	Dogs Cats	NOT APPROVED FOR USE IN CALIFORNIA		

ROUTES AND SITES OF INOCULATION IN DOGS: California specifies sites and routes indicated to be effective in efficacy trials. Administration via other sites or routes may reduce effectiveness or be unsafe. Approved canine vaccines must be administered to dogs according to the manufacturer's recommendations either intramuscularly (IM) at one site in the thigh, or subcutaneously (SC) just behind the upper shoulder. For species other than dogs, refer to the product label.

Adapted from the Compendium of Animal Rabies Prevention and Control, 2011, National Association of State Public Health Veterinarians, Incorporated

- Continued -

Part III.
California Department of Health Services
Compendium of U. S. Licensed Animal Rabies Vaccines - 2012,
and Their Application in Animals Under the California Rabies Control Program

Product Name	Produced By	Marketed By	For Use In	Dosage/Route*	Age at Primary Vaccination [†]	Booster Recommendation
B) MONOVALENT - RABIES GLYCOPROTEIN, LIVE CANARY POX VECTOR						
PUREVAX Feline Rabies	Merial, Incorporated License No. 298	Merial, Incorporated	Cats	1 ml SC	3 months	Annually
C) COMBINATION - INACTIVATED RABIES						
CONTINUUM DAP-R	Intervet, Incorporated License No. 165A	Intervet, Incorporated	Dogs	1 ml SC	4 months	1 year later & triennially
CONTINUUM Feline HCP-R	Intervet, Incorporated License No. 165A	Intervet, Incorporated	Cats	1 ml SC	3 months	1 year later & triennially
EQUINE POTOMAVAC + IMRAB	Merial, Incorporated License No. 298	Merial, Incorporated	Horses	1 ml IM	3 months	Annually
D) COMBINATION - RABIES GLYCOPROTEIN, LIVE CANARY POX VECTOR						
PUREVAX FELINE 3/ RABIES	Merial, Incorporated License No. 298	Merial, Incorporated	Cats	1 ml SC	8 weeks 3 months	Every 3 weeks until 3 months & annually 3 weeks later & annually
PUREVAX FELINE 4/ RABIES	Merial, Incorporated License No. 298	Merial, Incorporated	Cats	1 ml SC	8 weeks 3 months	Every 3 weeks until 3 months & annually 3 weeks later & annually

* Intramuscularly (IM) at one site in the thigh.
Subcutaneously (SC) just behind the upper shoulder.

[†] Minimum age (or older) and revaccinated one year later. A month = 28 days.