



VACCINATION STATION

Rabies Vaccination in Dogs

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PREVENTIVE ACTION

Diligent vaccination programs are essential in preventing rabies from becoming more common in dogs.

Rabies is a deadly zoonotic disease of mammals. It is now rarely reported in dogs in the United States owing to widespread vaccination programs effectively eliminating the canine variant. However, education of the public regarding the need to vaccinate dogs and the continued diligent practice of rabies vaccination in dogs will help to prevent re-emergence of this fatal zoonotic infection.

PUBLIC HEALTH SIGNIFICANCE

Rabies is responsible for tens of thousands of human deaths annually, with infection usually following a bite or scratch from a rabies-infected animal. According to the World Health Organization, rabies-infected dogs serve as the main source of human rabies transmission globally, contributing up to 99% of all rabies cases in humans, while in the Americas, bats are the most common source of human infections.¹ In the U.S., the dog rabies variant, once endemic in small animals, has now been nearly eradicated.² However, wildlife species, which carry their own rabies variants, present a constant danger of reintroduction of rabies to dogs.

RABIES DISEASE

Rabies is caused by viruses in the genus *Lyssavirus*.

Virtually all mammals are susceptible to rabies infection, including domestic animals (e.g., dogs, cats, cattle, horses) as well as wild mammalian reservoir populations (e.g., raccoons, skunks, foxes, bats) where multiple rabies virus variants are maintained.^{3,4} Regardless of the species affected, rabies causes an acute, progressive encephalitis.

Pathogenesis

Transmission most commonly occurs through a bite or scratch from an infected animal. The incubation period is highly variable and depends on the age of the individual bitten, the degree of innervation of the bite site, the distance from the point of inoculation to the spinal cord or brain, and the variant and amount of virus introduced, as well as other factors.⁵ In domestic animals, the incubation period is generally 3 to 12 weeks, but can range from several days to months, rarely exceeding 6 months.³ Once the virus is introduced in the body, it enters peripheral nerves and subsequently gains entry into the central nervous system (CNS). After replication within the CNS, the virus moves outward to other body tissues via the peripheral, sensory, and motor nerves (**FIGURE 1**).⁵

Clinical Signs

Rabies virus infection has classically been divided into 2 main clinical manifestations: the excitatory (“furious”) and the paralytic (“dumb”) forms.^{2,5} This classification system is arbitrary because rabies can be quite variable in its presentation, and not all animals progress through all 3 clinical stages: prodromal, excitatory, and paralytic.^{2,5}

Initial clinical signs (the prodromal period) are nonspecific and can include minor behavioral changes. These signs, if recognized, usually last 2 to 3 days in dogs.^{2,5} During the excitatory phase, dogs suddenly become vicious and behave erratically. They may become restless and irritable and have heightened sensitivities to visual and auditory stimuli.⁵ This stage usually lasts 1 to 7 days; however, some dogs may progress directly from the prodromal stage to the paralytic stage.² This final stage is characterized initially

by weakness and eventually by paralysis. The limb where the wound occurred is initially affected, followed by progression of paralysis to the neck and head. The paralytic phase usually lasts 2 to 4 days and ends in death from respiratory failure.^{2,5} The course of rabies typically lasts 3 to 8 days in dogs.²

Diagnosis and Treatment

There is no premortem test or effective treatment for rabies in dogs. Dogs that have sustained a bite from an unknown or unvaccinated animal should be immediately vaccinated and quarantined or euthanized, as recommended (TABLE 1).³ Elimination of feral animals or wildlife populations that harbor rabies is not economically feasible, nor is it socially or ecologically acceptable. As such, control through immunization is paramount to protecting dogs.

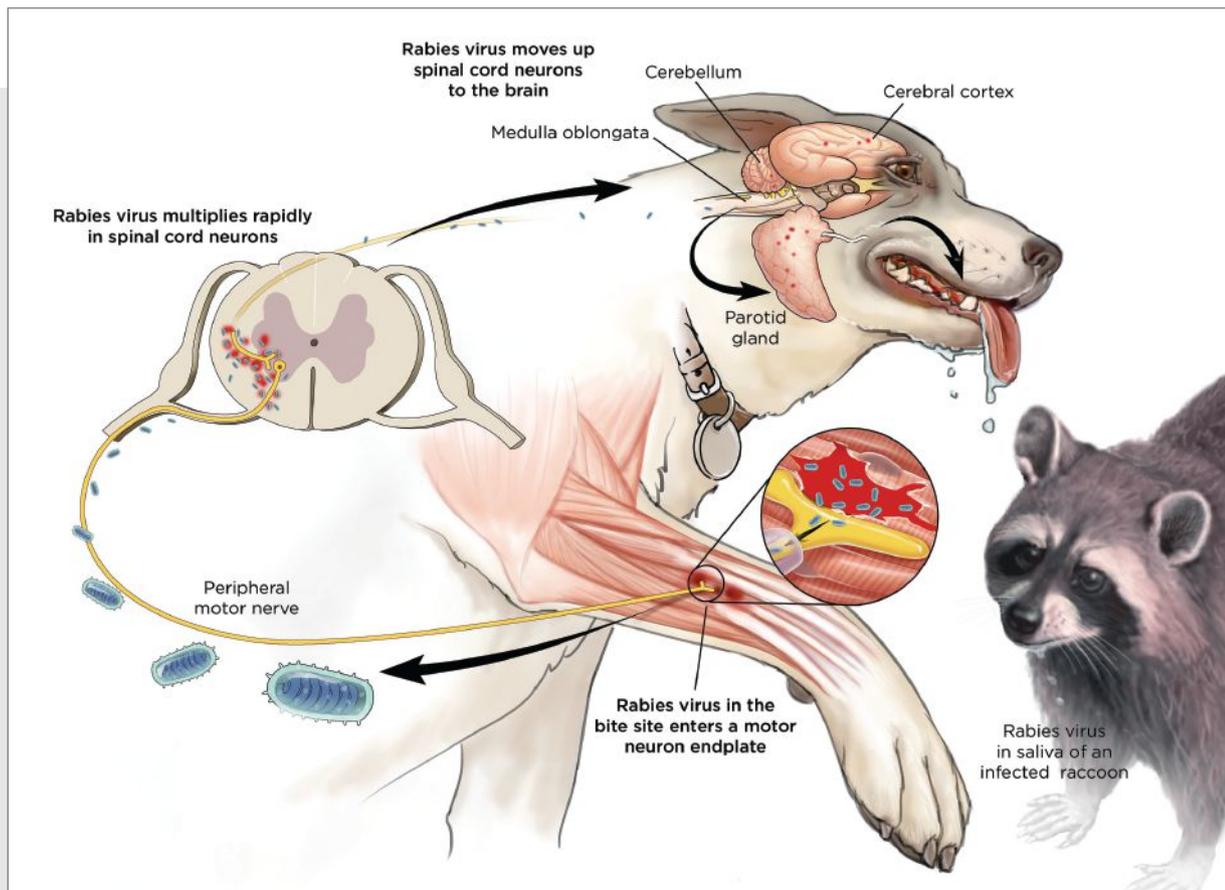


FIGURE 1. An example of the pathogenesis of rabies infection. A rabid animal transmits rabies virus through saliva into a bite wound. The virus travels up peripheral motor nerves to the spinal cord, where it rapidly divides and spreads throughout the nervous system. This produces lower motor neuron paralysis, behavior changes, and the cranial nerve deficits typically encountered during the various stages of rabies infection. The virus then spreads to salivary and additional tissues from which it can spread to other animals.

Vaccination efforts can provide protection for dogs exposed to potentially rabid animals even if they are overdue for a rabies booster vaccine.

RABIES VACCINES

Vaccines stimulate adaptive immunity, which is antigen-dependent and antigen-specific; therefore, rabies vaccination provides protection specifically from rabies infection. To be licensed in the United States, vaccines must protect at least 88% of vaccinated animals against challenge with virulent virus.⁵ Multiple vaccines are licensed for use in domestic animals, and inactivated (killed) vaccines are available for use in dogs (TABLE 2). Recombinant virus-vectored products are available for cats, and oral modified live vaccines are available for wild animals, but these options are not superior to the inactivated vaccine for dogs.

Vaccination Recommendations

Rabies vaccine is a core vaccine according to the American Animal Hospital Association (AAHA) and is the only companion animal vaccine required by law in most states.⁶ In Canada, rabies vaccination of dogs is only required in the province of Ontario.⁶ Licensed veterinarians are legally required to vaccinate dogs for rabies in most U.S. states. Some states also allow canine rabies vaccines to be administered by licensed or certified veterinary technicians or lay people working under the direct supervision of a licensed veterinarian.³

After vaccination, a rabies vaccination certificate verifying the vaccine, the health of the vaccinee, the product used, the booster interval, and the administering veterinarian is issued to identify vaccinated dogs.

While there are no clearly defined vaccination site recommendations for dogs as there are in cats, noting which vaccines are administered where is important in case of an adverse reaction. Inactivated rabies virus vaccines can be administered either intramuscularly or subcutaneously. The first vaccination is given per label recommendations at a minimum of 3 months of age due to the potential interference by maternally derived antibodies and a relatively poor immune response in the young.^{2,5} Regardless of the age of the first vaccination, a booster vaccine is repeated 1 year after the initial vaccine, with subsequent boosters given annually or triennially depending on the labeled duration of immunity of the vaccine used and local public health regulations.^{2,3,5} A recently published challenge study with virulent rabies virus demonstrated that the duration of immunity conferred by rabies vaccine extends beyond the 3-year label, which may change vaccination schedules in the future.⁷

Regardless of booster interval, within 28 days after initial vaccination, a peak rabies virus antibody titer is expected, and the animal can be considered immunized.³ The initial vaccine schedule (1 vaccine followed by a booster 1 year later) is inconsistent with other inactivated vaccine protocols, in which 2 sequential doses administered 2 to 4 weeks apart are required to stimulate adequate immunity. Like other inactivated vaccines, the initial dose of a rabies vaccine serves as the “priming” dose. If a dog, after having received only 1 dose of rabies vaccine, is subsequently exposed to virulent rabies virus, exposure to the virulent virus then serves as the second, or immunizing,

TABLE 1 Recommendations for Rabies Postexposure Management of Dogs and Cats Based on Vaccination Status⁴

VACCINATION STATUS	TYPE OF CONFINEMENT	VACCINATE
Current	Observation/owner's control for 45 days	Booster
Never vaccinated	A. None: euthanize B. 4-month strict quarantine: dogs and cats	A. N/A B. Vaccinate (<96 h)
Out of date/documented	Observation/owner's control for 45 days	Booster
Out of date/undocumented	A. None: euthanize B. 4-month strict quarantine: dogs and cats C. Observation/owner's control for 45 days ^a	A. N/A B. Vaccinate (<96 h) C. Booster

^aProvided serologic proof of prior rabies vaccination is obtained.



“dose.” Because the onset of signs of rabies is slow after exposure, there is adequate time for a protective, humoral immune response to develop.⁶

While no vaccine is 100% effective, rabies infection is rare in vaccinated dogs. In one study, 4.9% of cases of rabid dogs had a history of prior rabies vaccination.⁸ Vaccination efforts can provide protection for dogs exposed to potentially rabid animals even if they are overdue for a rabies booster vaccine. Results comparing the anamnestic response rate in currently vaccinated animals versus overdue animals indicated that dogs with an out-of-date vaccination status were not inferior in their antibody response following booster rabies vaccination compared with dogs with a current vaccination status.⁹ The findings of this study led to changes in recommendations for postexposure management of dogs exposed to an animal confirmed or suspected to be rabid, and to advisement that an animal is currently vaccinated and considered immunized immediately after any booster vaccination.³

Postexposure Management

A dog that has been exposed to a confirmed or suspected rabid animal should immediately receive veterinary medical care for assessment, wound cleansing, and booster vaccination.³ If the exposed dog is current on rabies vaccination, it should be quarantined and observed by the owner for 45 days.³ An exposed dog that is overdue for a rabies vaccine and has documentation of a past vaccine can also be quarantined and observed by the owner for 45 days. If the exposed dog is overdue for a booster vaccine without appropriate documentation, local public health

authorities should be consulted to determine the quarantine period and the utility of serologic testing to provide proof of an anamnestic response (TABLE 1).³

If the exposed dog has never been vaccinated for rabies, it should be euthanized immediately; however, if the owner is unwilling to euthanize, strict quarantine for 4 months or longer without direct contact with people may be an option after consultation with local public health authorities.³

For any of these situations, if at any time during the quarantine period signs suggestive of rabies develop (e.g., paralysis or seizures), the animal should be euthanized and submitted for rabies testing.³

Adverse Vaccine Reactions

Concerns about adverse vaccine reactions and overvaccination have occasionally caused reluctance to vaccinate dogs. The following are potential vaccine adverse reactions described in dogs and cats:⁴

- Injection-site reactions
- Allergic or immune-mediated reactions
- Tumorigenesis
- Vaccine-induced immunosuppression
- Anaphylaxis
- Injection-site sarcomas

The most common vaccine-associated adverse events reported in dogs in one study were allergic reactions, local vaccine-site reactions, and nonspecific systemic signs (fever, lethargy, or anorexia).¹⁰ In the same study, the reported rate of adverse events within 3 days of vaccination was 38.2 of 10 000 dogs, although it was

TABLE 2 Rabies Vaccines Licensed for Use in Dogs in the United States^a

PRODUCT FAMILY NAME ^b	MANUFACTURER	SPECIES	VACCINE TYPE	VOLUME (DOSE)	EARLIEST AGE FOR INITIAL INOCULATION	ROUTE OF INOCULATION	LABELED DURATION OF IMMUNITY
IMRAB	Boehringer Ingelheim Vetmedica	Dog, cat, ferret	Killed (adjuvanted)	1.0 mL	3 months	IM or SC	1 or 3 years
NOBIVAC	Merck Animal Health	Dog, cat	Killed (adjuvanted)	1.0 mL	3 months	IM or SC	1 or 3 years
RABVAC	Boehringer Ingelheim Vetmedica	Dog, cat	Killed (adjuvanted)	1.0 mL	3 months	IM or SC	1 or 3 years
DEFENSOR	Zoetis	Dog, cat	Killed (adjuvanted)	1.0 mL	3 months	SC (cats); IM or SC (dogs)	1 or 3 years

^aAdapted from Rabies Aware. Vaccines. rabiesaware.org/vaccines.php. Accessed September 5, 2020.

^bMultiple formulations of each vaccine exist. Always consult prescribing information for specific product for appropriate use.

The most common vaccine-associated adverse events reported in dogs in one study were allergic reactions, local vaccine-site reactions, and nonspecific systemic signs (fever, lethargy, or anorexia).¹⁰

noted that adverse events are likely underreported.¹⁰ If an acute adverse vaccine reaction is suspected, treatment may include antihistamines (e.g., diphenhydramine), anti-inflammatories (steroids or nonsteroidal anti-inflammatory drugs, depending on the reaction), or more targeted therapy (e.g., fluids and epinephrine for anaphylaxis). All adverse vaccine events should be reported to the vaccine manufacturer and the U.S. Department of Agriculture (USDA) Animal and Plant Health Inspection Service Center for Veterinary Biologics (aphis.usda.gov/aphis/home).

ANTIBODY TESTING

Although the rate of adverse events is low, many question the necessity of repeat vaccinations when serology, used to determine antibody titers and presumably protection, is available. Moreover, revaccination of an already protected animal does not enhance disease protection, further calling into question the necessity for revaccination. Antibody testing has been employed to assess immunity before revaccination for many canine viruses; however, most states in the United States mandate revaccination for rabies regardless of medical history or antibody levels.

Relation of Antibody Levels to Immunity

Rabies virus antibody titers are indicative of a response to rabies vaccine or infection.³ The major factors correlated with a robust rabies vaccine response are vaccination after maternal antibody has declined, patient size (larger breeds showed a higher percentage of inadequate vaccine response⁴), more than 1 vaccination, time interval since last vaccination, and

blood draw within 15 to 30 days of vaccination. Evidence from previous studies has indicated that type of vaccine (e.g., multivalent versus monovalent, manufacturer) can also play a role in the immune response to rabies vaccine.⁴ However, titers do not directly correlate with protection because other immunologic factors play a role in preventing rabies, and the ability to measure and interpret those other factors is not well developed.³ Therefore, evidence of circulating rabies virus antibodies in animals may not be used as a substitute for current vaccination in managing rabies exposures or determining the need for booster vaccination.³

For a rabies vaccine to be approved for use, it must demonstrate not only protection by survival of the challenged animals but also proof of immunogenicity by measurement of rabies antibody levels.⁴ Dogs and cats with rabies serology results greater than 0.5 IU/mL survive more often than dogs and cats with results less than 0.5 IU/mL. An almost 100% survival rate has been reported in animals with rabies virus neutralizing antibody (RVNA) levels greater than 0.5 IU/mL.⁴ Therefore, an RVNA level of 0.5 IU/mL typically demonstrates proof of adequate response to rabies vaccination.⁴ However, a few reported animals with an RVNA result greater than 0.5 IU/mL have succumbed to rabies in challenge studies.⁴

Available Tests

Many methods have been developed to detect rabies antibodies. The 2 most common methods in veterinary medicine are the rapid fluorescent focus inhibition test (RFFIT) and the fluorescent antibody virus neutralization (FAVN) test. The RFFIT is the method most often used to measure antibodies in dogs;² however, countries or regions that have been declared rabies-free and require antibody testing as confirmation of recent rabies vaccination only accept the FAVN test.

For canine samples, the RFFIT and the FAVN test are performed at Kansas State Veterinary Diagnostic Laboratory (ksvdl.org). A passing test result means that RVNA levels are greater than or equal to 0.5 IU/mL. The highest probability of obtaining a passing result is when a pet has been vaccinated a minimum of 2 times, and the best results are typically obtained 15 to 30 days after vaccination.⁴ Some countries, however, have strict requirements on the timing of the blood draw; therefore, the destination country or the state USDA office should be contacted for the most accurate



requirements.¹¹ For both tests, 1.0 to 2.0 mL of serum is required for submission and results are available approximately 3 to 4 weeks after the laboratory receives the sample.¹¹

Utility

Despite its utilization for pet travel and evidence presented in challenge studies, rabies serology cannot be used to forgo revaccinations where legally required in most states. Some states do allow a medical exemption from rabies booster vaccinations.¹² The lack of widespread adoption of antibody test results in lieu of revaccination is due in part to reported rabies vaccine failures and to inconsistency in testing strategies. Several critical parameters need to be defined before rabies serology can be confidently used as a correlate of protection, including definition of an adequate antibody response (correlation of protection level), method of measurement and validation (assay used), the reported value (IU/mL or titer), the timing of blood sampling, and approval for laboratories providing testing.⁴

This creates a dilemma for a veterinarian trying to balance the risks and benefits of vaccinating for rabies and public health interests. The use of serology for verification of rabies immunity should be reserved for well-vaccinated pets (dogs and cats that have received a primary vaccination, followed by 1 or 2 boosters).⁴ Rabies titer checks could also be used for prospective serologic monitoring to help determine whether an animal has been previously vaccinated or if it has low titers and needs a booster.^{3,4} In addition, titer checks can be used in pets for which routine vaccinations are contraindicated because of health concerns such as neoplasia or immune-mediated diseases.⁴ However, the veterinarian and the client must understand that serologic testing will not meet legal requirements in case of a bite or possible rabies exposure and be prepared to deal with those ramifications if necessary.

CONCLUSION

Rabies vaccination of dogs still remains one of the most effective strategies for preventing rabies in humans. Research is continuing to evaluate the duration of immunity with challenge studies, which may alter vaccine protocols in the future. While there are concerns regarding adverse vaccine reactions and overvaccination, current data limit the widespread usage of antibody titers to guide revaccination

strategies. Antibody levels can be used for dogs traveling into rabies-free areas to demonstrate prior rabies vaccination and may be useful when revaccination is contraindicated. **TVP**

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