Health Advisory

KITSAP PUBLIC HEALTH DISTRICT

March 28, 2016

New guidance for management of dogs/cats exposed to potentially rabid animals in the 2016 rabies Compendium

Actions Requested

- **Be aware that the NASPHV released a new version of the rabies Compendium,** which provides revised guidance on managing dogs and cats exposed to potentially rabid animals. Note that none of these changes apply to ferrets. Likewise, there are no changes to existing guidance for humans exposed to potentially rabid animals.
- **Familiarize yourself with the specifics of the new guidance**, particularly:
    - **Currently vaccinated dogs and cats** with documentation of vaccination status still need to receive a booster and undergo a 45 day observation under the owner's control. (No change).
    - **Unvaccinated dogs and cats** should either be euthanized or placed under strict quarantine for 4 months. Rabies vaccine must be given within 96 hours after the exposure; if delayed then the Health District may require the quarantine be extended to 6 months.
    - **Dogs and cats who are overdue** for their rabies booster but have appropriate documentation of being previously vaccinated at least once may be given a rabies booster immediately and observed under the owner's control for only 45 days. If the booster is delayed, the Health District may require an extended observation.
    - **Dogs and cats who lack documentation but have likely been previously vaccinated** should either be treated as unvaccinated (see above) *or* the veterinarian may request that the Health District allow prospective serologic monitoring to assess for an anamnestic response indicative of previous vaccination (see attached).
- **Continue to report domestic animal exposures** requiring observation/confinement and any human exposures to potentially rabid animals.
- **Consult our staff as needed for case-specific guidance on exposure assessment, quarantine, and testing.**

For questions or to report a rabies exposure, please contact our Communicable Disease staff at 360-337-5235.

Background

The revised guidelines from the National Association of Public Health Veterinarians (NASPHV) are derived from new evidence that shows dogs and cats with out-of-date rabies vaccine status had similar responses to boosters (i.e., non-inferior titers) as those who were current on their rabies vaccine. The studies were limited to dogs and cats, thus there is no evidence base for changing any of the existing recommendations for ferrets. The quarantine period has been reduced from 6 to 4 months for unvaccinated dogs and cats, which is based upon state/CDC unpublished data. The revised Compendium also strongly encourages an interdisciplinary approach to rabies control and provides an updated list of animal rabies vaccines.

We also want to remind you that if an animal needs to be euthanized and tested for rabies, we can approve testing at the WA Public Health Laboratories when there is human exposure. Generally, animal-only exposures are tested at Oregon State University Veterinary Diagnostic Laboratory at the owner's expense. Rare exceptions are made on a case-by-case basis. Note that freezing an animal is not recommended and may delay testing, but it does not necessarily preclude testing. Please call us to determine if testing is warranted prior to disposing of or freezing an animal involved in an exposure situation.

Resources

Attachments: (1) NASPHV Compendium of Animal Rabies Prevention and Control, 2016
(2) Moore, et al. Comparison of anamnestic responses to rabies vaccination in dogs and cats with current and out-of-date vaccination status. JAVMA 2015;246:205–211.
(3) NASPHV Prospective Serologic Monitoring Protocol, 2016

PROSPECTIVE SEROLOGIC MONITORING PROTOCOL: NASPHV COMPENDIUM OF ANIMAL RABIES PREVENTION AND CONTROL, 2016

This guidance on prospective serologic monitoring is for use with dogs and cats as referred to in Part I B.5(4b) of the NASPHV Compendium of Animal Rabies Prevention and Control, 2016.

NOTE: This guidance will be updated as needed. Please check the National Association of State Public Health Veterinarians website at www.nasphv.org for the most current guidance prior to any sample collection.

This protocol applies only to a dog or cat;

- that has been exposed to a confirmed or suspected rabid animal (as defined in Part I A.2 of the Compendium), and;
- that has been, or very likely has been, previously vaccinated with a USDA-licensed rabies vaccine, but for which there is no valid documentation, e.g. a rabies vaccination certificate, and;
- whose owner or guardian wants to avoid euthanasia or strict quarantine, and;
- that can immediately be managed by a veterinarian who can collect serum specimens as described below and administer a rabies vaccine.

The justification for this recommendation relies on the information presented in the following peer-reviewed publication:
Moore MC, Davis RD, Kang Q, et al. Comparison of anamnestic responses to rabies vaccination in dogs and cats with current and out-of-date vaccination status. J Am Vet Med Assoc 2015;246(2):205–211.

Dogs and cats that have previously received a USDA-licensed rabies vaccine which was administered in compliance with the manufacturers label insert, will mount a strong anamnestic (or secondary immune) response within days following the administration of a booster USDA-licensed rabies vaccine. The paper provides evidence that this is true regardless of the number of vaccines received (even a single vaccine) or the amount of time that has elapsed since the last vaccine was administered.

Recommended protocol for jurisdictions choosing to permit the use of prospective serologic monitoring for decision-making regarding 4 month quarantine versus 45 day observation (see also Figure 1)

The dog or cat must be seen by a veterinarian immediately following an exposure to a confirmed or suspected rabid animal. The veterinarian must report the case to public health authorities or whatever entity which serves as the local Rabies Control Authority (RCA). A RCA is the government agency or official at the state or local level, legally authorized and responsible for enforcement of rabies laws, regulations, and ordinances in a specific jurisdiction. RCAs vary by jurisdiction but are most frequently public health, animal health, or animal control officials. The RCA should be provided all relevant details on what is known about

the animal's vaccination history and the specifics of the current rabies exposure. The RCA will determine whether prospective serologic monitoring is indicated and permitted in their jurisdiction.

The RCA will work with the veterinarian and the owner to define a timeline during which the protocol must be implemented. The test, submission and all associated fees will be assumed by the animal owner and submitting veterinarian. The veterinary visit in which the first serum is collected and the rabies vaccine is administered must occur as soon as possible following the exposure and should not exceed 96 hours post exposure. The date of this visit will be counted as Day 0.

On Day 0:

1. Collect 1-2 mL of serum;
2. Label and keep the serum specimen refrigerated until the second specimen is collected. Serum held for more than 7 days may need to be frozen. Follow the instructions provided by the laboratory that will be performing the tests;
3. Administer a USDA-licensed rabies vaccine labeled for use in that species; and
4. Schedule a follow up appointment to ensure the pet will return in 5-7.

On Day 5 (but no later than day 7):

1. Collect a second (paired) serum specimen (1-2 mL).
2. Label and store the specimen appropriately according to the instructions from the laboratory where it will be submitted;
3. Submit the paired serum specimens to an approved Rabies Laboratory for Rapid Fluorescent Foci Inhibition Test (RFFIT) testing with the appropriate forms completed and **carefully following shipping instructions provided by the laboratory**; and
4. Contact the RCA to document submission of the specimens.

The paired serum specimens must be delivered to an approved Rabies Laboratory. At this time, the laboratories approved and available to perform the testing are:

- Atlanta Health Associates, Inc.;
- Kansas State University Rabies Laboratory (KSU-RL); and
- Wadsworth Rabies Laboratory (for New York State residents only).

The Centers for Disease Control and Prevention (CDC) may occasionally provide testing services by special arrangement only. The definition of an approved laboratory is one that is currently licensed by CLIA or NYSDOH and has been approved to participate in this Prospective Serological Monitoring Protocol by NASPHV's Rabies Compendium Committee.

The submission form for the appropriate laboratory must be complete, accurate, and accompany **properly labelled paired specimens** to avoid delays in testing. The submitting veterinarian is responsible for ensuring the accuracy of all specimen collection, submission form completion and shipping. Turn around time for results are dependent upon the laboratory and their current testing volume. The submitting veterinarian is responsible for

immediately contacting the RCA with the results to finalize recommendations for the animal.

The dog or cat shall remain in strict quarantine during the testing process unless and until otherwise approved by the RCA.

Interpretation of the results must be done in conjunction with the laboratory performing the testing as the determination of a statistically significant change in titer is determined by analysis of the laboratory's own data regarding testing performance. The test results will be used to determine whether the animal has evidence to suggest a previous rabies vaccine. Based on data analysis from the approved Rabies Laboratories, in general, the paired serum specimens must show both a statistically significant (usually defined as greater than two-fold at the currently approved Rabies Laboratories) rise in titer between the first and second specimens and the second titer must be above 0.5 IU/mL. If either of these conditions is not met, the animal must be treated as previously unvaccinated for the purposes of rabies control decisions.

Serology test results do not pre-empt the authority of the RCA to order continued strict quarantine of the animal if it judges such actions to be in the best interest of protecting the public's health. Nor do these recommendations supersede any applicable state laws and regulations or local ordinances.

FREQUENTLY ASKED QUESTIONS:

1. **What if the dog or cat did not receive care immediately (within 96 hours) after the exposure?**
   Such cases should be discussed with the RCA and managed on a case by case basis. Factors to consider include the number of days that have elapsed since the exposure, the severity of the exposure, number of previous vaccinations, the health of the animal and the local rabies epidemiology.

2. **What if the dog or cat cannot return to the veterinarian for collection of the second specimen on DAY 5?**
   The second specimens must be collected by Day 7. Delaying collection of the specimen prevents accurate interpretation of the test results as any increase in rabies antibody titer might be due to the rabies exposure itself or the booster vaccination rather than an anamnestic response to a previous vaccination.

3. **What test will be used to test the serum specimens?**
   The laboratory will test the specimens using a Rapid Fluorescent Focus Inhibition Test (RFFIT). It is a serum neutralization (inhibition) test, which means it measures the ability of rabies specific antibodies to neutralize rabies virus and prevent the virus from infecting cells. These antibodies are called rabies virus neutralizing antibodies (RVNA).

4. **What values will be used to determine if the dog or cat has evidence of a prior rabies vaccination and an acceptable anamnestic response?**
   A greater than two-fold rise in the titer values of the paired specimens, as well as a RVNA titer equal to or above 0.5 IU/mL for the second specimen, provides evidence of a robust anamnestic immune response after rabies vaccination.
   Considerable variability exists as to any individual's response to vaccination and the RCA should consult the laboratory for help in interpreting results that fall outside these guidelines.

   If an anamnestic response is demonstrated, the animal should be issued a vaccine certificate with an expiration date consistent with the vaccine label. If there is no evidence of an anamnestic response, the vaccine is considered the initial dose and the animal should be boostered in one year, consistent with the vaccine label.

5. **If the titer is equal to or above 0.5 IU/mL and there is evidence of an anamnestic response, is it impossible for the animal to go on to develop rabies?**
   A specific value equal to or above 0.5 IU/mL and evidence of an anamnestic response suggests the animal will be protected. However, there have been rare instances in which vaccinated animals have gone on to develop rabies. Contributing factors may include other immunological factors involved in the protection from rabies infection, or the location, viral dose, and severity of the wound. Because of this uncertainty, confinement with observation or quarantine is warranted regardless of the presence of antibodies.

6. **Where can I find the appropriate submission forms and shipping instructions?**
   - Atlanta Health Associates, Inc.: http://www.atlantahealth.net/
   - Kansas State University Rabies Laboratory: http://www.ksvdl.org/rabies-laboratory/rffit-test/rffit-submission-forms.html
   - New York State Wadsworth Center (New York residents only): http://www.wadsworth.org/programs/id/rabies

7. **Can this protocol be used for animals other than dogs or cats such as ferrets?**
   No. At this time, data regarding anamnestic responses following revaccination with rabies vaccine are available only for dogs and cats.

FIGURE 1: ALGORITHM FOR THE PROSPECTIVE SEROLOGIC MONITORING (PSM) PROTOCOL ON MANAGING DOGS AND CATS EXPOSED TO RABIES WITH A HISTORY OF RABIES VACCINATION, BUT NO DOCUMENTATION

Please Note, this protocol is intended only to apply to a dog or cat;
- that has been exposed to a confirmed or suspect rabid animal (as defined in Part I A.2 of the Compendium), and;
- that has been, or very likely has been, previously vaccinated with a USDA licensed rabies vaccine but for which there is no valid documentation, e.g. a rabies vaccination certificate, and;
- whose owner or guardian wants to avoid euthanasia or strict quarantine, and;
- that can immediately be managed by a veterinarian to collect serum specimens as described below and administer a rabies vaccine.

It is imperative that the veterinarian and the Rabies Control Authority (RCA) notify one another of rabies exposure cases in order to ensure appropriate follow up in a coordinated manner. Immediately following an exposure to a confirmed or suspect rabid animal, the dog or cat must be seen by a veterinarian.

VETERINARIAN

RABIES CONTROL AUTHORITY (RCA)†

DOG OR CAT EXPOSED TO RABIES

THE VETERINARIAN WILL IMMEDIATELY contact the local or state public health or appropriate Rabies Control Authority (RCA)[1].

If the RCA is not available after hours, weekends or holiday, veterinarians whose clients want to pursue PSM should initiate the process.
Rabies vaccine and serum collection must be initiated within 96 hours of the exposure.

The veterinarian and the RCA shall work together to determine if prospective serologic monitoring is an option, taking into consideration the date of exposure and time elapsed before the animal is rabies vaccinated.

THE RCA will discuss the case with the veterinarian and when indicated, the dog/cat owner or guardian.

Was the animal previously rabies vaccinated?

YES / NO

Consult compendium and RCA for other management options

Is there valid documentation? YES

NO

Will PSM be pursued?

YES / NO

The dog or cat shall remain in strict quarantine pending test results unless and until otherwise approved by the RCA. Test results will dictate the final management recommendation.

DAY 0 – *this is the day the first serum specimen is collected and the dog or cat is rabies vaccinated*:

1. Collect 1-2 mL of serum, label[2] and store according to instructions from the Approved Laboratory.
2. Administer USDA licensed rabies vaccine.
3. Schedule a follow up appointment for 5 to 7 days after.

BASED ON ASSESSMENT, THE RCA WILL:

1. Determine whether dog/cat requires continued quarantine or can be observed by the owner/guardian for 45 days from the date of exposure.
2. Communicate results and recommendations to veterinarian and dog/cat owner.

DAY 5 (*up to but no later than day 7*):

1. Collect second serum specimen (1-2 mL)
2. Label[2] and distinguish as second sample
3. Package appropriately labeled paired specimens together as required by the approved Rabies Laboratory with a completed specimen submission form.
4. Contact the RCA to document the visit.

Submit specimens to participating rabies laboratory[3]

The veterinarian must immediately report results to the RCA. Results will be used to guide management decisions based on evidence of previous rabies vaccination as demonstrated by a strong anamnestic response as well as an acceptable RVNA[4] titer. Results should be interpreted in consultation with the laboratory performing the testing.

[1]**RCA** = Rabies Control Authority. This is typically a government agency at the State or Local level that is legally authorized and responsible for enforcement of rabies ordinances. Often it is the Local or State Health Department, but may also be the Local or State Department of Agriculture.

[2]**LABEL INFORMATION**
Please include the following information on each specimen tube being submitted:
1. Animal's Name; 2. Date of collection

[3]**PARTICIPATING RABIES LABORATORIES**
1. Atlanta Health Associates, Inc. http://www.atlantahealth.net/
2. Kansas State University Rabies Laboratory http://www.ksvdl.org/rabies-laboratory/rffit-test/rffit-submission-forms.html
3. Wadsworth Rabies Laboratory for New York State residents only http://www.wadsworth.org/programs/id/rabies

[4]**RVNA** = Rabies virus neutralizing antibodies

Comparison of anamnestic responses to rabies vaccination in dogs and cats with current and out-of-date vaccination status

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Objective—To compare anamnestic antibody responses of dogs and cats with current versus out-of-date vaccination status.

Design—Cross-sectional study.

Animals—74 dogs and 33 cats.

Procedures—Serum samples were obtained from dogs and cats that had been exposed to rabies and brought to a veterinarian for proactive serologic monitoring or that had been brought to a veterinarian for booster rabies vaccination. Blood samples were collected on the day of initial evaluation (day 0) and then again 5 to 15 days later. On day 0, a rabies vaccine was administered according to label recommendations. Paired serum samples were analyzed for antirabies antibodies by means of a rapid fluorescent focus inhibition test.

Results—All animals had an antirabies antibody titer ≥ 0.5 IU/mL 5 to 15 days after booster vaccination. Dogs with an out-of-date vaccination status had a higher median increase in titer, higher median fold increase in titer, and higher median titer following booster vaccination, compared with dogs with current vaccination status. Most (26/33) cats, regardless of rabies vaccination status, had a titer ≥ 12 IU/mL 5 to 15 days after booster vaccination.

Conclusions and Clinical Relevance—Results indicated that dogs with out-of-date vaccination status were not inferior in their antibody response following booster rabies vaccination, compared with dogs with current vaccination status. Findings supported immediate booster vaccination followed by observation for 45 days of dogs and cats with an out-of-date vaccination status that are exposed to rabies, as is the current practice for dogs and cats with current vaccination status. (*J Am Vet Med Assoc* 2015;246:205–211)

Each year in the United States, approximately 6,000 cases of rabies are documented in animals, primarily in the major wildlife reservoir species (ie, raccoons, bats, skunks, and foxes). These confirmed cases are invariably associated with 1 or more human and animal exposures to rabies. In addition, many domestic animals come into contact with sick wildlife or other animals that cannot be captured for rabies diagnostic testing and, depending on the geographic location and species of animal involved, may be considered potentially exposed to rabies. As a result, thousands of dogs and cats are known to be exposed or are potentially exposed to rabies each year in the United States.

From the Veterinary Diagnostic Laboratory (Moore, Davis, Hanlon) and the Department of Diagnostic Medicine and Pathobiology (Mosier), College of Veterinary Medicine, and the Department of Statistics, College of Arts and Sciences (Vahl), Kansas State University, Manhattan, KS 66506; Statistical Intelligence Group LLC, 117 Firethorn Ln, Manhattan, KS 66503 (Kang); and the CDC, 1600 Clifton Rd, Atlanta, GA 30333 (Wallace, Hanlon).

This manuscript represents a portion of a thesis submitted by Dr. Moore to the Kansas State University Graduate School as partial fulfillment of the requirements for a Master of Public Health degree.

Presented to the Compendium of Animal Rabies Prevention and Control Committee of the National Association of State Public Health Veterinarians, Nashville, Tenn, June 2014.

The authors thank Drs. Sue Nelson, John Teeter, and Don Dinges for assistance in procuring samples.

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Regulations have been developed to minimize the public health risks that dogs and cats exposed or potentially exposed to rabies and potentially incubating the virus may pose. These regulations vary, depending on locality, but most public health officials refer to or rely on the Compendium of Animal Rabies Prevention and Control[1] for guidance in these situations.

According to the current version of the compendium, dogs and cats with current rabies vaccination status that have been exposed to an animal confirmed or suspected to be rabid should immediately receive a rabies booster vaccination and be observed for 45 days, most often, as allowed by jurisdictional authorities, under the owner's supervision with no contact restrictions. The recommendation for dogs and cats that have never been vaccinated against rabies and that have been exposed to a rabid animal is euthanasia or quarantine for 6 months in a specialized facility.

In contrast, the compendium guidelines are less clear when it comes to recommendations for dogs and cats overdue for a booster vaccination (ie, dogs and cats with out-of-date rabies vaccination status), suggesting that these animals be evaluated on a case-by-case basis that takes into account the severity of the exposure, time since the last rabies vaccination, number of rabies vaccinations received previously, current health status of the animal, and local rabies epidemiology.[1] Unfortunately, this recommendation for a case-by-case risk as-

sessment coupled with concerns for public safety, a fear of liability, and the lack of published clinical data regarding response to rabies vaccination in dogs and cats with an out-of-date rabies vaccination status commonly leads to conservative handling of these animals. Most often, this means that public health officials consider these animals to be unvaccinated, resulting in either euthanasia or a 6-month quarantine.

The present study was designed to provide greater insight into the appropriate handling of dogs and cats with out-of-date rabies vaccination status that have been exposed to rabid animals. Specifically, the purpose of the study reported here was to compare anamnestic antibody responses of dogs and cats with current versus out-of-date rabies vaccination status.

Materials and Methods

Sample acquisition—The first phase of the study involved serum samples from 10 dogs and 2 cats, from 8 states, that had been exposed to rabies and for which the attending veterinarian or owner had contacted the Rabies Diagnostic Laboratory at Kansas State University between March 2010 and June 2012 for help in assessing the immune state of the animal. The remainder of the study involved serum samples from an additional 64 dogs and 31 cats that had been exposed to rabies and brought to a veterinarian for proactive serologic monitoring or that had not been exposed to rabies and had been brought to a veterinarian for booster rabies vaccination. In total, serum samples from 74 dogs and 33 cats from 13 states collected over a period of 3.75 years were included. The study protocol was approved by the Kansas State University Institutional Animal Care and Use Committee (protocol No. 3193).

For each animal included in the study, a 2-mL serum sample was obtained at the time of initial evaluation (day 0) and then again 5 to 15 days later. On day 0, a rabies vaccine of the attending veterinarian's choice was administered to the animal according to label recommendations. Serum samples were shipped fresh to the Rabies Diagnostic Laboratory and analyzed for antirabies antibody titer by means of a rapid fluorescent focus inhibition test.

Classification of rabies vaccination status—All dogs and cats included in the study were classified as having a current or out-of-date rabies vaccination status. Rabies vaccination status was classified as current if the animal had received initial rabies vaccination and the initial (ie, day 0) serum sample was obtained < 1 year after the initial vaccination or if the animal had received both an initial rabies vaccination and a rabies booster vaccination and the initial (day 0) serum sample was obtained < 3 years after the last vaccination. Otherwise, rabies vaccination status was classified as out of date.

A cutoff of 3 years since the last vaccination was used regardless of whether the last vaccine administered had been licensed for a 1-year or 3-year duration, because the antigenic mass, carrier, adjuvant, and other characteristics of 1-year and 3-year vaccines from 2 companies[2,a] were reportedly identical. One animal that received a 1-year vaccine was excluded from the data analysis because the company[b] that manufactured the vaccine would neither confirm nor deny that their 1-year and 3-year formulations were identical.

Rapid fluorescent focus inhibition test—The rapid fluorescent focus inhibition test,[3] a serum neutralization test, was used to determine the titer of rabies neutralizing antibodies in all serum samples. Briefly, rabies virus was mixed with serial dilutions of each serum sample, and the resulting mixture was incubated at 37°C for 90 minutes. Baby hamster kidney cells suspended in Eagle minimum essential medium with 10% fetal bovine serum were then added, and the mixture was incubated for 20 to 24 hours at 37°C. Following fixation with 80% acetone, a conjugate of antirabies antibody labeled with fluorescein isothiocyanate was added to the cells. After washing, cells were counted by means of fluorescent microscopy to determine the ratio of infected to noninfected cells at each dilution. Results were compared with results for a standard control sample containing a known neutralizing antibody concentration to determine the titer for each test sample.

End point dilution was not used to determine the specific antibody titer for samples that resulted in complete neutralization of the virus at the highest serum dilution used. However, the maximum possible titer varied between test runs depending on the control sample's ability to neutralize the challenge virus. Standard operating procedures for the test method defined a priori an acceptable range of titers for the control sample, with testing repeated if the titer for the control sample was outside the acceptable range. Because the lowest titer for control samples used in the present study was 12 IU/mL, for calculation purposes, we reported results for test samples > 12 IU/mL as 12 IU/mL. In the statistical analysis, all titers reported as ≥ 12 IU/mL were treated as right censored. For comparison, a rabies neutralizing antibody titer ≥ 0.5 IU/mL is considered by the World Health Organization to be an adequate vaccine response for dogs and cats traveling to rabies-free areas.[4]

Data analysis—Rabies neutralizing antibody titers following booster vaccination (ie, days 5 to 15) were compared between dogs with current versus out-of-date vaccination statuses by modeling the proportions of animals with titers exceeding various given values (sometimes referred to as a reverse cumulative distribution). This approach was selected to account for the right censoring of titers for some animals. A proportional hazards model[c] was used to compare distributions of titers between the 2 groups (current vaccination status versus out-of-date vaccination status), with current vaccination status as the reference. In essence, the proportional hazards ratio represented the comparative ability of the 2 groups to reach a particular titer after booster vaccination on day 0. If the ratio was equal to 1, the 2 groups were considered identical. If the ratio was > 1, then the response to booster vaccination in animals with an out-of-date vaccination status was considered to be not as robust as the response in animals with a current vaccination status. Conversely, if the ratio was < 1, the response to booster vaccination in animals with an out-of-date vaccination status was considered superior to the response in animals with a

current vaccination status. For purposes of the present study, we assumed the response to booster vaccination in animals with an out-of-date vaccination status was not clinically worse than the response in animals with a current vaccination status if the hazard ratio was < 1.25. On the basis of an analysis of data from Mansfield et al,[5] this choice of noninferiority margin was determined to be conservative. Formally, in the hypothesis test of noninferiority, the null hypothesis was that the ratio was ≥ 1.25 (ie, out-of-date vaccination status was inferior to current vaccination status), and the alternative hypothesis was that the ratio was < 1.25 (ie, out-of-date vaccination status was noninferior to current vaccination status). Diagnostic graphs indicated the proportional hazard model was appropriate for these data.

Results

Rabies neutralizing antibody titers for the 10 dogs and 2 cats in the first phase of the study were summarized (**Table 1**). For all 12 animals, antibody titers 5 to 15 days after booster vaccination were > 0.5 IU/

Table 1—Rabies neutralizing antibody titers immediately prior to (baseline) and 5 to 15 days after booster vaccination in 10 dogs and 2 cats that had been exposed to an animal confirmed or suspected to be rabid.

Species	Exposure description	> 1 vaccine dose previously	Label duration of last vaccine (y)	Time since last vaccination (mo)	Rabies vaccination status	Baseline titer (IU/mL)	Titer after booster vaccination (IU/mL)
Dog*	Contact with skunk	Yes	3	39.0	OOD	9.7	12
Dog	Exposed to rabid skunk	Yes	UK	9.0	C	0	12
Dog*	Raccoon bite	Yes	3	41.4	OOD	12	12
Dog*	Raccoon bite	Yes	1	18.1	C	0.7	3.4
Dog*	Exposed to rabid skunk	No	1	36.0	OOD	0.6	12
Dog	Exposed to rabid skunk	Yes	3	15.6	C	12	12
Dog*	Exposed to rabid skunk	No	1	15.6	OOD	0.2	12
Dog*	Exposed to rabid skunk	No	1	15.4	OOD	0.6	12
Dog*	Raccoon bite	Yes	1	30.5	C	1.8	12
Dog	Exposed to rabid skunk	Yes	3	10.7	C	3.1	12
Cat*	Raccoon bite	Yes	3	38.7	OOD	0.3	12
Cat*	Exposed to bat	Yes	3	44.9	OOD	12	12

*Quarantined for 6 months after rabies exposure; no animals developed signs of rabies-associated disease during quarantine, and all 12 animals survived.

C = Current. OOD = Out of date. UK = Unknown.

Rabies vaccination status was classified as current if the animal had received an initial rabies vaccination and the initial serum sample was obtained < 1 year after the initial vaccination or if the animal had received both an initial rabies vaccination and a rabies booster vaccination 1 year later and the baseline serum sample was obtained < 3 years after the last vaccination. Otherwise, rabies vaccination status was classified as out of date. A cutoff of 3 years since the last vaccination was used regardless of whether the last vaccine administered had been licensed for a 1-year or 3-year duration, because formulations of the 1-year and 3-year vaccines were confirmed by the manufacturer to be identical.

Table 2—Rabies neutralizing antibody titers immediately before (baseline) and 5 to 15 days after booster vaccination in 74 dogs and 33 cats classified as having a current or out-of-date rabies vaccination status.

Species and vaccination status	Baseline titer (IU/mL)*	Titer after booster vaccination (IU/mL)*	Median increase (IU/mL)	Median fold rise
Dog				
Current (n = 55)	2.6 (0–12)	11.1 (0.5–12)	3.1	0
Out of date (n = 19)	2.0 (0–12)	12.0 (0.5–12)	8.1	2
Cat				
Current (n = 7)	2.4 (0.1–12)	12.0 (2.6–12)	9.4	2
Out of date (n = 26)	6.3 (0.3–12)	12.0 (2.9–12)	2.4	0

*Data are given as median (range).
See Table 1 for remainder of key.

Table 3—Number (percentage) of dogs and cats in Table 2 with rabies neutralizing antibody titers 5 to 15 days after booster vaccination that equaled or exceeded various benchmarks above 0.5 IU/mL.

	Titer (IU/mL)					
Species and vaccination status	0.5	1.0	2.0	4.0	8.0	12.0
Dog						
Current (n = 55)	55 (100)	53 (96)	50 (90)	40 (72)	34 (61)	26 (47)
Out of date (n = 19)	19 (100)	18 (94)	18 (94)	16 (84)	13 (68)	13 (68)
Cat						
Current (n = 7)	7 (100)	7 (100)	7 (100)	6 (85)	6 (85)	6 (85)
Out of date (n = 26)	26 (100)	26 (100)	26 (100)	23 (88)	23 (88)	21 (80)

Data are given as number (%).
See Table 1 for remainder of key.

mL. Five of the animals were classified as having a current vaccination status, and 7 were classified as having an out-of-date vaccination status. All 7 animals with an out-of-date vaccination status and 2 animals with a current vaccination status were quarantined for 6 months, during which time no rabies-associated clinical disease was reported. All 12 animals survived following rabies exposure. The 2 animals with current vaccination status that were quarantined had been exposed > 1 year (but < 3 years) after receiving a rabies vaccine labeled for 1-year duration. However, the manufacturer confirmed that the 1-year and 3-year formulations of this product were identical; therefore, for purposes of the present study, both animals were classified as having a current vaccination status.

Table 4—Rabies neutralizing antibody titers immediately before (baseline) and 5 to 8 days after booster vaccination in 14 dogs and 2 cats with a titer < 0.5 IU/mL prior to booster vaccination.

Species and vaccination status	Baseline titer (IU/mL)	Time between samples (d)	Titer after booster vaccination (IU/mL)
Dog			
Out of date	0.2	8	12
	0.2	7	12
	0	5	12
	0.4	7	2.4
	0	8	0.5
Current	0	7	12
	0.4	7	4.4
	0.3	5	11.1
	0.4	7	0.5
	0.1	7	1.3
	0.1	7	6.1
	0	7	2
	0.1	5	4
	0.3	6	0.5
Cat			
Out of date	0.3	5	12
Current	0.1	6	12

Median titer after booster vaccination was 12 IU/mL for dogs with an out-of-date vaccination status and 4 IU/mL for dogs with a current vaccination status.

See Table 2 for key.

Rabies neutralizing antibody titers before (day 0) and after (day 5 to 15) booster vaccination for all 74 dogs and 33 cats included in the study were summarized, along with median increase in titer and median fold increase (**Table 2**). Dogs with out-of-date vaccination status had a higher median increase in titer, higher median fold increase in titer, and higher median titer following booster vaccination, compared with dogs with current vaccination status. However, statistical analyses were not performed on these parameters.

The percentages of dogs and cats in each vaccine category with titers that equaled or exceeded various benchmarks above 0.5 IU/mL were summarized (**Table 3**). All animals in the study had a titer ≥ 0.5 IU/mL 5 to 15 days after booster vaccination. This included the 14 dogs (9 with current vaccination status and 5 with out-of-date vaccination status) and 2 cats (1 with current vaccination status and 1 with out-of-date vaccination status) that had titers < 0.5 IU/mL prior to booster vaccination (day 0; **Table 4**). Median increase in titer for dogs (**Table 5**) and cats (**Table 6**) with an out-of-date vaccination status was higher for those that had previously received only a single dose of vaccine, compared with those that had previously received ≥ 2 doses of vaccine. Again, however, no statistical analyses were performed on this parameter.

Reverse cumulative distributions of titers 5 to 15 days after booster vaccination were calculated for dogs with current vaccination status and dogs with out-of-date vaccination status (**Figure 1**). The hypothesis test for noninferiority was significant ($P = 0.029$), with out-of-date dogs shown to be noninferior to current dogs, and the proportional hazards ratio (with current vaccination status as the reference) was 0.53 (95% confidence interval, 0.20 to 1.12). Because the upper limit of the 95% confidence interval was < 1.25, the response to booster vaccination in dogs with an out-of-date vaccination status was considered to be noninferior to the response in dogs with a current vaccination status.

Table 5—Rabies neutralizing antibody titers immediately before (baseline) and 5 to 15 days after booster vaccination for 15 dogs with an out-of-date vaccination status classified on the basis of number of rabies vaccinations received previously.

No. of vaccine doses received previously	Baseline titer (IU/mL)	Time between samples (d)	Titer after booster vaccination (IU/mL)	Time overdue for vaccination (mo)	Increase in titer (IU/mL)
≥ 2	0.6	6	2.8	0.2	2.2
	0.4	7	2.4	0.3	2
	9.7	15	12	3	2.3
	4	7	5.9	4.8	1.9
	12	6	12	7.5	0
	3.9	7	12	10.6	8.1
	2.9	7	7.8	14.9	4.9
	0	8	0.5	19.7	0.5
	2	7	12	22.8	10
1	3.4	7	12	0.3	8.6
	0.6	10	12	3.4	11.4
	0.2	8	12	3.6	11.8
	0	5	12	5.9	12
	0.6	7	12	24	11.4
	0.2	7	12	36.1	11.8

Median increase in titer was 2.2 IU/mL for dogs that had previously received ≥ 2 doses of vaccine and was 11.6 IU/mL for dogs that had previously received only a single dose of vaccine.

Table 6—Rabies neutralizing antibody titers immediately before (baseline) and 5 to 15 days after booster vaccination for 24 cats with an out-of-date vaccination status classified on the basis of number of rabies vaccinations received previously.

No. of vaccine doses received previously	Baseline titer (IU/mL)	Time between samples (d)	Titer after booster vaccination (IU/mL)	Time overdue for vaccination (mo)	Increase in titer (IU/mL)
≥ 2	12	8	12	0.1	0
	6.1	7	11.3	0.1	5.2
	12	8	12	0.1	0
	3.4	7	12	0.2	8.6
	12	7	12	0.2	0
	5.4	6	12	0.9	6.6
	6.4	7	9	1.1	2.6
	12	7	12	2.3	0
	12	7	12	2.5	0
	0.3	5	12	2.7	11.7
	3.4	7	3.7	2.9	0.3
	12	7	12	2.9	0
	8.9	7	12	3.2	3.1
	12	7	12	3.7	0
	12	7	12	5.6	0
	2.5	7	12	5.6	9.5
	2.4	7	12	8.4	9.6
	12	8	12	8.9	0
	2.4	6	12	15.9	9.6
	3	6	3.3	34.6	0.3
	0.6	7	2.9	46.1	2.3
1	0.6	5	12	4.9	11.4
	9.6	6	12	21.2	2.4
	2.7	6	12	38.5	9.3

Median increase in titer was 0.3 IU/mL for cats that had previously received ≥ 2 doses of vaccine and was 9.3 IU/mL for cats that had previously received only a single dose of vaccine.

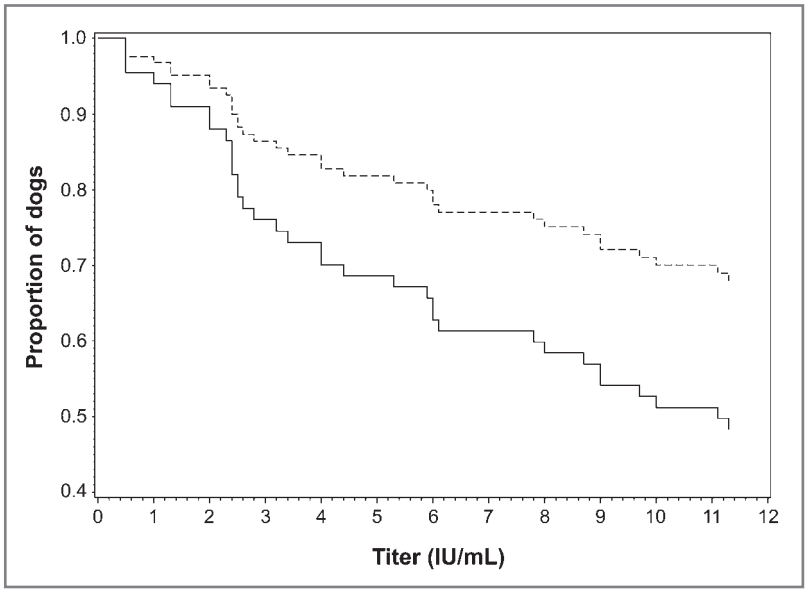

Figure 1—Reverse cumulative distributions of rabies neutralizing antibody titers 5 to 15 days after booster vaccination in dogs with a current (n = 55; solid line) or out-of-date (19; dashed line) rabies vaccination status. The reverse cumulative proportion represents, for any given titer, the proportion of dogs with a titer equal to or greater than that titer. The hypothesis test for noninferiority was significant (P = 0.029), with out-of-date dogs shown to be noninferior to current dogs.

Because of the small number of cats in the study and the fact that most cats, regardless of whether they had a current (6/7) or out-of-date (21/26) vaccination status, had a titer ≥ 12 IU/mL 5 to 15 days after booster vaccination, proportional hazards analysis could not be used to analyze the response to booster vaccination in cats with current versus out-of-date vaccination status.

Discussion

Results of the present study indicated that the anamnestic responses of dogs and cats with an out-of-date rabies vaccination status were similar to the responses in animals with a current rabies vaccination status. Specifically, titers 5 to 15 days after booster vaccination in dogs with an out-of-date vaccination status were shown to be noninferior to titers in dogs with a current vaccination status. Also, dogs with an out-of-date vaccination status had a higher median increase in titer, higher median fold increase in titer, and higher median titer following booster vaccination, compared with dogs with current vaccination status; however, statistical analyses were not performed to compare these parameters between groups.

The noninferiority margin of 1.25 used in the present study was selected because it has commonly been used in other studies as a conservative margin for hazard ratio analyses. On the basis of an analysis of results reported by Mansfield et al[5] for dogs and cats vaccinated with 3 rabies vaccines, we determined that a margin of 1.25 corresponded to a difference in titer between animals with an out-of-date vaccination status and naïve

animals that was at least 88% of the difference in titer between animals with current vaccination status and naïve animals. Ng[6] recommends that the noninferiority margin preserve at least 80% of the advantage the active treatment holds over placebo. Therefore, we believe that the noninferiority margin of 1.25 used in the present study was conservative.

In the present study, we used 3 methods to compare anamnestic responses to rabies vaccination in dogs and cats with current versus out-of-date vaccination status: fold rise in titer, absolute increase in titer, and absolute titer following booster vaccination. Evaluating the fold rise in titer gives an advantage to animals with a low starting titer. Therefore, because many animals in the present study with an out-of-date vaccination status had lower starting titers, we were not surprised that they had a higher fold rise in titer, compared with animals with a current vaccination status.

Although absolute increase in titer following booster vaccination provides some information on the anamnestic response to vaccination, it may not represent a true measure of protection. Assuming that neutralizing antibody titer is a measure of protection,[7,8] then a rabies neutralizing antibody titer of 5.5 IU/mL should afford better protection than a titer of 0.5 IU/mL. However, when evaluating absolute increase in titer, an increase from 0.1 to 0.5 IU/mL is the same as an increase from 5.1 to 5.5 IU/mL.

In contrast to fold rise or absolute increase in titer, absolute titer following booster vaccination should provide a good indication of the level of protection achieved. In the present study, we found that the response for dogs with an out-of-date vaccination status was noninferior to the response for dogs with a current vaccination status ($P = 0.029$). Unfortunately, we could not perform the same analyses for cats in the present study because of the low number of cats enrolled and the fact that most cats, regardless of whether they had a current or out-of-date vaccination status, achieved the maximum titer (≥ 12 IU/mL) after booster vaccination. Given these high titers, even if a difference had been found between groups, it likely would not have been clinically meaningful.

Results of the present study may help clarify recommendations in the Compendium of Animal Rabies Prevention and Control[1] for postexposure management of dogs and cats overdue for a booster vaccination that are exposed to an animal confirmed or suspected to be rabid. Currently, the guidelines recommend that such animals be evaluated on a case-by-case basis on the basis of the following 5 criteria: severity of the exposure, time since the last rabies vaccination, number of rabies vaccinations received previously, current health status of the animal, and local rabies epidemiology.

Importantly, the guidelines do not recommend altering postexposure management for dogs and cats with a current vaccination status on the basis of severity of the exposure. Considering that dogs and cats in the present study responded to rabies booster vaccination in a similar manner regardless of whether they had a current or out-of-date vaccination status, we believe that postexposure management should be the same for dogs and cats with current versus out-of-date vaccination status, regardless of the severity of exposure.

With respect to time since the last rabies vaccination, we did not identify a difference in anamnestic response between animals with current versus out-of-date vaccination status. In fact, dogs with an out-of-date vaccination status generally had higher responses than did dogs with a current vaccination status.

Similarly, with respect to the number of rabies vaccinations received previously, we did not find a substantial difference in anamnestic responses between dogs and cats that had previously received only a single dose of vaccine and those that had received ≥ 2 doses previously. However, age could have been a confounding factor, given that animals vaccinated only once had a median age of 3 years, whereas animals vaccinated multiple times had a median age of 6 years, and immunosenescence in dogs and cats is well documented.[9]

We did not evaluate the effect of health status on anamnestic responses in the present study, and all animals were generally healthy. However, we recommend that, regardless of vaccination status, public health officers should be cautious when managing immunocompromised dogs and cats that have been exposed to rabid animals.

Finally, in suggesting that public health officials take local rabies epidemiology into consideration in the postexposure management of dogs and cats with an out-of-date vaccination status that have been exposed to an animal suspected to be rabid, the compendium acknowledges that although rabies is endemic in the United States, the incidence varies widely from one location to the next. Thus, without confirmatory testing, the risk that a dog bitten by a wild raccoon has truly been exposed to rabies is much lower in, for example, Illinois than in Alabama. Nevertheless, given that the response to rabies booster vaccination in the present study was similar regardless of rabies vaccination status, we believe that postexposure management should be the same.

In conclusion, results of the present study indicated that the anamnestic response to rabies booster vaccination in dogs and cats with an out-of-date vaccination status is similar to the response for dogs and cat with a current vaccination status. Thus, we believe that postexposure management of any previously vaccinated dog or cat exposed to a confirmed or suspected rabid animal should be the same, regardless of vaccination status. Specifically, we believe that appropriate postexposure management for dogs and cats with an out-of-date vaccination status is immediate booster vaccination followed by observation for 45 days, rather than euthanasia or quarantine for 6 months. If additional reassurance is needed, titers could be measured prior to and again 5 to 7 days after booster vaccination to determine whether an anamnestic response has occurred.

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From this month's *AJVR*

Associations between early radiographic and computed tomographic measures and canine hip joint osteoarthritis at maturity

Anemone A. Andronescu et al

Objective—To evaluate associations of measures assessed by radiography, 2-D CT, and 3-D CT of the hip joints of immature dogs with osteoarthritis in the same joints at maturity.

Animals—46 hound-type dogs from a colony predisposed to osteoarthritis.

Procedures—Images of hip joints (1/dog) were obtained at 16, 32, and 104 weeks of age. Radiographic measures included Norberg angle, distraction index, and osteoarthritis score. Two-dimensional CT measures included acetabular index; percentage of femoral head coverage; and center edge, horizontal toit externe, acetabular anteversion, and ventral, dorsal, and horizontal acetabular sector angles. Three-dimensional CT measures were femoral head and neck volume, femoral neck angle, and femoral head and neck radius. Differences among measures at 16 and 32 weeks in dogs with different osteoarthritis scores at later time points, relationships among variables at each time point, and relationships of single and combined measures with the presence of osteoarthritis at 104 weeks were evaluated.

Results—The 16- and 32-week distraction index, center edge angle, dorsal acetabular sector angle, horizontal acetabular sector angle, percentage of femoral head coverage, acetabular index, and Norberg angle and the 32-week femoral neck angle varied significantly with osteoarthritis severity at 104 weeks. Presence of osteoarthritis in mature dogs was most strongly associated with 16-week combined measures of distraction index and center edge angle and 32-week combined measures of dorsal acetabular sector angle and Norberg angle.

Conclusions and Clinical Relevance—Changes in hip joint morphology associated with radiographic signs of osteoarthritis were detectable as early as 16 weeks of age and varied with osteoarthritis severity in adult dogs. The use of combined hip joint measures may improve early identification of dogs predisposed to hip joint osteoarthritis. (*Am J Vet Res* 2015;76:19–27)

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See the midmonth issues of *JAVMA* for the expanded table of contents for the *AJVR* or log on to avmajournals.avma.org for access to all the abstracts.

Compendium of Animal Rabies Prevention and Control, 2016

National Association of State Public Health Veterinarians Compendium of Animal Rabies Prevention and Control Committee

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Endorsed by the AVMA, American Public Health Association, Association of Public Health Laboratories, Council of State and Territorial Epidemiologists, and National Animal Care and Control Association.

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Rabies is a fatal viral zoonosis and serious public health problem.[1] All mammals are believed to be susceptible to the disease, and for the purposes of this document, use of the term animal refers to mammals. The disease is an acute, progressive encephalitis caused by viruses in the genus *Lyssavirus*.[2] Rabies virus is the most important lyssavirus globally. In the United States, multiple rabies virus variants are maintained in wild mammalian reservoir populations such as raccoons, skunks, foxes, and bats. Although the United States has been declared free from transmission of canine rabies virus variants, there is always a risk of reintroduction of these variants.[3-7]

The rabies virus is usually transmitted from animal to animal through bites. The incubation period is highly variable. In domestic animals, it is generally 3 to 12 weeks, but can range from several days to months, rarely exceeding 6 months.[8] Rabies is communicable during the period of salivary shedding of rabies virus. Experimental and historic evidence documents that dogs, cats, and ferrets shed the virus for a few days prior to the onset of clinical signs and during illness. Clinical signs of rabies are variable and include inappetance, dysphagia, cranial nerve deficits, abnormal behavior, ataxia, paralysis, altered vocalization, and seizures. Progression to death is rapid. There are currently no known effective rabies antiviral drugs.

The recommendations in this compendium serve as a basis for animal rabies prevention and control programs throughout the United States and facilitate standardization of procedures among jurisdictions, thereby contributing to an effective national rabies control program. The compendium is reviewed and revised as necessary, with the most current version replacing all previous versions. These recommendations do not supersede state and local laws or requirements. Principles of rabies prevention and control are detailed in Part I, and recommendations for parenteral vaccination procedures are presented in Part II. All animal rabies vaccines licensed by the USDA and marketed in the United States are listed and described in Appendix 1, and contact information for manufacturers of these vaccines is provided in Appendix 2.

Modifications of note in this updated version of the compendium, compared with the previous version,[9] include clarification of language, explicit en-

couragement of an interdisciplinary approach to rabies control, a recommendation to collect and report at the national level additional data elements on rabid domestic animals, changes to the recommended management of dogs and cats exposed to rabies that are either unvaccinated or overdue for booster vaccination, reduction of the recommended 6-month quarantine period for certain species, and updates to the list of marketed animal rabies vaccines.

Part I. Rabies Prevention and Control

A. Principles of rabies prevention and control

1. Case definition. An animal is determined to be rabid after diagnosis by a qualified laboratory as specified (*see* Part I.A. 10. Rabies diagnosis).The national case definition for animal rabies requires laboratory confirmation on the basis of either a positive result for the direct fluorescent antibody test (preferably performed on CNS tissue) or isolation of rabies virus in cell culture or a laboratory animal.[10]

2. Rabies virus exposure. Rabies is transmitted when the virus is introduced into bite wounds, into open cuts in skin, or onto mucous membranes from saliva or other potentially infectious material such as neural tissue.[11] Questions regarding possible exposures should be directed promptly to state or local public health authorities.

3. Interdisciplinary approach. Clear and consistent communication and coordination among relevant animal and human health partners across and within all jurisdictions (including international, national, state, and local) is necessary to most effectively prevent and control rabies. As is the case for the prevention of many zoonotic and emerging infections, rabies prevention requires the cooperation of animal control, law enforcement, and natural resource personnel; veterinarians; diagnosticians; public health professionals; physicians; animal and pet owners; and others. An integrated program must include provisions to promptly respond to situations; humanely restrain, capture, and euthanize animals; administer quarantine, confinement, and observation periods; and prepare samples for submission to a testing laboratory.

4. Awareness and education. Essential components of rabies prevention and control include ongoing public education, responsible pet ownership, routine veterinary care and vaccination, and professional continuing education. Most animal and human exposures to rabies can be prevented by raising awareness concerning rabies transmission routes, the importance of avoiding contact with wildlife, and the need for appropriate veterinary care. Prompt recognition and reporting of possible exposures to medical and veterinary professionals and local public health authorities are critical.

5. Human rabies prevention. Rabies in humans can be prevented by eliminating exposures to rabid animals or by providing exposed persons prompt postexposure prophylaxis consisting of local treatment of wounds in combination with appropriate administration of human rabies immune globulin and vaccine. An exposure assessment should occur before rabies postexposure prophylaxis is initiated and should include discussion between medical providers and public health officials. The rationale for recommending preexposure prophylaxis and details of both preexposure and postexposure prophylaxis administration can be found in the current recommendations of the Advisory Committee on Immunization Practices.[11,12] These recommendations, along with information concerning the current local and regional epidemiology of animal rabies and the availability of human rabies biologics, are available from state health departments.

6. Domestic animal vaccination. Multiple vaccines are licensed for use in domestic animal species. Vaccines available include inactivated and modified-live virus vectored products, products for IM and SC administration, products with durations of immunity for periods of 1 to 3 years, and products with various minimum ages of vaccination. Recommended vaccination procedures are specified in Part II of this compendium; animal rabies vaccines licensed by the USDA and marketed in the United States are specified in Appendix 1. Local governments should initiate and maintain effective programs to ensure vaccination of all dogs, cats, and ferrets and to remove stray and unwanted animals. Such procedures have reduced laboratory-confirmed cases of rabies among dogs in the United States from 6,949 cases in 1947 to 89 cases in 2013.[3] Because more rabies cases are reported annually involving cats (247 in 2013) than dogs, vaccination of cats should be required.[3] Animal shelters and animal control authorities should establish policies to ensure that adopted animals are vaccinated against rabies.

An important tool to optimize public and animal health and enhance domestic animal rabies control is routine or emergency implementation of low-cost or free clinics for rabies vaccination. To facilitate implementation, jurisdictions should work with veterinary medical licensing boards, veterinary associations, the local veterinary community, animal control officials, and animal welfare organizations.

7. Rabies in vaccinated animals. Rabies is rare in vaccinated animals.[13–15] If rabies is suspected in a vaccinated animal, it should be reported to public health officials, the vaccine manufacturer, and the USDA APHIS Center for Veterinary Biologics

(www.aphis.usda.gov; search for "adverse event reporting"). The laboratory diagnosis should be confirmed and the virus variant characterized by the CDC's rabies reference laboratory. A thorough epidemiologic investigation including documentation of the animal's vaccination history and potential rabies exposures should be conducted.

8. Rabies in wildlife. It is difficult to control rabies among wildlife reservoir species.[16] Vaccination of free-ranging wildlife or point infection control is useful in some situations,[17] but the success of such procedures depends on the circumstances surrounding each rabies outbreak (See Part I. C. Prevention and control methods related to wildlife). Because of the risk of rabies in wild animals (especially raccoons, skunks, coyotes, foxes, and bats), the AVMA, American Public Health Association, Council of State and Territorial Epidemiologists, National Animal Care and Control Association, and National Association of State Public Health Veterinarians strongly recommend the enactment and enforcement of state laws prohibiting the importation, distribution, translocation, and private ownership of wild animals.

9. Rabies surveillance. Laboratory-based rabies surveillance and variant typing are essential components of rabies prevention and control programs. A comprehensive surveillance program should not be limited to testing only those animals that have potentially exposed people or domestic animals to rabies. Accurate and timely information and reporting are necessary to guide decisions regarding postexposure prophylaxis in potentially exposed humans, determine appropriate management of potentially exposed animals, aid in the discovery of emerging variants, describe the epidemiology of the disease, and assess the effectiveness of vaccination programs for domestic animals and wildlife. Every animal submitted for rabies testing should be reported to the CDC to evaluate surveillance trends. Public health authorities should implement electronic laboratory reporting and notification systems.[18] Information reported on every animal submitted for rabies testing should include species, point location, vaccination status, rabies virus variant (if rabid), and human or domestic animal exposures. To enhance the ability to make evidence-based recommendations from national surveillance data, additional data should be collected and reported on all rabid domestic animals. In this regard, essential data elements include age, sex, neuter status, ownership status, quarantine dates (if any), date of onset of any clinical signs, and complete vaccination history. Rabid animals with a history of importation into the United States within the past 60 days are immediately notifiable by state health departments to the CDC; for all indigenous cases, standard notification protocols should be followed.[19]

10. Rabies diagnosis.

a) The direct fluorescent antibody test is the gold standard for rabies diagnosis. The test should be performed in accordance with the established national standardized protocol (www.cdc.gov/rabies/pdf/rabiesdfaspv2.pdf) by a qualified laboratory that has been designated by the local or state health department.[20,21] Animals submitted for rabies testing should be euthanized[22,23] in such a way as to maintain the integrity of the brain so that the laboratory can recognize anatomic structures. Except in the case of very small animals, such as bats, only the head or entire brain (including brainstem) should be submitted to the laboratory. To facilitate prompt laboratory testing, submitted specimens should be stored and shipped under refrigeration without delay. The need to thaw frozen specimens will delay testing. Chemical fixation of tissues should be avoided to prevent significant testing delays and because such fixation might preclude reliable testing. Questions about testing of fixed tissues should be directed to the local rabies laboratory or public health department.

b) Rabies testing should be available outside of normal business hours at the discretion of public health officials to expedite exposure management decisions.[20] When confirmatory testing is needed by state health departments (eg, in the event of inconclusive results, unusual species, or mass exposures), the CDC rabies laboratory can provide additional testing and results within 24 hours of sample receipt.[24]

c) Professional associations such as the Association of Public Health Laboratories should advocate for, distribute, and promote the development of guidelines for routinely assessing testing practices within rabies laboratories to ensure maintenance of quality and safety.

d) A direct rapid immunohistochemical test (referred to as dRIT) is being used by trained field personnel in surveillance programs for specimens not involved in human or domestic animal exposures.[25–28] All positive direct rapid immunohistochemical test results need to be confirmed by means of direct fluorescent antibody testing at a qualified laboratory.

e) Currently, there are no commercially available, USDA-licensed rapid test kits for rabies diagnosis. Unlicensed tests should not be used owing to the following concerns: sensitivity and specificity of these tests are not known, the tests have not been validated against current standard methods, the excretion of virus in the saliva is intermittent and the amount varies over time, any unlicensed test result would

need to be confirmed by validated methods such as direct fluorescent antibody testing on brain tissue, and the interpretation of results from unlicensed tests may place exposed animals and persons at risk.

11. Rabies serology. Some jurisdictions require evidence of vaccination and rabies virus antibodies for animal importation purposes. Rabies virus antibody titers are indicative of a response to vaccine or infection. Titers do not directly correlate with protection because other immunologic factors also play a role in preventing rabies and our abilities to measure and interpret those other factors are not well-developed. Therefore, evidence of circulating rabies virus antibodies in animals should not be used as a substitute for current vaccination in managing rabies exposures or determining the need for booster vaccination.[29–32]

12. Rabies research. Information derived from well-designed studies is essential for the development of evidence-based recommendations. Data are needed in several areas, including viral shedding periods for domestic livestock and lagomorphs, potential shedding of virus in milk, the earliest age at which rabies vaccination is effective, protective effect of maternal antibody, duration of immunity, postexposure prophylaxis protocols for domestic animals, models for treatment of clinical rabies, extralabel vaccine use in domestic animals and wildlife rabies reservoir species, host-pathogen adaptations and dynamics, and the ecology of wildlife rabies reservoir species, especially in relation to the use of oral rabies vaccines.

B. Prevention and control methods in domestic and confined animals

1. Preexposure vaccination and management. Adherence to a regular rabies vaccination schedule is critical to protect animals against recognized and unrecognized rabies exposures. Parenteral animal rabies vaccines should be administered only by or under the direct supervision of a licensed veterinarian on premises. Rabies vaccines may be administered under the supervision of a licensed veterinarian to animals held in animal shelters before release.[33,34] The veterinarian signing a rabies vaccination certificate must ensure that the person who administered the vaccine is identified on the certificate and has been appropriately trained in vaccine storage, handling, and administration and in the management of adverse events. This ensures that a qualified and responsible person can be held accountable for properly vaccinating the animal.

Within 28 days after initial vaccination, a peak rabies virus antibody titer is expected, and the animal can be considered immunized.[31,35–37] Regardless of the age of the animal at initial vaccination, a booster vaccination should be administered 1 year later (*see* Part II and Appendix 1). An animal is currently vaccinated and is considered immunized immediately after any booster vaccination.[38,39]

a) Booster vaccination. Following the initial vaccination, booster vaccinations should be given in a manner consistent with the manufacturer's label. If a previously vaccinated animal is overdue for any booster vaccination, including the first booster vaccination due 1 year after initial vaccination, it should be given a booster vaccination. Immediately after this booster vaccination, the animal is considered currently vaccinated and should be placed on a booster vaccination schedule consistent with the label of the vaccine used. There are no laboratory or epidemiological data to support the annual or biennial administration of 3-year vaccines after completion of the initial vaccine series (ie, the initial vaccination and 1-year booster vaccination).

b) Dogs, cats, and ferrets. All dogs, cats, and ferrets should be vaccinated against rabies and revaccinated in accordance with recommendations in this compendium (Appendix 1).

c) Livestock. All horses should be vaccinated against rabies.[40] Livestock, including species for which licensed vaccines are not available, that have frequent contact with humans (eg, in petting zoos, fairs, and other public exhibitions) should be vaccinated against rabies.[41,42] Consideration should also be given to vaccinating livestock that are particularly valuable.

d) Captive wild animals and wild animal hybrids (the offspring of wild animals crossbred to domestic animals).

(1) Wild animals and wild animal hybrids should not be kept as pets.[43,44] No parenteral rabies vaccines are licensed for use in wild animals or wild animal hybrids.[45]

(2) Animals that are farmed (eg, for food, fur, or fiber) or maintained in exhibits or zoological parks and that are not completely excluded from all contact with rabies vectors can become infected.[46] Moreover, wild animals might be incubating rabies when initially captured. Therefore, wild-caught animals susceptible to rabies should be quarantined for a minimum of 6 months.

(3) Employees who work with animals in exhibits or zoological parks should receive preexposure rabies vaccination. The use of preexposure or postexposure rabies vaccination for handlers who work with animals at such facilities might reduce the need for euthanasia of captive animals that expose handlers. Carnivores and bats should be housed in a manner

that precludes direct contact with the public.[41,42] Consideration may be given to vaccinating animals that are particularly valuable (*see* Part II. D. Vaccination of wildlife and wild animal hybrids).

2. Stray animals. Stray dogs, cats, and ferrets should be removed from the community, and mechanisms should be put in place to facilitate voluntary surrender of animals to prevent abandonment. Local health departments and animal control officials can enforce the removal of strays more effectively if owned animals are required to have identification and be confined or kept on leash. Strays should be impounded for at least 3 business days to determine whether human exposure has occurred and to give owners sufficient time to reclaim animals.

Stray and feral cats serve as a significant source of rabies exposure risk.[47] If communities allow maintenance of feral cat colonies despite this risk, they should safeguard the health of the cats and the communities in which they reside by requiring that cats receive initial rabies vaccinations and appropriately scheduled booster vaccinations.

3. Importation and interstate movement of animals.

a) Areas with dog-to-dog rabies transmission. Canine rabies virus variants have been eliminated from the United States[3,7]; however, rabid dogs and a rabid cat have been introduced into the continental United States from areas with dog-to-dog rabies transmission.[4–6,48,49] The movement of dogs for the purposes of adoption or sale from areas with dog-to-dog rabies transmission increases the risk of introducing canine-transmitted rabies to areas where it does not currently exist, and this practice should be prohibited.

b) International importation. Current federal regulations are insufficient to prevent the introduction of rabid animals into the United States and must be strengthened and appropriately enforced.[4–6,48,49] The CDC and USDA APHIS have regulatory authority over the importation of dogs and cats into the United States.[6] Importers of dogs must comply with rabies vaccination requirements.[50,51] These regulations require that dogs from rabies-endemic countries be currently vaccinated against rabies prior to importation. The appropriate health official of the state of destination should be notified by the appropriate federal authorities within 72 hours of the arrival of any unvaccinated imported dog required to be placed in confinement (as defined by the CDC[52]) under these regulations. Failure of the owner to comply with these confinement requirements should be promptly reported to the CDC's Division of Global Migration and Quarantine (CDCAnimalImports@cdc.gov).

All imported dogs and cats are also subject to state and local laws governing rabies and should be currently vaccinated against rabies with USDA-licensed products in accordance with this compendium. Failure of the owner to comply with state or local requirements should be referred to the appropriate state or local official.

c) Interstate movement (including commonwealths and territories). Before interstate movement occurs, dogs, cats, ferrets, and horses should be currently vaccinated against rabies in accordance with this compendium. Animals in transit should be accompanied by a current, valid rabies vaccination certificate such as Form 51 from the National Association of State Public Health Veterinarians.[53] When an interstate health certificate or certificate of veterinary inspection is required, it should contain the same rabies vaccination information as Form 51.

4. Adjunct procedures. Methods or procedures that enhance rabies control include the following[54]:

a) Identification. Dogs, cats, and ferrets should be identified (eg, metal or plastic tags or microchips) to allow for verification of rabies vaccination status.

b) Licensure. Registration or licensure of all dogs, cats, and ferrets is an integral component of an effective rabies control program. A fee is frequently charged for such licensure, and revenues collected are used to maintain rabies or animal control activities. Evidence of current vaccination should be an essential prerequisite to licensure.

c) Canvassing. House-to-house canvassing by animal control officials facilitates enforcement of vaccination and licensure requirements.

d) Citations. Citations are legal summonses issued to owners for violations, including the failure to vaccinate or license their animals. The authority for officers to issue citations should be an integral part of animal control programs.

e) Animal control. All local jurisdictions should incorporate training and continuing education of personnel regarding stray-animal control, leash laws, animal bite prevention, and rabies prevention and control into their programs.

f) Public education. All local jurisdictions should incorporate education covering responsible pet ownership, bite prevention, and appropriate veterinary care into their programs.

5. Postexposure management. This section refers to any animal exposed (*see* Part I. A. 2. Rabies virus exposure) to a confirmed or suspected rabid animal. Wild mammalian carnivores, skunks, and bats that are not available or suitable for testing should be regarded as rabid. The rationale for

observation, confinement, or strict quarantine periods of exposed animals despite previous vaccination is based in part on the potential for overwhelming viral challenge, incomplete vaccine efficacy, improper vaccine administration, variable host immunocompetence, and immune-mediated death (ie, early death phenomenon).[13,55–57]

a) Dogs, cats, and ferrets. Any illness in an exposed animal should be reported immediately to the local health department. If signs suggestive of rabies develop (eg, paralysis or seizures), the animal should be euthanized, and the head or entire brain (including brainstem) should be submitted for testing (*see* Part I.A. 10. Rabies diagnosis).

(1) Dogs, cats, and ferrets that are current on rabies vaccination should immediately receive veterinary medical care for assessment, wound cleansing, and booster vaccination. The animal should be kept under the owner's control and observed for 45 days.

(2) Dogs, cats, and ferrets that have never been vaccinated should be euthanized immediately. There are currently no USDA-licensed biologics for postexposure prophylaxis of previously unvaccinated domestic animals, and there is evidence that the use of vaccine alone will not reliably prevent the disease in these animals.[58] If the owner is unwilling to have the animal euthanized, the animal should be placed in strict quarantine for 4 (dogs and cats) or 6 (ferrets) months. Strict quarantine in this context refers to confinement in an enclosure that precludes direct contact with people and other animals. A rabies vaccine should be administered at the time of entry into quarantine to bring the animal up to current rabies vaccination status. Administration of vaccine should be done as soon as possible. It is recommended that the period from exposure to vaccination not exceed 96 hours.[59,60] If vaccination is delayed, public health officials may consider increasing the quarantine period for dogs and cats from 4 to 6 months, taking into consideration factors such as the severity of exposure, the length of delay in vaccination, current health status, and local rabies epidemiology.

(3) Dogs and cats that are overdue for a booster vaccination and that have appropriate documentation of having received a USDA-licensed rabies vaccine at least once previously should immediately receive veterinary medical care for assessment, wound cleansing, and booster vaccination. The animal should be kept under the owner's control and observed for 45 days.[39] If booster vaccination is delayed, public health officials may consider increasing the observation period for the animal, taking into consideration factors such as the severity of exposure, the length of delay in booster vaccination, current health status, and local rabies epidemiology.

(4) Dogs and cats that are overdue for a booster vaccination and without appropriate documentation of having received a USDA-licensed rabies vaccine at least once previously should immediately receive veterinary medical care for assessment, wound cleansing, and consultation with local public health authorities.

(a) The animal can be treated as unvaccinated, immediately given a booster vaccination, and placed in strict quarantine (*see* Part I. B. 5. a) (2)).

(b) Alternatively, prior to booster vaccination, the attending veterinarian may request guidance from the local public health authorities in the possible use of prospective serologic monitoring. Such monitoring would entail collecting paired blood samples to document prior vaccination by providing evidence of an anamnestic response to booster vaccination. If an adequate anamnestic response is documented, the animal can be considered to be overdue for booster vaccination (*see* Part I. B. 5. a) (3)) and observed for 45 days.[39] If there is inadequate evidence of an anamnestic response, the animal is considered to have never been vaccinated and should be placed in strict quarantine (*see* Part I. B. 5. a) (2)).

(5) Ferrets that are overdue for a booster vaccination should be evaluated on a case-by-case basis, taking into consideration factors such as the severity of exposure, time elapsed since last vaccination, number of previous vaccinations, current health status, and local rabies epidemiology, to determine need for euthanasia or immediate booster vaccination followed by observation or strict quarantine.

b) Livestock. All species of livestock are susceptible to rabies; cattle and horses are the most frequently reported infected species.[3] Any illness in an exposed animal should be reported immediately to the local health department and animal health officials. If signs suggestive of rabies develop, the animal should be euthanized, and the head or entire brain

(including brainstem) should be submitted for testing (*see* Part I.A. 10. Rabies diagnosis).

(1) Livestock that have never been vaccinated should be euthanized immediately. Animals that are not euthanized should be confined and observed on a case-by-case basis for 6 months.

(2) Livestock that are current on rabies vaccination with a USDA-licensed vaccine approved for that species should be given a booster vaccination immediately and observed for 45 days.

(3) Livestock overdue for a booster vaccination should be evaluated on a case-by-case basis, taking into consideration factors such as severity of exposure, time elapsed since last vaccination, number of previous vaccinations, current health status, and local rabies epidemiology, to determine need for euthanasia or immediate booster vaccination followed by observation or strict quarantine.

(4) Multiple rabid animals in a herd and herbivore-to-herbivore transmission of rabies are uncommon.[61] Therefore, restricting the rest of the herd if a single animal has been exposed to or infected with rabies is usually not necessary.

(5) Rabies virus is widely distributed in the tissues of rabid animals.[62–64] Tissues and products from a rabid animal should not be used for human or animal consumption[65,66] or transplantation.[67] However, pasteurization and cooking will inactivate rabies virus.[68] Therefore, inadvertently drinking pasteurized milk or eating thoroughly cooked animal products does not constitute a rabies exposure.

(6) Handling and consumption of uncooked tissues from exposed animals might carry a risk for rabies transmission.[69] Persons handling exposed animals, carcasses, and tissues should use appropriate barrier precautions.[69,70] State and local public health authorities, state meat inspectors, and the USDA Food Safety and Inspection Service should be notified if exposures occur in animals intended for commercial use. Animals should not be presented for slaughter in a USDA-regulated establishment if such animals originate from a quarantine area and have not been approved for release by the proper authority. If an exposed animal is to be custom slaughtered or home slaughtered for consumption, it should be slaughtered immediately after exposure, and all tissues should be cooked thoroughly.

c) Other animals. Other mammals exposed to a rabid animal should be euthanized immediately. Animals maintained in USDA-licensed research facilities or accredited zoological parks should be evaluated on a case-by-case basis in consultation with public health authorities. Management options may include quarantine, observation, or administration of rabies biologics.

6. Management of animals that bite humans.

a) Dogs, cats, and ferrets. Rabies virus is excreted in the saliva of infected dogs, cats, and ferrets during illness and for only a few days before the onset of clinical signs or death.[71–73] Regardless of rabies vaccination status, a healthy dog, cat, or ferret that exposes a person should be confined and observed daily for 10 days from the time of the exposure[74]; administration of rabies vaccine to the animal is not recommended during the observation period to avoid confusing signs of rabies with rare adverse vaccine reactions.[15] Any illness in the animal should be reported immediately to the local health department. Such animals should be evaluated by a veterinarian at the first sign of illness during confinement. If signs suggestive of rabies develop, the animal should be euthanized, and the head or entire brain (including brainstem) should be submitted for testing (*see* Part I.A. 10. Rabies diagnosis). Any stray or unwanted dog, cat, or ferret that exposes a person may be euthanized immediately, and the head or entire brain (including brainstem) should be submitted for testing (*see* Part I.A. 10. Rabies diagnosis).

b) Other animals. Other animals that might have exposed a person to rabies should be reported immediately to the local health department. Management of animals other than dogs, cats, and ferrets depends on the species, the circumstances of the exposure, the epidemiology of rabies in the area, the exposing animal's history and current health status, and the animal's potential for exposure to rabies. The shedding period for rabies virus is undetermined for most species. Previous vaccination of these animals might not preclude the necessity for euthanasia and testing.

7. Outbreak prevention and control. The emergence of new rabies virus variants or the introduction of nonindigenous viruses poses a significant risk to humans, domestic animals, and wildlife.[75–82] A rapid and comprehensive response involves coordination of multiple agencies (*see* Part I.A. 3. Interdisciplinary approach) to accomplish the following outcomes[83]:

- Characterize the virus at the national reference laboratory.
- Identify and control the source of the introduction.

- Enhance laboratory-based surveillance in wild and domestic animals.
- Increase animal rabies vaccination rates.
- Restrict the movement of animals.
- Evaluate the need for wildlife intervention activities (eg, point infection control, trap-vaccinate-release programs, and oral rabies vaccination programs).
- Provide public and professional outreach and education.

8. Disaster response. Animals might be displaced during and after man-made or natural disasters and require emergency sheltering.[84–86] Animal rabies vaccination and exposure histories are often not available for displaced animals, and disaster response can create situations where animal caretakers might lack appropriate training or preexposure vaccination. In such situations, it is critical to implement and coordinate rabies prevention and control measures to reduce the risk of rabies transmission and the need for human postexposure prophylaxis. Such measures include the following actions:

- Coordinate relief efforts of individuals and organizations with the local emergency operations center before deployment.
- Examine each animal at a triage site for possible bite injuries or signs of rabies.
- Isolate animals exhibiting signs of rabies pending evaluation by a veterinarian.
- Ensure that all animals have a unique identifier.
- Administer a rabies vaccine to all dogs, cats, and ferrets unless reliable proof of current vaccination exists.
- Adopt minimum standards for animal caretakers as feasible, including use of personal protective equipment, completion of the preexposure rabies vaccination series prior to deployment, and provision of appropriate training.[87]
- Maintain documentation of animal disposition and location (eg, returned to owner, died or euthanized, adopted, or relocated to another shelter with address of new location).
- Provide facilities to confine and observe animals involved in exposures (*see* Part I. B. 6. Management of animals that bite humans).
- Report human exposures to appropriate public health authorities (*see* Part I. A. 2. Rabies virus exposure).

C. Prevention and control methods related to wildlife

The public should be warned not to handle or feed wild mammals. Wild mammals and wild animal hybrids that expose persons, pets, or livestock should be considered for euthanasia and rabies testing. A person exposed by any wild mammal should immediately wash the wound thoroughly and report the incident to a health-care provider who, in consultation with public health authorities, can evaluate the need for postexposure prophylaxis.[11,12]

Translocating infected wildlife has contributed to the spread of rabies,[75–80,88] and animals that appear healthy can still be rabid. Therefore, translocation (ie, moving live animals from their point of capture and releasing them) of known rabies reservoir species should be prohibited.[89] Whereas state-regulated wildlife rehabilitators and nuisance-wildlife control operators should play a role in a comprehensive rabies control program, minimum standards for these persons who handle wild mammals should include rabies preexposure vaccination, specific rabies prevention and control training, and ongoing continuing education.

1. Carnivores. The use of oral rabies vaccines for mass vaccination of free-ranging wildlife should be considered in selected situations, with the approval of appropriate state and local agencies.[16,90] There have been documented successes using oral rabies vaccines to control rabies in wildlife in North America.[90–93] The currently licensed vaccinia-vectored oral rabies vaccine is labeled for use in raccoons and coyotes. Research to improve existing oral rabies vaccine and baits and to develop and test novel products to determine safety and efficacy must be encouraged. The distribution of oral rabies vaccines should be based on scientific assessments of the target species and followed by timely and appropriate analysis of surveillance data, with results provided to all stakeholders. In addition, parenteral vaccination (trap-vaccinate-release) of wildlife rabies reservoir species may be integrated into coordinated oral rabies vaccine programs to enhance their effectiveness. Continuous and persistent programs for trapping or poisoning wildlife are not effective in reducing populations of wildlife rabies reservoir species on a statewide basis. However, limited population control in high-contact areas (eg, picnic grounds, camps, and suburban areas) might be indicated for the removal of selected high-risk species of wildlife. State agriculture, public health, and wildlife agencies should be consulted for planning, coordination, and evaluation of vaccination or point infection control programs.[16]

2. Bats. From the 1950s to today, indigenous rabid bats have been reported from every state except Hawaii and have caused rabies in at least 54 humans in the United States.[94–103] Bats should be excluded, using appropriate methods, from houses, public buildings, and adjacent structures to prevent direct association with humans.[104,105] Such structures should then be made bat-proof by sealing entrances used by bats. Controlling rabies in bats through programs designed to reduce bat populations is neither feasible nor desirable.

Part II. Recommendations for Parenteral Rabies Vaccination Procedures

A. Vaccine administration

All animal rabies vaccines should be restricted to use by or under the direct supervision of a veterinar-

ian,[106] except as recommended otherwise (*see* Part I. B. 1. Preexposure vaccination and management).

B. Vaccine selection

All vaccines licensed by the USDA and marketed in the United States at the time of publication of this compendium are listed (Appendix 1). Newly approved vaccines and changes in label specifications made subsequent to publication should be considered as part of this list. Any of the listed vaccines can be used for revaccination, even if the product is not the same as the one previously administered. Vaccines used in state and local rabies control programs should have at least a 3-year duration of immunity. This constitutes the most effective method of increasing the proportion of immunized dogs and cats in any population.[107]

C. Adverse events

Currently, no epidemiological association exists between any particular licensed vaccine product and adverse events.[15,34,108–110] Although rare, adverse events such as vomiting, injection site swelling, lethargy, hypersensitivity, and the occurrence of rabies despite previous vaccination of an animal have been reported. Adverse events should be reported to the vaccine manufacturer and to USDA APHIS's Center for Veterinary Biologics (www.aphis.usda.gov; search for "adverse event reporting"). Although ill animals may not have a full immunologic response to vaccination, there is no evidence to suggest that adverse events are more likely to occur with rabies vaccination of ill than healthy animals. A veterinarian choosing to temporarily delay vaccinating an animal with an acute illness or condition should ensure that the animal is vaccinated as soon as possible. Animals with a previous history of anaphylaxis can be medically managed and observed after vaccination.[56] Severe adverse events related to rabies vaccination are extremely rare in animals. Decisions concerning rabies vaccination of animals with well-documented severe adverse events to rabies vaccine must be made within the context of a valid veterinarian-client-patient relationship. Due consideration should be given to the attendant risks and benefits of not vaccinating, including regulatory noncompliance. Animals not currently vaccinated that experience a rabies exposure are at greater risk for infection and death and also put their owners and the community at risk.

D. Vaccination of wildlife and wild animal hybrids

The safety and efficacy of parenteral rabies vaccines in wildlife and wild animal hybrids have not been established, and no rabies vaccines are currently licensed for use in these animals. Thus, any use of rabies vaccines in these animals is considered extralabel use. Zoos or research institutions may establish vaccination programs in an attempt to protect valuable animals, but these should not replace appropriate public health activities that protect humans (*see* Part I. B. 1. d) (3)).

E. Accidental human exposure to rabies vaccines

Human exposure to parenteral animal rabies vaccines listed in Appendix 1 does not constitute a risk for rabies virus infection. Human exposure to vaccinia-vectored oral rabies vaccines should be reported to state health officials.[111,112]

F. Rabies certificates

All agencies and veterinarians should use Form 51, the rabies vaccination certificate recommended by the National Association of State Public Health Veterinarians,[53] or should use an equivalent. The form must be completed in full and signed by the administering or supervising veterinarian. Computer-generated forms containing the same information are also acceptable.

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Appendix 1

Rabies vaccines licensed and marketed in the United States, 2016.

Product name	Produced by	Marketed by	For use in	Dose	Age at primary vaccination*	Booster vaccination	Route of inoculation
Monovalent (inactivated)							
RABVAC 1	Boehringer Ingelheim Vetmedica Inc License No. 124	Boehringer Ingelheim Vetmedica Inc	Dogs and cats	1 mL	3 mo	Annually	IM or SC
RABVAC 3	Boehringer Ingelheim Vetmedica Inc License No. 124	Boehringer Ingelheim Vetmedica Inc	Dogs and cats	1 mL	3 mo	1 year later and triennially	IM or SC
			Horses	2 mL	3 mo	Annually	IM
EQUI-RAB with Havlogen	Merck Animal Health License No. 165A	Merck Animal Health	Horses	1 mL	4 mo	Annually	IM
DEFENSOR 1	Zoetis License No. 190	Zoetis	Dogs	1 mL	3 mo	Annually	IM or SC
			Cats	1 mL	3 mo	Annually	SC
DEFENSOR 3	Zoetis License No. 190	Zoetis	Dogs	1 mL	3 mo	1 year later and triennially	IM or SC
			Cats	1 mL	3 mo	1 year later and triennially	SC
			Sheep and cattle	2 mL	3 mo	Annually	IM
NOBIVAC: 1-Rabies	Zoetis License No. 190	Merck Animal Health	Dogs	1 mL	3 mo	Annually	IM or SC
			Cats	1 mL	3 mo	Annually	SC
NOBIVAC: 3-Rabies and 3-Rabies CA	Zoetis License No. 190	Merck Animal Health	Dogs	1 mL	3 mo	1 year later and triennially	IM or SC
			Cats	1 mL	3 mo	1 year later and triennially	SC
			Sheep and cattle	2 mL	3 mo	Annually	IM
IMRAB 1	Merial Inc License No. 298	Merial Inc	Dogs and cats	1 mL	3 mo	Annually	SC
IMRAB 1 TF	Merial Inc License No. 298	Merial Inc	Dogs and cats	1 mL	3 mo	Annually	SC
IMRAB 3	Merial Inc License No. 298	Merial Inc	Dogs and cats	1 mL	3 mo	1 year later and triennially	IM or SC
			Sheep	2 mL	3 mo	1 year later and triennially	IM or SC
			Cattle and horses	2 mL	3 mo	Annually	IM or SC
			Ferrets	1 mL	3 mo	Annually	SC
IMRAB 3 TF	Merial Inc License No. 298	Merial Inc	Dogs and cats	1 mL	3 mo	1 year later and triennially	IM or SC
			Ferrets	1 mL	3 mo	Annually	SC
IMRAB Large Animal	Merial Inc License No. 298	Merial Inc	Dogs and cats	1 mL	3 mo	1 year later and triennially	IM or SC
			Cattle and horses	2 mL	3 mo	Annually	IM or SC
			Sheep	2 mL	3 mo	1 year later and triennially	IM or SC
Monovalent (rabies glycoprotein; live canary pox vector)							
PUREVAX Feline Rabies	Merial Inc License No. 298	Merial Inc	Cats	1 mL	3 mo	Annually	SC
PUREVAX Feline Rabies 3YR	Merial Inc License No. 298	Merial Inc	Cats	1 mL	3 mo	1 year later and triennially	SC
Combination (inactivated)							
Equine POTOMAVAC + IMRAB	Merial Inc License No. 298	Merial Inc	Horses	1 mL	3 mo	Annually	IM
Combination (rabies glycoprotein; live canary pox vector)							
PUREVAX Feline 3/Rabies	Merial Inc License No. 298	Merial Inc	Cats	1 mL	8 wk	Every 3 to 4 wk until 3 mo and annually	SC
					3 mo	3 to 4 wk later and annually	SC
PUREVAX Feline 4/Rabies	Merial Inc License No. 298	Merial Inc	Cats	1 mL	8 wk	Every 3 to 4 wk until 3 mo and annually	SC
					3 mo	3 to 4 wk later and annually	SC
Oral (rabies glycoprotein; live vaccinia vector)†							
RABORAL V-RG	Merial Inc License No. 298	Merial Inc	Raccoons and coyotes	NA	NA	As determined by local authorities	Oral

*One month = 28 days. †Oral rabies vaccines are restricted for use in federal and state rabies control programs.
NA = Not applicable.
Information is provided by the vaccine manufacturers and USDA APHIS's Center for Veterinary Biologics and is subject to change.

Appendix 2

Rabies vaccine manufacturer contact information

Manufacturer	Phone No.	URL
Boehringer Ingelheim Vetmedica Inc	800–638–2226	www.bi-vetmedica.com
Merck Animal Health Inc	800–521–5767	www.merck-animal-health-usa.com
Merial Inc	888–637–4251	us.merial.com
Zoetis	800–366–5288	www.zoetis.com