

Nebraska Department of Health and Human Services

Health Alert Network

UPDATE

June 21, 2023

Rabies Postexposure Prophylaxis (PEP): Recommendations for Healthcare Providers to Ensure Proper Prevention & Treatment

Summary

Rabies is a fatal but preventable viral disease. Despite significant progress in reducing risk of rabies exposures through domestic animal vaccination and other prevention efforts, rabies remains persistent in wildlife reservoirs across the United States and continues to pose a serious threat to public health. Domestic animals and humans commonly interact with rabies reservoir species (e.g., bats, skunks, raccoons) thereby increasing the opportunity for cross-species transmission to occur. Once clinical symptoms of rabies begin in humans, there is no effective treatment. Thus, rapid and appropriate response to known exposures is crucial. Identifying and understanding inconsistencies in appropriate treatment could help improve management efforts and guidance for this otherwise fatal disease.

This Health Alert Network (HAN) Advisory provides clinicians and public health officials with guidance for prioritizing appropriate rabies postexposure prophylaxis following either known or possible rabies exposures for the at-risk public.

Background

According to the Advisory Committee on Immunization Practices, “administration of rabies postexposure prophylaxis is a medical urgency, not a medical emergency, but decisions must not be delayed.” Rabies postexposure prophylaxis (PEP) consists of human rabies immune globulin (HRIG) and rabies vaccine ideally given as close to the day of the exposure as possible. Repeat doses of vaccine should also be given 3, 7, and 14 days after the first vaccine dose. People with suppressed immune systems should follow a 5-dose vaccine regimen with an additional dose administered on day 28 [1]. Such individuals should also have their virus-neutralizing antibody responses checked. The combination of HRIG and vaccine is *always* recommended for those without previous vaccination, even for non-bite exposures, regardless of the interval between exposure and initiation of treatment. However, it is recommended to start the series as soon as possible since the incubation period for the virus is highly variable and can range from a few days to a few years [2]. HRIG should be administered at the start of vaccine treatment but can be given up to 7 days after the first rabies vaccine dose without significantly diminishing antibody suppression [3].

The Nebraska Department of Health and Human Services (NDHHS) is responsible for managing the state’s Rabies Program as part of the agency’s public health mission. NDHHS works closely with Nebraska’s local health departments to provide recommendations and document human exposures. For program improvement, we created a questionnaire that was distributed to all Nebraskans reported to NDHHS as being potentially exposed to rabies and subsequently recommended by public health officials to get rabies PEP during 2012–2021. Our objectives were to better understand how many completed the series, where they received it, the costs, and what factors might influence failure to complete a recommended treatment series.



Of the 117 respondents, 62 (53%) were female and the average age was 49 years old; 102 (87%) reported receiving medical care following their potential exposure to rabies. Of these, 92 (90%) reported receiving rabies PEP. Of 15 (13%) who reported not seeking any type of medical care or treatment, nine (60%) decided to not receive any kind of medical care because they did not think it was necessary, 3 (20%) avoided treatment due to cost of care including the deductible or copay being too high, and 3 (20%) did not recall being advised to receive rabies PEP following their exposure. Upon further examination of our data, the latter three did indeed have the Local Health Department's PEP recommendations documented in our records. This reinforces need for effective communication surrounding PEP recommendations so at-risk people comprehend the importance of this treatment for disease prevention.

Of the 92 respondents who reported receiving PEP with rabies vaccine, 88 should have also received HRIG. However, 10 of these reported not receiving HRIG. It is important to recognize this concerning omission of appropriate PEP. Treatment is not considered complete without HRIG, which provides immediate passive immunity during the initial stages of viral invasion when post-vaccination endogenous antibody production remains delayed for 7–10 days. This window without HRIG protection could allow the virus to establish infection despite administration of the vaccine series. An abbreviated series without HRIG would only be appropriate for those individuals who had previously either received PEP following a past exposure or received pre-exposure prophylaxis (PrEP) vaccines. The following table provides reported examples of patient reasoning for not seeking care and possible recommendations that clinicians could offer to justify the need for treatment.

Patient reasoning for not seeking care:	Clinician recommendation to justify need for treatment:
Not able to find bite or scratch	Contact of infectious material in saliva with mucous membranes can constitute possible exposure: https://www.cdc.gov/rabies/exposure/index.html
Only brief interaction with possible rabid animal	Inapparent exposure is commonly reported for disease caused by bat rabies variants [4].
No symptoms	Once symptoms become apparent, it is too late for PEP treatment to be effective as the infection has already been established.
Cost of treatment	Patient assistance programs provide support to uninsured or underinsured patients: https://www.cdc.gov/rabies/medical_care/programs.html
The possible rabid animal appeared healthy	Infected animals might shed rabies virus for up to 2 weeks before onset of clinical signs with variability depending on species [5].
Have had a lot of previous wildlife exposures	Since rabies is nearly always 100% fatal, acquisition of natural immunity is not possible. Even in patients with prior PrEP or prior PEP administration following previous exposures, abbreviated PEP is still indicated for any subsequent known exposures.
Young bats don't harbor the virus	Although juvenile bats are less likely to be infected with rabies than adults (due to behavioral characteristics thus decreasing exposure and maternal antibodies adding protections for 6—8 weeks), they can still carry the virus and spread it to humans [6].
Painful course of treatment	While existing vaccines might cause mild, local reactions with minimal pain, redness, swelling, or itching at the injection site, more serious adverse reactions to rabies vaccine and immune globulin are not common. Local pain and low-grade fever may follow injection of HRIG.

Recommendations for Health Care Providers

Optimal management of potential rabies exposure requires a collaborative effort among multiple professional disciplines including veterinarians, public health authorities, physicians, natural resource personnel, virologists, diagnosticians, and animal control or law enforcement officers. Please refer to the Nebraska Rabies Investigation Guideline for more comprehensive, detailed information:

<https://dhhs.ne.gov/epi%20docs/Rabies%20Investigation%20Guidelines.pdf>

- Human Rabies Vaccine: Single dose vial of vaccine should be reconstituted with accompanying sterile diluent to a volume of 1 mL before administration. Advised injection site is intramuscular in the deltoid area for adults or in the anterolateral aspect of the thigh for children.
 - Human diploid cell vaccine (HDCV) or purified chick embryo cell vaccine (PCECV): ≥ 2.5 international units (IU) of rabies antigen.
- Human Rabies Immunoglobulin (HRIG): Local infiltration of 20 IU/kg around the wound as is anatomically feasible, with remaining immunoglobulin administered intramuscularly (IM) in an anatomical site distant from where vaccine was placed using a separate syringe from the vaccine. If no wound is evident, the entire volume is administered IM.
- Wound cleansing with soap and water +/- virucidal agent (povidine-iodine solution).
- For bite wounds, consider a tetanus shot if not immunized in preceding ten years +/- antibiotics (clinician discretion).
 - Although a rare occurrence, tetanus bacteria can enter the site of a bite through puncture if animal saliva is contaminated by infective soil spores.
 - Additionally, antibiotics can decrease risk of coinfection at the wound site depending on severity.
- PEP Treatment of Rabies per ACIP:
 - No previous rabies vaccination history: HRIG + vaccine (days 0*, 3, 7, and 14).
 - 5th dose of vaccine for immunocompromised people as well as antibody titer check
 - Previous rabies vaccine history (previous PrEP or complete PEP series): Abbreviated vaccine series only (days 0* and 3). Do not administer HRIG.
- Veterinarians:
 - Stay up to date with the *Compendium of Animal Rabies Prevention and Control* published by the National Association of State Public Health Veterinarians: <http://www.nasphv.org/Documents/NASPHVRabiesCompendium.pdf>
 - Maintain accurate records of rabies vaccination to keep animals up to date on boosters.
 - Provide rabies vaccination, serologic titers, and interstate travel health certificates.
 - Dogs & cats: Administer 1st vaccine at 12 weeks of age then booster vaccine one year later, additional boosters should follow manufacturer label.
 - Horses: All horses should be vaccinated.
 - Livestock: Livestock (of species for which vaccine is approved) that have frequent contact with humans should be vaccinated.
 - If rabies testing is necessary, euthanasia should be performed in a manner that sustains the anatomical integrity of brain tissue.

Prevention

Rabies prevention and control can be improved with further education and awareness of rabies transmission routes, responsible pet ownership, and routine veterinary care. Prompt recognition and reporting of possible exposures to local health professionals and authorities is also essential to minimize risk of rabies in Nebraska.

*Day 0 indicates the 1st day vaccine given not necessarily the day of exposure.

- Pet owners: Vaccinate pets, follow leash laws, obtain bite prevention training.
- Avoid direct interaction with wildlife and do not harbor wildlife as pets.
- Management of animals that potentially expose (bite) humans.
 - Healthy owned dogs and cats should be under strict quarantine and observed for 10 days at the minimum to rule out signs of infection regardless of vaccination status.
 - Strays can be observed for up to 72 hours while waiting to find an owner.
 - If animal (other than dog or cat under observation) isn't available for testing, PEP is strongly advised; download and refer Nebraska Rabies Investigation Guideline for flow diagrams for decision support.
<https://dhhs.ne.gov/epi%20docs/Rabies%20Investigation%20Guidelines.pdf>
- Receive rabies pre-exposure vaccination (PrEP) if recommended.
 - The Advisory Committee on Immunization Practices (ACIP) has recently changed their PrEP recommendations to approve a 2-dose (days 0 and 7) intramuscular rabies vaccination series superseding the previous 3-dose schedule [7].
 - Receiving PrEP eliminates subsequent need for rabies immunoglobulin and decreases the number of vaccine doses required for PEP.
 - Clinical guidance was recently updated to ensure effective PrEP administration for certain populations including delayed treatment until immunocompromising conditions have been resolved or immunosuppressive medications are withheld [8].
 - A subsequent titer check is advised regardless of immune status.
 - High incidence of work-related exposure.
 - Risk categories and PrEP recommendations:
https://www.cdc.gov/rabies/prevention/pre-exposure_vaccinations.html
 - Traveling to a high-risk country:
 - Rabies status assessment by country:
<https://www.cdc.gov/rabies/resources/countries-risk.html>

Nebraska Local Health Departments: <https://dhhs.ne.gov/CHPM%20Maps/LHDcontactMaster.pdf>

Nebraska Rabies Program: 402-471-2937

References:

1. CDC. Recommendations of the Advisory Committee on Immunization Practices (ACIP): Use of a Reduced (4-Dose)Vaccine Schedule for Postexposure Prophylaxis to Prevent Human Rabies. *MMWR*, March 19, 2010, Vol 59, #RR-02.
2. World Health Organization. *WHO expert consultation on rabies: third report*. WHO Technical Report Series, No. 1012. Geneva: World Health Organization, 2018.
3. Manning SE, Rupprecht CE, Fishbein D, et al.; Advisory Committee on Immunization Practices Centers for Disease Control and Prevention. Human rabies prevention—United States, MMWR Recomm Rep 2008;57(No. RR-3):1–28. PMID:18496505
4. Ma, X et al. "Rabies surveillance in the United States during 2021". *Journal of the American Veterinary Medical Association*. < <https://doi.org/10.2460/javma.23.02.0081>>. Web. 5 May. 2023.
5. 7. Spickler, Anna Rovid. "Rabies and Rabies-Related Lyssaviruses." *CFSPH*, Jan. 2021. Retrieved from www.cfsph.iastate.edu/Factsheets/pdfs/rabies.pdf.
6. Dah et al. (2022). Prevalence and public health significance of Lyssavirus in bats in North region of Cameroon. 10.1101/2022.09.12.507528.
7. Rao AK, Briggs D, Moore SM, et al. Use of a Modified Preexposure Prophylaxis Vaccination Schedule to Prevent Human Rabies: Recommendations of the Advisory Committee on Immunization Practices — United States, 2022. *MMWR Morb Mortal Wkly Rep* 2022;71:619–627.
8. CDC. Recommendations of the Advisory Committee on Immunization Practices (ACIP): use of vaccines and immune globulins for persons with altered immunocompetence. y42(No. RR-4). 28.

Natalie Bauer, MS
 CDC EEP Student
 (402) 471-2937

Timothy Tesmer, MD
 CMO Public Health
 (402) 471-8566

Matthew Donahue, MD
 NE State Epidemiologist
 (402) 471-8566

Bryan F. Buss, DVM, MPH
 NE State Public Health Veterinarian
 (402) 471-8820