

INFORMATION PAPER

DHA-IHD
18 May 2022

SUBJECT: Rabies Disease and Rabies Vaccines

1. Purpose. To describe rabies disease and the vaccines that prevent it.
2. Facts.
 - a. Microbiology. Rabies is a zoonotic disease (transmitted from animals to humans) caused by viruses in the family Rhabdoviridae, genus Lyssavirus.
 - b. Epidemiology. Lyssaviruses have been found on all continents except Antarctica. Rabies is the most common lyssavirus infection in humans. Transmission of rabies virus occurs when saliva or nerve tissue from an infected mammal is introduced into a person or another animal, generally through a bite or contact with mucous membranes. Rabies virus variants exist in dogs and wildlife, such as bats, foxes, jackals, mongooses, raccoons, and skunks. Dogs are the main reservoir in developing countries, and canine rabies virus variant (CRVV) remains enzootic (endemic in certain animals) in many areas of the world, including Africa, Asia, and Central and South America. Bat bites anywhere in the world are a cause of concern and an indication to consider prophylaxis. Accurate information about global rabies occurrence is difficult to find. It is estimated that the rabies exposure rate is 16-200 of every 100,000 travelers, with 59,000 human deaths each year.
 - c. Disease. After infection, the incubation period is variable, but is often several weeks to several months. Early symptoms of rabies in people are similar to that of many other illnesses: pain and numbness at the bite site, fever, headache, and general weakness or discomfort. As the disease progresses, more specific neurologic symptoms appear, such as anxiety, difficulty swallowing, fear of water (hydrophobia), paralysis, delirium, and convulsions, followed rapidly by coma and death. Once symptoms of rabies appear, the disease is nearly always fatal.
 - d. Vaccines. Imovax® (Sanofi Pasteur) and RabAvert® (GlaxoSmithKline) are the only two rabies vaccines currently FDA-licensed for use in the United States. Both vaccines can be used for pre-exposure (PrEP) or post-exposure (PEP) prophylaxis.

- (1) Imovax® is a human diploid cell vaccine (HDCV) derived from a human cell line, and contains human albumin, neomycin, phenol, and trace amounts of beta-propiolactone.
- (2) RabAvert® is a purified chick embryo cell (PCEC) vaccine derived from chicken fibroblasts, and contains bovine gelatin, human albumin, potassium glutamate, sodium EDTA, chicken protein (ovalbumin), neomycin, chlortetracycline, and amphotericin B.

e. Contraindications.

- (1) PrEP: contraindicated in people with a history of a serious reaction (e.g., anaphylaxis) after vaccination or to any vaccine component, to include neomycin.
- (2) PEP: as rabies is virtually 100% fatal once symptoms appear, there is no contraindication to PEP. Patients with a history of hypersensitivity who require PEP may be given antihistamines and vaccinated under observation by an Allergist. Equipment and medications to manage a medical emergency should be readily available.
- (3) For information on vaccine components, refer to the [manufacturer's package insert](#) or <http://www.cdc.gov/vaccines/pubs/pinkbook/downloads/appendices/b/excipient-table-2.pdf>.

f. Precautions.

- (1) Moderate or severe acute illness with or without fever.
- (2) Syncope (fainting) can occur in association with administration of injectable vaccines. Have procedures in place to avoid a falling injury (e.g. observation after administration) and to restore cerebral perfusion following syncope.

g. Special Populations: These individuals should discuss vaccine receipt timing and medication management with their primary or specialty healthcare provider(s).

- (1) Pregnancy: There is no evidence of adverse fetal effects from vaccinating pregnant women with inactivated virus, bacterial vaccines, or toxoids, and a growing body of data demonstrate the safety of such use.

- (2) Lactation: Inactivated vaccines have not been shown to affect the safety of breastfeeding for women or their infants.
- (3) Infants and children: although limited safety data are available, PrEP and PEP may be administered if patients meet current clinical criteria. Administer indicated product(s) using the same dosing and timing as for other high-risk groups.
- (4) Immunocompromised: In persons with [primary or secondary immunodeficiencies](#), delay PrEP vaccination (when possible) until a temporary immunocompromising condition has resolved or immunosuppressive medications can be withheld. Do not delay PEP treatment for these patients.

h. Immunization.

- (1) PrEP vaccination with Imovax® or RabAvert® for persons in certain risk categories consists of a 2-dose primary series given intramuscularly (IM) at 0 and 7 days. (See Table 1). Both vaccines are supplied by the manufacturer in a pre-packaged single-dose (1mL) kit. Booster doses are indicated based on risk category and titer level. For Risk Category 3, patients may elect to receive a booster dose between 21 days and 3 years after the primary series in lieu of a one-time titer check.
 - (2) PEP vaccination with Imovax® or RabAvert® consists of a multiple-dose series with the addition of rabies immune globulin (RIG) for patients who did not receive PrEP. (See Table 2.)
 - (3) Do not start PrEP if the series cannot be completed before travel: limited data exists to guide PEP after a partial immunization series.
- i. Adverse Events. The most common adverse reactions after any vaccination are fever and injection site complaints such as soreness, warmth, redness, swelling, or induration. Mild systemic reactions such as headache, nausea, muscle aches, or dizziness may also occur. Serious reactions are very rare. Approximately 6% of people who receive HDCV booster vaccinations may experience systemic reactions characterized by urticaria (rash), pruritus (itching), and malaise. The likelihood of these reactions may be less with PCEC. Do not interrupt or discontinue PEP because of local or mild systemic reactions: consider switching to the alternative vaccine for the remainder of the series. Clinically-significant adverse events following vaccination should be reported to the Vaccine Adverse Event Reporting System (VAERS), even if a causal relation to vaccine is not certain. Reports can be submitted to VAERS online at

<https://vaers.hhs.gov>. Information about VAERS is also available by telephone at (800) 822-7967.

- j. DOD Policy. Administer rabies vaccines to DOD beneficiaries who are in a high-risk category per current ACIP recommendations, local Public Health guidance for disease outbreak prevention, or IAW Service-specific guidelines.

3. References.

- a. Centers for Disease Control and Prevention. (2020). CDC Yellow Book 2020: Health Information for International Travel. Oxford University Press. <https://wwwnc.cdc.gov/travel/page/yellowbook-home-2020>.
- b. Centers for Disease Control and Prevention. (2021). Epidemiology and Prevention of Vaccine-Preventable Diseases (14th ed.). Public Health Foundation. <https://www.cdc.gov/vaccines/pubs/pinkbook/index.html>.
- c. Rao, A. K., Briggs, D., Moore, S. M., Whitehill, F., Campos-Outcalt, D., Morgan, R. L., Wallace, R. M., Romero, J. R., Bahta, L., Frey, S. E., & Blanton, J. D. (2022). Use of a Modified Preexposure Prophylaxis Vaccination Schedule to Prevent Human Rabies: Recommendations of the Advisory Committee on Immunization Practices - United States, 2022. MMWR. Morbidity and Mortality Weekly Report, 71(18), 619–627. <https://doi.org/10.15585/mmwr.mm7118a2>.

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Table 1. Rabies Pre-Exposure Prophylaxis (PrEP) Recommendations

Risk Category	Typical population*	Primary Series (2 doses)	Titer / Booster (1 dose)
1. Elevated risk for unrecognized [†] or recognized ^{††} exposures, including unusual or high-risk exposures	Work with live rabies virus in research or vaccine production facilities; perform rabies testing in diagnostic laboratories	Vaccine on days 0 and 7	Titer: every 6 months Booster: if titer < 0.5 IU/mL [§]
2. Elevated risk for unrecognized [†] or recognized ^{††} exposures	Frequently handle or have contact with bats; enter high-density bat environments; perform animal necropsies (e.g., biologists who frequently enter bat roosts or who collect suspected rabies samples)	Vaccine on days 0 and 7	Titer: every 2 years Booster: if titer < 0.5 IU/mL [§]
3. Elevated risk for recognized ^{††} exposures, sustained risk [¶]	Interact with animals that could be rabid [#] (e.g., veterinarians, vet techs, animal control officers; wildlife biologists, rehabilitators, and trappers); spelunkers	Vaccine on days 0 and 7	Titer: once, 1–3 years after PrEP Booster: if titer < 0.5 IU/mL [§] OR These patients may elect to receive a booster dose 3 weeks-3 years after PrEP in lieu of a one-time titer check.
	Travelers with increased risk for exposure to potentially rabid animals (particularly dogs) who might not have prompt access to safe PEP (e.g., rural area, far from closest PEP clinic)		
4. Elevated risk for recognized ^{††} exposures, risk not sustained [¶]	Same as Risk Category 3, but risk duration ≤ 3 years (e.g., short-term animal care, no expected high-risk travel > 3 years after PrEP)	Vaccine on days 0 and 7	None
5. Low risk for exposure	Typical person living in the United States	None	None

Adapted from CDC MMWR 71(18), 619-627 (06 May 2022):

<https://www.cdc.gov/mmwr/volumes/71/wr/mm7118a2.htm>.

Abbreviations: IU = international units; PEP = post-exposure prophylaxis

* Nature of exposure is the most important variable to consider when determining risk category. Examples provided are only a guide; categorizations should be done on a case-by-case basis. If an individual falls into more than one category, follow guidance for the highest-risk category. Risk categories may change over an individual's lifetime.

† Example: a small scratch during an inconspicuous personal protective equipment breach while testing neural tissue from a rabid animal or conducting studies on bats in the field, etc.

†† Noticed because the exposure is unusual (e.g., contact with a bat, splash with contaminated fluids) or painful (e.g., bite or scratch from a raccoon).

§ Give a booster when rabies antibody titers are < 0.5 IU/mL. For immunocompetent patients, titers to verify booster response are not needed. For immunocompromised patients, verify response with a titer ≥ 1 week (ideally, 2–4 weeks) after every booster dose.

- ¶ Elevated risk for rabies > 3 years after the completion of the primary rabies PrEP series.
- # Rabies virus is unlikely to persist outside a deceased animal's body for an extended time. Risk of transmission to persons handling animal products (e.g., hunters or taxidermists) is unknown but presumed to be low (risk category 5); direct skin contact with saliva or neural tissue of mammals should be avoided regardless of profession or activity.
- || Titer after recommended booster dose(s) not indicated unless patient has altered immunity.

Table 2. Rabies Post-Exposure Prophylaxis (PEP) Recommendations*					
Status	Product	Dose	# of Doses	Schedule (Days) [†]	Route
Not previously vaccinated	RIG	20 IU/kg body weight	1	0	Infiltrated at bite site (if possible); remainder IM
	HDCV or PCEC	1.0 mL	4 or 5 [‡]	0, 3, 7, 14 (and 28) [‡]	IM
Previously vaccinated ^{§, ¶}	HDCV or PCEC	1.0 mL	2	0, 3	IM

Adapted from CDC Yellow Book (2020): <https://wwwnc.cdc.gov/travel/yellowbook/2020/travel-related-infectious-diseases/rabies>.

Abbreviations: RIG: rabies immune globulin; IM: intramuscular; HDCV: human diploid cell vaccine; PCEC: purified chick embryo cell.

* All PEP should begin with immediate, thorough wound cleansing with soap and water, povidone iodine, or other substances with virucidal activity.

† For most minor schedule deviations (delays of a few days), resume vaccination as though the traveler were on schedule. If substantial deviations occur, assess immune response with a titer 7–14 days after the final dose is administered.

‡ Five vaccine doses for the immunocompromised patient. The first 4 vaccine doses are given on the same schedule as for an immunocompetent patient, and the fifth dose is given on day 28. Verify immune response with a titer ≥ 1 week (ideally, 2–4 weeks) after the final dose is administered. For more information, see

www.cdc.gov/mmwr/preview/mmwrhtml/rr5902a1.htm.

§ Prior PrEP or PEP immunization with HDCV or PCEC, or previously received any other type of rabies vaccine and have a subsequent documented protective titer response (> 0.5 IU/mL).

¶ RIG not recommended.