Rabies Pre-Exposure and Post-Exposure Prophylaxis

DESCRIPTION

This fact sheet highlights pertinent information regarding rabies pre-exposure prophylaxis (PrEP) and post-exposure prophylaxis (PEP), including vaccination schedules and human rabies immune globulin (HRIG) administration resources.

EPIDEMIOLOGY[1]

Cases of human rabies in the United States are rare, with approximately only 1 to 3 cases reported annually. The number of deaths attributed to rabies in the U.S. has declined steadily since the 1970's as a result of animal control and vaccination programs, public health efforts and the availability of modern rabies biologics and creation of prophylaxis strategies. Between 30,000 to 60,000 individuals receive rabies post-exposure prophylaxis annually.

RABIES VACCINES/IMMUNOGLOBULINS

PrEP strategies utilize rabies vaccine given as a standard 2-dose series (see Table 2). Two vaccine products are currently available on the U.S. market: RabAvert and Imovax. Imovax is non-formulary at UNC Health and will not be discussed in this document. Table 1 outlines pertinent drug information for RabAvert.

PEP strategies utilize both vaccine products and HRIG. There are 4 HRIG products on the market: HyperRAB, HyperRAB S/D, Imogam Rabies-HT, and Kedrab. HyperRAB is the only formulary HRIG product; the other agents will not be discussed in detail.

It should be noted that **rabies vaccines are interchangeable with one another**. This means a vaccine series may be initiated with one product but finished with another without any ill-effects. Similarly, HRIG products are interchangeable; this is less important as HRIG is given as a one-time dose (see Figure 1).

TABLE 1. Rabies Vaccine/HRIG Products **on UNC Health Formulary**

Type	Product	Form	Dose	Storage	Preparation	Comments
Vaccine	RabAvert	2.5 IU/vial for reconstitution	2.5 IU	2°C to 8°C Do not freeze	Use supplied diluent & swirl until dissolved; will be opaque to light pink after recon; use immediately	Contains amphotericin B, bovine gelatin, egg & chicken protein, chlortetracycline, and neomycin
HRIG	HyperRAB	300 IU/1 mL 1500 IU/5 mL[A]	20 mg/kg[B]	2°C to 8°C Do not freeze Store at RT up to 6 mos.	N/A – drug in solution	HyperRAB I more concentrated (300 IU/mL) vs comparator products and uses less volume

[A] A 900 IU/3 mL vial is also available on the market but non-formulary at UNC Health

[B] UNC Health utilizes a dose-rounding protocol to minimize the use of partial vials when possible; this logic is built into Epic and no action is needed

PRE-/POST-EXPOSURE PROPHYLAXIS DOSING SCHEDULES

PrEP vaccine recommendations are dependent on patient risk category (Table 2). PEP dosing schedules are dependent on previous vaccination status and immunocompetency.

Adverse reactions to PrEP/PEP regimens are generally mild. The most common vaccine reactions include local reactions (pain, redness, swelling at injection site); less common reactions include headache, nausea, muscle aches, and dizziness. For HRIG, the most common adverse events are local injection site pain, low-grade fever, and headache.

Pre-Exposure Prophylaxis – Dose Recommendations[2,3]

TABLE 2. Recommendations for Pre-Exposure Prophylaxis Vaccination by risk category

Risk Category	Individuals at Risk	Vaccine Recs	Titer Recs[A]
Category 1 (Highest Risk)	Those who work with live or concentrated rabies virus in laboratories	1st dose on Day 0 2nd dose on Day 7	Check every 6 months
Category 2	Those who frequently handle bats, have contact with bats, enter high-density bat environments like caves, or perform animal necropsies	1st dose on Day 0 2nd dose on Day 7	Check every 2 years
Category 3	Those who regularly or frequently interact with mammals that could be rabid for a duration of 3+ years after receiving PrEP, including the following: • Most veterinarians, vet techs, animal control officers, wildlife biologists, rehabilitators, trappers, and spelunkers • Travelers to regions outside of the US where rabid dogs are regularly encountered	1st dose on Day 0 2nd dose on Day 7 ***PLUS EITHER*** One-time titer (see right) ***or*** 1-dose booster 3 weeks to 3 years after the 2nd dose	1-3 years post-vaccination with 2-dose series (if no booster)
Category 4	Same population as risk category 3, BUT in whom exposure duration is expected to be ≤ 3 years after they receive PrEP	1st dose on Day 0 2nd dose on Day 7	N/A
Category 5 (Lowest Risk)	General U.S. population	Not Indicated	N/A

[A] Titer ≥0.5 IU/mL indicates sufficient neutralizing response

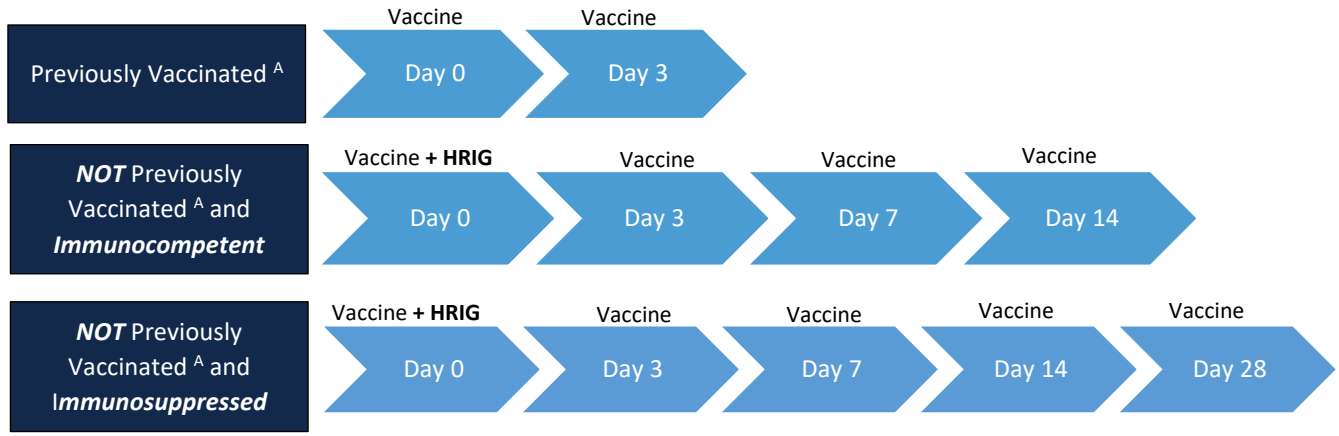
Post-Exposure Prophylaxis – Dose Recommendations[4-7]

For patients exposed to rabies, standard practice is to **immediately and thoroughly cleanse wounds with soap and water**. If available, a virucidal agent (e.g., povidone-iodine solution) should be used to irrigate wounds. Patients should also be evaluated for tetanus prophylaxis.

PEP (Figure 1) should immediately be initiated post-exposure, preferably on the day of exposure or as soon as possible.

- Vaccines are given as 2-5 doses (**2.5 IU/dose**) depending on patient history/characteristics.
- HRIG dose is one-time, weight-based (**20 IU/kg**); for UNC Health, dose rounding is applied as outlined in Table 2.

FIGURE 1. PEP Vaccine/HRIG Schedule Dosing



[A] Previously vaccinated defined as having completed an ACIP-recommended PEP or PrEP regimen (Table 2, Figure 1) OR having received another vaccine regimen with a documented rabies virus neutralizing antibody response (titer ≥0.5 IU/mL)

ADMINISTRATION INSTRUCTIONS[15,16]

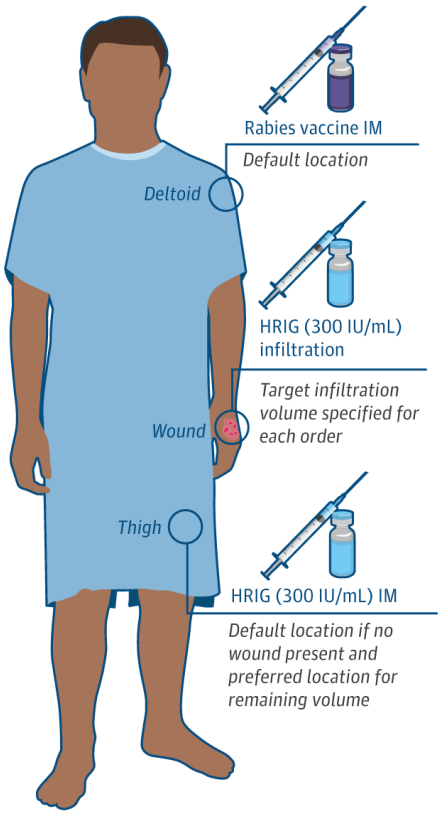
Vaccines

Rabies vaccines are given intramuscularly (IM) into the deltoid muscle [see Fig 2, right). While the deltoid is the preferred location, the anterolateral aspect of the thigh may be considered in pediatrics

Vaccines should NOT be administered into the gluteal region, as data indicate this location is associated with impaired immune response and may result in low titers. **If rabies vaccine is administered into the gluteal region, the dose does not count must be repeated with correct injection technique.**

Vaccines should NOT be administered in the same site as HRIG, as HRIG may interrupt/attenuate the natural immune response to vaccination.

Figure 2. Administration Locations



HRIG

HRIG is administered via infiltration into the wound/bite site(s). If possible, the entire dose should be infiltrated at the wound site. If wound site is not apparent, or if excess volume remains following infiltration, HRIG should be given IM ***at a site distant from vaccine injection site***.

Do NOT administer HRIG into the gluteal region *unless* that is the site of exposure. HRIG may cause sciatic nerve damage when administered gluteally.

FREQUENTLY ASKED QUESTIONS[2,5,17-18]

FAQs: General

1. **Do pediatrics need lower doses of HRIG/vaccines?**
   No, dosing recommendations and administration volumes are identical between pediatrics and adults.
2. **For patients undergoing titer monitoring, what level indicates "protection"?**
   Titers ≥0.5 IU/mL indicate protection. Older guidance utilized a lower cutoff of 0.1 to 0.3 IU/mL and may be reflected in literature but is no longer the ACIP-recommended limit to define adequate response.
3. **Can HRIG and rabies vaccine be mixed in the same syringe and administered together?**
   No. Products should be administered separately at regions distant to one another.
4. **After administration of Day 0 HRIG + vaccine, do subsequent vaccine doses need to be administered at different site from where HRIG was given?**
   No. Subsequent doses may be administered in the same anatomic location of HRIG if needed.
5. **Are HRIG/rabies vaccine safe to give in pregnant/lactating individuals?**
   Yes. Pregnant/lactating individuals should receive PEP/PrEP as clinically indicated without harm to fetus/baby.
6. **Are patient-assistance programs available for patients unable to afford PEP/PrEP?**
   Yes. The following programs are available:
   - Sanofi-Pasteur Patient Assistance Program: 1-866-801-5655 or Link Here
     - Covered products: Imogam HRIG, Imovax Rabies Vaccine [NON-FORMULARY]
   - Grifols Patient Assistance Program: 1-833-504-9983
     - Covered products: HyperRAB HRIG
   - Kedrion Biopharma Patient Assistance Program: 1-866-234-3732 or Link Here
     - Covered products: Kedrab HRIG

7. **Who should I contact with questions not answered in this Fact Sheet or for guidance on schedule deviations?**
   Contact the Communicable Disease Branch of the NC DHHS at 919-733-3419.

FAQs: Pre-Exposure Prophylaxis (PrEP)

8. **Can immunosuppressed patients receive PrEP? If so, is the schedule different from the general population?**
   For *temporary* immunocompromising conditions, vaccination should be delayed until condition has resolved.

   For conditions that cannot be resolved/temporarily reversed, antibody titers should be checked 2-4 weeks after completion of the 2-dose series. If titer is <0.5 IU/mL, a booster dose should be given followed by another titer check. If two such checks are <0.5 IU/mL, please consult with the local or state health authorities for guidance.

9. **How should I manage deviations in the PrEP vaccine schedule?**
   Missed doses of <2 weeks are inconsequential; vaccination can be resumed on a regular schedule. More substantial deviations in the dosing schedule may require assessment by local or state health authorities. The 2nd dose of the series should NOT be given early – if inadvertently given early, consult health authorities.

FAQs: Post-Exposure Prophylaxis (PEP)

10. **Should PEP be given if exposure is suspected but uncertain**?
    Unless rabies can be ruled out by diagnostic testing of the bat/other animal, rabies PEP is recommended

11. **Why is HRIG not administered for PEP in patients with adequate vaccination history?**
    HRIG provides immediate antibodies in previously unvaccinated patients but may inhibit anamnestic (i.e., immune) response in vaccinated patients. To avoid inhibition of an appropriate immune response, HRIG should not be given.

12. **Does administration of HRIG depend on when exposure occurred?**
    No, HRIG is recommended in combination with the vaccine (if clinically indicated; see Fig.1) regardless of interval between exposure and PEP initiation.

13. **My patient is indicated for HRIG but this was not given/missed on Day 0. Can it still be given?**
    If not given on Day 0, HRIG may be given through Day 7 after start of the series. Past this window, HRIG is not recommended since the antibody response to vaccine is presumed to have occurred.

14. **How should I manage deviations in the PEP vaccine schedule?**
    Minor deviations (~≤1 week) are inconsequential; vaccination can be resumed on a regular schedule, maintaining the same interval between doses. Schedules should be resumed even in the case of more substantial delays (~>1-2 weeks), but serologic testing should be completed at 7-14 days after the final dose to assess status.

15. **Should I draw antibody titers after completion of a PEP vaccine series?**
    Routine testing is not recommended or required in patients who complete a series; testing may be necessary with extended dose interruptions (see FAQ #14)

REFERENCES

1. Human Rabies. Centers for Disease Control and Prevention (CDC). September 22, 2021. Accessed May 12, 2023. https://www.cdc.gov/rabies/location/usa/surveillance/human_rabies.html
2. 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(18):619-627.
3. Pre-Exposure Prophylaxis (PrEP). Centers for Disease Control and Prevention (CDC). May 4, 2022. Accessed May 12, 2023. https://www.cdc.gov/rabies/prevention/pre-exposure_vaccinations.html
4. Rabies Post-Exposure Prophylaxis (PEP). Centers for Disease Control and Prevention (CDC). May 4, 2022. Accessed May 12, 2023. https://www.cdc.gov/rabies/medical_care/index.html
5. Rupprecht CE, Briggs D, Brown CM, et al. Use of a reduced (4-dose) vaccine schedule for postexposure prophylaxis to prevent human rabies: recommendations of the advisory committee on immunization practices. *MMWR Recomm Rep*. 2010;59(RR-2):1-9.
6. Human Rabies Immune Globulin. Centers for Disease Control and Prevention (CDC). April 22, 2011. Accessed May 12, 2023. https://www.cdc.gov/rabies/medical_care/hrig.html
7. Rabies Vaccine. Centers for Disease Control and Prevention (CDC). September 24, 2014. Accessed May 12, 2023. https://www.cdc.gov/rabies/medical_care/vaccine.html
8. Vaccine and Immune Globulin Availability. Centers for Disease Control and Prevention (CDC). August 24,2020. Accessed May 12, 2023. https://www.cdc.gov/rabies/resources/availability.html
9. HyperRAB (Rabies Immune Globulin Human) [package insert]. Grifols Therapeutics, LLC. Research Triangle Park, NC; 2023.
10. HyperRAB S/D (Rabies Immune Globulin Human Solvent/Detergent Treated) [package insert]. Grifols Therapeutics, LLC. Research Triangle Park, NC; 2022.
11. Imogam Rabies- HT (Rabies Immune Globulin Human) [package insert]. Sanofi Pasteur, Inc. Swiftwater, PA; 2021.
12. KEDRAB (Rabies Immune Globulin Human) [package insert]. Kedrion Biopharma, Inc. Fort Lee, NJ; 2021.
13. RabAvert (Rabies Vaccine) [package insert]. GlaxoSmithKline. Research Triangle Park, NC; 2019.
14. Imovax (Rabies Vaccine) [package insert]. Sanofi Pasteur, Inc. Swiftwater, PA; 2023.
15. Rabies Biologics. Centers for Disease Control and Prevention (CDC). October 2, 2019. Accessed May 12, 2023. https://www.cdc.gov/rabies/specific_groups/hcp/biologic.html?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Frabies%2Fspecific_groups%2Fdoctors%2Fbiologic.html
16. Yuan F, Iso T, Rizk E, et al. Implementation of Clinical Decision Support on Emergency Department Delivery of Human Rabies Immune Globulin. *JAMA Netw Open*. 2022;5(6):e2216631.
17. Ask the Experts- Rabies. Immunization Action Coalition. October 22, 2020. Accessed May 12, 2023. https://www.immunize.org/askexperts/experts_rab.asp#:~:text=Both%20vaccines%20contain%20inactivated%20rabies,considered%20equally%20safe%20and%20effective.
18. Programs for Uninsured and Underinsured Patients. Centers for Disease Control and Prevention (CDC). May 4, 2022. Accessed May 12, 2023.