Type of exposure
Rabies is transmitted by introducing the virus into open cuts or wounds in skin or via mucous membranes. The likelihood of rabies infection varies with the nature and extent of exposure. Two categories of exposure should be considered, bite and nonbite.

Bite
Any penetration of the skin by teeth. Nonbite
Scratches, abrasions, open wounds, or mucous membranes contaminated with saliva or other potentially infectious material, such as brain tissue, from a rabid animal. Casual contact, such as petting a rabid animal, (without a bite or nonbite exposure as described above), does not constitute an exposure and is not an indication for prophylaxis. Rare cases of exposure to the saliva of an airborne rabies have been received from laboratory and bat-infested cave settings. (11)

Rabies cases from human-to-human transmission have occurred in patients in the US and overseas who received organ transplanted from persons who died of rabies undiagnosed at the time of death. No documented laboratory-diagnosed cases of human-to-human rabies transmission have been documented from a bite or nonbite exposure other than the transplant cases. At least two cases of human-to-human rabies transmission in Ethiopia have been suggested, but rabies as the cause of death was not confirmed by laboratory testing. The reported route of exposure in both cases was direct salivary contact from another human (ie, a bite and a kiss). Routine delivery of health care to a patient with rabies is not an indication for post-exposure prophylaxis unless the healthcare worker is reasonably certain that he or she was bitten by the patient or that his or her mucous membranes or nonintact skin was exposed directly to potentially infectious saliva or mucous membranes.

2. Pre- and post-exposure prophylaxis of rabies

A. Pre-exposure
Pre-exposure prophylaxis should be offered to rabies researchers, certain laboratory personnel and other persons in high-risk groups, such as veterinarians and their staff, and animal handlers. Pre-exposure vaccination also should be considered for persons whose activities bring them into frequent contact with rabies virus or potentially rabid bats, raccoons, skunks, cats, dogs, or other species at risk for having rabies. In addition, some international travelers might be candidates for pre-exposure vaccination if they are likely to come in contact with animals in areas where dog or other animal rabies is enzootic and immediate access to adequate medical care, including rabies vaccine and immune globulin, might be limited. (11)

Vaccination is recommended for children living in or visiting countries where exposure to rabid animals is a constant threat. Worldwide statistics indicate children are more at risk than adults.

Pre-exposure prophylaxis is administered for several reasons. First, although pre-exposure vaccination does not eliminate the need for additional medical evaluation after a rabies exposure, it simplifies management by eliminating the need for Rabies Immune Globulin (RIG) and decreases the number of doses of vaccine needed. This is particularly important for persons at high risk for being exposed to rabies in areas where modern immunizing products might not be available or where cruder, less safe biologics might be used, placing the exposed person at increased risk for adverse events. Second, pre-exposure prophylaxis might offer partial immunity to persons whose post-exposure prophylaxis is delayed. Finally, pre-exposure prophylaxis might provide some protection to persons at risk for exposure to wild terrestrial carnivores.

B. Post-exposure prophylaxis

Post-exposure prophylaxis consists of three 1.0 mL doses of Imovax Rabies vaccine administered intramuscularly, using a sterile needle and syringe, one injection per day on Days 0, 7, and 21 or 28. In adults and older children, the vaccine should be administered in the deltoid muscle. In infants and small children, the anterolateral aspect of the thigh may be preferable, depending on age and body mass.

Administration of booster doses of vaccine depends on exposure risk category and serologic testing as noted in Table 1. Immunosuppressed persons should postpone pre-exposure vaccination and consider avoiding activities for which rabies pre-exposure prophylaxis is indicated. When this course is not possible, immunosuppressed persons who are at risk for rabies should have their viral neutralizing antibody titers checked after completing the pre-exposure series. If no acceptable antibody response is detected, the patient should be managed in consultation with their physician and appropriate public health officials. (11)

<table>
<thead>
<tr>
<th>Risk category</th>
<th>Nature of risk</th>
<th>Typical populations</th>
<th>Pre-exposure recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Continuous</td>
<td>Virus present continuously and often in high concentrations. Specific exposures likely unrecognized. Bite, nonbite, or aerosol exposure.</td>
<td>Rabies research laboratory workers; rabies biologists; production workers.</td>
<td>Primary course. Serologic testing every 6 months; booster vaccination if antibody titer is below acceptable level.</td>
</tr>
<tr>
<td>Frequent</td>
<td>Exposure usually episodic, with source recognized. But exposure also might be unrecognized. Bite, nonbite, or aerosol exposure.</td>
<td>Rabies diagnostic laboratory workers, veterans, farmers, veterinarians and staff, and animal control and wildlife workers in areas where rabies is enzootic. All persons who frequently handle bats.</td>
<td>Primary course. Serologic testing every 2 years; booster vaccination if antibody titer is below acceptable level.</td>
</tr>
</tbody>
</table>

In the United States, postexposure prophylaxis is recommended for all human exposures. (11)
Minimum acceptable antibody level is complete virus neutralization at a 1:5 serum dilution by the rapid fluorescent focus inhibition test. A booster dose should be administered in the titer falls below this level.

**B. Post-exposure**

The essential components of rabies post-exposure prophylaxis are wound treatment and, for previously unvaccinated persons, the administration of both human rabies immune globulin (HRIG) and vaccine. (11)

1. **Local treatment of wounds**

Thorough washing and flushing (for about 15 minutes, if possible) with soap or a cleansing agent and copious amounts of water of all bite wounds and scratches should be washed immediately or as early as possible. Where available, an iodine-containing, or similarly viricidal, topical preparation should be applied to the wound. (12)

Tetanus prophylaxis and measures to control bacterial infection should be given as indicated. 2. **Specific treatment**

The sooner treatment is begun after exposure, the better. Post-exposure antirabies vaccine should always include administration of both passive antibody and vaccine, with the exception of persons who have ever previously received complete vaccination regimens (pre-exposure or post-exposure) with a cell culture vaccine or persons who have been vaccinated with other types of vaccines and have previously had a documented rabies virus neutralizing antibody titer. These persons should receive only vaccine (ie, post-exposure for a person previously vaccinated). The combination of HRIG and vaccine is recommended for both bite and nonbite exposures reported by persons who have never been previously vaccinated for rabies, regardless of the interval between exposure and initiation of prophylaxis. If post-exposure prophylaxis has been initiated and appropriate laboratory diagnostic testing (ie, the direct fluorescent antibody test) indicates that the exposing animal was not rabid, post-exposure prophylaxis can be discontinued. (11)

3. **Treatment outside the United States**

If post-exposure is begun outside the United States with locally produced biologics, it may be desirable to provide additional treatment when the patient reaches the US. State or local health departments should be contacted for specific advice in such cases. (11)

**POST-EXPOSURE RABIES PROPHYLAXIS GUIDE**

The following recommendations are only a guide. In applying them, take into account the animal species involved, the circumstances of the bite or other exposure, the vaccination status of the animal, the availability of the exposing animal for observation or rabies testing, and the presence of rabies in the region (see Table 2). Local or state public health officials should be consulted if questions arise about the need for rabies prophylaxis. (11)

**CONTRAINDICATIONS**

Pre-exposure Prophylaxis

Do not administer to anyone with a known life-threatening systemic hypersensitivity reaction to any component of the vaccine (see WARNINGS, PRECAUTIONS, and DESCRIPTION sections).

Post-exposure Prophylaxis

None.

**WARNINGS**

- Do not inject the vaccine into the gluteal area as administration in this area may result in lower neutralizing antibody titers. (11)
- The product is provided in a single dose vial. Because the single dose vial contains no preservative, it is not to be used as a multidose vial for intradermal injection.
- In both pre-exposure and post-exposure immunization, the full 1.0 mL dose should be given intramuscularly.
- Serum sickness type reactions have been reported in persons receiving booster doses of rabies vaccine for pre-exposure prophylaxis. The reaction is characterized by onset approximately 2 to 21 days post-booster, presents with a generalized urticaria, and may also include arthralgia, arthritis, angioedema, nausea, vomiting, fever, and malaise. None of the reported reactions were life-threatening. This has been reported in up to 7% of persons receiving booster vaccination. (13)
- Rare cases of neurologic illness resembling Guillain-Barré syndrome, (14) (15) a transient neuroparalytic illness, that resolved without sequelae in 12 weeks and a focal subacute central nervous system disorder temporally associated with HDCV, have been reported. (16)
- This product contains albumin, a derivative of human blood. Based on effective donor screening and product manufacturing processes, it carries an extremely remote risk for transmission of viral diseases, CJD, or vCJD. There is a theoretical risk for transmission of Creutzfeldt-Jakob disease (CJD), but if that risk actually exists, the risk of transmission would also be considered extremely remote. No cases of transmission of viral diseases, CJD, or vCJD have ever been identified for licensed albumin or albumin contained in other licensed products.

All serious systemic neuroparalytic or anaphylactic reactions to a rabies vaccine should be immediately reported to VAERS at 1-800-822-7967 (http://vaers.hhs.gov) or Sanofi Pasteur Inc., 1-800-VACCINE (1-800-822-2463).

Vaccination with Immovax Rabies vaccine may not protect 100% of vaccinated individuals.

**PRECAUTIONS**

- IN ADULTS AND CHILDREN THE RABIES VACCINE SHOULD BE INJECTED INTO THE DELTOID MUSCLE. IN INFANTS AND SMALL CHILDREN, THE ANTEROLATERAL ASPECT OF THE THIGH MAY BE PREFERABLE.*
- When a person with a history of hypersensitivity must be given rabies vaccine, antihistamines may be given. Epinephrine (1:1000) and other appropriate agents should be readily available to counteract anaphylactic reactions, and the person should be carefully observed after immunization.
- While the concentration of antibiotics in each dose of vaccine is extremely small, persons with known hypersensitivity to any of these agents, or any other component of the vaccine, could manifest an allergic reaction. While the risk is small, it should be weighed in light of the potential risk of contracting rabies.

**DRUG INTERACTIONS**

Corticosteroids, other immunosuppressive agents or treatments, and immunosuppressive illnesses can interfere with the development of active immunity and predispose the patient to developing rabies. Immunosuppressive agents should not be administered during post-exposure therapy, unless essential for the treatment of other conditions. When rabies post-exposure prophylaxis is administered to persons receiving steroids or other
immunosuppressive therapy, it is especially important that serum be tested for rabies antibody to ensure that an adequate response has developed. (11)

**USAGE IN PREGNANCY**

Pre-exposure
Animal reproduction studies have not been conducted with Imovax Rabies vaccine. It is also not known whether Imovax Rabies vaccine can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. Imovax Rabies vaccine should be given to a pregnant woman only if potential benefits outweigh potential risks. If there is substantial risk of exposure to rabies, pre-exposure prophylaxis may also be indicated during pregnancy. (11)

Post-exposure
Because of the potential consequences of inadequately treated rabies exposure and limited data that indicate that fetal abnormalities have not been associated with rabies vaccination, pregnancy is not considered a contraindication to post-exposure prophylaxis. (11) (17)

**USAGE IN NURSING MOTHERS**

It is not known whether Imovax Rabies vaccine is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Imovax Rabies vaccine is administered to a nursing woman.

**PEDIATRIC USE**

Both safety and efficacy in children have been established.

**ADVERSE REACTIONS**

- Once initiated, rabies prophylaxis should not be interrupted or discontinued because of local or mild systemic adverse reactions to rabies vaccine. Usually such reactions can be successfully managed with anti-inflammatory, antihistaminic, and antipyretic agents. (11)
- Reactions after vaccination with HDCV have been observed. (13) In a study using five doses of HDCV, local reactions such as pain, erythema, swelling or itching at the injection site were reported in about 25% of recipients of HDCV, and mild systemic reactions such as headache, nausea, abdominal pain, muscle aches, and dizziness were reported in about 20% of recipients. (8)
- Serious systemic anaphylactic or neuropsychiatric reactions occurring during the administration of rabies vaccines pose a dilemma for the attending physician. A patient’s risk of developing rabies must be carefully considered before deciding to discontinue vaccination. Moreover, the use of corticosteroids to treat life-threatening neuropsychiatric reactions carries the risk of inhibiting the development of active immunity to rabies. It is especially important in these cases that the serum of the patient be tested for rabies antibodies. Advice and assistance on the management of serious adverse reactions in persons receiving rabies vaccines may be sought from the local or state health department. (8)
- SEE WARNINGS AND CONTRAINdications sections for additional statements.

**Data from post-marketing experience**

The following additional adverse events have been identified during postapproval use of Imovax Rabies vaccine. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to Imovax Rabies vaccine exposure.

- **Blood and Lymphatic System Disorders**
  - Lymphadenopathy
- **Immune System Disorders**
  - Anaphylactic reaction, serum sickness type reaction, dermatis allergic, pruritus (itching), edema
- **Nervous System Disorders**
  - Paresthesia, neuropathy, convulsion, encephalitis
- **Gastrointestinal Disorders**
  - Vomiting, diarrhea
- **Musculoskeletal and Connective Tissue Disorders**
  - Arthralgia
- **General Disorders and Administration Site Conditions**
  - Asthenia, malaise, fever and chills (shivering), injection site hematoma
- **Respiratory, Thoracic, and Mediastinal Disorders**
  - Wheezing, dyspnea

**DOSE AND ADMINISTRATION**

The package contains a vial of freeze-dried vaccine, a Luer-Lok™ syringe containing 1.0 mL of diluent with a plunger rod either inserted into the syringe or provided separately, and a sterile reconstitution needle. The syringe and its package should be inspected prior to use for evidence of leakage, premature activation of the plunger rod, or a faulty tip seal. If evidence of such defects is observed, the product should not be used.

**Instructions for vaccine reconstitution**

Luer-Lok™ syringe components (with plunger rod inserted)

1. **Step 1:** Remove plastic cover from the vial. Cleanse the vial stopper with a suitable germicide. Do not remove the stopper or the metal seal holding it in place.
2. **Step 2:** Screw the plunger rod into the syringe, if it is provided separately.
3. **Step 3:** Hold the syringe cap in one hand (avoid holding the plunger rod or syringe barrel), and unscrew the tip cap by twisting it counterclockwise.
4. **Step 4:** Attach the reconstitution needle to the syringe, by gently twisting the needle clockwise into the syringe until slight resistance is felt.
5. **Step 5:** Reconstitute the freeze-dried vaccine by injecting the diluent from the syringe into the vial. While the syringe and reconstitution needle are still attached, gently swirl the contents of the vial until completely dissolved and proceed to Step 6.
6. **Step 6:** Prior to withdrawing vial contents and without removing the reconstitution needle from the vial, unscrew the syringe to eliminate negative pressure (as the vial is sealed under vacuum). Reattach the syringe to the reconstitution needle which has remained in the vial.
7. **Step 7:** Withdraw the total contents of the vial into the syringe. Remove the reconstitution needle and discard it.
8. **Step 8:** Attach a new sterile needle (as per step 4) of a proper length and gauge suitable for intramuscular injection.

The supplied syringe is intended for single use only, must not be reused, and must be disposed of properly and promptly following its use. To help avoid transmission of infectious diseases due to accidental needle sticks, needles should not be recapped but disposed of according to recommended guidelines. The reconstituted vaccine should not be mixed with any other vaccine and should be used immediately.

**Vaccine administration**

Parenteral drug products should be inspected for particulate matter and discoloration prior to administration, whenever solution and container permit. If evidence of such defects is observed, the product should not be used.

After preparation of the injection site with an appropriate germicide, immediately inject the vaccine intramuscularly. For adults and older children, the vaccine should be injected into the deltoid muscle. (10) (18) (19) In infants and small children, the anterolateral aspect of the thigh may be preferable, depending on age and body mass. Care should be taken to avoid injection into or near blood vessels and nerves. If blood or any suspicious discoloration appears in the syringe, do not inject but discard contents and repeat procedure using a new dose of vaccine at a different site.

The gluteal area should not be used for administration of the vaccine as administration in this area may result in lower neutralizing antibody titers. (11)

**NOTE:** The freeze-dried vaccine is creamy white to orange. After reconstitution, it is pink to red.

**Dosage schedules**

A. Pre-exposure dosage

1. **Primary vaccination**

   In the United States, the Advisory Committee on Immunization Practices (ACIP) recommends three injections of 1.0 mL each, one injection on Day 0, one on Day 7, and one either on Day 21 or 28. (11)

2. **Booster dose**

   A booster dose consists of one injection of 1.0 mL of Imovax Rabies vaccine. To ensure the presence of a primed immune response over time among persons at higher than normal risk for exposure, titers should be checked periodically, with booster doses administered only as needed. Persons working with live rabies virus in research laboratories and in vaccine production facilities (continuous risk category) should have rabies antibody titers checked every six months and boosters given as needed to maintain an adequate titer defined as virus neutralization at a 1:5 dilution by a RFFIT. Other laboratory workers (eg, those performing rabies diagnostic testing), cavers, veterinarians and staff, animal-control and wildlife officers in areas where rabies is enzootic, and bat handlers regardless of location, (requent risk category), should have their serum tested for rabies antibody every 2 years. If their titer is inadequate, they should receive a single booster dose of vaccine. Veterinarians, veterinary students, and terrestrial animal-control and wildlife officers, working in areas of low rabies endemicity (infrequent risk category) and certain at-risk international travelers who have completed a full pre-exposure vaccination series with licensed vaccines and according to schedule do not require routine booster serologic verification of detectable antibody titers or routine pre-exposure booster doses of vaccine (see Table 1). (11)

   Persons who have experienced "immune complex-like" hypersensitivity reactions should receive no further doses of Imovax Rabies vaccine unless they are exposed to rabies or they are truly likely to be inapparently and/or unavoidably exposed to rabies virus and have unsatisfactory antibody titers.
REFERENCES


15. CDC. Adverse reactions to human diploid cell rabies vaccine. MMWR. 1980;29:609-10.


Product information as of December 2019.
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