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Vaccine Shortage in Light of a Rise in Rabies Exposure By: Connie Cheng, Pharm.D.

What is rabies?

Rabies is a life-threatening disease caused by viruses that belong to the genus *Lyssavirus*.¹ Onset of symptoms can occur up to months after a bite, which include pain, fatigue, headaches, fever, and irritability followed by development of seizures, hallucinations, and paralysis.²

How prevalent is rabies in the United States today?

Overall, there were 6,031 rabid animals (e.g., raccoons, skunks, foxes) reported to the Centers for Disease Control and Prevention (CDC) in 2011; this was a 1.9% decrease from 2010 when 6,153 rabid animals and two human cases were reported.¹ However, CDC epidemiologists estimate up to 7,000 rabid animals may be confirmed by the end of 2012; this increase can be attributed to a milder winter causing an earlier start to bat season and an increase in rabid animal attacks.² In the United States, an estimated 23,000 to 38,000 people annually receive post-exposure vaccinations after having possible or confirmed exposure to rabid animals.³

What are the Advisory Committee on Immunization Practices' (ACIP) current recommendations for pre- and post-exposure prophylaxis?

The ACIP, an advisory committee to the CDC, recommends pre-exposure vaccination for people who are at an increased risk for rabies exposure and to protect those who may experience a delay in obtaining post-exposure prophylaxis.⁴ Pre-exposure vaccination reduces the number of post-exposure vaccine doses required and eliminates the need for rabies immune globulin.⁴ Recommendations approved by the ACIP for pre-exposure and post-exposure prophylaxis are summarized in Table 1 and Table 2, respectively.

How soon should rabies vaccine (RV) and human rabies immunoglobulin (HRIG) be given for post-exposure prophylaxis in patients who have not been previously immunized? Is there a maximum window of time that the RV and/or HRIG can be administered following an exposure?

Rabies vaccine and HRIG should be given as early as possible following an exposure.⁵⁻⁷ Regardless of when treatment is initiated, HRIG along with the RV series should be given to persons who have not been previously immunized (See Table 2). The HRIG must be administered within 7 days after the first dose of RV is given. Beyond the seventh day, HRIG is not recommended since an antibody response to the vaccine is presumed to have occurred by that time point. Patients who received pre-exposure RV prophylaxis do not require HRIG. Although a maximum window of time for post-exposure prophylaxis has not been established, treatment has been given 6 months or longer following a previously unrecognized exposure.⁶

Table 1: Rabies Pre-exposure Prophylaxis Guide²⁻⁶

Risk Category	Typical Population	Pre-exposure Recommendations
<p>Continuous Virus present continuously, often in high concentrations</p> <p>Specific exposures likely to go unrecognized</p> <p>Bite, nonbite or aerosol exposures*</p>	<ul style="list-style-type: none"> Rabies research laboratory workers Rabies biologics production workers 	<p>Primary course[†]</p> <p>Serologic rabies antibody testing every 6 months; booster vaccination if antibody titer is below acceptable level[†]</p>
<p>Frequent Exposure usually episodic, with source recognized</p> <p>Exposure might be unrecognized bite, nonbite or aerosol exposure</p>	<ul style="list-style-type: none"> Rabies diagnostic lab workers Spelunkers Veterinarians and staff Animal-control and wildlife workers in rabies-enzootic areas Persons who frequently handle bats 	<p>Primary course[†]</p> <p>Serologic rabies antibody testing every 2 years; booster vaccination if antibody titer is below acceptable level[†]</p>
<p>Infrequent (Greater than population-at-large)</p> <p>Exposure nearly always episodic with source recognized</p> <p>Bite or nonbite exposure</p>	<ul style="list-style-type: none"> Veterinarians and terrestrial animal-control workers in areas where rabies is uncommon to rare Veterinary students Travelers visiting areas where rabies is enzootic and immediate access to medical care is limited 	<p>Primary course[†]</p> <p>No serologic testing or booster vaccination needed</p>
<p>Rare (Population-at-large)</p> <p>Exposures always episodic with source recognized</p> <p>Bite or nonbite exposure</p>	<ul style="list-style-type: none"> U.S. population at large, including persons in rabies-epizootic areas 	<p>No vaccination necessary</p>

*Bite is referred to as any skin penetration by teeth. Nonbite exposure can be scratches, abrasions, open wounds, or mucous membranes contaminated with saliva or other potentially infectious material like brain tissue from a rabid animal.

[†]Three 1 mL injections of RabAvert[®] or Imovax[®] Rabies vaccine should be administered intramuscularly (IM) in the deltoid area for a total of three doses, given at the following times:
Dose 1: As appropriate (day 0)
Dose 2: 7 days after dose 1 (day 7)
Dose 3: 21 days or 28 days after dose 1 (day 21 or 28)

[‡]Minimal acceptable antibody level is complete viral neutralization at a 1:5 serum dilution by the rapid fluorescent focus inhibition test. A booster dose of one IM injection of 1 mL of RabAvert[®] or Imovax[®] Rabies vaccine should be administered if the titer falls below this level.

Table 2: Rabies Post-exposure Prophylaxis Guide^{2,7-10}

	Wound Cleansing	Human Rabies Immune Globulin (HRIG)	Vaccine
Not Previously Immunized	<p>All post-exposure prophylaxis should begin with immediate thorough cleansing of all wounds with soap and water</p> <p>If available, a virucidal agent (e.g., povidine-iodine solution) should be used for wound irrigation</p>	<ul style="list-style-type: none"> Full dose (20 international units/kg or 0.133 mL/kg of actual body weight) of Imogam Rabies[®]-HT or HyperRAB[®] S/D should be infiltrated around any wound(s), any remaining volume should be given intramuscularly (IM) at a distant site* from vaccine administration Do not administer more than recommended dose Do not administer in same syringe as vaccine 	<p>Inject 1 mL IM of RabAvert[®] or Imovax[®] Rabies in deltoid area[†] given at the following times: Dose 1: As appropriate (day 0)[‡] Dose 2: 3 days after dose 1 (day 3) Dose 3: 7 days after dose 1 (day 7) Dose 4: 14 days after dose 1 (day 14) Dose 5: If needed, 28 days after dose 1 (day 28)[§]</p>
Previously Immunized	<p>All post-exposure prophylaxis should begin with immediate thorough cleansing of all wounds with soap and water</p> <p>If available, a virucidal agent (e.g., povidine-iodine solution) should be used for wound irrigation</p>	<p>Do NOT administer</p>	<p>Inject 1 mL IM of RabAvert[®] or Imovax[®] Rabies in deltoid area[†] given at the following times: Dose 1: As appropriate (day 0)[‡] Dose 2: 3 days after dose 1 (day 3)</p>

*Deltoid muscle of the upper arm or lateral thigh muscle. The gluteal region should not be used as an injection site due to risk of injury to sciatic nerve. Human rabies immune globulin (HRIG) should never be administered at the same anatomical site as first vaccine dose. However, subsequent doses of vaccine in the four-dose series can be given in same anatomic location where HRIG dose was administered.

[†]Deltoid area is the only acceptable site of vaccination for adults and older children. For younger children, outer aspect of the thigh may be used. Vaccine should never be administered in the gluteal area.

[‡]Day 0 is the day dose 1 of vaccine is administered.

[§]For persons with immunosuppression, rabies post-exposure prophylaxis should be administered using five doses of vaccine on days 0, 3, 7, 14, and 28.

^{||}Any person with a history of rabies vaccine and a documented history of antibody response to the prior vaccination.

Are there different pre- and post-exposure ACIP recommendations for immunocompromised patients?

If a patient's immunocompromised state is temporary and can be resolved, rabies pre-exposure prophylaxis should be postponed.⁹ However, post-exposure prophylaxis should be initiated as soon as possible following exposure. If feasible, immunosuppressive agents should also be avoided while patients receive rabies post-exposure prophylaxis therapy. A fifth dose of RV for post-exposure should be administered on day 28 for immunosuppressed patients.

How does the product labeling approved by the Food and Drug Administration (FDA) for RV differ from the ACIP recommendation for post-exposure prophylaxis in individuals who have not been previously immunized?

The original product labeling for RV recommends that five doses of RV be given for post-exposure prophylaxis regardless of the patient's immune status.^{5,6} However based on clinical studies demonstrating comparable efficacy and safety between the four- and five-dose RV regimens, the ACIP currently recommends a four-dose RV regimen for immunocompetent individuals and a five-dose RV regimen for patients with immunosuppression.⁹

Do patients who have not been bitten but may have been exposed to a potentially rabid animal need post-exposure prophylaxis?

Post-exposure prophylaxis should also be considered for anyone who might be unaware of a possible bite or direct contact that may have occurred (e.g., a sleeping person awakens to find a bat in the room).⁶

What RVs and HRIGs products are available? Are different brands of RV interchangeable?

Imovax[®] Rabies (Sanofi Pasteur) and RabAvert[®] (Novartis) are the two inactivated rabies virus vaccines currently available.^{5,6} The two brands of HRIG available for post-exposure prophylaxis are Imogam[®] Rabies-HT (Sanofi Pasteur) and HyperRAB[®] S/D (Talecris Biotherapeutics).^{8,11}

Imovax[®] Rabies and RabAvert[®] are considered generically equivalent and interchangeable for pre- and post-exposure prophylaxis.¹² Therefore, a different brand can be used if the brand used for previous doses becomes unavailable before completion of the vaccination series. However, it is generally recommended that the same brand be used for the entire vaccination series if possible, since the origin and excipients vary between the two products.^{5,6}

What are the recommended doses for RV and HRIG? Are the pediatric and adult doses the same? Can these products be used in pregnant women?

The dosage recommendations for pre-exposure and post-exposure vaccination with RabAvert[®] and Imovax[®] Rabies are the same for all age groups; infants and children receive an intramuscular (IM) injection of 1 mL as do adults.^{5,6}

The weight-based dosing regimens for Imogam[®] Rabies-HT and HyperRAB[®] S/D are also the same for all age groups, which is 20 international units/kg (0.133 mL/kg) based on actual body weight.^{8,11} Active immunization to the vaccine may be impaired (e.g., interference of active antibody production) if the administered dose of HRIG exceeds the recommended dose.⁶

All RV and HRIG products are classified as pregnancy-risk category C.^{5,6,8,11} Due to lack of animal reproduction studies, it is not known whether the administration of these products will cause fetal harm. Therefore, RV and HRIG should be given to a pregnant woman when potential benefits outweigh the risks.

How and where are RV and HRIG administered?

The RV is administered by IM injection.^{5,6} The deltoid area is the only acceptable site of vaccination for adults and older children. For younger children, outer aspect of the thigh may be used. The vaccine should never be administered in the gluteal area due to potential reduction in immunological response.⁹

The full dose of HRIG should be infiltrated around any wound(s), any remaining volume should be given IM at a distant site from vaccine administration.^{8,11} If a wound is not present, alternate sites for IM injection include deltoid muscle of the upper arm or lateral thigh muscle. The same site can be selected for each HRIG IM injection provided that the sites are spaced at least one inch apart. The gluteal region should not be used as an injection site due to risk of injury to the sciatic nerve.⁹ Human rabies immune globulin should never be administered at the same anatomical site as the first vaccine dose.⁸ However, subsequent doses of RV in the four-dose series can be given in the same anatomic location separated by at least one inch where the HRIG dose was administered. A volume of 5 mL of HRIG should not be exceeded at any one site.¹³ However, patient-specific factors including age and muscle mass should be considered in determining an appropriate volume to be administered at one site.

What is the current drug shortage situation with RV? Is there also a shortage of HRIG?

The increased incidence of rabid animals reported this past year has affected the availability of the two RVs (RabAvert[®] and Imovax[®] Rabies) in the United States.

Due to limited overall supply, Novartis, the manufacturer of RabAvert[®], is currently unable to directly supply RabAvert[®] for pre-exposure prophylaxis.¹⁴ However, wholesale distributors who have RabAvert[®] in stock will continue to provide this product for pre-exposure prophylaxis. These supplies are expected to adequately meet the demand for pre-exposure vaccination until new product is released from the manufacturer.

Sanofi Pasteur, the manufacturer of Imovax[®] Rabies-HT, is currently unable to supply the RV for pre-exposure prophylaxis and is releasing the product for post-exposure emergency use only.^{14,15}

Sanofi Pasteur, the manufacturer of Imogam[®] Rabies-HT, is directing requests for HRIG to Grifols/Talecris Biotherapeutics, the supplier of HyperRAB[®] S/D.¹⁶ Recommendations for post-exposure prophylaxis with HRIG should remain unaffected as supplies of HyperRAB[®] S/D are expected to meet the demand for post-exposure vaccination.

Are there any restrictions/requirements for obtaining RV? How long will it take to receive an order for RV?

Each brand of RV is associated with different requirements. At this time, there is no limitation in supply of RabAvert[®] for post-exposure prophylaxis and Novartis can directly fill such orders. No paperwork is required to confirm post-exposure prophylaxis before placing an order for RabAvert[®]. However, requests can only be made on a case-by-case basis in which the healthcare provider must answer a series of questions regarding the patient's exposure (e.g., type of bite) and treatment received. For each patient, up to five doses of the vaccine can be supplied by the manufacturer if the provider requests them. After submitting the order to Novartis, the vaccine should arrive within 24 to 48 hours; however if the order is placed on a Friday, normal delivery would be on Tuesday, unless Saturday delivery is requested. Novartis expects additional lots of RabAvert[®] to be released in the coming months.¹⁴

Due to a significant increase in demand along with manufacturing delays over the past summer, Sanofi Pasteur has notified healthcare providers that a Rabies Post-exposure Form must be submitted in order to obtain Imovax[®] Rabies vaccine for post-exposure prophylaxis.¹⁷ The prescriber must complete the Rabies Post-exposure Form. Although Sanofi Pasteur offers overnight delivery, the turnaround time during the week is 24 to 48 hours. If the order is placed on Friday, Saturday delivery can be arranged, otherwise the order will be received on Tuesday. The company estimates that Imovax[®] Rabies will be readily available by the end of 2012, but a definite release date has not been determined.

Federal, state, and local public health personnel will continue to monitor the availability of the rabies vaccines and immunoglobulin to determine if additional strategies are needed to prevent future shortages. Updates regarding the supply constraints are posted to the CDC Rabies News website as available: <http://www.cdc.gov/rabies/resources/news/>

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Formulary Update

The CCHS Medical Staff P&T Committee met on November 28, 2012, and the Cleveland Clinic Local P&T Committee met on December 12, 2012, and the following decisions were made.

Pediatrics:

There were no changes made to the Children's Hospital/Pediatric Formulary for the 4th quarter 2012.

Adults:

Additions to the CCHS Formulary:

Critical Care/Surgery/Anesthesia:

1) **Oxymorphone immediate-release (IR) and extended-release (ER) (Opana[®] IR and ER)**

- a) It is an opioid analgesic and currently a therapeutic interchange is in place to convert this agent to morphine in equipotent doses; however, the drug is being added to Formulary to improve patient care and satisfaction issues with maintaining opioid therapy from home.
 - b) Oxymorphone IR and ER use is **restricted** to continuation of therapy from home (i.e., no initiation of therapy in the hospital).
 - c) The existing therapeutic interchange will still be used to convert *initiation of oxymorphone therapy* to morphine IR and ER (the therapeutic interchange would not apply for continuation of therapy from home).
- 2) **Tranexamic acid injection:** It is a synthetic lysine amino acid derivative which forms a reversible complex that displaces plasminogen from fibrin resulting in inhibition of fibrinolysis. Intravenous tranexamic acid is already on the Formulary for an off-label indication to decrease post-operative bleeding in total joint arthroplasty (TJA). Now, the **topical route** of administration (topical application of the injection) will be allowed to be given based on published data to reduce post-operative bleeding in orthopedic procedures and decrease adverse events.

Hematology and Medical Oncology:

- 1) **Liposomal cytarabine (Depocyt[®]):** It is FDA-approved for intrathecal treatment of lymphomatous meningitis. It has also been studied in neoplastic meningitis from solid tumor malignancies such as breast cancer and other primary brain cancers. Liposomal cytarabine is a sustained-release formulation that can only be administered intrathecally. Less frequent administration is required with liposomal cytarabine (every 2 weeks) compared to conventional intrathecal cytarabine (twice per week) since conventional cytarabine has a much shorter half-life (3 to 4 hours) versus the liposomal formulation (5.9 to 82.4 hours). The drug is being added to Formulary because in some patients, the liposomal form is preferred to conventional cytarabine (e.g., in breast cancer patients who do not have an ommaya due to less frequent administration of the drug).
 - a) Liposomal cytarabine is **restricted** to the Department of Hematology/Oncology for outpatient use only.

Did Not Add to the CCHS Formulary:

- 1) **Ziv-aflibercept (Zaltrap[®]):** This agent was not added to the Formulary for the treatment of metastatic colorectal cancer because of its similar efficacy to a current Formulary agent [bevacizumab (Avastin[®])], and it is significantly more expensive.

Changes in Current CCHS Formulary Restrictions:

1) **Telaprevir (Incivek[™]) and Boceprevir (Victrelis[®]):**

- a) Telaprevir and boceprevir restrictions have been updated to include Infectious Diseases. Therefore, telaprevir and boceprevir will be restricted to Hepatology, Transplant Services, or Infectious Diseases for continuation of therapy from home.

Practice Guidelines:

- 1) For Smart Pumps, the upper hard limit for IV diltiazem is 15 mg/hr, and there is no soft upper limit for diltiazem because there are no data to support doses greater than 15 mg/hr.

Policy/ Practice Changes:

1) **Latex Policy (Nursing Units and Operating Rooms):**

- a) All vials used in latex allergic patients will be considered single-dose vials. Pharmacy does not need to be called to determine latex content of medication. Medications will be removed from vials using the “one-stick” method described below.
- b) Latex-containing vial stoppers may be punctured only once using the “one-stick” method with an 18-gauge or smaller needle to remove the medication from a new, unopened vial.
 - i) If the vial stopper has been previously punctured, the “one-stick” method cannot be utilized.
 - ii) Following removal of the initial dose from a vial using the “one-stick” method, discard any remaining medication in the vial. It cannot be used for subsequent administration to the patient.
 - (1) Exception: In Ambulatory Clinics, if a latex allergic patient needs a vaccine dose from a multi-dose vial, a brand new vial must be used. *However, the remainder of the vaccine in the multi-dose vial can be used for non-latex allergic patients* (this is due to the fact that some of the vaccines are expensive).
- c) For medications that require reconstitution, the stopper of the vial may be punctured only once to both reconstitute the medication and remove the solution from the vial. The needle must remain in place in the vial stopper during reconstitution.

2) **Pain Ease:**

- a) Pain Ease is not permitted for use on inpatients.
- b) Pain Ease is permitted for use on outpatients (in Ambulatory Clinics) EXCEPT for the following:
 - i) Blood culture draws [may be used for other types of blood draws associated with labs (e.g., BMP, CMP)]
 - ii) Sterile device insertion, including line placement
 - iii) Sterile procedures (e.g., joint space aspiration)
- c) Nursing is working on a policy and procedure specifically for using Pain Ease in the Ambulatory Setting.

3) **Heparin Infusions To Be Mixed In Dextrose 5% in Water (D5W) Only**

- a) For medication safety and to reduce medication errors, heparin infusions will only be prepared and dispensed in D5W by the pharmacy.