Background to Rabies Pre-exposure Prophylaxis, Vaccine Safety, and Work Group Considerations

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Advisory Committee on Immunization Practices
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Rabies in humans

- Acute, progressive encephalomyelitis that is nearly always fatal
- Transmitted from infected mammals by bite, scratch, or exposure to saliva or neural tissue
- Not transmitted by exposures to blood, urine, or feces of infected animals
- No known laboratory confirmed cases of human-to-human transmission through exposure to infected persons
- Rare cases in U.S.; ~0-4 cases / year
Transmission

- Few animal species are reservoirs for rabies
- Rabies virus variants (RVV)
  - Named for animal reservoir species in which they circulate
  - Confined to geographically definable regions
- Infection can be transmitted from the reservoir species to other species
  - Example, Raccoon RVV can spread from a raccoon → a cat → a human
  - RVV does not denote the animal to which the human was exposed
Distribution of RVV in United States

- Canine RVV successfully eliminated
- Terrestrial (or wildlife) rabies
  - Wildlife are reservoirs
  - Eg., skunk, fox, mongoose, raccoon
- Non-terrestrial rabies
  - Bats are reservoirs
  - Endemic in all states except Hawaii

**Distribution of terrestrial RVV—United States, 2018**

Skunk RVV: Orange = South central, Blue = North central, Brown = California; Fox RVV: Red = Arctic fox, Hash = Gray fox; Raccoon RVV: Green; Mongoose RVV: Yellow.
Activities that have led to confirmed human cases in U.S.

- **Domestic**
  - Recreational
  - Occupational including laboratory and field work
  - Contacts in everyday life
    - Bats in home
    - Residence in wooded areas with opportunities for exposure
  - Organ and tissue transplants

- **International travel**
  - Recreational
  - Occupational including laboratory and field work
Prevention of human rabies

- Vaccinating domestic and wild animals
- Vaccinating humans
  - Pre-exposure prophylaxis (PrEP)
    - Comprised of rabies vaccine schedule
    - >15,000 persons receive PrEP / year in U.S.
  - Post-exposure prophylaxis (PEP)
U.S. rabies vaccines
## Vaccines licensed in U.S.

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Product name</th>
<th>Manufacturer</th>
<th>Licensed for Administration</th>
</tr>
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<tbody>
<tr>
<td>Human diploid cell vaccine (HDCV)</td>
<td>Imovax®</td>
<td>Sanofi Pasteur</td>
<td>Intramuscularly</td>
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<tr>
<td>Purified chick embryo cell vaccine (PCECV)</td>
<td>RabAvert</td>
<td>GlaxoSmithKline (In future: Bavarian Nordic)</td>
<td>Intramuscularly</td>
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Vaccine Adverse Event Reporting System (VAERS) safety data for HDCV; Imovax*

- VAERS received 1,666 reports following HDCV (1/1/1990-12/31/2019)
  - 1,571 (94.3%) were non-serious
- Systemic reactions were observed
  - Headache (18.8%), pyrexia (18.1%), and nausea (17.1%)
- Angioedema rarely reported
- Findings are consistent with pre-licensure and post-marketing studies

VAERS: Vaccine Adverse Event Reporting System
VAERS safety data for PCECV; RabAvert*

- VAERS received 739 reports following PCEC
  - 686 (92.8%) were non-serious

- Most common systemic reactions observed were headache (19.5%), pyrexia (18.5%), nausea (18.1%)

- Findings consistent with findings of pre-licensure studies and a previous evaluation of PCECV vaccine in VAERS during 1997-2005 †

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† Dobardzic A et al. Vaccine. 2007;25:4244–51
VAERS: Vaccine Adverse Event Reporting System
Safety data from 25 trials published since 2008 ACIP recommendations

- Publications involved comparison of
  - New vaccine and one of the 2 US vaccines
  - Intradermal administration and intramuscular
  - Co-administration with other vaccines (e.g., Japanese Encephalitis vaccine)
  - Varying schedules
  - Use in pregnant persons and children

- Safety findings
  - Similar to that of VAERS data and package insert
  - Unchanged and favorable safety profile
Persons who should receive PrEP
Purpose of PrEP

- Provide partial immunity to persons who are at risk for rabies
- Persons who receive PrEP still need PEP after an exposure
  - Rabies immune globulin not given
  - Vaccine series shorter
- Intended for persons who may have unrecognized or frequent exposures to rabies virus or delays in starting PEP
- Recommendations for PrEP vary depending on level of risk to unrecognized exposures
Risk categories for PrEP

- Developed to outline
  - Populations that should receive PrEP
  - Recommendations for schedules and frequency of titer checks
- Named for level of risk for unrecognized exposures
  - Continuous: highest risk
  - Frequent
  - Infrequent
  - Rare: least risk (general U.S. population)
# Rabies PrEP guide

## Table 6: Rabies pre-exposure prophylaxis guide — United States, 2008

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<td>Exposure usually episodic, with source recognized, but exposure also might be unrecognized. Bite, nonbite, or aerosol exposure.</td>
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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 if the titer falls below this level.
Factors to consider when applying risk categories to populations

- Activity performed
- Geographic region of mammal to which there might be exposure
- Access to safe and effective PEP
Activity performed

- **Occupation:**
  - Handling live rabies virus in diagnostic, research or vaccine production capacities (e.g., rabies diagnostician)
  - Contact with bats (e.g., bat ecologist)
  - Contact with terrestrial mammals (e.g., veterinarian or wildlife biologists)

- **Recreation:**
  - Contact with bats (e.g., spelunker)
  - International travel involving potential exposure to rabid animals
Geographic region of mammals to which there might be exposure

- **Domestic**
  - Wildlife work in WA state may involve lower risk than same work in PA
  - Spelunker entering only caves in Hawaii may have lower risk than spelunker entering caves in AB

- **International**
  - Determine if canine rabies is present for general traveler
Access to PEP

- An important consideration for international travel
- Nearly all major cities have rabies vaccine and rabies immune globulin
  - For most, the available vaccine is safe
  - Rabies immune globulin typically also available
- Persons traveling in rural areas may not have easy access to PEP
## Rabies PrEP guide

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<td>Veterinarians and animal-control staff working with terrestrial animals in areas where rabies is uncommon to rare. Veterinary students. Travelers visiting areas where rabies is enzootic and immediate access to appropriate medical care including biologics is limited.</td>
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<td>U.S. population at large, including persons in areas where rabies is epizootic.</td>
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* 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 if the titer falls below this level.
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# Proposed PrEP clinical guidance

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<tr>
<th>Risk category</th>
<th>Nature of Risk</th>
<th>Disease Biogeography</th>
<th>Typical Population</th>
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| Continuous    | Risk of virus exposure is continuous. Exposure is often in high concentrations and may go unrecognized. Direct and indirect exposures. | Laboratory | Laboratory personnel working with live rabies virus in research, diagnostic, or vaccine production capacities (e.g., necropsy of suspect rabid animal or working with rabies virus cultures) | • ? schedule  
• ? Frequency of serologic monitoring³ |
| Frequent      | Risk of virus exposure is episodic. Exposure typically recognized but could be unrecognized. Direct exposures and rarely indirect exposures | Geographic regions where bats are the only reservoirs for rabies** | Persons who frequently handle or come into contact with bats (e.g., bat biologist) | • ? schedule  
• ? Frequency of serologic monitoring³ |
| Infrequent    | Risk of virus exposure greater than population at large. Exposure is a recognized one. Direct exposures. | Geographic regions where bats are the only reservoir for rabies | Animal care professionals (e.g., veterinarians, technicians, animal control officers) 
Others who repeatedly handle terrestrial reservoir species (e.g., wildlife biologists, rehabilitators, and trappers) | • ? schedule  
• No serologic monitoring |
|               | | Geographic regions where terrestrial mammals are reservoirs for rabies | Animal care professionals 
Others who repeatedly handle terrestrial reservoir species 
Spelunkers | |
|               | | Geographic regions internationally with canine rabies | Veterinary students 
Short-term / volunteer hands-on animal care workers where increased risk is expected for short time periods | |
| Rare (i.e., general population) | Risk of virus exposure is uncommon. Bite or non-bite exposure | Nationwide | U.S. population at large | • No pre-exposure prophylaxis  
• No serologic monitoring |

*Direct exposures are bite and non-bite (e.g., contamination of fresh open wound or mucous membranes with saliva), indirect exposures (i.e., droplet)

³For questions about the disease biogeography of the region where an exposure occurred, please contact your local or state health department

³Minimal acceptable antibody level is 0.5 IU/mL

⁴Terrestrial mammals are non-bat species (e.g., racoons, skunks, livestock). If you are uncertain which mammals in your region may circulate rabies, please contact your local or state health department

**Bats are reservoirs for rabies in all US states except Hawaii

**Geographic regions where bats are the only reservoirs for rabies**

**Geographic regions where terrestrial mammals are reservoirs for rabies**

**Geographic regions internationally with canine rabies**
Continuous and frequent risk categories: Disease biogeography and typical population

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|               |               | Geographic regions where terrestrial mammals³ are reservoirs for rabies | • Animal care professionals (e.g., veterinarians, technicians, animal control officers)  
• Others who repeatedly handle terrestrial reservoir species (e.g., wildlife biologists, rehabilitators, and trappers) |

- Laboratorians in the highest risk category
- Disease biogeography determines whether animal care professionals, others who handle terrestrial reservoir species is listed in “Frequent” or Infrequent” Risk categories
### Infrequent risk category: Disease biogeography and typical population

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Spelunkers |
|               | Geographic regions where terrestrial mammals are reservoirs for rabies | | Veterinary students  
Short-term / volunteer hands-on animal care workers where increased risk is expected for short time periods |
|               | Geographic regions internationally with canine rabies | | Travelers who will be performing activities (e.g., occupational or recreational) that put them at increased risk for exposure to rabid dogs and may have difficulty getting access to safe PEP (e.g., in rural area). Children may receive PrEP depending on the country to which they will travel (see CDC Traveler’s Health destination pages) |
| Rare (i.e., general population) | Risk of virus exposure is uncommon. Bite or non-bite exposure | Nationwide | U.S. population at large |

- Moved spelunkers / cavers from “frequent” to “infrequent” risk category
- Added “short-term / volunteer hands-on animal care workers where increased risk is expected for short time periods”
- Rephrased guidance for travelers which will align with CDC Traveler’s health destination pages and 2022 Yellow Book
## Proposed PrEP recommendations and clinical guidance

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²Minimal acceptable antibody level is 0.5 IU/mL.

³Terrestrial mammals are non-bat species (e.g., raccoons, skunks, livestock). If you are uncertain which mammals in your region may circulate rabies, please contact your local or state health department.

**Bats are reservoirs for rabies in all US states except Hawaii.
Vaccine series and frequency of titer checks
**Vaccination route**

- Intradermal (ID) globally recommended since 1980s
- **WHO recommends ID because**
  - Dose- and cost-sparing
  - Could make the difference between person receiving vaccine and not receiving vaccine
- **U.S. population**
  - U.S. rabies vaccine not licensed for ID use
  - Packaged for single-use IM
  - Less need for many people to be vaccinated concurrently
  - No preservatives and multiple punctures → infections
  - Mostly associated with occupations which might pay cost
2008 ACIP PrEP recommendations

- PrEP schedule
  - IM [0, 7, 21/28 days] for Continuous, Frequent, and Infrequent Risk Categories
  - No PrEP for Rare Risk Category

- Frequency of titer checks*
  - Every 6 months for Continuous
  - Every 2 years for Frequent
  - No titer checks for Infrequent

*Booster is recommended if titer is below minimum acceptable antibody level (complete virus neutralization at a 1:5 serum dilution by the rapid fluorescent focus inhibition test.)
Frequency of titer checks

- Rabies antibody titer is used as an indicator of adequate immune response to vaccine
- However, an acceptable titer is not an indication of protection; it is used as a surrogate
  - Person with a low titer may still be immune
  - Person may mount anamnestic response if exposed
- Titer higher than the minimum acceptable antibody level needed for persons involved in some activities; example, handling rabies virus
  - That is because these persons (e.g., laboratorians) have a risk for unrecognized exposure to high titer viruses
  - Out of caution, higher titers are the target
WG’s task

- Evaluate whether vaccine series’ could be different depending on risk category
  - Data for 2-dose IM series
  - Booster for those at higher risk for rabies

- Evaluate whether frequency of titer checks could be different depending on the risk exposure category
  - Data that helps determine whether titer checks for persons in the continuous category should be more often than those in the frequent category
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Rabies Vaccine Work

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Questions?