



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

**Agam Rao, MD**

**CDR, US Public Health Service**

**Co-Lead, ACIP Rabies WG**

**Advisory Committee on Immunization Practices  
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# Rabies in humans

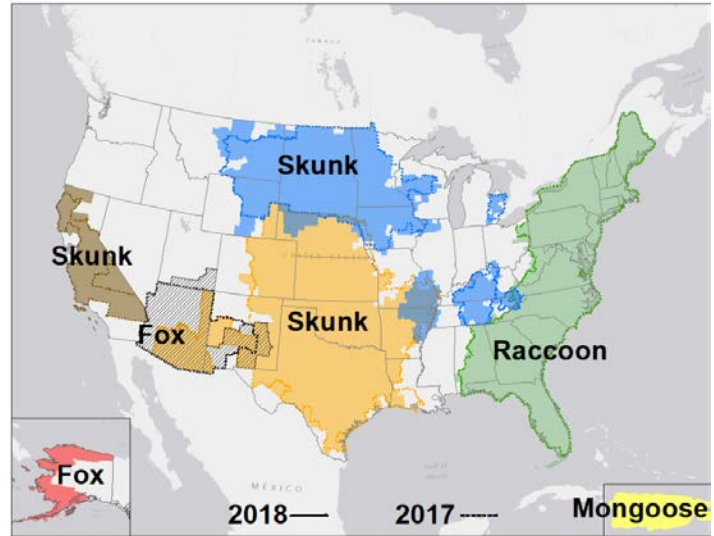
- Acute, progressive encephalomyelitis that is nearly always fatal
- Transmitted from infected mammals by bite, scratch, or exposure to saliva or neural tissue
- Not transmitted by exposures to blood, urine, or feces of infected animals
- No known laboratory confirmed cases of human-to-human transmission 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.

Vaccine	Product name	Manufacturer	Licensed for Administration
Human diploid cell vaccine (HDCV)	Imovax®	Sanofi Pasteur	Intramuscularly
Purified chick embryo cell vaccine (PCECV)	RabAvert	GlaxoSmithKline (In future: Bavarian Nordic)	Intramuscularly



# 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 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<sup>†</sup>

\*Moro PL et al. Travel Med Infect Dis. 2019 May - Jun;29:80-81.

†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

Risk category	Nature of risk	Typical populations	Pre-exposure recommendations
Continuous	Virus present continuously, often in high concentrations. Specific exposures likely to go unrecognized. Bite, nonbite, or aerosol exposure.		Recommended schedules and frequency of titer checks
Frequent	Exposure usually episodic, with source recognized, but exposure also might be unrecognized. Bite, nonbite, or aerosol exposure.		
Infrequent (greater than population at large)	Exposure nearly always episodic with source recognized. Bite or nonbite exposure.		
Rare (population at large)	Exposure always episodic with source recognized. Bite or nonbite exposure.		

Increasing Risk

\* 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

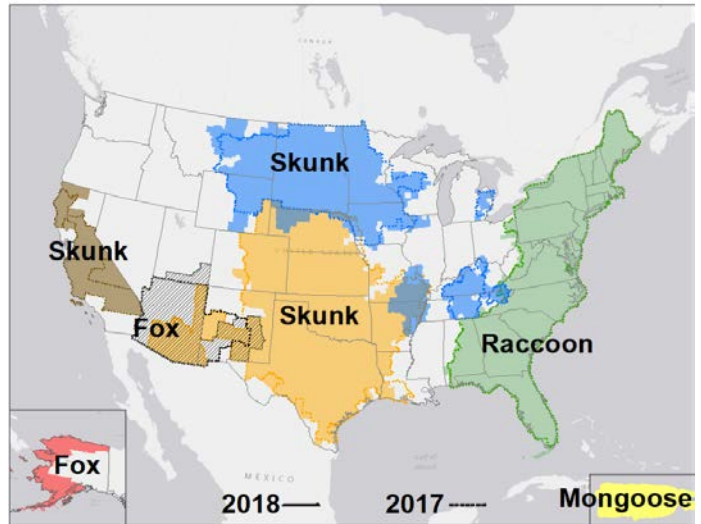


# Activity performed

- 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

TABLE 6. Rabies pre-exposure prophylaxis guide — United States, 2008

Risk category	Nature of risk	Typical populations	Pre-exposure recommendations
Continuous	Virus present continuously, often in high concentrations. Specific exposures likely to go unrecognized. Bite, nonbite, or aerosol exposure.	Rabies research laboratory workers; rabies biologics production workers.	Recommended schedules and frequency of titer checks
Frequent	Exposure usually episodic, with source recognized, but exposure also might be unrecognized. Bite, nonbite, or aerosol exposure.	Rabies diagnostic laboratory workers, cavers, veterinarians and staff, and animal-control and wildlife workers in areas where rabies is enzootic. All persons who frequently handle bats.	
Infrequent (greater than population at large)	Exposure nearly always episodic with source recognized. Bite or nonbite exposure.	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.	
Rare (population at large)	Exposure always episodic with source recognized. Bite or nonbite exposure.	U.S. population at large, including persons in areas where rabies is epizootic.	

\* 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.

# Confusing aspects of rabies PrEP guide

## Risk category

## Typical populations

Continuous

Rabies research laboratory workers; rabies biologics production workers

Frequent

Rabies diagnostic laboratory workers, cavers, veterinarians, and staff, and animal-control and wildlife workers in areas where rabies is enzootic.

All persons who frequently handle bats

Infrequent

Veterinarians and animal-control staff working with terrestrial animals in areas where rabies uncommon to rare. Veterinary students.

Travelers visiting areas where rabies is enzootic and immediate access to appropriate medical care including biologics is limited

Rare

US population at large

# Proposed PrEP clinical guidance

Risk category	Nature of Risk	Disease Biogeography <sup>1</sup>	Typical Population	Pre-exposure recommendations
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)	<ul style="list-style-type: none"> <li>? schedule</li> <li>? Frequency of serologic monitoring<sup>‡</sup></li> </ul>
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)	<ul style="list-style-type: none"> <li>? schedule</li> <li>? Frequency of serologic monitoring<sup>‡</sup></li> </ul>
		Geographic regions where terrestrial mammals <sup>§</sup> are reservoirs for rabies	<ul style="list-style-type: none"> <li>Animal care professionals (e.g., veterinarians, technicians, animal control officers)</li> <li>Others who repeatedly handle terrestrial reservoir species (e.g., wildlife biologists, rehabilitators, and trappers)</li> </ul>	
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	<ul style="list-style-type: none"> <li>Animal care professionals</li> <li>Others who repeatedly handle terrestrial reservoir species</li> <li>Spelunkers</li> </ul>	<ul style="list-style-type: none"> <li>? schedule</li> <li>No serologic monitoring</li> </ul>
		Geographic regions where terrestrial mammals are reservoirs for rabies	<ul style="list-style-type: none"> <li>Veterinary students</li> <li>Short-term / volunteer hands-on animal care workers where increased risk is expected for short time periods</li> </ul>	
		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	<ul style="list-style-type: none"> <li>No pre-exposure prophylaxis</li> <li>No serologic monitoring</li> </ul>

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

<sup>1</sup>For questions about the disease biogeography of the region where an exposure occurred, please contact your local or state health department

<sup>‡</sup>Minimal acceptable antibody level is 0.5 IU/mL

<sup>§</sup>Terrestrial 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

# Continuous and frequent risk categories: Disease biogeography and typical population

Risk category	Nature of Risk	Disease Biogeography <sup>!</sup>	Typical Population
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)

- Laboratorians in the highest risk category

Risk category	Nature of Risk	Disease Biogeography <sup>!</sup>	Typical Population
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)
		Geographic regions where terrestrial mammals <sup>§</sup> are reservoirs for rabies	<ul style="list-style-type: none"> <li>• Animal care professionals (e.g., veterinarians, technicians, animal control officers)</li> <li>• Others who repeatedly handle terrestrial reservoir species (e.g., wildlife biologists, rehabilitators, and trappers)</li> </ul>

- 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

Risk category	Nature of Risk	Disease Biogeography <sup>1</sup>	Typical Population
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	<ul style="list-style-type: none"> <li>Animal care professionals</li> <li>Others who repeatedly handle terrestrial reservoir species</li> <li>Spelunkers</li> </ul>
		Geographic regions where terrestrial mammals are reservoirs for rabies	<ul style="list-style-type: none"> <li>Veterinary students</li> <li>Short-term / volunteer hands-on animal care workers where increased risk is expected for short time periods</li> </ul>
		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 <u>PrEP</u> 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

Risk category	Nature of Risk	Disease Biogeography <sup>1</sup>	Typical Population	Pre-exposure recommendations
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)	<ul style="list-style-type: none"> <li>? schedule</li> <li>? Frequency of serologic monitoring<sup>2</sup></li> </ul>
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 <u>come into contact with</u> bats (e.g., bat biologist)	<ul style="list-style-type: none"> <li>? schedule</li> <li>? Frequency of serologic monitoring<sup>2</sup></li> </ul>
		Geographic regions where terrestrial mammals <sup>3</sup> are reservoirs for rabies	<ul style="list-style-type: none"> <li>Animal care professionals (e.g., veterinarians, technicians, animal control officers)</li> <li>Others who repeatedly handle terrestrial reservoir species (e.g., wildlife biologists, rehabilitators, and trappers)</li> </ul>	
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		Geographic regions where terrestrial mammals are reservoirs for rabies	<ul style="list-style-type: none"> <li>Veterinary students</li> <li>Short-term / volunteer hands-on animal care workers where increased risk is expected for short time periods</li> </ul>	
		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).	
Rare (i.e., general population)	Risk of virus exposure is uncommon. Bite or non-bite exposure	Nationwide	U.S. population at large	<ul style="list-style-type: none"> <li>No pre-exposure prophylaxis</li> <li>No serologic monitoring</li> </ul>

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

<sup>1</sup>For questions about the disease biogeography of the region where an exposure occurred, please contact your local or state health department

<sup>2</sup>Minimal acceptable antibody level is 0.5 IU/mL

<sup>3</sup>Terrestrial 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

### Group

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## CDC Technical Team

*Jesse Blanton*

*Brett Petersen*

*Ryan Wallace*

*Sathesh Panayampalli*

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Questions?