



Rabies Pre-exposure Prophylaxis in the United States and Work Group Considerations

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October 29, 2020

Human rabies

- Acute, progressive encephalomyelitis that is nearly always fatal
- Transmitted from infected mammals
- Worldwide
 - Dogs are most common cause
 - 59,000 human cases / year
- United States
 - Bats are most common cause
 - Canine rabies virus variant (RVV) eliminated in 2007
 - 0-4 human cases / year

Rabies biogeography in U.S.

- ~5,000 animals test positive for rabies / year
- Mammal reservoirs vary by geography
 - Terrestrial (or wildlife) rabies: RVV for which wildlife are reservoir
 - Non-terrestrial rabies: RVV for which bats are only reservoir
- Terrestrial rabies restricted to specific U.S. regions
- Non-terrestrial rabies in all U.S. states except Hawaii

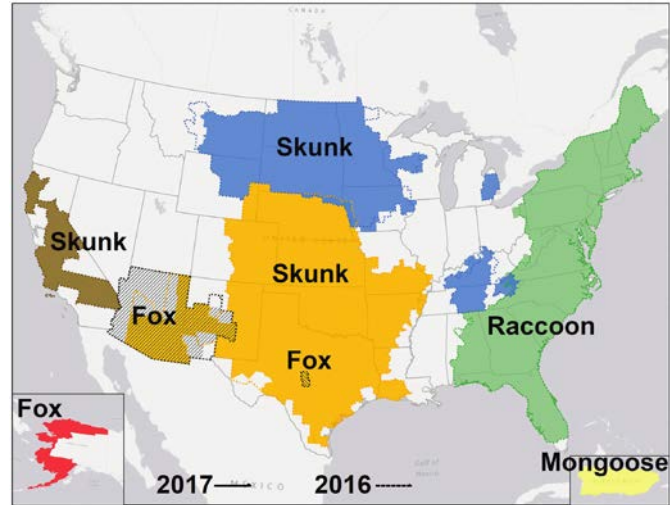


Figure: Terrestrial rabies virus variants (RVV) in U.S.: **Skunk RVV:** Orange = South central, Blue = North central, Brown = California; **Fox RVV:** Red = Arctic fox, Hash = Gray fox; **Raccoon RVV:** Green; **Mongoose RVV:** Yellow.

Rabies and general U.S. population

- Risk during occupational or recreational activities in U.S.
- Exposure is “recognized”
 - Bite or scratch (e.g., from raccoon, mongoose, fox)
 - Person with intact mental status would realize that they had the exposure and could seek post-exposure prophylaxis (PEP)
- Pre-exposure prophylaxis (PrEP)
 - Not advantageous and has never been recommended by ACIP
 - Expensive and typically not covered by insurance

Rabies PrEP

- Is not a substitute for PEP
- Current vaccine series for healthy persons who have an exposure
 - With PrEP: 5 vaccine doses and no rabies immunoglobulin (RIG), i.e., 3 vaccine doses for PrEP + 2 vaccine doses for PEP
 - Without PrEP: 4 vaccine doses for PEP + RIG
- Benefits
 - Eliminates need for RIG which is expensive and may not be easily available during some international travel
 - Shortens PEP series for persons who may have multiple rabies exposures in their lifetime
 - Provides some coverage if a delay in PEP is anticipated

Rabies risks that warrant PrEP are higher than those of general population

- Unrecognized exposures*, i.e., Person with intact mental status may not notice exposure and does not seek PEP
- Potential for high potency or unusual exposures
 - High concentration, research grade rabies virus
 - Aerosolized rabies virus
 - Non-rabies lyssaviruses
- Opportunities for frequent contact with potentially rabid mammals
 - E.g., bat biologist, veterinarian, or spelunker
- Travel to canine rabies endemic country
 - e.g., travel to rural region where exposures are possible and PEP may not be easily accessible in a timely manner

* “Unrecognized” exposure is not one when a person knows they were bitten/scratched but were unaware that rabies can occur from these exposures

U.S. populations for whom rabies risk above those of general population

- Laboratorians
- Persons who frequently handle bats or enter environments with high concentrations of bats, e.g., bat biologists and some pest control workers
- Persons who work with animals (e.g., wildlife workers and veterinarians) or who may come in contact with dogs in canine-rabies endemic country (e.g., travelers)

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 - Frequent opportunities for recognized exposure

U.S. populations for whom rabies risk above those of general population

- 
- Increasing Risk
- Laboratorians
 - High potency or unusual exposures
 - Unrecognized exposures
 - Frequent contact with potentially rabid mammals
 - Persons who frequently handle bats or enter environments with high density of bats, e.g., bat biologists and some pest control workers
 - Unrecognized exposures
 - Frequent contact with potentially rabid mammals
 - Persons who frequently work with mammals other than bats (e.g., wildlife workers) or who may come in contact with dogs in canine-rabies endemic country (e.g., travelers)
 - Frequent opportunities for unrecognized exposure

Recognized and unrecognized exposures

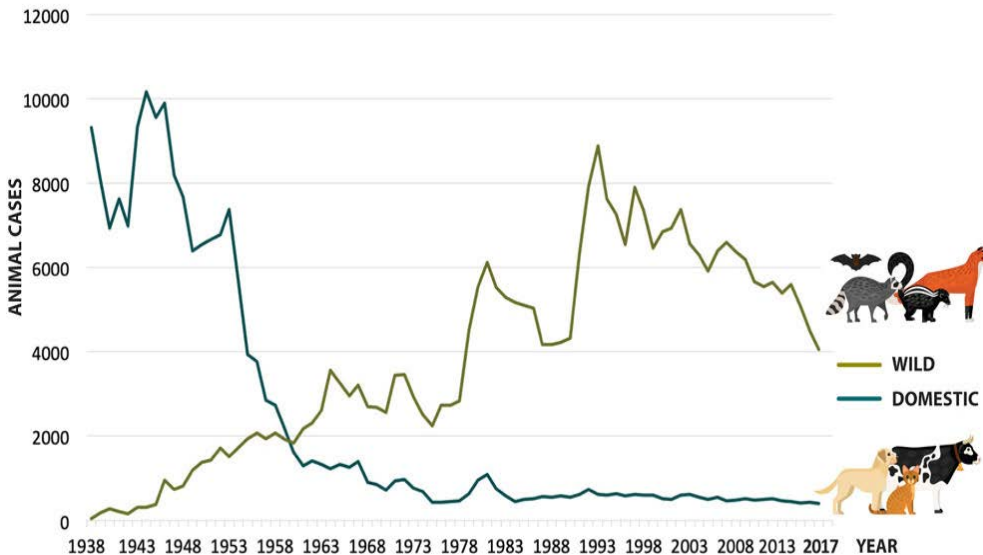


- Exposures from terrestrial mammals (above): Canine tooth size 15-50mm and bite strength ~320 lbs of pressure causing “recognized” trauma when exposures occur
- Exposure from bats (below): Canine tooth size: 2-10mm and bite strength ~2 lbs of pressure which can cause both recognized and unrecognized exposures



Rabies exposure risk among persons who work with domestic animals: A changing landscape

Reports of Rabid Animals in the United States, 1938 - 2017



Rabid **Domestic Animals** per US Population (1,000,000):
1955 – 2007
0.55

Rabid **Domestic Animals** per US Population (1,000,000):
2008 – 2018
0.21

Persons who work with animals: Terrestrial vs. non-terrestrial RVV regions

- Increased opportunities for exposure to rabies for persons who work with animals (e.g., wildlife, dogs and cats) in terrestrial RVV regions than in non-terrestrial RVV regions
- Type of exposure that could lead to rabies is “recognized” for all persons with the same occupation
- Whether exposure occurred in terrestrial or non-terrestrial RVV matters for PEP but not for PrEP

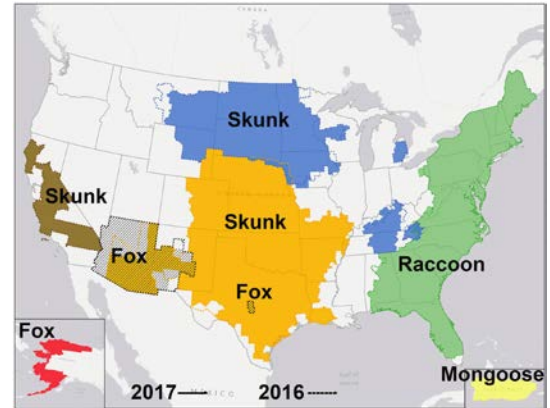


Figure: Terrestrial rabies virus variants (RVV) in U.S.: **Skunk RVV**: Orange = South central, Blue = North central, Brown = California; **Fox RVV**: Red = Arctic fox, Hash = Gray fox; **Raccoon RVV**: Green; **Mongoose RVV**: Yellow.

2008 ACIP risk categories for PrEP

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.	Primary course. Serologic testing every 6 months; booster vaccination if antibody titer falls below acceptable level.*
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.	Primary course. Serologic testing every 2 years; booster vaccination if antibody titer falls below acceptable level.*
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.	Primary course. No serologic testing or booster vaccination.
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.	No vaccination necessary.

PrEP: IM[0, 7, 21 days]
Titers at varying frequencies

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.

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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.	Primary series: IM[0, 7, 21 days] for three risk groups. Titrations for only those in the top two risk groups and at different frequencies.
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.	Primary series: IM[0, 7, 21 days] for three risk groups. Titrations for only those in the top two risk groups and at different frequencies.
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.	No vaccination necessary.

Increasing Risk

- Primary series: IM[0, 7, 21 days] for three risk groups
- Titrations for only those in the top two risk groups and at different frequencies

* 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.

Proposed revisions

Risk category	Nature of Risk	Typical Population	Disease Biogeography ¹	Primary Immunogenicity PrEP	Long-term immunogenicity
#1: Elevated risk for unrecognized and recognized exposures and	Risk of virus exposure is continuous. Exposure is often in high concentrations and may go unrecognized. Direct and indirect <u>exposures</u> .*	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)	Laboratory	Goal: Same primary series for 3 risk groups	Goal: Titers maintained high in case of unrecognized exposures
#2: Elevated risk of both unrecognized and recognized exposures	Risk of virus exposure is episodic. Exposure typically recognized but could be unrecognized and is greater than for those in the #3 risk group. Direct exposures and rarely indirect exposures	Persons who frequently handle bats or at frequent risk for <u>coming into contact with</u> bats because of entrance to high density bat environments (e.g., bat biologist)	All geographic regions where bats are a reservoir for rabies**		
#3: Elevated risk of recognized exposures	Risk of virus exposure greater than population at large. Exposure is a recognized one. Direct exposures.	<p>Persons who work with animals</p> <ul style="list-style-type: none"> Animal care professionals (e.g., veterinarians, technicians, animal control officers) Others who repeatedly handle terrestrial reservoir species (e.g., wildlife biologists, rehabilitators, and trappers) Spelunkers Veterinary students Short-term / volunteer hands-on animal care workers where increased risk is expected for short time periods* <p>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)*</p>	<p>All geographic regions where terrestrial and non-terrestrial mammals are reservoirs for rabies</p> <ul style="list-style-type: none"> Geographic regions internationally with canine rabies 		Goal: Anamnestic response elicitation to recognized exposure
#4: Low risk of exposure / (i.e., general population)	Risk of virus exposure is uncommon. Bite or non-bite exposure	U.S. population at large	<ul style="list-style-type: none"> Nationwide 	<ul style="list-style-type: none"> No pre-exposure prophylaxis No serologic monitoring 	n/a

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

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

²Terrestrial mammals are non-bat species (e.g., racoons, skunks, livestock). **Bats are reservoirs for rabies in all US states except Hawaii

WG considerations throughout discussions about approach to PrEP

- ACIP PrEP recommendations were initially many more doses and with suboptimal vaccines
- 2008 ACIP recommendations have been effective
- Rabies is nearly 100% fatal
- Proposed changes
 - Supported by robust data
 - Address evolving rabies landscape
 - Reflect new data and increased confidence in modern cell culture vaccines
 - Not have suboptimal immunogenicity to current PrEP
- WHO and ACIP recommendations do not have to align
 - Dose and cost-sparing options are top priority for WHO

Additional background presentations before presentations about proposed recommendations

- 1) Minimum Acceptable Rabies Antibody Titer and Implications on ACIP Recommendations
 - **Purpose:** Share concerns about current ACIP cut-off titer, proposed solution, and potential implications of change
- 2) Pertinent Fundamentals of Rabies Immunology
 - ACIP recommendations limited to intramuscular (IM) schedules
 - Worldwide, intradermal schedules (ID) commonly used
 - Rabies experts believe ID data can be extrapolated to inform IM schedules
 - **Purpose:** Show the efficacy of current rabies vaccines and that data for ID can be used to inform decisions about IM administration

Conclusions

- Risk for rabies has decreased but rabies is ~100% fatal
- WG revised table outlining risk categories
 - Biogeography
 - Changing landscape of rabies
 - Purpose of PrEP
 - Indications for PrEP
- Highest risk for rabies among laboratorians
- Second highest risk among persons who frequently handle bats or enter high density bat environments
- Third highest risk in a) persons who work with animals or b) travelers to canine rabies endemic regions
- WG proposed recommendations for primary PrEP series and frequency of titer checks will be presented

Acknowledgements

Rabies Vaccine Work

Group

Sharon Frey (chair)

Lynn Bahta

José R. Romero

Deborah Briggs

James Stevermer

Matt Zahn

Karl Hess

Paula Agger

Jesse Blanton

Robin Levis

Katie Brown

Elizabeth Barnett

Sally Slavinski

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David Shlim

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CDC Technical Team

Ryan Wallace

Jesse Blanton

Brett Petersen

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Florence Whitehill

Sathesh Panayampalli

Caroline Schrodt



Questions?