

Background: Recommendations to Prevent Human Rabies

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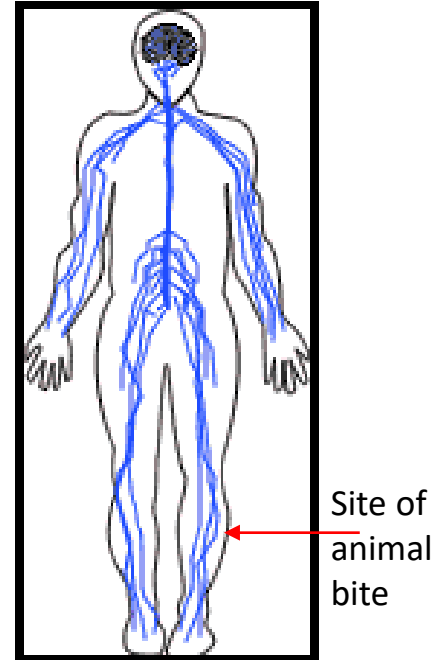
Advisory Committee on Immunization Practices meeting
October 24, 2019

Rabies in humans

- Caused by viruses in genus *Lyssavirus*
- Acute, progressive encephalomyelitis
- Occurs worldwide
- Nearly always fatal after onset of clinical signs
- 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

Viral pathogenesis

- Neurotrophic virus
 - Enters peripheral nerves
 - Travels centripetally to Central Nervous System
 - Flows centrifugally to innervated organs, including salivary glands
- Incubation period weeks to months
- Death typically within 2 weeks of illness onset

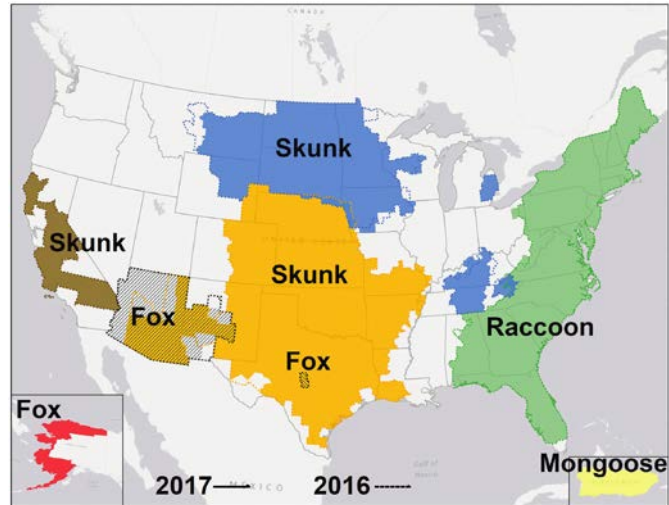


Rabies transmission

- 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

Surveillance in United States

- Canine RVV successfully eliminated
- Terrestrial (or wildlife) rabies
 - Wildlife are reservoirs
- Non-terrestrial rabies
 - Bats are reservoirs
 - Endemic in all states except Hawaii
- ~5,000 animals test positive for rabies / year



Skunk RVV: Orange = South central, Blue = North central, Brown = California; Fox RVV: Red = Arctic fox, Hash = Gray fox; Raccoon RVV: Green; Mongoose RVV: Yellow.

Exposures that have led to confirmed human cases in U.S.

- Domestic
 - Recreational
 - Occupational including laboratory work
 - Contacts in everyday life
 - Bats in home
 - Residence in wooded areas with increased opportunities for contact
 - Organ and tissue transplants
- International travel
 - Leisure and occupational animal exposures
 - Dogs are most important animal reservoir

Human rabies—United States, 2009-2019 (N=25)

- ~2-4 cases / year
- Domestic exposures (n=17)
 - 12 bat RVV
 - 3 raccoon RVV (including kidney donor and recipient)
 - 1 mongoose RVV
 - 1 unknown RVV
- International exposures (n=8)
 - 7 dog RVV (Philippines, Guatemala, Brazil, Afghanistan, Haiti, India)
 - 1 bat RVV (Mexico)
- None due to occupational exposures

Prevention of human rabies

- Primary prevention: Avoiding animal exposures, vaccinating domestic and wild animals
- Secondary prevention
 - Pre-exposure prophylaxis (PrEP)
 - Vaccine series
 - >15,000 people receive PrEP / year in U.S.
 - Post-exposure prophylaxis (PEP)
 - Washing wound with soap and water, rabies immune globulin, vaccine series
 - 50,000 people receive rabies PEP / year in U.S.
- None of the confirmed cases in the last 10 years received PrEP or PEP

Factors that contribute to PrEP and PEP recommendations

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 1-2 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. |

Recommended schedules and frequency of titer checks

* 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.

Increasing Risk

Decision to administer PEP

- Type of exposure
 - Is the exposure a bite or non-bite (i.e., aerosol, organ / tissue transplant, contamination of wounds or mucous membranes with saliva or neural tissue)?
 - Is the exposure to urine, feces, skin, or blood?
- Bio-Geo-Behavioral Risk Assessment
 - Is the animal a reservoir species for rabies?
 - What is the rabies epidemiology in the area?
 - Was the animal showing signs of rabies?

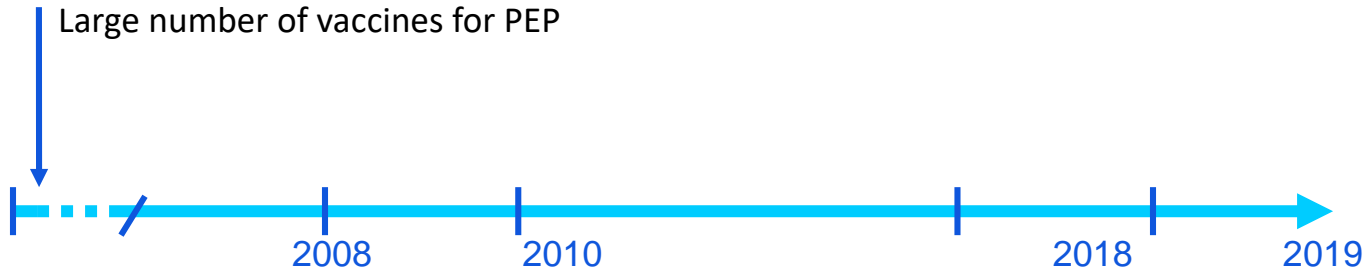
Schedules and Titer Checks for PEP

- Was PrEP administered?
- Were there any deviations in PEP administration?
- Does the patient require special considerations? Example immunocompromised?

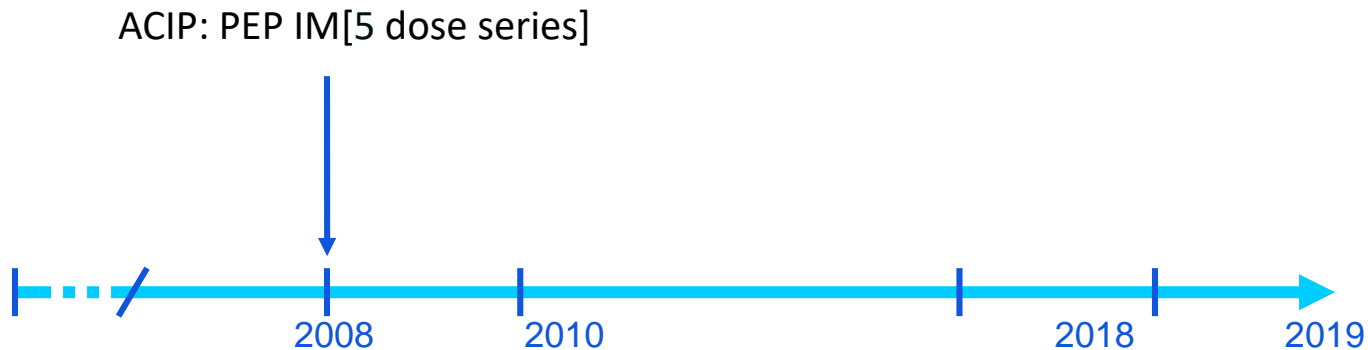
**National and global rabies
recommendations and products**

Timeline of recent national and global recommendations for PrEP and PEP schedules

Remote U.S. rabies management:
Impaired vaccine quality
Decreased potency
Increased adverse events
Intradermal and Intramuscular licensed vaccines
Large number of vaccines for PEP



Timeline of recent national and global recommendations for PrEP and PEP schedules in healthy, nonpregnant persons

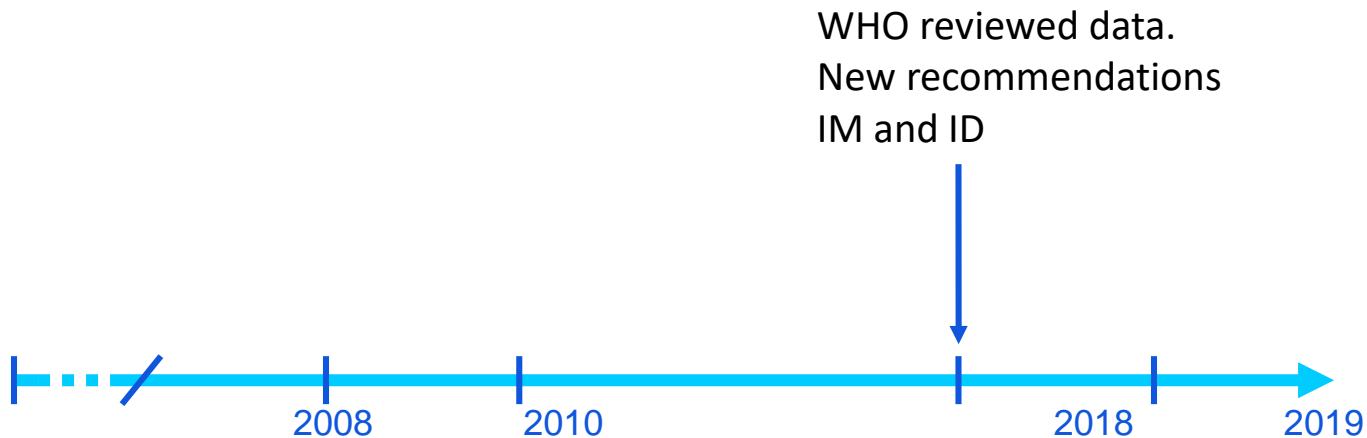


Timeline of recent national and global recommendations for PrEP and PEP schedules in healthy, nonpregnant persons

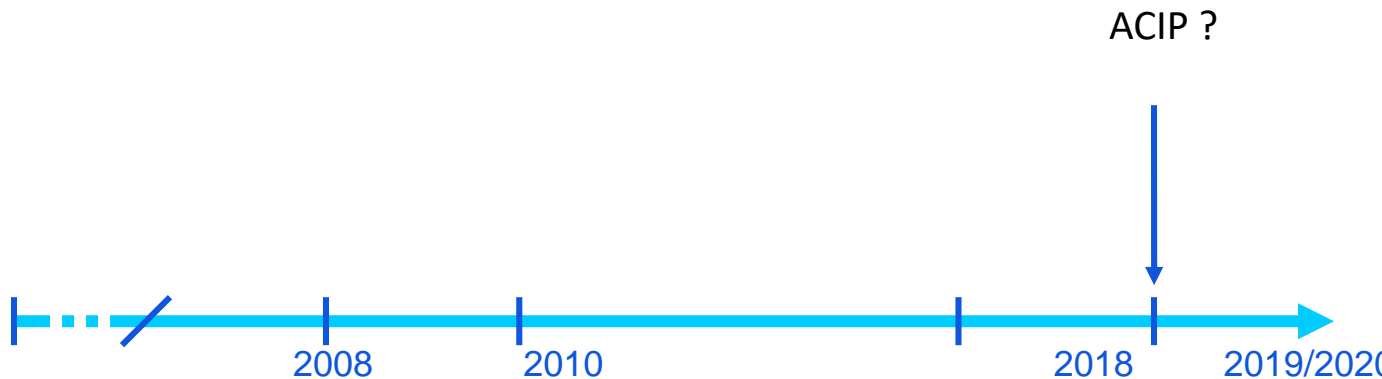
Prompted by vaccine shortage, data was reviewed
ACIP: PEP IM[4 dose series]



Timeline of recent national and global recommendations for PrEP and PEP schedules in healthy, nonpregnant persons



Timeline of recent national and global recommendations for PrEP and PEP schedules in healthy, nonpregnant persons



Vaccines and human immunoglobulins licensed in U.S.

| Biologic | 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 |
| Human immune globulin | Imogam® | Sanofi Pasteur | Intramuscularly and Infiltrated around wound |
| | Kedrab™/Kedrion | Biopharma and Kamada Ltd | Intramuscularly and infiltrated around Wound |
| | HyperRab™ S/D and HyperRab® | Grifols | Intramuscularly and Infiltrated around wound |

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Thank you