

Background: Post-exposure Prophylaxis

Agam Rao, MD

CAPT, United States Public Health Service

CDC Lead for Rabies ACIP Update

Advisory Committee on Immunization Practices meeting

May 5, 2021

Agenda

- Components of rabies post-exposure prophylaxis (PEP)
- Role of rabies epidemiology in decisions about PEP
- Propose approach to PEP for clinicians

Post-exposure prophylaxis (PEP) for persons who never received PEP (for a prior exposure) or PrEP

Human Rabies
Immunoglobulin
(RIG)



Rabies Vaccine

Rabies Vaccines

Day 0

Days 3, 7, 14

Previously vaccinated persons

- Defined, in the 2008 ACIP recommendations as a person who received:
 - One of the recommended PrEP regimens of HDCV*, PCECV[†], or RVA #
 - One of the recommended PEP regimens of HDCV*, PCECV[†], or RVA #
 - Another vaccine and had a documented rabies virus neutralizing antibody titer
- Implications
 - Eliminates need for rabies immune globulin (RIG)
 - Decreases number of PEP vaccine doses needed after an exposure

*Human diploid cell vaccine

† Purified chick embryo cell vaccine

#Rabies vaccine, Adsorbed

Management of an exposure in persons who previously received PEP (for a prior exposure) or PrEP

Rabies Vaccine

Rabies Vaccines

Day 0

Day 3



Overuse of PEP

- ~55,000 people received PEP / year in U.S., 2012-2017
- Impact
 - Unnecessary administration of vaccines
 - High costs
 - Emotional distress
 - Less availability to persons who really need it during vaccine shortage events

Inappropriate Administration of Rabies Postexposure Prophylaxis, Cook County, Illinois, USA

Hannah D. Steinberg, Kelley Bemis, Mabel M. Frias, Demian Christiansen

Appropriateness of Rabies Postexposure Prophylaxis Treatment for Animal Exposures

Gregory J. Moran, MD
David A. Talan, MD
William Mower, MD, PhD
Michael Newdow, MD, MPH
Samuel Ong, MD
Janet Y. Nakase, MPH
Robert W. Pinner, MD
James E. Childs, ScD
for the Emergency ID Net Study Group

Context Rabies postexposure prophylaxis (RPEP) treatments and associated costs have increased in the United States. The extent to which RPEP use is consistent with guidelines is not well understood.

Objective To characterize animal contacts and determine the frequency and factors associated with inappropriate RPEP use.

Design, Setting, and Patients Prospective case series study of patients presenting with an animal exposure-related complaint from July 1996 to September 1998 at 11 university-affiliated, urban emergency departments (the Emergency ID Net).

Main Outcome Measures Exposure type, circumstances, and RPEP use (appropriateness defined by local public health departments).

Results Of 2030 exposures, 1635 (81%) were to dogs; 268 (13%) to cats; 88 (4%) to rodents/rabbits; 10 (0.5%) to raccoons; 5 (0.2%) to bats; and 24 (1.2%) to other

Rabies epidemiology

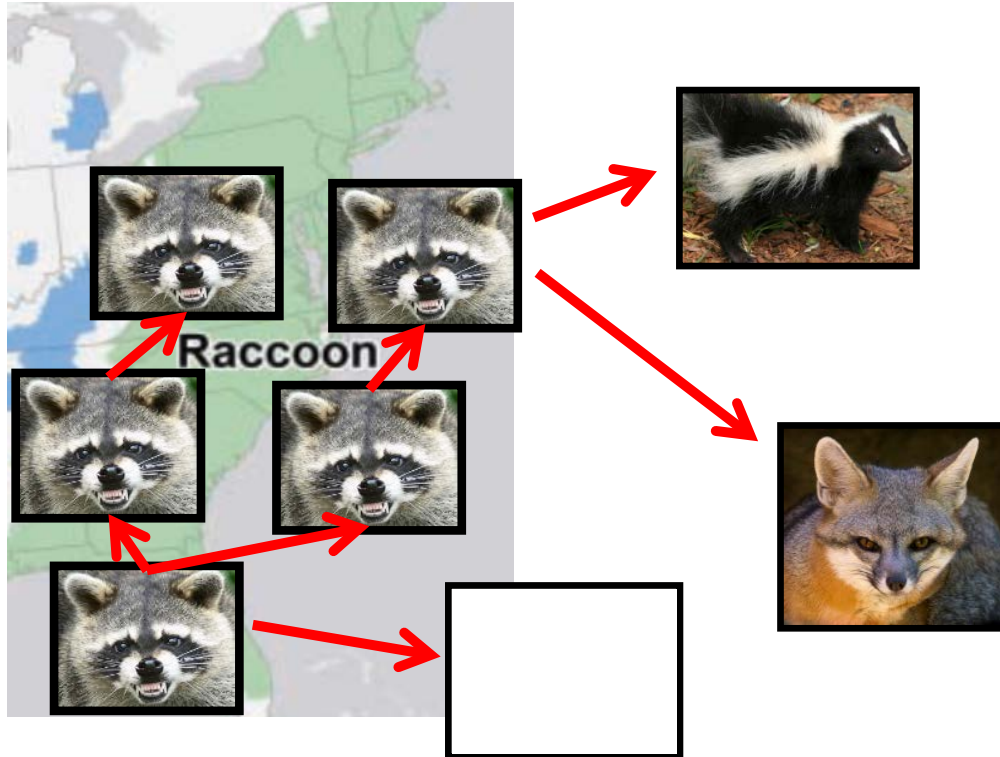
Human rabies

- Transmitted from infected mammals
 - Bite
 - Scratch
 - Mucous membrane or open wound contamination with saliva or neural tissue
- Not transmitted by exposures to blood, urine, or feces of infected animal
- Some cases after organ and tissue transplants

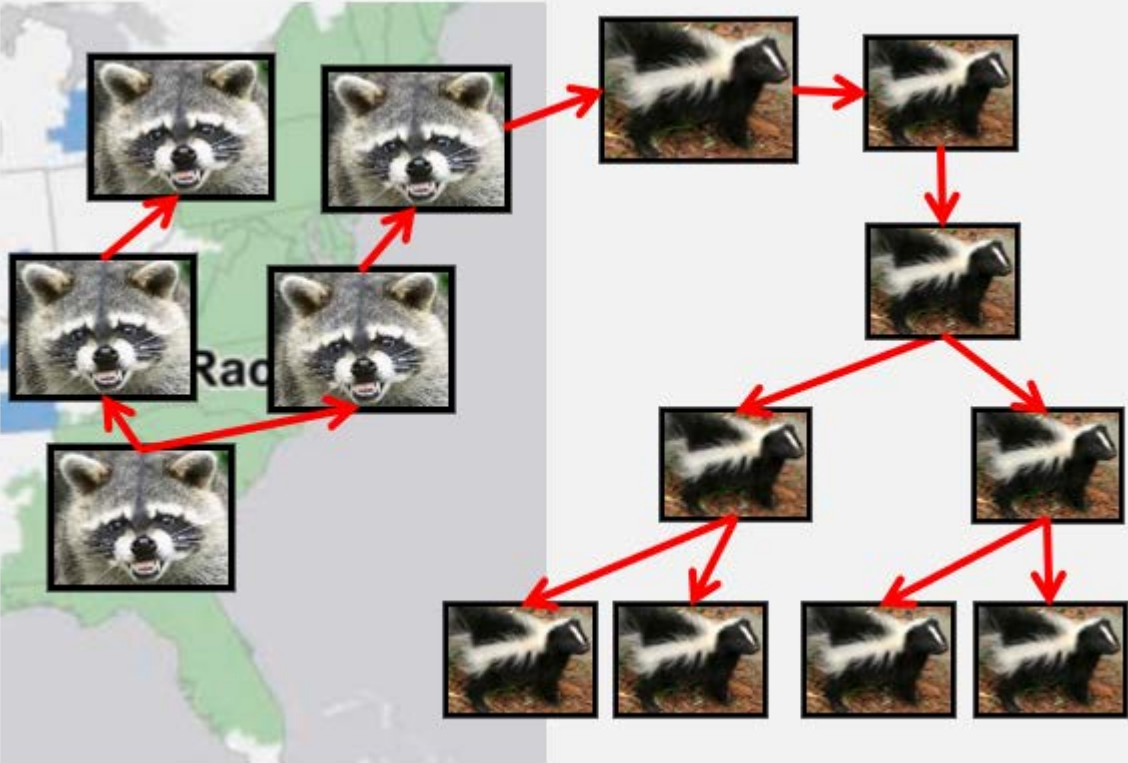
Rabies transmission

- Few animal species are reservoirs for rabies (i.e., species that can sustain circulation of 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 any other mammal
 - Example, Raccoon RVV can spread from a raccoon
→ a cat → a human
 - RVV does not denote the animal to which the human was exposed

Rabies reservoir species and cross-species transmission



Host shift event



Host shift and effects on rabies epidemiology



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 biogeography in U.S.

- 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

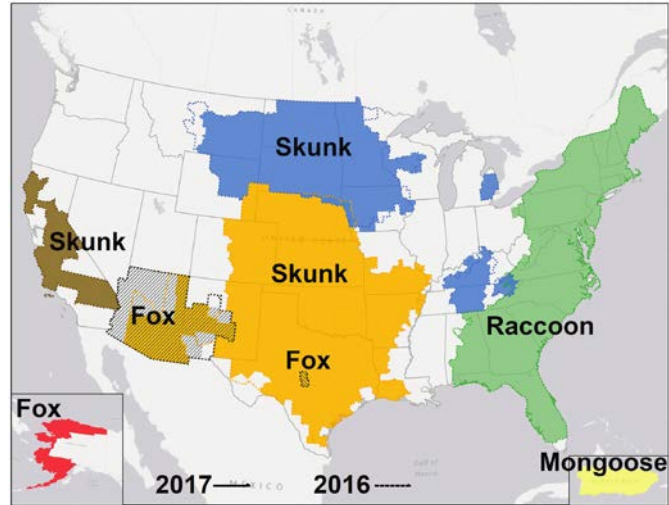


Figure: Terrestrial rabies virus variants (RVV) in U.S.: **Skunk RVV**: Orange = South central, Blue = North central, Brown = California; **Fox RVV**: Red = Arctic fox, Hash = Gray fox; **Raccoon RVV**: Green; **Mongoose RVV**: Yellow.

Cases in the United States, 2009-2020 (N=25)

- ~0-4 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 (Philippines, Guatemala, Brazil, Afghanistan, Haiti, India)
 - 1 bat RVV (Mexico)
- None due to occupational exposures
- None received rabies PrEP or PEP

Approach to post-exposure prophylaxis

Challenges of drafting PEP algorithm

- Differing epidemiology in 50 U.S. states
 - Concern for exposure in terrestrial rabies region differs from that in non-terrestrial rabies regions
 - Rabies vectors and RVV differ by region
- Differing management styles among health departments
 - E.g., In regions without Fox RVV, health departments differ in recommendation about PEP after an exposure
 - E.g., Many (but not all) health departments advise against PEP for exposures to squirrels, chipmunks, and mice

Differences in health department guidance for PEP

- Impacted by degree of oversight and case management of animal bite investigations
- Guidance on websites
 - Some provide detailed algorithms recommending or not recommending administration of PEP
 - Others provide limited guidance and recommend calling health department
- Comprehensiveness
 - Some omit guidance about caged rabbits, hamsters, and other “pocket pets”
 - Some provide long list of animals that could be risky

Consultations with health department

- Multiple factors considered when deciding whether to administer PEP
- Provide authoritative input about local biogeography and rabies epidemiology
- Available after hours

General approach to PEP in 50 U.S. states

- Enables clinicians to handle “easy” cases quickly; no need to contact health department
- Intended to defer to health department guidance for most definitive answers; consultations with health department known to decrease odds of inappropriate PEP administration by 87%*
- Considerations outlined for decisions that depend on multiple factors
 - Collection of important history before health department consultation
 - Transparency of factors that weigh into decision
 - Improved patient counseling

*Reference: Steinberg HD, Bemis K, Frias MM, Christiansen D. Inappropriate administration of rabies postexposure prophylaxis, Cook County, Illinois, USA. Emerg Infect Dis. 202 Oct; 26 (10): 2515-2517

Considerations outlined in text of 2008 ACIP recommendations

- Bite and non-bite exposures
- Exposure mammal
 - Bats
 - Domestic dogs, cats, and ferrets
 - Wild animals
- Animal rabies epidemiology
- Circumstances of biting incident
 - Provoked vs. not provoked
 - Behavior of animal
 - Vaccination status of exposing animal

2008 ACIP guide to rabies PEP

Table 3

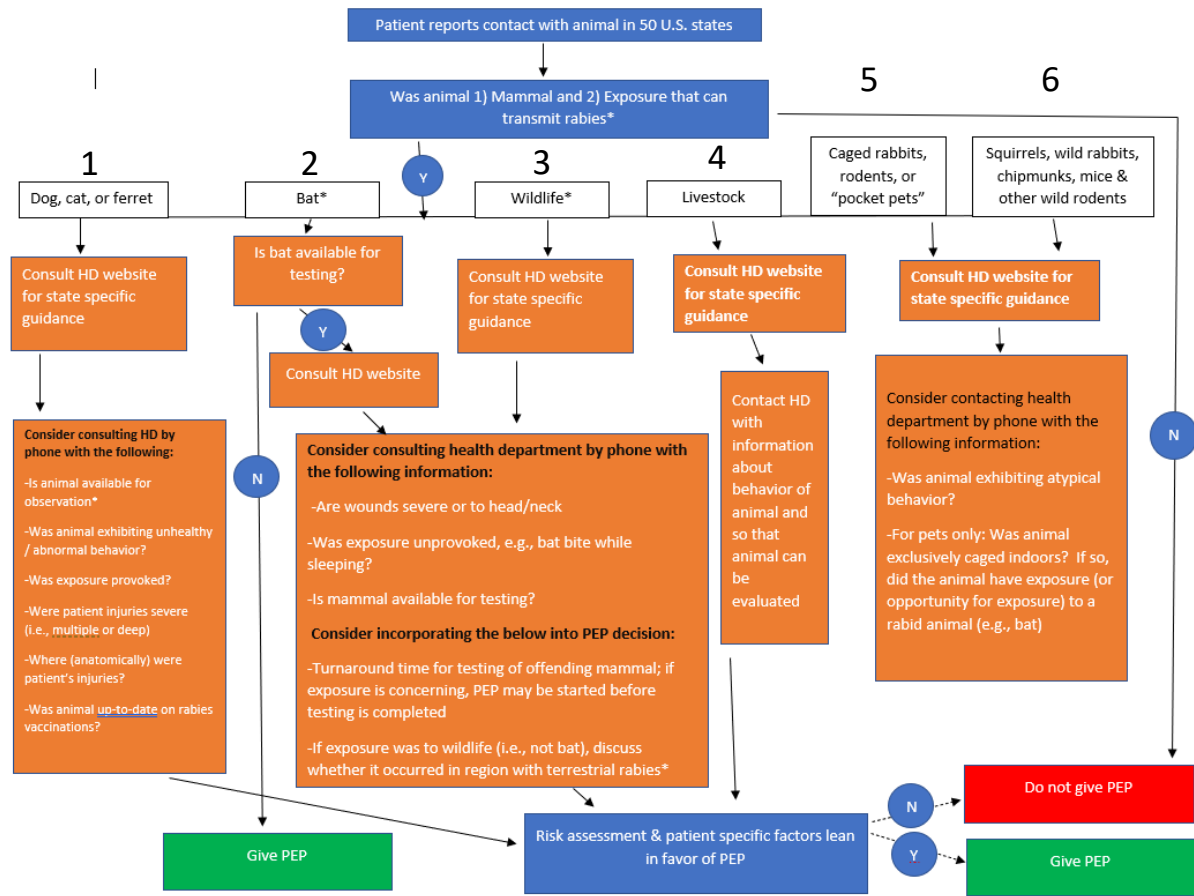
TABLE 3. Rabies postexposure prophylaxis guide — United States, 2008

Animal type	Evaluation and disposition of animal	Postexposure prophylaxis recommendations
Dogs, cats, and ferrets	Healthy and available for 10 days observation	Persons should not begin prophylaxis unless animal develops clinical signs of rabies.*
	Rabid or suspected rabid	Immediately begin prophylaxis.
	Unknown (e.g., escaped†)	Consult public health officials.
Skunks, raccoons, foxes, and most other carnivores; bats‡	Regarded as rabid unless animal proven negative by laboratory tests§	Consider immediate prophylaxis.
Livestock, small rodents (rabbits and hares), large rodents (woodchucks and beavers), and other mammals	Consider individually	Consult public health officials. Bites from squirrels, hamsters, guinea pigs, gerbils, chipmunks, rats, mice, other small rodents, rabbits, and hares almost never require antirabies postexposure prophylaxis.

* During the 10-day observation period, begin postexposure prophylaxis at the first sign of rabies in a dog, cat, or ferret that has bitten someone, if the animal exhibits clinical signs of rabies, it should be euthanized immediately and tested.

† Postexposure prophylaxis should be initiated as soon as possible following exposure to such wildlife unless the animal is available for testing and public health authorities are facilitating expeditious laboratory testing or it is already known that brain material from the animal has tested negative. Other factors that might influence the urgency of decision-making regarding initiation of postexposure prophylaxis before diagnostic results are known include the species of the animal, the general appearance and behavior of the animal, whether the encounter was provoked by the presence of a human, and the severity and location of bites. Discontinue vaccine if appropriate laboratory diagnostic test (i.e., the direct fluorescent antibody test) is negative.

§ The animal should be euthanized and tested as soon as possible. Holding for observation is not recommended.



Approach to exposure from domestic dog, cat, or ferret

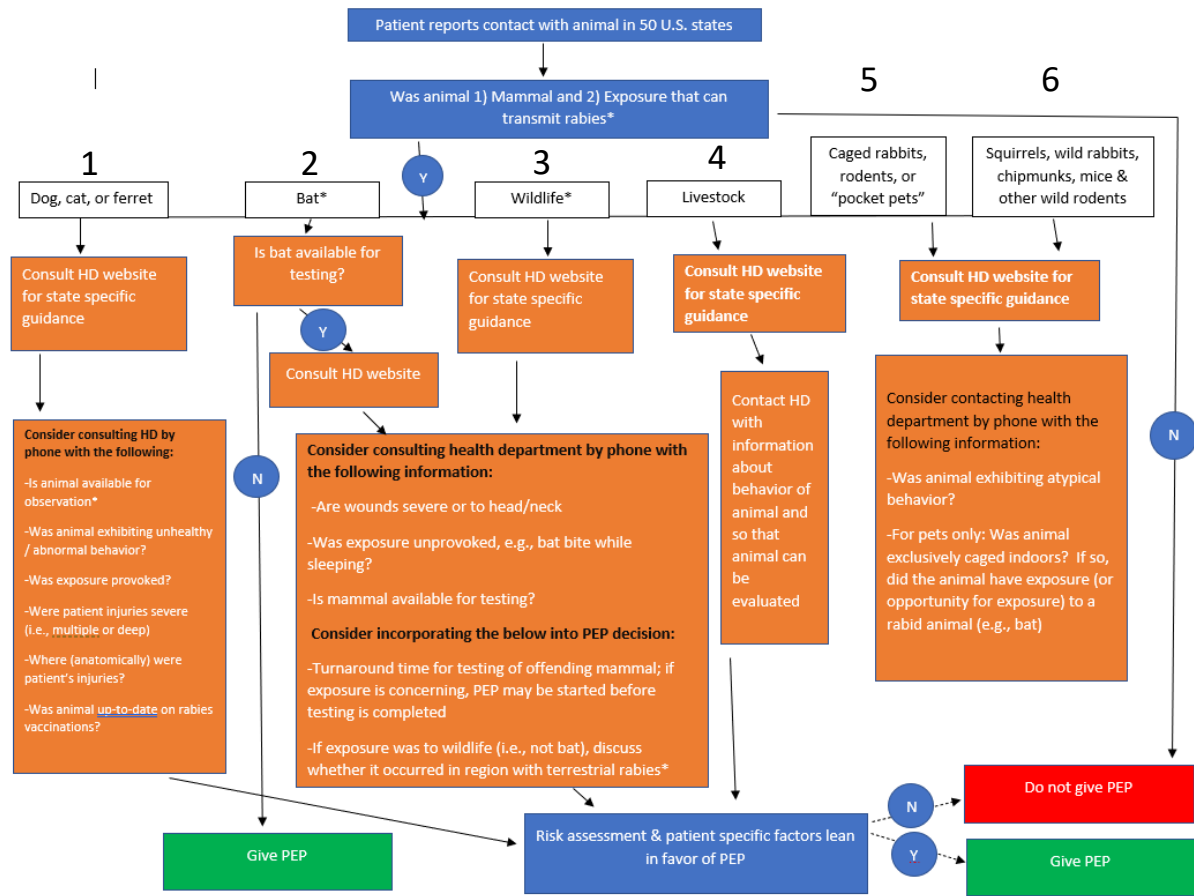
Consult HD website for state specific guidance. Need more guidance?



Consider consulting HD by phone with the following:

- Is animal available for observation*
- Was animal exhibiting unhealthy / abnormal behavior?
- Was exposure provoked?
- Were patient injuries severe (i.e., multiple or deep)
- Where (anatomically) were patient's injuries?
- Was animal upto-date on rabies vaccinations?

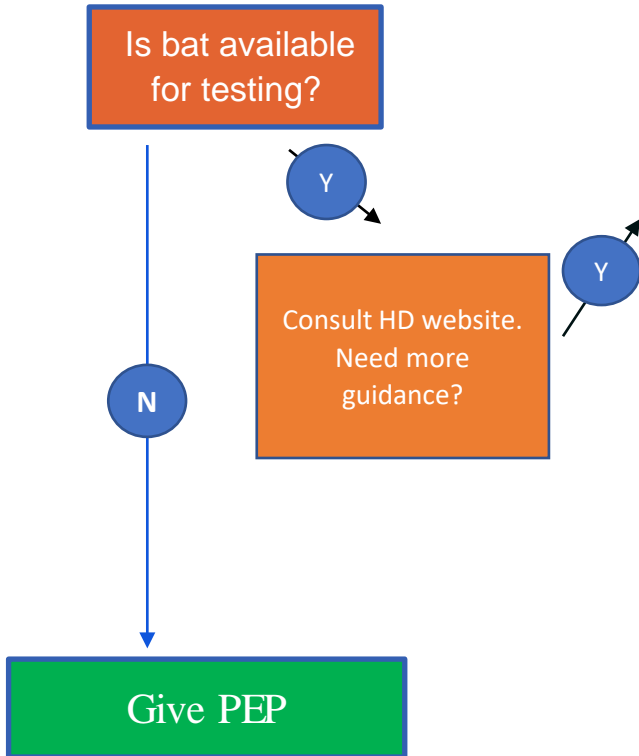
*Animal escaped / is not owned by anyone



Bat exposures can be challenging to assess

- Most common RRV that causes human rabies in the U.S.
- Risk can be difficult to assess because of limited injury from bat bite compared to terrestrial animals
 - Bats involved in potential human exposures should be caught and tested when possible
 - Patient should be interviewed to determine if bite, scratch, or mucous membrane exposure could have occurred
- Bat in room of concern in specific situations
 - Deep sleeping person awakens to find bat in room
 - Adult witness to bat in room with previously unattended child
 - Intoxicated person
 - Person with altered mental status

Approach to exposure from bat

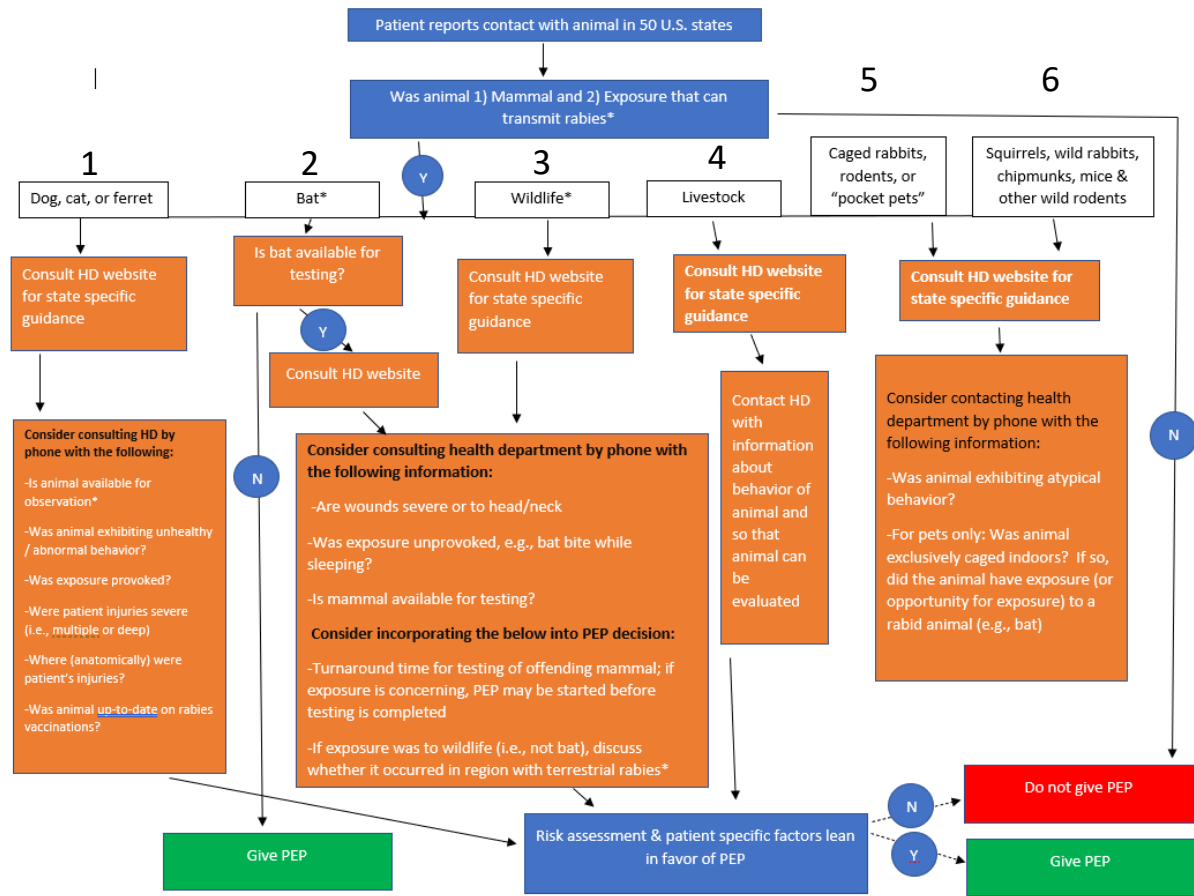


Consider consulting health department by phone with the following information:

- Are wounds severe or to head/neck
- Was exposure unprovoked, e.g., bat bite while sleeping?
- Is mammal available for testing?

Consider incorporating the below into PEP decision:

- Turnaround time for testing of offending mammal; if exposure is concerning, PEP may be started before testing is completed



Wildlife*

Consult HD website for state specific guidance. Need more guidance?

Y

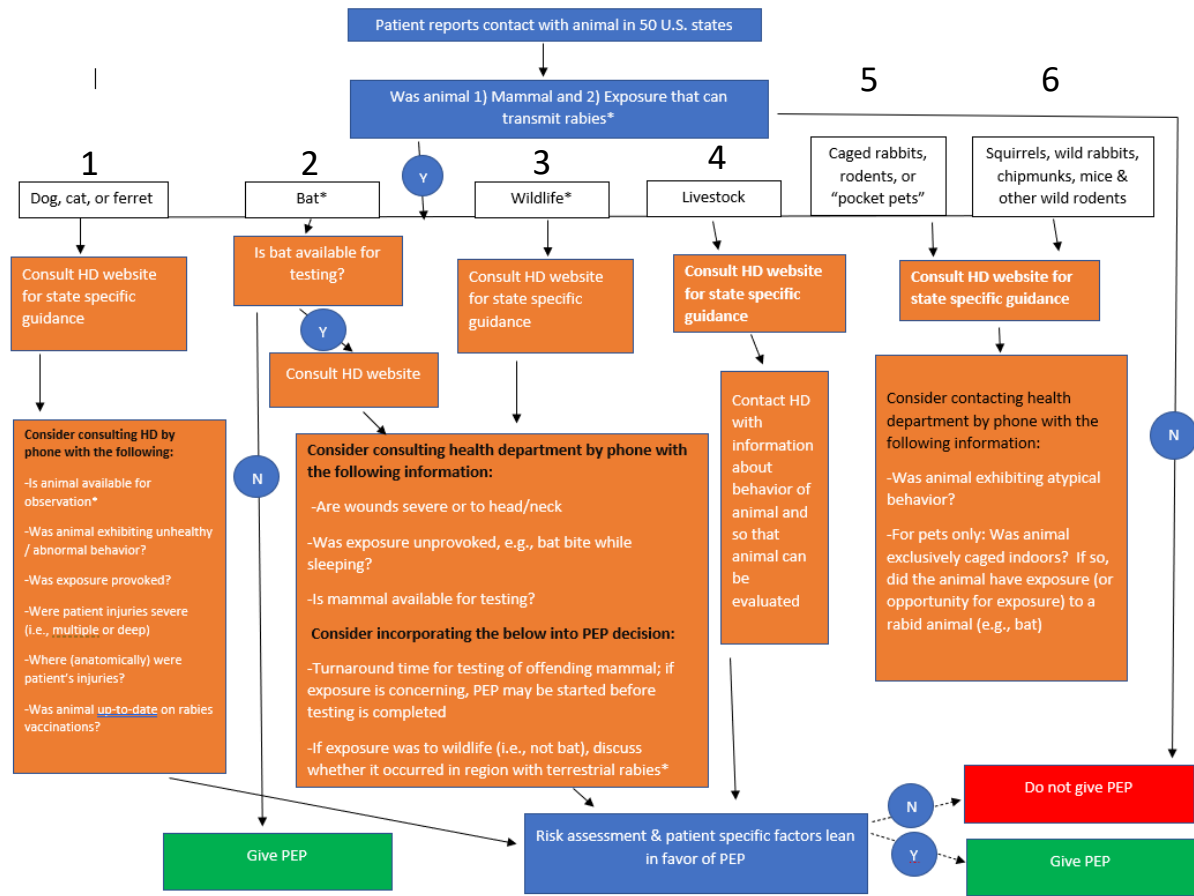
Consider consulting health department by phone with the following information:

- Are wounds severe or to head/neck
- Was exposure unprovoked
- Is mammal available for testing?

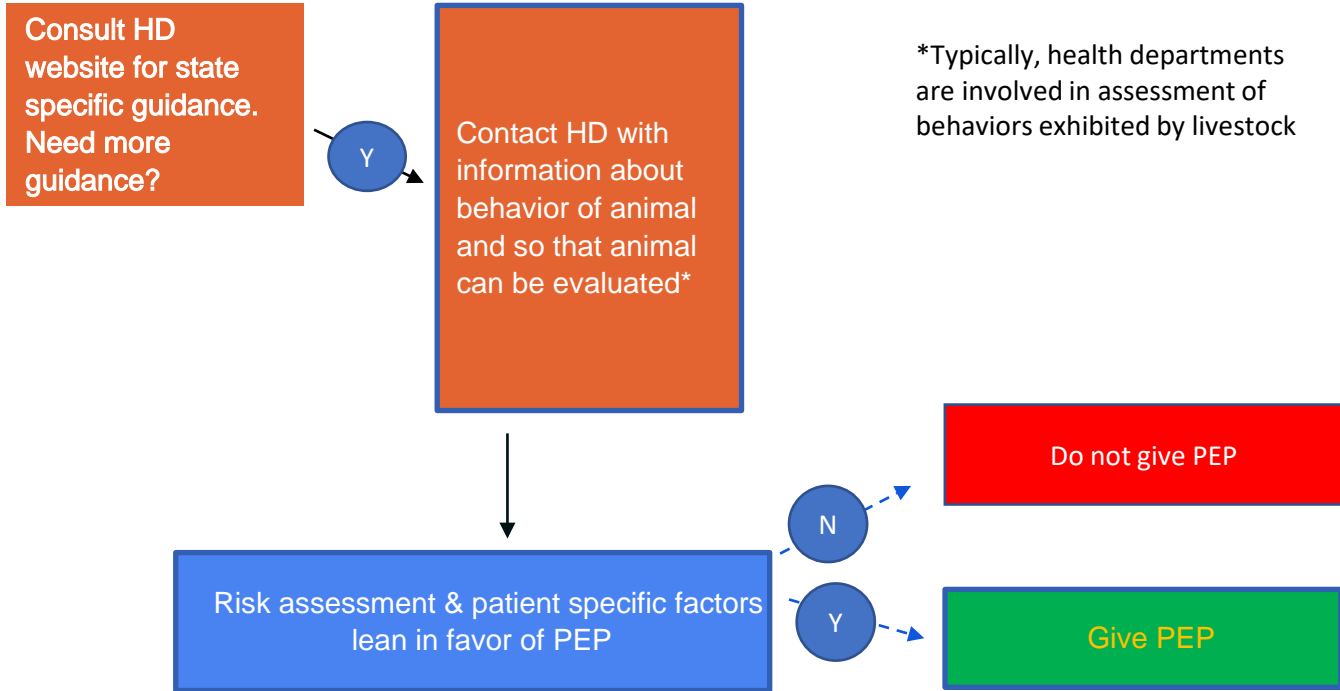
Consider incorporating the below into PEP decision:

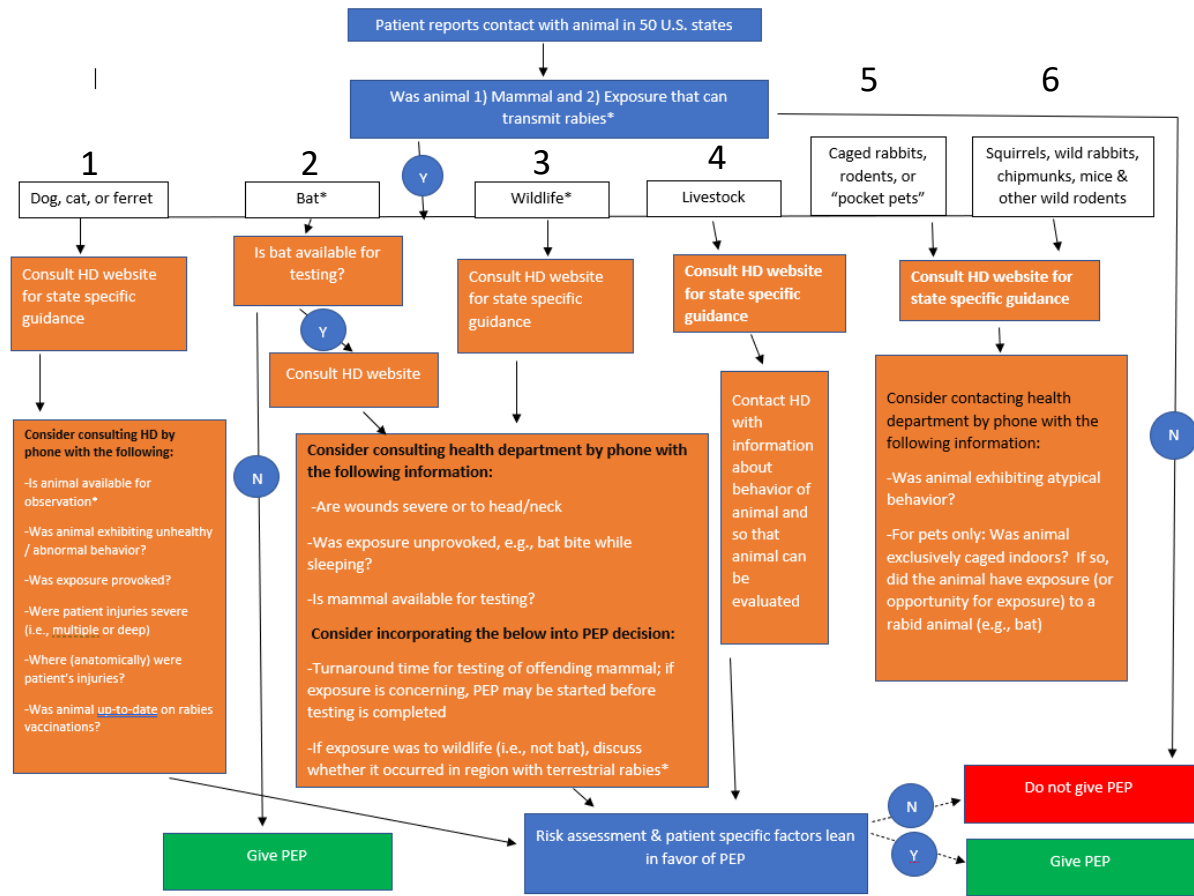
- Turnaround time for testing of offending mammal; if exposure is concerning, PEP may be started before testing is completed
- If exposure was to wildlife, discuss whether it occurred in region with terrestrial rabies

*Wildlife is a diverse group with different animals being of concern for different regions in the country



Livestock





Caged rabbits, rodents, “pocket pets”, squirrels, wild rabbits, chipmunks, mice and other wild rodents

Consult HD website for state specific guidance.
Need more guidance?

Y

Consider contacting health department by phone with the following information:

Was animal exhibiting atypical behavior?

For pets only: Was animal exclusively caged indoors? If so, did the animal have exposure (or opportunity for exposure) to a rabid animal (e.g., bat)

Exposures outside of 50 U.S. states

- ~30 known reservoirs for rabies worldwide
 - Mongoose
 - Dog in a canine-rabies endemic region
 - Bat outside of the U.S.
 - Monkey
 - Exotic animal (e.g., Australian Dassie)
- General guidance
 - Consult health department for case specific advice
 - Collect information about type of exposure, whether exposure was provoked or not provoked, and behavior of animal

Acknowledgements

Rabies Vaccine Work Group

Sharon Frey (chair)

Lynn Bahta

Deborah Briggs

James Stevermer

Matt Zahn

Karl Hess

Paula Agger

Robin Levis

Katie Brown

Elizabeth Bennett

Sally Slavinski

Greg Moran

Michael Pentella

Susan Moore

David Shlim

Julie Emili

Linlu Zhao

Pedro Moro

Kristina Angelo

Eunchung Park

CDC Technical Work Group

Ryan Wallace

Jesse Blanton

Brett Petersen

Sathesh Panayampalli

James Ellison

Florence Whitehill

Caroline Schrodt



Thank you