Background: Post-exposure Prophylaxis

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Advisory Committee on Immunization Practices meeting
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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

Day 0:  RIG + Rabies Vaccine

Days 3, 7, 14: Rabies Vaccines
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

<table>
<thead>
<tr>
<th>Rabies Vaccine</th>
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<tbody>
<tr>
<td>Day 0</td>
<td>Day 3</td>
</tr>
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</table>
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
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

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
Table 3

<table>
<thead>
<tr>
<th>Animal type</th>
<th>Evaluation and disposition of animal</th>
<th>Postexposure prophylaxis recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dogs, cats, and ferrets</td>
<td>Healthy and available for 10 days observation</td>
<td>Persons should not begin prophylaxis unless animal develops clinical signs of rabies.*</td>
</tr>
<tr>
<td></td>
<td>Rabid or suspected rabid</td>
<td>Immediately begin prophylaxis.</td>
</tr>
<tr>
<td></td>
<td>Unknown (e.g., escaped)</td>
<td>Consult public health officials.</td>
</tr>
<tr>
<td>Skunks, raccoons, foxes, and most other carnivores; bats†</td>
<td>Regarded as rabid unless animal proven negative by laboratory tests‡</td>
<td>Consider immediate prophylaxis.</td>
</tr>
<tr>
<td>Livestock, small rodents (rabbits and hares), large rodents (woodchucks and beavers), and other mammals</td>
<td>Consider individually</td>
<td>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.</td>
</tr>
</tbody>
</table>

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.
Patient reports contact with animal in 50 U.S. states

Was animal 1) Mammal and 2) Exposure that can transmit rabies*

1. Dog, cat, or ferret
   - Consult HD website for state specific 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., mutilation or deep)
     - Where (anatomically) were patient's injuries?
     - Was animal up-to-date on rabies vaccinations?
   - 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
     - If exposure was to wildlife (i.e., not bat), discuss whether it occurred in region with terrestrial rabies*

   - Give PEP

2. Bat*
   - Is bat available for testing?
   - Consult HD website
   - Consider consulting 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)

   - Give PEP

3. Wildlife*
   - Consult HD website
   - Consider consulting 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)

   - Give PEP

4. Livestock
   - Consult HD website for state specific guidance
   - Contact HD with information about behavior of animal and so that animal can be evaluated
   - Do not give PEP

5. Caged rabbits, rodents, or "pocket pets"
   - Consult HD website for state specific guidance
   - 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)

   - Give PEP

6. Squirrels, wild rabbits, chipmunks, mice & other wild rodents
   - Consult HD website for state specific guidance
   - 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)

   - Give PEP
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 up-to-date on rabies vaccinations?

*Animal escaped / is not owned by anyone
Bat exposures can be challenging to assess

- Most common RVV 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

Is bat available for testing?

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

Give PEP
Patient reports contact with animal in 50 U.S. states

Was animal 1) Mammal and 2) Exposure that can transmit rabies*

1. Dog, cat, or ferret
   - Consult HD website for state specific guidance
   - Consider consulting HD by phone with the following:
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     - Was animal exhibiting unhealthy/abnormal behavior?
     - Was exposure provoked?
     - Were patient injuries severe (i.e., multi-tissue or deep)?
     - Where (anatomically) were patient's injuries?
     - Was animal up-to-date on rabies vaccinations?

2. Bat*
   - Is bat available for testing?
   - 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?
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   - 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 (i.e., not bat), discuss whether it occurred in region with terrestrial rabies*
   - Contact HD with information about behavior of animal and so that animal can be evaluated

3. Wildlife*
   - Consult HD website for state specific guidance

4. Livestock
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5. Caged rabbits, rodents, or “pocket pets”
   - Consult HD website for state specific guidance
   - 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)

6. Squirrels, wild rabbits, chipmunks, mice & other wild rodents
   - Consult HD website for state specific guidance

Do not give PEP

Risk assessment & patient specific factors lean in favor of PEP

Give PEP
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*
Patient reports contact with animal in 50 U.S. states

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   - Consider consulting HD by phone with the following:
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     - Was exposure provoked?
     - Were patient injuries severe (i.e., multiple or deep)
     - Where (anatomically) were patient’s injuries?
     - Was animal up-to-date on rabies vaccinations?

2. Bat*
   - Is bat available for testing?
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   - Consult HD website for state specific guidance

Risk assessment & patient specific factors lean in favor of PEP

Give PEP

Do not give PEP
Livestock

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

*Typically, health departments are involved in assessment of behaviors exhibited by livestock*

Contact HD with information about behavior of animal and so that animal can be evaluated*

Risk assessment & patient specific factors lean in favor of PEP

Y

Do not give PEP

N

Give PEP

Y

N
Patient reports contact with animal in 50 U.S. states

Was animal 1) Mammal and 2) Exposure that can transmit rabies*

1. Dog, cat, or ferret
   - Consult HD website for state specific 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 up-to-date on rabies vaccinations?
   - Give PEP

2. Bat*
   - Is bat available for testing?
     - Yes
       - Consult HD website
     - No
       - Consider consulting 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)
       - Give PEP

3. Wildlife*
   - Consult HD website for state specific guidance

4. Livestock
   - Consult HD website for state specific guidance

5. Caged rabbits, rodents, or “pocket pets”
   - Consult HD website for state specific guidance

6. Squirrels, wild rabbits, chipmunks, mice & other wild rodents
   - Consult HD website for state specific guidance
   - 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)
   - Do not give PEP

Risk assessment & patient specific factors lean in favor of PEP

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

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

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
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