Evidence to Recommendations for Rabies Pre-Exposure Prophylaxis

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Poxvirus and Rabies Branch
Centers for Disease Control and Prevention

Advisory Committee on Immunization Practices

October 29, 2020
Policy question #1

Should a 2 dose pre-exposure prophylaxis (PrEP) series involving HDCV* or PCECV† IM [0, 7 days] replace the 3 dose series IM [0, 7, 21/28 days] for all those for whom rabies vaccine PrEP is recommended?

*Human diploid cell vaccine
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Policy question: Should a two dose pre-exposure prophylaxis (PrEP) series involving HDCV* or PCECV† IM [0, 7 days] replace the 3 dose series IM[0, 7, 21/28 days] for all those for whom rabies vaccine PrEP is recommended?

*Human diploid cell vaccine
† Purified chick embryo cell vaccine
Problem: Rabies and Pre-exposure Prophylaxis for Rabies

- Rabies is nearly always fatal
- PrEP is important component of preventing human rabies in U.S.
- Indicated for persons with rabies risk > than that of general population
- PrEP critically important for persons with:
  - Unusual exposures
  - Unrecognized exposures
  - Frequent exposure to potentially rabid animals
  - Travel abroad to canine-rabies endemic regions without quick access to PEP
Primary Immunogenicity of Pre-Exposure Prophylaxis Series for Rabies

- No cases of rabies have occurred among persons who received modern cell culture vaccines in the U.S.
- ACIP has recommended PrEP for decades
- Many persons for whom ACIP recommends PrEP, do not receive it
  - Rabies PrEP is very expensive
    - Insurance typically does not cover the cost
    - Occupations often do not cover the cost
  - Some occupations do not enforce compliance with ACIP recommendations even though risk is typically because of occupation
Problem: Pre-exposure prophylaxis for rabies

- PrEP indicated for many persons in U.S.: All U.S. animal care professionals (e.g., veterinarians, technicians, animal control officers), veterinary students, short-term and volunteer workers with hands-on animal care, persons who frequently handle bats or enter high density bat environments, various laboratory personnel, and travelers to canine-rabies endemic regions who may not have quick and easy access to PEP if needed.

- Fewer people receive PrEP than ACIP recommends because series involves 3 vaccine doses and out-of-pocket costs.
Problem: Pre-exposure prophylaxis for rabies

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- Fewer people receive PrEP than ACIP recommends because series involves 3 vaccine doses and out-of-pocket costs

Is the problem of public health importance?

- No
- Probably no
- Uncertain
- Probably yes [X] Yes
- Varies
Benefits

How substantial are the desirable anticipated effects?

- Minimal  Small  Moderate  Large  Don’t know  Varies

- Out of 264 persons receiving 2-dose primary series, 100% achieved titer ≥0.5 IU/mL 2-4 weeks after second dose

- 100% of 264 persons receiving 3-dose primary series achieved a titer level ≥0.5 IU/mL

- Seroconversion is target outcome of PrEP and is achieved with proposed 2-dose series just as it is with the [0, 7, 21/28 days] series
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Harms

How substantial are the undesirable anticipated effects?

- Minimal
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- No expected safety concerns associated with U.S. rabies cell culture vaccines
- Safety data recently compiled from VAERS reports for HDCV and PCECV vaccines* †, those mentioned in the package insert, and those reported in 25 trials published since the 2008 ACIP recommendations are unchanged from previous reports
- These rabies vaccines have been used for decades and considered to have favorable safety profile

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## Overall Certainty for Evidence: Effectiveness

### Effectiveness of the intervention

- No included studies
- Very low
- Low
- Moderate
- High

- Moderate certainty of evidence (Level 2) due to concerns for risk of bias
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Target Population Sentiments

Does the target population feel that the desirable effects are large relative to undesirable effects

- No
- Probably no
- Uncertain
- Probably yes
- Yes
- Varies

- No research evidence identified
- Target population would likely appreciate a shorter series that requires fewer vaccines, is less expensive, and provides the same primary immunogenicity as the current 3-dose series
- Educational materials may be needed to ensure the target audience understands that the immunogenicity is unchanged from that of the current series for up to 3 years
- KAP surveys may be considered to assess perceptions of target population
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- Target population values “protection” from rabies and there is likely no important variability in how people value it
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Is there important uncertainty about or variability in how much people value the main outcomes

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Acceptability

Is the intervention acceptable to key stakeholders

- A shorter series would be appreciated by clinical providers, public health officials, and patients who all prefer a simpler vaccine schedule that is less expensive than the current schedule
- It will be easier to schedule appointments for 2 vaccines than for 3 vaccines
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Resource Use

Is the intervention a reasonable and efficient allocation of resources

- Estimated cost of a 3-dose PrEP series is ~$18,000 for than that for a 2-dose vaccination series; these costs are often out-of-pocket
- Fewer costs would be incurred by patients with shorter series, thereby making intervention a reasonable and efficient allocation of resources to all populations for which it is indicated
- Rabies vaccine shortages have occurred in U.S. Shorter vaccine schedule may prevent impact of these to PrEP demands
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### Equity

**What would be the impact on health equity?**

- Reduced
- Probably Reduced
- Probably no impact
- Probably increased
- Increased
- Varies
- Don’t know

- No research evidence identified
- Costs for rabies PrEP often out-of-pocket so shorter series could potentially make PrEP series more accessible to persons who would not otherwise be able to afford costs
### Equity

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- Costs for rabies PrEP often out-of-pocket so shorter series could potentially make PrEP series more accessible to persons who would not otherwise be able to afford costs
Feasibility

Is the intervention feasible to implement

- No research evidence identified
- No barrier expected to implement shorter series
  - With 3-dose series, often difficult to ensure 3rd dose is administered before travel or start of work which requires pre-vaccination
  - Implementing shorter series will be easier to implement
- Management challenges expected to be equivocal to those currently faced when deviations occur to PrEP schedule
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# Type of recommendation

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<th>Draft recommendation</th>
<th>Work Group Interpretation</th>
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<tr>
<td>In persons for whom rabies vaccine PrEP is indicated,</td>
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<tr>
<td>ACIP recommends 2-dose PrEP series IM [0, 7 days]</td>
<td>WG preference is for intervention</td>
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<td>Involving HDCV or PCECV rather than a 3-dose PrEP series IM [0, 7, 21/28 days]</td>
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Policy question #2

Should an IM booster dose of rabies vaccine (*PCECV or †HDCV) be recommended as an alternative to a titer check no sooner than day 21 and no later than 3 years after the two dose pre-exposure (PrEP) series IM [0, 7 days] for those in the #3 risk category who receive PrEP?

*Human diploid cell vaccine
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**PrEP policy question #2**

Policy question: Should an IM booster dose of rabies vaccine (*PCECV or †HDCV) be recommended as an alternative to a titer check no sooner than day 21 and no later than 3 years after the two dose pre-exposure prophylaxis (PrEP) series IM [0, 7 days] for those in the #3 risk category of people who receive PrEP?

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<td>No rabies vaccine booster after [0, 7 days] rabies vaccine PrEP schedule</td>
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<td>Outcome</td>
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*Human diploid cell vaccine  
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Problem: Long-term Immunogenicity for Rabies

- Some persons have sustained risk for rabies, i.e., risk >3 years after completion of the primary series.

- For those in #1 and #2 risk groups for rabies, serial titer checks is currently recommended by ACIP because of the risk to those groups for “unrecognized” exposures.

- In the absence of data to confirm long-term immunogenicity >3 years after primary series, titer check or booster for those in the #3 risk group can confirm long-term immunogenicity.
  - Single titer check is indicated 1-3 years after primary series because this value is indicative of long-term immunogenicity.
  - Recommendation for titer check would be new ACIP recommendation for those in #3 risk group.
Problem: Long-term Immunogenicity for Rabies

- Some persons in #3 risk group may prefer booster to titer check
  - Titer is much less costly than booster
  - However, titer may indicate need for booster
  - Some persons may prefer going straight away to booster so as to avoid the inconvenience of multiple clinic visits
  - Some persons may have cost of booster absorbed by occupation

- Facilitating the booster dose as soon as when the 3rd dose of the current ACIP [0, 7, 21/28 days] series is administered will amount to no change for those accustomed to that schedule
Problem: Long-term Immunogenicity for Rabies

- Facilitating the booster dose as soon as when the 3rd dose of the current ACIP [0, 7, 21/28 days] series is administered will amount to no change for those accustomed to that schedule.

- Providing flexibility for when the booster dose can be given (i.e., up to 3 years after primary series), may be appreciated by recipients:
  - Some may not know whether they will have risk for long-term immunogenicity and may prefer waiting for 3 years to receive the additional dose.
  - Some may not be able to receive the third dose for an extended time period because of travel and will appreciate having a large time period to receive the booster.

- WHO approved [0, 7 days] series without booster in 2018.
Problem: Long-term immunogenicity for rabies

- Data about immunogenicity will likely be available in coming years
- Europe may have data in coming years
- If policy question is recommended by ACIP, the recommendation facilities collection of data U.S. before next update of ACIP recommendations
  - In #1 risk group among laboratorians at CDC
  - Among those in #3 risk group through collaborations with veterinary schools where PrEP is required
- If data shows IM [0, 7 days] series provides long-term immunogenicity alone, future ACIP update may easily drop booster dose requirement which is an easy change to make
- The proposed recommendation would be step toward simplified series
Problem: Long-term immunogenicity

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- Many persons in #3 risk category may require long-term immunogenicity (e.g., career veterinarian). While 2-dose [0, 7 days] series may provide long-term immunogenicity, in the absence of data to confirm this, a titer check to determine if booster is needed OR booster straight away, provides added insurance for this nearly 100% fatal illness.

- Allowing for option of booster straight away is important because for some persons in target population, it is preferable to save time to bypass titer and go directly to booster; for these persons, cost is typically absorbed by occupation.
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- Allowing for option of booster straight away is important because for some persons in target population, it is preferable to save time to bypass titer and go directly to booster; for these persons, cost is typically absorbed by occupation.
An anamnestic response to vaccine challenge, as measured by increase in antibody titer level $\geq 0.5$ IU/mL, occurred for 100% of persons who receive rabies vaccine booster at the 1-year time point and 3-year time point. These time points are markers of long-term immunogenicity.

We suspect persons who receive 2-dose [0, 7 days] series will be able to mount an anamnestic response many years later regardless of booster; however, for high stakes infection, in the absence of human data to confirm long-term immunogenicity after 3 years, desirable effects are moderate.
Benefits

How substantial are the desirable anticipated effects?

- Minimal
- Small
- Moderate [X]
- Large
- Don’t know
- Varies

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Harms

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- No expected safety concerns associated with booster dose
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- 100% response rate among those receiving a booster
- Likely few additional adverse events from receipt of booster
Benefit/Harms

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- Favors intervention
- Favors comparison
- Favors both
- Favors neither
- Unclear

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## Overall Certainty for Evidence: Effectiveness

### Effectiveness of the intervention

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- Low certainty evidence (Level 3)
Overall Certainty for Evidence: Effectiveness

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- Low certainty evidence (Level 3)
### Target Population Sentiments

**Does the target population feel that the desirable effects are large relative to undesirable effects**

- No
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- Target population likely wants to ensure long-term immunogenicity: Given limited data that 2-dose series alone will provide long-term immunogenicity, we expect benefits to outweigh any inconvenience.

- Persons may experience less anxiety about acquiring this high-mortality infection by having the option of booster or titer confirming titers $\geq 0.5$ IU/mL.

- Some persons may experience discomfort or inconvenience of having to get booster.
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- No research evidence identified
- Target population likely desire PrEP series that provides long-term immunogenicity
- No important uncertainty or variability because target population is at increased risk for exposure to life-threatening illness
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Acceptability

Is the intervention acceptable to key stakeholders

- No research evidence identified
- Stakeholders are invested in ensuring target population has long-term immunogenicity for rabies
- Stakeholders accustomed to accommodating for third dose of rabies vaccine and will find it acceptable to have titer option or booster dose provided after the proposed [0, 7 days] primary series
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**Is the intervention a reasonable and efficient allocation of resources**

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- Cost of rabies booster and appointment for booster is $1800 while cost of a titer is ~$100

- However, given added insurance booster would give for long-term immunogenicity, it would be reasonable and efficient allocation of resources

- Since not all persons who received primary 2-dose series will require a booster, titer check confirming titers $\geq 0.5$ IU/mL would be less costly and could be used to avoid booster
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<td><img src="#" alt="No" />  <img src="#" alt="Probably no" /> <img src="#" alt="Uncertain" /> <img src="#" alt="Probably yes" /> <img src="#" alt="Yes" /></td>
</tr>
</tbody>
</table>

- Cost of rabies booster and appointment for booster is !$1800 while cost of a titer is ~$100
- However, given added insurance booster would give for long-term immunogenicity, it would be reasonable and efficient allocation of resources
- Since not all persons who received primary 2-dose series will require a booster, titer check confirming titers \(\geq 0.5 \text{ IU/mL} \) would be less costly and could be used to avoid booster
### Equity

**What would be the impact on health equity?**

- Reduced
- Probably Reduced
- Probably no impact
- Probably increased
- Increased
- Varies
- Don’t know

- No research evidence identified
- Costs for rabies PrEP often out-of-pocket. There is potential for inequity because of high costs of vaccine
- Because titer is offered as an alternative to booster, the inequity could be resolved by choosing titer option which is many times less expensive than booster
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## Feasibility

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- Administrators of the booster are accustomed to accommodating multiple doses of PrEP beyond a [0, 7 days] series. They will have no difficulty with feasibility of booster dose after 2-dose series.

- Recommending booster may improve feasibility of maintaining occupational compliance with rabies PrEP, including among those noncompliant with current ACIP recommendation for titer checks.
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</tr>
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<td><strong>Desirable consequences clearly outweigh undesirable consequences in most settings</strong></td>
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<tr>
<td>There is insufficient evidence to determine the balance of consequences</td>
</tr>
</tbody>
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Sufficiency of Information

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## Type of recommendation

<table>
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<th>Work Group Interpretation</th>
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<td>For those in the #3 risk category for rabies with sustained risk for rabies, ACIP recommends an IM booster dose of rabies vaccine (PCECV or HDCV) as an alternative to a titer check no sooner than day 21 but no later than 3 years after the 2-dose PrEP series IM [0, 7 days]</td>
<td>WG preference is for intervention</td>
</tr>
</tbody>
</table>
For more information, contact CDC
1-800-CDC-INFO (232-4636)

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.