



# 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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# PrEP policy question #1

	<b>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?</b>
<b>Population</b>	Persons for whom rabies vaccine PrEP is recommended
<b>Intervention</b>	[0, 7 days] rabies vaccine PrEP schedule
<b>Comparison</b>	[0, 7, 21/28 days] rabies vaccine PrEP schedule
<b>Outcome</b>	Primary immunogenicity

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# 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

Is the problem of public health importance?

No     Probably no     Uncertain     Probably yes     Yes     Varies

- 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

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

# 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  $\geq 0.5$  IU/mL 2-4 weeks after second dose
- 100% of 264 persons receiving 3-dose primary series achieved a titer level  $\geq 0.5$  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   Moderate  Large  Don't know  Varies

- 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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# Benefit/Harms

**Do the desirable effects outweigh the undesirable effects?**

Favors intervention    Favors comparison    Favors both    Favors neither    Unclear

- Both 2-dose and 3-dose primary series achieve complete immunogenicity at 2-4 weeks following completion of series

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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 Sentiments

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- No research evidence identified
- Target population values “protection” from rabies and there is likely no important variability in how people value it

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# Acceptability

Is the intervention acceptable to key stakeholders

No  Probably no  Uncertain  Probably yes  Yes  Varies

- 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**

No    Probably no    Uncertain    Probably yes    Yes

- 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



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# Feasibility

Is the intervention feasible to implement

No    Probably no    Uncertain    Probably yes    Yes    Varies

- No research evidence identified
- No barrier expected to implement shorter series
  - With 3-dose series, often difficult to ensure 3<sup>rd</sup> 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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# Balance of Consequences

- ☐ Undesirable consequences clearly outweigh desirable consequences in most settings
- ☐ Undesirable consequences probably outweigh desirable consequences in most settings
- ☐ Balance between desirable and undesirable consequences is closely balanced or uncertain
- X** **Desirable consequences probably outweigh undesirable consequences in most settings**
- ☐ Desirable consequences clearly outweigh undesirable consequences in most settings
- ☐ There is insufficient evidence to determine the balance of consequences

# Sufficiency of Information

Is there sufficient information to move forward with a recommendation?

Yes

No

# Sufficiency of Information

Is there sufficient information to move forward with a recommendation?

Yes

No

# Type of recommendation

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## Draft recommendation

In persons for whom rabies vaccine PrEP is indicated, ACIP recommends 2-dose PrEP series IM [0, 7 days] involving HDCV or PCECV rather than a 3-dose PrEP series IM [0, 7, 21/28 days]

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## Work Group Interpretation

WG preference is for intervention

## 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

	<b>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?</b>
<b>Population</b>	Persons in the #3 risk category for whom rabies vaccine PrEP is recommended
<b>Intervention</b>	Day 21- year 3 rabies vaccine booster after [0, 7 days] rabies vaccine PrEP schedule
<b>Comparison</b>	No rabies vaccine booster after [0, 7 days] rabies vaccine PrEP schedule
<b>Outcome</b>	Long-term immunogenicity

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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 3<sup>rd</sup> 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 3<sup>rd</sup> 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 facilitates 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

Is the problem of public health importance?

No    Probably no    Uncertain    Probably yes    Yes    Varies

- 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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# Benefits

**How substantial are the desirable anticipated effects?**

Minimal  Small  Moderate  Large  Don't know  Varies

- 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



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- 100% response rate among those receiving a booster
- Likely few additional adverse events from receipt of booster

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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 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    Probably no    Uncertain    Probably yes    Yes    Varies

- 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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# Resource Use

**Is the intervention a reasonable and efficient allocation of resources**

No    Probably no    Uncertain    Probably yes    Yes

- 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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# Equity

## What would be the impact on health equity?

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- 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

**Is the intervention feasible to implement**

No    Probably no    Uncertain    Probably yes    Yes    Varies

- 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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# Balance of Consequences

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# Sufficiency of Information

Is there sufficient information to move forward with a recommendation?

Yes

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# Sufficiency of Information

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No

# Type of recommendation

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## Draft recommendation

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]

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## Work Group Interpretation

WG preference is for intervention

For more information, contact CDC  
1-800-CDC-INFO (232-4636)  
TTY: 1-888-232-6348 [www.cdc.gov](http://www.cdc.gov)

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.