Evidence to Recommendations for Rabies Pre-Exposure Prophylaxis

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Advisory Committee on Immunization Practices

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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
† Purified chick embryo cell vaccine

PrEP policy question #1

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

*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

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 ≥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 ☐ ☐ 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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Effectiveness of the intervention				
☐ No included studies	☐ Very low	☐ Low	☒ Moderate	☐ High

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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

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
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Target Population Sentiments

Is there important uncertainty about or variability in how much people value the main outcomes				
☐ Important uncertainty or variability	☐ Possibly important uncertainty or variability	☐ Probably no important uncertainty or variability	☐ No important uncertainty or variability	☐ No known undesirable outcomes

- 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

Acceptability

Is the intervention acceptable to key stakeholders

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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 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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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?	
[X] **Yes**	[ ] No

Type of recommendation

Draft recommendation	Work Group Interpretation
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]	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
† Purified chick embryo cell vaccine

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

*Human diploid cell vaccine

† Purified chick embryo cell vaccine

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

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 ≥ 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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Do the desirable effects outweigh the undesirable effects?

☐ Favors intervention ☐ Favors comparison ☐ Favors both ☐ Favors neither ☐ Unclear

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

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Overall Certainty for Evidence: Effectiveness

Effectiveness of the intervention

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

☐ No ☐ Probably no ☐ Uncertain ☐ Probably yes ☐ Yes ☐ Varies

- 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 ≥0.5 IU/mL
- Some persons may experience discomfort or inconvenience of having to get booster

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Target Population Sentiments

Is there important uncertainty about or variability in how much people value the main outcomes

Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability	No known undesirable outcomes

- No research evidence identified
- Target population likely desire PrEP series that provides long-ter 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

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- 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 ≥0.5 IUmL would be less costly and could be used to avoid booster

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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. 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

☐ 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
☐ 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?	
[X] **Yes**	[ ] No

Type of recommendation

Draft recommendation	Work Group Interpretation
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]	WG preference is for intervention

For more information, contact CDC
1-800-CDC-INFO (232-4636)
TTY: 1-888-232-6348 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.