Summary of Evidence to Recommendations Framework for Rabies Pre-Exposure Prophylaxis Vote

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Rabies antibody response

- Target response, i.e., ≥ minimum antibody titer, 0.5 IU/mL, regardless of series
  - Children
  - Pregnant women
  - Persons ≥ 65 years of age

- Persons with altered immunity
  - Efficacy can be a concern
  - Titer check after primary series (and boosters until ≥ 0.5 IU/mL)

Rabies vaccines licensed in U.S.

Biologic	Product name	Manufacturer	Administration	Potency
Human diploid cell vaccine (HDCV)	Imovax	Sanofi Pasteur	intramuscularly	≥2.5 IU of rabies antigen
Purified chick embryo cell vaccine (PCECV)	RabAvert	Bavarian Nordic	intramuscularly	≥2.5 IU of rabies antigen

- Been used in the U.S. for decades
- No change in favorable safety profile

Estimated* PrEP use in the United States

- Doses: 170,000 including 500 booster doses
- Categories of people receiving PrEP: 60,535 / year
  - Travelers and “other risk groups”: 41,117
  - Veterinary technicians: 13,860
  - Veterinary students: 3,500
  - Animal control: 1,178
  - Rabies laboratory personnel: 480
  - Wildlife biologists: 400

* Mathematical model based on workforce statistics produced by Bureau of Labor Statistics and market research provided by Bavarian Nordic

Adherence to ACIP PrEP recommendations*

- Veterinary students: 100% (required for clinics)
- Laboratory personnel: 100% (required)
- Animal control: 78.5%
- Veterinary technicians/staff: 69.3% (in other published studies, 30-40% adherence)
- Wildlife biologists: ~50%
- Other risk groups: ?
- Travelers: ?

*Some results from unpublished CDC data; Blanton et al.

Includes data obtained from ~2,000 persons

Survey sent to members of professional organizations who were certified providers and were likely more compliant with the ACIP recs than persons not captured by the survey

EtR for policy question #1: Primary immunogenicity

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 PrEP

- Rabies is nearly always fatal
- PrEP is important component of preventing human rabies in U.S.
- PrEP critically important to some persons
  - Unusual exposures (e.g., aerosolized) or high concentration virus
  - Unrecognized exposures
  - Frequent exposure to potentially rabid animals
  - Travel abroad to canine-rabies endemic regions without quick PEP access

Primary immunogenicity of PrEP for rabies

- Rabies modern cell culture vaccines are effective
- ACIP has recommended PrEP for decades
- Noncompliance among some for whom it is recommended
  - Out-of-pocket costs
  - Some occupations do not require it
  - Insufficient time to complete 3-dose series before international travel

EtR: Policy question #1

Domains	WG interpretation
Benefits: How substantial are the desired anticipated effects	Minimal; 100% of people seroconvert for proposed and for previous schedule
Harms: How substantial are undesirable anticipated effects?	Minimal; No expected safety concerns
Benefit / Harm: Do desirable effects outweigh undesirable effects?	Favors both
Overall certainty for evidence: effectiveness	Moderate certainty of evidence (Level 2) due to concerns for risk of bias

PrEP costs

- Reimbursement price for vaccine dose: $331*(Source: CMS/ASP)

- Additional costs are variable depending on location PrEP is administered
- We estimate $1100- $3500 for PrEP series

  (3 vaccines + additional costs)

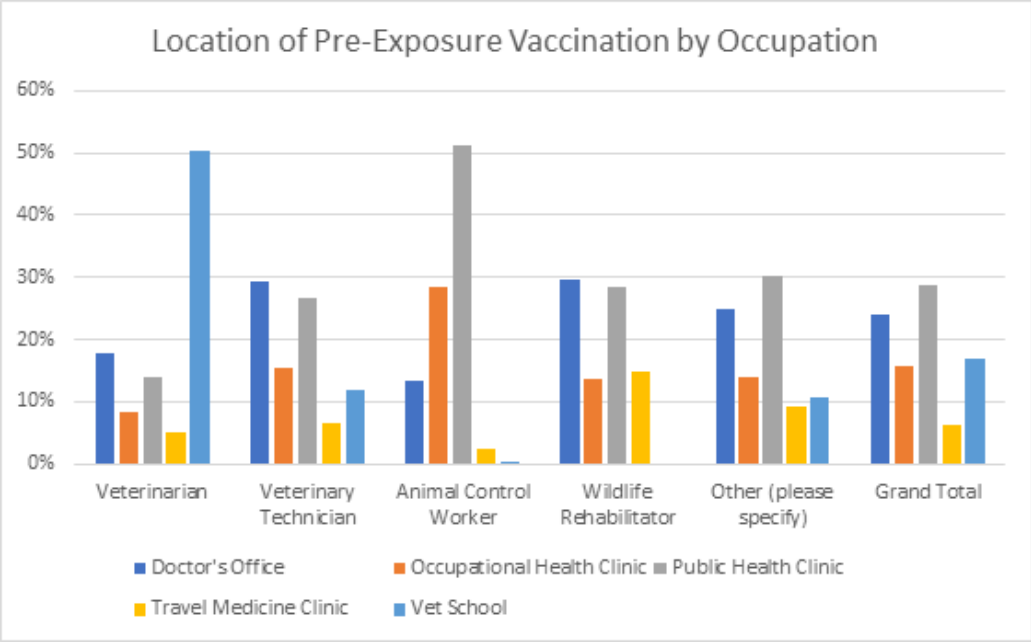


Figure: Location of pre-exposure vaccine administration by occupation in the United States; not shown is PrEP received in Emergency Departments which was the location for PrEP in 2% of respondents
(Source: Blanton et al, unpublished data from CDC survey)

Proportion of PrEP costs that are out-of-pocket

Vaccination indication	# reporting insurance would cover at least part of cost		# reporting employer would cover at least part of cost		# reporting EITHER would cover at least part of the cost	
	Booster	Titer	Booster	Titer	Booster	Titer
Veterinary professionals	25%	25%	20%	40%	25%	30%
Animal control	50%	40%	54%	20%	60%	60%
Animal rehabilitationists	25%	33%	12%	20%	25%	40%

Source: Unpublished CDC data; Blanton et al

EtR: Policy question #1

Domains	WG interpretation
Target population sentiments: uncertainty about or variability in how much people value outcomes?	No: Target population values "protection" from rabies and there is likely no important variability
Acceptability to stakeholders?	Yes: Shorter schedule preferred by patients & providers
Reasonable and efficient allocation of resources?	Yes: Cost savings and because rabies vaccine shortages have occurred in U.S.
Impact on equity?	Probably reduced because of decreased costs
Feasible to implement?	Yes: Shorter series than current series

EtR: Policy question #1

Domains	WG interpretation
Target population sentiments: Does the target population feel desirable effects are large relative to undesirable effects	Probably yes • Data supports high costs incurred by PrEP recipients • Persons who should receive PrEP for travel are known to not receive it because <21 days from clinic appointment to travel

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

Proposed recommendation for vote

Recommendation	**Work Group Interpretation**
ACIP recommends a 2-dose [0, 7 days] intramuscular rabies vaccine series in immunocompetant persons >= 18 years of age for whom rabies vaccine pre-exposure prophylaxis (PrEP) is indicated	WG preference is for intervention

EtR for policy question #2: Long-term immunogenicity

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

- Immunology suggests that anamnestic response to an exposure occurs
- WHO approved 2-dose series (no booster or titers)
- Rabies is nearly 100% fatal
- WG opted for most cautious route to ensure long-term immunogenicity for [0, 7 days] series
  - Strong data for long-term immunogenicity only exists for up to 3 years
  - Data shows that titer at ≥ 1 year, is marker of long-term immunogenicity
  - WG proposed titer at 1-3 years (and boost accordingly) OR
  - Booster no sooner than day 21 and no later than year 3

Long-term immunogenicity reported in recently published article*

- 6 persons who received [0, 7 days] IM series, were evaluated after 10-11 years
  - 3 male; 3 female
  - Ages 34-46
  - 5 had titers ≥ 0.5 IU/mL
  - All had 4-fold increase in titers after booster

- More data expected about long-term immunogenicity of 2-dose series because WHO recommendations made in 2018

*De Pijper et al, Long-term memory response after a single intramuscular rabies booster vaccination, 10-24 years after primary vaccination. Journal of Infectious Diseases. Epub January 2021

EtR: Policy question #2

Domains	WG interpretation
Benefits: How substantial are the desired anticipated effects	Moderate • Booster at day 21 is equivalent to current 3-dose series and is known to provide long-term immunogenicity • 100% of subjects mounted anamnestic response to booster at 1-3 years
Harms: How substantial are undesirable anticipated effects?	Minimal; No expected safety concerns
Benefit / Harm: Do desirable effects outweigh undesirable effects?	Favors intervention
Overall certainty for evidence: effectiveness	Low certainty of evidence (Level 3)

EtR: Policy question #2

Domain	WG interpretation
Target population sentiments: Does the target population feel desirable effects are large relative to undesirable effects	Probably yes • Stakeholders want to avoid acquiring high-stakes infection • Booster provides reassurance that outweighs any inconvenience
Target population sentiments: uncertainty about or variability in how much people value outcomes?	No: Target population values "protection" from rabies and there is likely no important variability
Acceptability to stakeholders?	Yes: Stakeholders accustomed to accommodating third dose of rabies vaccine and will find it acceptable to have booster as an option
Reasonable and efficient allocation of resources?	Yes: Cost savings

Costs of titer compared to booster

- Titer: Cost ~$50-$75* + cost of blood draw / clinic appointment

- Booster: ~$331 for cost of booster + additional costs

*KSU website and word of mouth

EtR: Policy question #2

Domains	WG interpretation
Impact on equity?	Don't know: some PrEP costs are out-of-pocket; because titer is offered as option, inequity could be resolved by choosing that option
Feasible to implement?	Yes: Administrators could opt to schedule booster dose at the time of primary vaccination

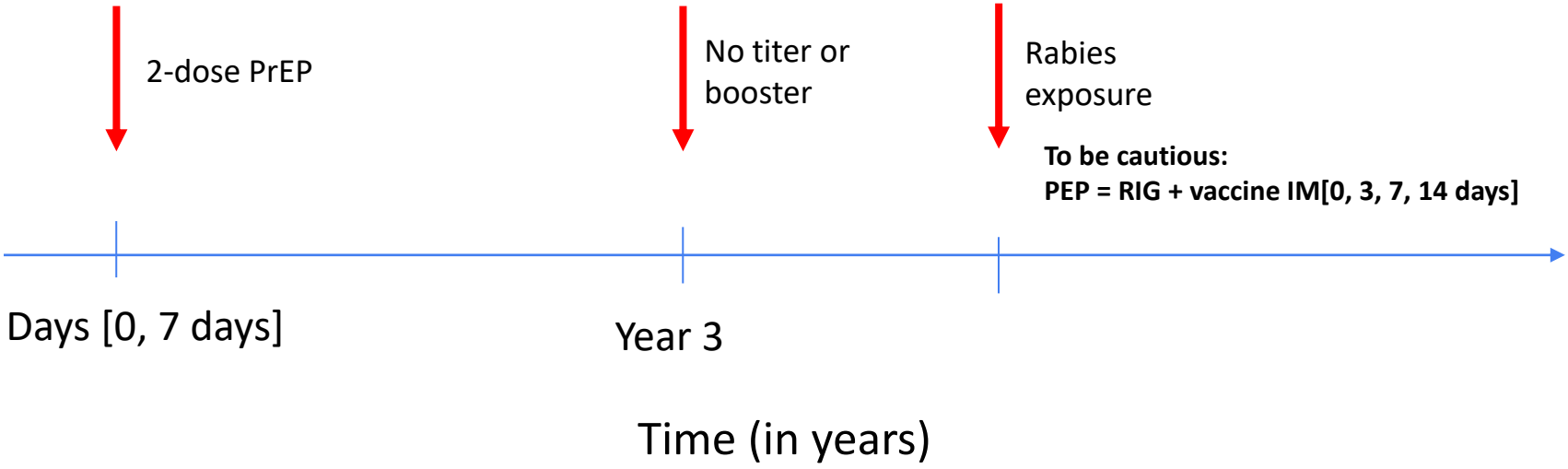
Balance of Consequences

- [ ] 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
- [x] **Desirable consequences clearly outweigh undesirable consequences in most settings**
- [ ] There is insufficient evidence to determine the balance of consequences

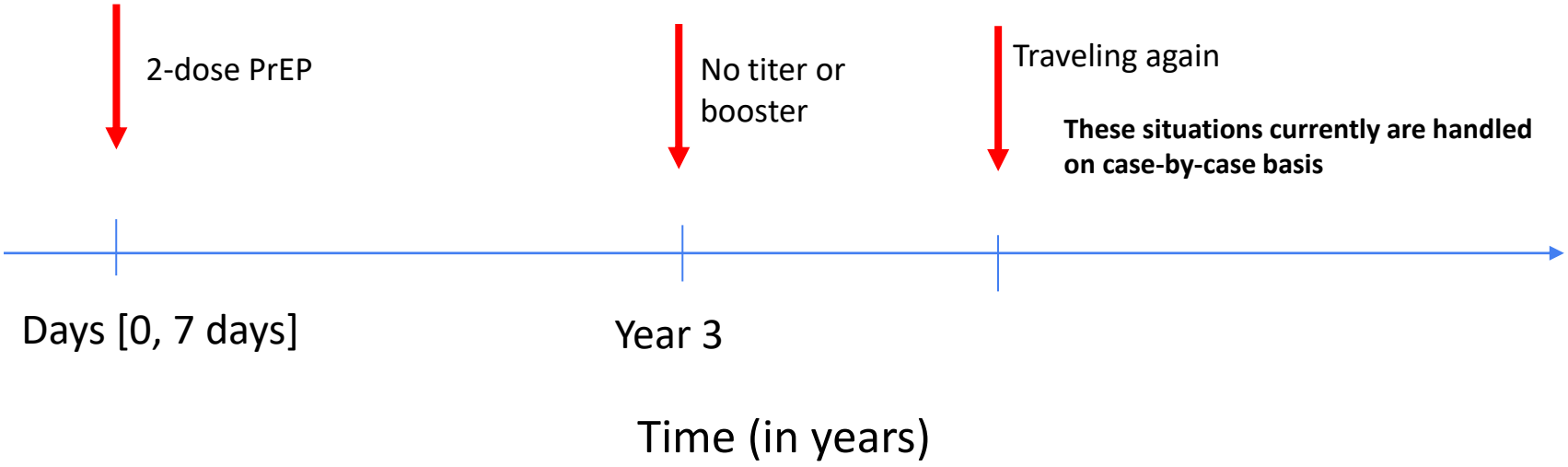
Proposed recommendation for vote

Recommendation	Work Group Interpretation
ACIP recommends an intramuscular booster dose of rabies vaccine, as an alternative to a titer check, for immunocompetent persons >=18 years who have sustained and elevated risk for only recognized rabies exposures (i.e., those in risk category #3 of rabies PrEP recommendations table). The booster dose should be administered no sooner than day 21 but no later than 3 years after the 2-dose PrEP series.	WG preference is for intervention

Clinical guidance scenarios



Clinical guidance scenarios



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Questions?

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.

Implications of proposed changes

Risk group	Population	Primary immunogenicity	Implications	Long-term immunogenicity	Implications
#1	Research laboratorians	IM [0, 7 days]	Fewer vaccine doses but equivalent efficacy	Titer check ever 6 months[1]	No change
	Diagnostic laboratorians			Titer every 6 months	Makes sense to consider all laboratorians equally
#2	Bat biologists			Titer check every 2 years[2]	No change
#3	Animal care professionals in terrestrial rabies regions			Titer once (1-3 years after primary series) OR Booster no sooner than day 21 and no later than year 3	Fewer vaccine doses and/or fewer titer checks
	Animal care professionals in non-terrestrial rabies regions, students, spelunkers, persistent travelers				Same number of vaccine doses OR instead of 3rd vaccine, a titer
	Short-term animal care professionals and persons without sustained risk for rabies				No additional vaccine and no titers

PrEP Policy Question #1

Table 3a: Summary of Randomized Control Trial Studies Reporting Outcome

Authors last name, pub year	Age (years)	N intervention	N comparison	Vaccine	Risk Ratio [95% CI]	Study limitations (Risk of Bias)
Endy, 2019	Mean 32.4, Range 18 - 59	22	24	PCEC, IM, ID	1.00 [0.89, 1.12]	Some concerns[1]
Soentjens, 2019	Median 29.0, Range NR	242	240	HDCV, ID	1.00 [0.99, 1.01]	Some concerns[2]

[1]Allocation concealment not reported. Study did not blind participants or healthcare personnel; however, unlikely that co-interventions would have influenced the outcome.

[2]Method of randomization and allocation not reported. Study did not blind participants or healthcare personnel; however, unlikely that co-interventions would have influenced the outcome.

PrEP Policy Question #1

Table 3b: Summary of Observational Studies Reporting Outcome

Authors last name, pub year	Age (years)	N intervention	N comparison	Vaccine	Risk Ratio [95% CI][1]	Study limitations (Study quality[2])
Ajjan, 1989	Mean 22, Range 19-41	72	69	HDCV, IM	1.00 [0.97, 1.03]	9/9 No concerns
Arora, 2004	Mean 26.2, NR	44	44	HDCV, IM	1.00 [0.96, 1.04]	9/9 No concerns
Briggs, 1996	NR	146	146	HDCV, IM	1.00 [0.99, 1.01]	9/9 No concerns
Cramer 2016	Mean 36.7, SD 12.9	371	364	PCEC, IM	0.99 [0.98, 1.01][4]	7/9 Minimal concerns
Hacibektasoglu, 1992	Mean 20, Range 18 - 24	30	30	HDCV, IM	0.90 [0.79, 1.03]	9/9 No concerns
Jaijaroensup, 1999	NR, Range 17 - 22	138	129	PCEC, IM, ID	0.94 [0.87, 1.02][4]	9/9 No concerns
Kitala, 1990	NR	37	37	HDCV, IM	1.00 [0.95, 1.05]	8/9 Minimal concerns
Recuenco, 2017	Median 41.0, Range 20 - 62	60	59	PCEC, IM, ID	1.00 [0.96, 1.05][4]	9/9 No concerns
Sabchareon, 1999	Mean 10, SD 1.3[3]	190	190	HDCV, IM	1.00 [0.99, 1.01]	7/9 Minimal concerns
Vodopija, 1986	NR	49	46	HDCV, PCEC, IM	1.00 [0.94, 1.06][4]	9/9 No concerns

[1]Data from observational studies, where intervention and comparison data were taken from the same people at different time points, were analyzed using M-H Risk Ratio random effects procedure. Due to unavailable raw data on pairing, a matched analysis was not possible.

[2]Study quality for observational studies was assessed using the Newcastle Ottawa Scale.

[3]Age for total study population was not reported in this paper. Numbers in this cell are from the study arm from which data were extracted.

[4]Studies contained multiple arms relative to the analysis. Risk ratio reflects pooled analysis from eligible arms.

PrEP Policy Question #2

Table 3: Summary of Studies Reporting Outcome

Authors last name, pub year	Age (years)	N intervention	N comparison	Comparator vaccine	Risk Ratio [95% CI]	Study limitations (Study quality[3])
Endy, 2019	Mean 32.4, Range 18 - 59	20	No comparison[1]	PCEC, IM	Not able to calculate[2]	8/9 Minimal concerns
Soentjens, 2019	Median 29.0, NR	183	No comparison[1]	HDCV, IM	Not able to calculate[2]	8/9 Minimal concerns

[1]No comparison data available for this policy question available in these studies.

[2]No comparison data available to calculate effect estimate.

[3]Study quality for observational studies was assessed using the Newcastle Ottawa Scale.

Reminder: proposed changes

	Primary immunogenicity	Long-term immunogenicity
#1 risk group (i.e., laboratorians)	IM [0, 7 days]	Titers every 6 months after primary series
#2 risk group (i.e., persons who handle bats or enter high density bat environments)	IM [0, 7 days]	Titers every 2 years after primary series
#3 risk group (i.e., veterinarians, vet assistants, animal handlers, vet students, travelers etc.)	IM [0, 7 days]	Titer once at 2 years after primary series OR Booster once no sooner than day 21 and no later than 3 years[ŧ]

Highlighted: Proposed changes to 2008 ACIP recommendations

Red box: Today's votes