



# Rabies Pre-exposure Prophylaxis and Children

Advisory Committee on Immunization Practices Meeting

May 5, 2021

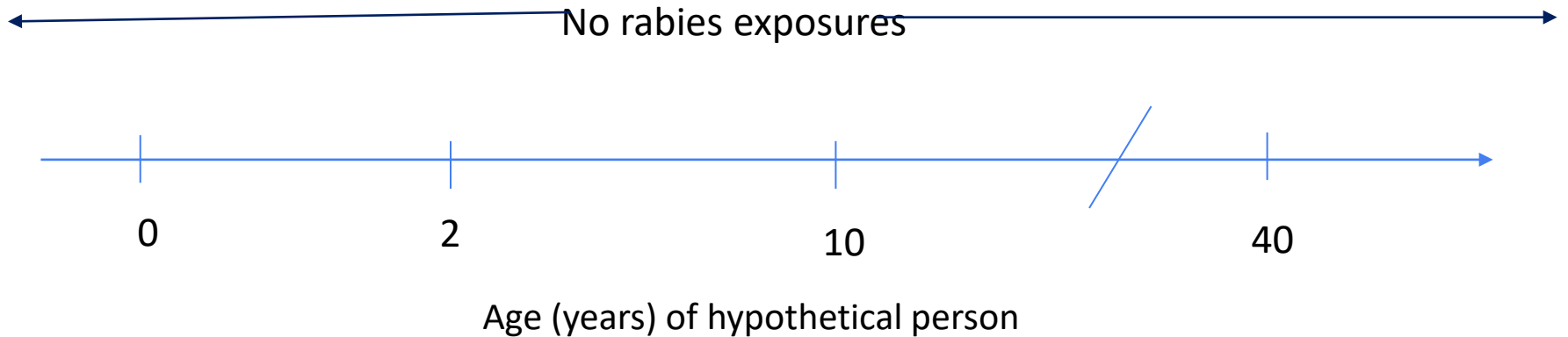
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# Strategies to prevent rabies exposures

- Avoidance of risky behaviors
- Vaccination of pets and wildlife
- Proper use of personal protective equipment



# Strategies to prevent human rabies when an exposure occurs

- Post exposure prophylaxis (PEP)
  - Rabies immune globulin + 4-dose vaccine series
  - Alone, saves lives
- Pre-exposure prophylaxis (PrEP)
  - Does not negate the need for PEP
  - Recommended for select populations for specific reasons

# Reasons PrEP is recommended for select populations

- Rapid PEP administration is not enough
  - High concentration rabies virus exposure
  - Unusual rabies virus exposures
  - E.g., laboratorians
- Unrecognized rabies exposures
  - Bite from bat can sometimes go undetected\*
  - E.g., bat biologist commonly entering high density bat caves



\*Bat tooth size 2-10mm and bite strength ~2lbs of pressure ; exposure can go unrecognized if swarmed by bats (which occurs when entering high density bat region)

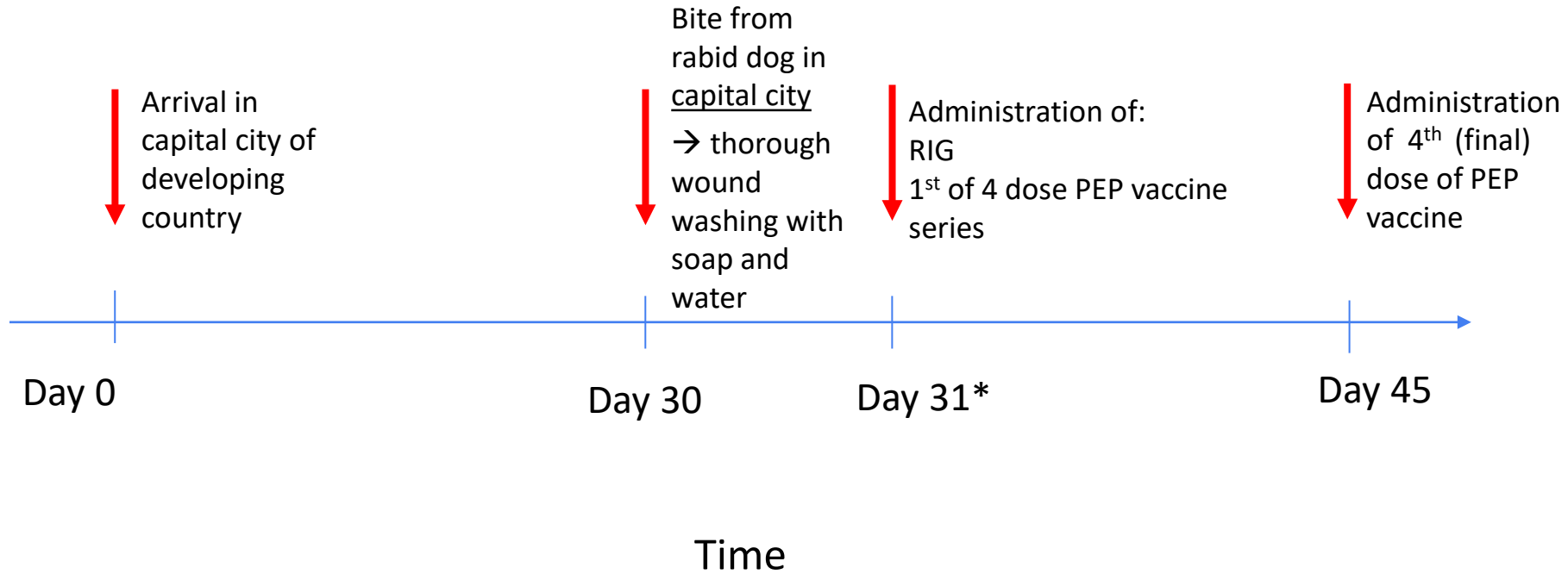
# Reasons PrEP is recommended for select populations

- Challenges with access to PEP
  - RIG is not available in some developing countries
  - Rabies vaccines may only be available in capital city of developing country resulting in a delay to PEP administration
  - E.g., travelers, particularly children



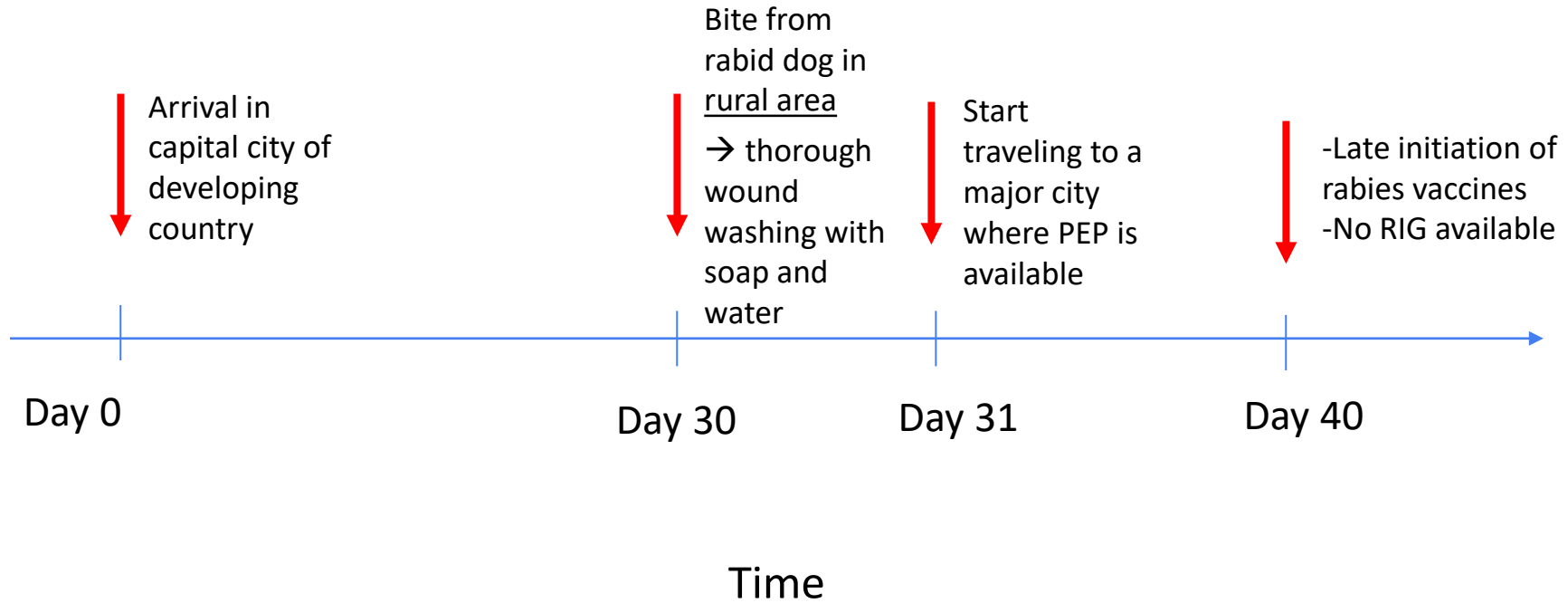
# Sequence of events for many travelers

\*PEP should be administered promptly but there is no specified time period within which PEP should be administered after an exposure



# Sequence of events for some travelers

\*PEP should be administered promptly but there is no specified time period within which PEP should be administered after an exposure



# Rabies PrEP and travelers\*

- Recommended for certain international travelers
  - Based on occurrence of animal rabies in the country of destination
  - Availability of antirabies biologics
  - Intended activities of traveler, especially in remote areas
  - Traveler's duration of stay
- Children, in particular, should be offered PrEP when indicated

## Preexposure Vaccination

Children are at higher risk for rabies exposure and subsequent illness because of their inquisitive nature and inability to read behavioral cues from dogs and other animals. The smaller stature of children makes them more likely to experience severe bites to high-risk areas, such as the face and head. Also contributing to the higher risk is their attraction to animals and the possibility that they may not report an exposure.

\*Yellow Book; <https://wwwnc.cdc.gov/travel/yellowbook/2020/travel-related-infectious-diseases/rabies>; accessed on 4/20/21



# Benefits of receiving PrEP

- No RIG if exposure occurs
- 2-dose PEP rabies vaccine series, [0, 3 days] instead of 4-dose PEP rabies vaccine series [0, 3, 7, 14 days]
  
- Beneficial for travelers to some developing countries
  - Where RIG may not be available
  - Where rabies vaccines may take time to access
  - Where 2-dose series is easier to get than 4-dose series

**Data reviewed by WG**

# Expectations for PrEP schedule (regardless of age group) to ensure effectiveness

- Primary immunogenicity is achieved (i.e, minimum acceptable antibody titers achieved within 14 days of series completion)
  - If primary immunogenicity is achieved
    - Rapid anamnestic response occurs after an exposure
    - Anamnestic response occurs regardless of time from PrEP to exposure
- High proportion of persons achieve primary immunogenicity

## Factors that do not impact anamnestic response

- Vaccine doses over that needed to achieve primary immunogenicity
- Number of bites / scratches
- Severity of bites / scratches
- Location of bites / scratches
- Size of exposed person

Anamnestic response is an all-or-none response that occurs quickly after an exposure

# WG discussion: Is there any reason to believe that children have a different response to rabies vaccines than adults?

- 2019, systematic review performed to determine if pediatric response to various rabies vaccine series is inferior to that of adults
- >12 papers identified through search of multiple databases
  - Papers addressing children < 2 years: 7
  - Papers addressing children 2-18 years: 7
  - Age range: 2 months – 17 years of age
- Conclusion:
  - GMTs in children are the same or higher than those in adults for any given series
  - GMTs stay higher for longer in children; no reason to suspect suboptimal immunogenicity in children compared to adults

# Manuscripts reviewed by WG that indicated robust response in children

Article	Pertinent study details	Conclusion
<p>Chatchen et al; 2017            “Long-term protective rabies antibodies in Thai children after preexposure rabies vaccination”; SE Asian Journal of Trop Med &amp; Public Health</p>	<p>Titers 48 years after IM and ID rabies PrEPseries + booster had been administered to <u>children &lt;2 years of age</u>; <u>68 subjects</u></p>	<p>-In comparison to 18-24 year old subjects in Thailand studied similarly, “these findings suggest that the immune responses of the toddlers were better than those of young adults.”            -Evidence for long-term induction of protective antibodies by PrEP</p>
<p>Fridell et al; 1984            “Pre-exposure prophylaxis against rabies in children by human diploid cell vaccine”; Lancet</p>	<p>Titers checked 2wks after [0, 28] SQ HDCVPrEPor 2 wks after booster given 1-3 years (or more) later in some; Sera from adults getting same schedule was control; aged <u>&lt;5mths-15 yrs</u>; <u>9</u> (titers after primary)+ 17 (titers after booster).</p>	<p>- ” There was good antibody response with titers (EU/mL) higher than those in adults.”</p>
<p>Kamoltham et al; 2011            “Immunogenicity of simulated PCECV Post-exposure doses 1, 3, and 5 years after 2-dose and 3-dose primary rabies vaccination in schoolchildren; Advances in Preventive Medicine</p>	<p>Assessed immunogenicity of 2dose ID 0, 3 days] booster (PCECV) 1, 3, and <u>5</u> after PrEPseries (2dose and 3-dose); ID boosters known to last shorter than IM doses; <u>children aged 58 yrs</u>; <u>703 kids</u></p>	<p>-100% of children had titers &gt;0.5 IU/mL 1, 3, and 5 years after ID booster to 2 or 3 dose ID primary series 14 days after booster            -Safe and immunogenic</p>

# Manuscripts about children reviewed by WG

Article	Pertinent study details	Conclusion
<p>Lang et al; 1999 and 1997            “Booster vaccination at 1yr with rabies vaccine associated with DTRPV in infants living in rabies endemic country” Journal of tropical pediatrics            “Randomized feasibility trial of preexposure rabies vaccination with DTPIPv in infants” The Lancet</p>	<p>Vero-cell rabies vaccine series concomitant with DTP-IPV to 24 months old Vietnamese children; booster at 1 year. <u>-84 kids</u></p>	<p>-100% had titers &gt;0.5 IU/mL after primary series, 75% of children had titers &gt;0.5 IU/mL before the 1yr booster and 100% had titers &gt;0.5 IU/mL after booster; in comparison a study in France on 111 adults primed with 2 doses of PVRV Vero Cell revealed that 47% had titers &gt;0.5 IU/mL before booster</p>
<p>Lang et al; 1999            “Immunogenicity and safety of low-dose ID rabies vaccination given during an Expanded Programme on Immunization session in VietNam: results of a comparative randomized trial; Transactions of the Royal Society of Tropical Medicine and Hygiene</p>	<p>RCT about safety and immunogenicity of 3-dose ID with 2-dose IM [0, 60 days] of Vero Cell rabies vaccine with routine vaccines given at 2, 3, and 4 months of age (DTPIPv); <u>240 kids in Vietnam</u></p>	<p>ID route is as safe and immunogenic as the 2-dose IM route and can be given with routine peds immunizations without affecting safety or immunogenicity of standard childhood vaccines.</p>
<p>Kamoltham et al; 2007            “Pre-exposure Rabies Vaccination Using Purified Chick Embryo Cell Rabies Vaccine Intradermally is Immunogenic and Safe.” Journal of Pediatrics</p>	<p><u>School-aged children in Thailand</u>, PrEP ID 2 and 3 dose PCECV produced adequate immune responses <u>206 kids</u>.</p>	<p>-100% of children had titers &gt;0.5 IU/mL after primary vaccination; all demonstrated a rapid increase in RVNA titers to 0.5 IU/mL by day 14 after 2 simulated post-exposure booster immunizations 1 year after primary vaccination series</p>

# Manuscripts about children reviewed by WG

Article	Pertinent study details	Conclusion
<p>Lang et al; 2009            “Pre-exposure purified vero cell rabies vaccine and concomitant routine childhood vaccinations: 5-year post-vaccination follow-up study of an infant cohort in Vietnam”            Journal of trop Pediatrics</p>	<p>DTP-IPV at <u>2, 3, 4 mths and 1 yr</u> + rabies Vero Cell vaccine (PVRV) at <u>2 mths, 4 mths, and 1 year</u>. Titers were evaluated 5 years after the series; 63.3% of children had titers &gt;0.5 IU/mL <u>72 children</u></p>	<p>Titers were &gt;0.5 IU/mL for 90% of children at 1 year after the series and 60% at 5 years. This is comparable to levels in adults.            -”In conclusion, the integration of aPrEPregimen of 2 IM doses at 2 and 4 months of age, followed by a booster at 1 year resulted in long-term persistence of seroprotective antirabies antibody concentrations in the majority of vaccinated children without interfering with the immune responses to concomitant DTwP-IPV immunizations.”            -RabiesPrEP should be given along with routine childhood schedule to ensure long-term immunogenicity likely &gt;10 yrs from primary series</p>
<p>Li et al; 2015            “Immunogenicity and safety of purified chick-embryo cell rabies vaccine under Zagreb 2-1-1 or 5-dose Essen regimen in Chinese children &lt;17 yrs old and adults &gt;50 yrs: a randomized open-label study            Human vaccines and immunotherapeutics</p>	<p>Phase IIIb open label RT to demonstrate non-inferiority of immune responses and safety from PCECV series in Chinese children compared to adults &gt;50 years (i.e., 2 populations that are of concern, the latter because of immunosenescence); <u>243 kids aged 6-17 yrs</u></p>	<p>Children’s titers at various checkpoints were a mean of 124 IU/mL (i.e., much higher than the 0.5 IU/mL goal). For older adults at the same time points, the mean titers were 7.893 IU/mL which is still much higher than the 0.5 IU/mL goal. Children reached much higher titers for the same series than adults &gt;age 50.</p>



# Manuscripts reviewed by WG that indicated robust response in children

Article	Pertinent study details	Conclusion
<p>Pengsaaet al; 2009            “A Three-Year Clinical Study On Immunogenicity, Safety, and Booster Response of Purified Chick Embryo Cell Rabies Vaccine Administered Intramuscularly or Intradermally to 12 to 18-Month-Old Thai Children, Concomitantly With Japanese Encephalitis Vaccine “            Pediatric Infectious Diseases Journal</p>	<p>Concomitant PCECV and JE vaccine to toddler; the children were randomized into 4 groups of different IM and ID rabies schedules including a 2dose [0, 28 days] ID rabies schedule. All received a rabies booster; <u>200 healthy children aged 12-18 months in Thailand</u></p>	<p>All 4 rabies groups had RVNA concentrations &gt; 0.5 IU/mL at day 49. Regardless of prebooster antibody level, all the children had an anamnestic response to booster at the 1 year point with titers &gt;0.5 IU/mL</p>
<p>Sabchareonet al; 1998            “Persistence of antibodies in children after ID or IM administration of PrEP primary and booster immunizations with purified Vero cell rabies vaccine.”            The Pediatric Infectious Disease Journal</p>	<p>Children in Thailand <u>aged 512 received PVRV ID or IM on [0, 7, 28 days]; 190 schoolchildren</u></p>	<p>-2 weeks after primary series, 100% had titers &gt;0.5 IU/mL            -After 1 year booster, 100% had titers &gt;0.5 IU/mL            -82% of children at year 1 (after primary series but before booster) still had titers &gt;0.5 IU/mL.</p>

# Manuscripts about children reviewed by WG

Article	Pertinent study details	Conclusion
<p>Sabchareonet al; 1999            "A New Vero Cell Rabies Vaccine: Results of a Comparative Trial with Human Diploid Cell Rabies Vaccine in Children"            Clinical Infectious Diseases</p>	<p>Immunogenicity of chromatographically purified rabies vaccine (CPRV) to HDCV after IM[0, 7, 28 days] and 365 booster. <u>400 schoolchildren</u> (but some withdrew because of change of school)</p>	<p>-100% of children had titers &gt;0.5 IU/mL at day 21 (i.e., 14 days after the 2<sup>nd</sup> vaccine)            -All children had an anamnestic response to booster regardless of their titers before booster at the 1 year mark            -For those who received HDCV, GMT mean was 34.1 before 3 dose on day 28 (range 3.8-24 and 95% CI 30-37.9)</p>
<p>Shanbaget al; 2008            Protecting Indian schoolchildren against rabies: preexposure vaccination with purified chick embryo cell vaccine (PCECV) or purified verocell rabies vaccine (PVRV); Human Vaccines</p>	<p>Safety and immunogenicity of PCECV and PVRV as 3-dose IMPREP series [0, 7, 28 days]  <u>175 school children (613 years of age)</u></p>	<p>-100% had RVNA concentrations above 0.5 IU/mL after completion of the 3 dose series. There was no titer checked earlier than when the 3<sup>d</sup> dose would have become effective</p>
<p>Vien et al; 2008            Long-term anti-rabies antibody persistence following intramuscular or low-dose intradermal vaccination of young Vietnamese children            Transactions of the Royal Society of Tropical Medicine &amp; Hygiene</p>	<p><u>4-8 months at primary series and 16-20 months at receipt of PVRV n booster at 1 year.</u> Assessed 14 days after booster and annually for 5 yrs.</p>	<p>-Number of children with titers persistently higher than 0.5 IU/mL was more in the IM groups compared to ID groups            -All children mounted an anamnestic response to challenge</p>

# PrEP and children from Yellow Book\* and 2008 ACIP recommendations

## PRECAUTIONS AND CONTRAINDICATIONS

Pregnancy is not a contraindication to PEP. In infants and **children**, the dose of HDCV or PCEC for preexposure or PEP is the same as that recommended for adults. The dose of RIG for PEP is based on body weight ([Table 4-18](#)).

“Children should receive the same vaccine dose (i.e., vaccine volume) as recommended for adults”

\*<https://wwwnc.cdc.gov/travel/yellowbook/2020/travel-related-infectious-diseases/rabies>; accessed on 4/20/21

# PrEP recommendations

# Proposed recommendations during February ACIP meeting\*

- ACIP recommends a 2-dose [0, 7 days] intramuscular rabies vaccine series in immunocompetent persons for whom rabies vaccine pre-exposure prophylaxis (PrEP) is indicated
- ACIP recommends an intramuscular booster dose of rabies vaccine, as an alternative to a titer check, for immunocompetent persons who have sustained and elevated risk for only recognized rabies exposures (i.e., those in risk category #3 of rabies PrEP recommendations table J). The booster dose should be administered no sooner than day 21 but no later than 3 years after the 2-dose PrEP series

\*These were voted on (and passed) for persons  $\geq 18$  years of age only

JRisk category table in extra slides

# WG thought process in developing recommendation #1

- Primary series: [0, 7 days] IM
  - Robust data demonstrating boostability for up to 3 years (presented in GRADE table at October 2020 and February 2021 ACIP meetings)
  - Advantages for travelers:
    - Travelers typically do not have enough time to receive the 3 dose series (dose 3 is due no sooner than day 21)
    - This proposed recommendation will facilitate more travelers getting vaccinated

# Evidence table

## Immunogenicity after [0, 7 days] PrEP series with HDCV or PCECV

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	[0, 7 days] rabies vaccine PrEP schedule	[0, 7, 21/28 days] rabies vaccine PrEP schedule	Relative (95% CI)	Absolute (95% CI)		
Immunogenicity (RCTs) (follow up: range 2 weeks to 3 weeks; assessed with: titer level above 0.5)												
2 <sup>1,2</sup>	randomized trials	serious <sup>a</sup>	not serious	not serious	not serious	none	264/264 (100.0%)	64/264 (100.0%)	RR 1.00 (0.99 to 1.01)	0 fewer per 1,000 (from 10 fewer to 10 more)	Level 2	CRITICAL
Immunogenicity (observational studies) (follow up range: 2 to 3 weeks, assessed with titer level above 0.5)												
10 <sup>3,4,5,6,7,8,9,10,11,12</sup>	observational studies	not serious	not serious	not serious <sup>b</sup>	not serious	none	1090/1137 (95.9%)	1081/1114 (97.0%)	RR 1.00 (0.99 to 1.00)	0 fewer per 1,000 (from 10 fewer to 0 fewer)	Level 3	CRITICAL

CI: Confidence interval; RR: Risk ratio

### Explanations

a. Method of randomization and allocation not reported in Soentjens 2019 and allocation concealment not reported in Endy 2019. Neither study blinded participants or healthcare personnel; however, unlikely that co-interventions would have influenced the outcome.

b. Sabchareon 1999 study was conducted among children and the response may be more robust than in adults, which would potentially overestimate the immune response.

# PrEP Policy Question #1

## Summary of Observational Studies Reporting Outcome

Authors last name, pub year	Age (years)	N intervention	N comparison	Vaccine	Risk Ratio [95% CI] <sup>1</sup>	Study limitations (Study quality <sup>2</sup> )
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, Range 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, Range 18 – 65	371	364	PCEC, IM	0.99 [0.98, 1.01] <sup>4</sup>	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	Mean NR, Range 17 – 22	138	129	PCEC, IM, ID	0.94 [0.87, 1.02] <sup>4</sup>	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] <sup>4</sup>	9/9 No concerns
Sabchareon, 1999	Mean 10, Range 5 -13	190	190	HDCV, IM	1.00 [0.99, 1.01]	7/9 Minimal concerns
Vodopija, 1986	Mean NR, Range 19 -25	49	46	HDCV, PCEC, IM	1.00 [0.94, 1.06] <sup>4</sup>	9/9 No concerns

<sup>1</sup>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.

<sup>2</sup>Study quality for observational studies was assessed using the Newcastle Ottawa Scale.

<sup>3</sup>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.

<sup>4</sup>Studies contained multiple arms relative to the analysis. Risk ratio reflects pooled analysis from eligible arms.



# Sabchareon et al

- HDCV in 190 school children
- After [0, 7 days] series, 100% of children had antibody titers  $\geq 0.5$  IU/mL

Group, variable	Day 28
CPRV	
<i>n</i>	195
Antibody titer $\geq 0.15$ IU/mL*	100
Antibody titer $\geq 0.5$ IU/mL <sup>†</sup>	100
HDCV	
<i>n</i>	190
Antibody titer $\geq 0.15$ IU/mL*	100
Antibody titer $\geq 0.5$ IU/mL <sup>†</sup>	100

Table from: Sabchareon A, Lang J, Attanath P et al. A new vero cell rabies vaccine: Results of a comparative trial with human diploid cell rabies vaccine in children. Clin Infect Dis. 1999; 29: 141-9.

## WG thought process for recommendation #2

- Every expectation (from knowledge of immunology) is that beyond 3 years, boostability is preserved
- However, rabies is nearly 100% fatal and ACIP requested robust data for any proposed recommendation
- Titer value at 1-3 years, is indicative of long-term titer levels
- Titer check (and booster if titer is under cut-off) at 1-3 years will ensure long-term immunogenicity
- Titer cut-off will be raised to 0.5 IU/mL; this option will ensure high titers
- As an option to titer check, booster can be given instead of titer check
- Booster can be given as soon as day 21 and as late as year 3

# Evidence table

## Duration of immunogenicity after [0, 7 days] PrEP series with HDCV or PCECV

Certainty assessment							Impact	Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Anamnestic response after booster (follow up: range 1 weeks to 3)									
2 <sup>1,2</sup>	observational studies	not serious	not serious	not serious	not serious	none	A historical control of trial participants receiving 2 doses of rabies vaccine resulting in 100% immunogenicity (n=264) at 1-3 weeks following vaccination schedule (Endy 2019, Soentjens 2019) : 203/203 (100%) seroconversion with booster	Level 3	CRITICAL

CI: Confidence interval

# Summary

- Primary immunogenicity
  - No difference between primary immunogenicity in children compared to adults (including for young children) for any given schedule
  - One observation study showed 190 (100%) children aged 5-13 mounting titers over 0.5 IU/mL cut-off after primary series
- Long-term immunogenicity
  - Titers in children may stay higher for longer; since boostability is not a concern for adults, it should not be a concern for children

# Implications of not aligning recommendations for children with those of adults

- ACIP rabies PrEP recommendations have always been the same for children and adults
- Implications of new precedent
  - Adult travelers may get [0, 7 days] IM series before travel
  - Child travelers may not have enough time for [0, 7, 21/28 days] IM series and may not get vaccinated
  - Adults will have received PrEP and children will not have received PrEP even though children are the population with higher risk

# Proposed recommendations for June ACIP vote

- ACIP recommends a 2-dose [0, 7 days] intramuscular rabies vaccine series in immunocompetent persons <18 years of age for whom rabies vaccine pre-exposure prophylaxis (PrEP) is indicated
- ACIP recommends an intramuscular booster dose of rabies vaccine, as an alternative to a titer check, for immunocompetent persons < 18 years of age who have sustained and elevated risk for only recognized rabies exposures (i.e., those in risk category #3 of rabies PrEP recommendations table<sup>‡</sup>). The booster dose should be administered no sooner than day 21 but no later than 3 years after the 2-dose PrEP series

<sup>‡</sup>Risk category table in extra slides

Thank you!

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.

Risk category	Nature of Risk	Typical Population	Disease Biogeography <sup>1</sup>	Primary Immunogenicity PrEP	Long-term immunogenicity
<b>#1: Elevated risk for unrecognized and recognized exposures including unusual / high risk exposures (e.g., aerosol exposures and high concentration rabies virus exposures)</b>	Risk of virus exposure is continuous. Exposure is often in high concentrations and may go unrecognized, and can be unusual (e.g., aerosolized virus).	Laboratory personnel working with live rabies virus in research, diagnostic, or vaccine production capacities (e.g., necropsy of suspect rabid animal or working with rabies virus cultures)	Laboratory	IM [0, 7 days]	Titers every 6 months (booster if titer <0.5 IU/mL)
<b>#2: Elevated risk of both unrecognized and recognized exposures</b>	Risk of virus exposure is episodic. Exposure typically recognized but could be unrecognized. Unusual exposures do not occur	Persons who frequently handle bats or at frequent risk for coming into contact with bats because of entry into high density bat environments (e.g., bat biologist)	All geographic regions where bats are a reservoir for rabies <sup>2</sup>	IM [0, 7 days]	Titers every 2 years (booster if titer <0.5 IU/mL)
<b>#3: Elevated risk of recognized exposures that is sustained</b>	Risk of virus exposure greater than for population at large. Exposure is a recognized one.	Persons who work with animals <ul style="list-style-type: none"> <li>Animal care professionals (e.g., veterinarians, technicians, animal control officers)</li> <li>Others who repeatedly handle terrestrial reservoir species (e.g., wildlife biologists, rehabilitators, and trappers)</li> <li>Spelunkers</li> <li>Veterinary students</li> </ul>	All geographic regions where terrestrial <sup>3</sup> and non-terrestrial mammals are reservoirs for rabies	IM [0, 7 days]	Titer once at 1-3 years (booster if titer <0.5 IU/mL)  OR Booster no sooner than day 21 and no later than year 3.
		Travelers who will be performing activities (e.g., occupational or recreational) that put them at increased risk for exposure to rabid dogs and may have difficulty getting access to safe PEP (e.g., in rural area). Children may receive PrEP depending on the country to which they will travel (see CDC Traveler's Health destination pages)	Geographic regions internationally with endemic rabies		
<b>#4: Elevated risk of recognized exposures that is not sustained (i.e., ≤ 3 years)</b>	Risk of virus exposure greater than for population at large. Exposure is a recognized one and only present for up to 3 years after primary vaccination	Same as for #3 but with risk ≤ 3 years (e.g., short-term volunteer providing hands-on animal care or a traveler with no risky travel planned beyond 3 years)	Same as for #3	IM [0, 7 days]	None
<b>#5: Low risk of exposure / (i.e., general population)</b>	Risk of virus exposure is uncommon. Bite or non-bite exposure	U.S. population at large	Nationwide	None	None

<sup>1</sup>For questions about the disease biogeography of the region where an exposure occurred, please contact your local or state health department

<sup>2</sup>Bats are reservoirs for rabies in all US states except Hawaii

<sup>3</sup>Terrestrial mammals are non-bat species (e.g., racoons, skunks, livestock)