



# PEP vaccine series: Change to the series for healthy and immunocompromised persons

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# Post-exposure prophylaxis (PEP) for persons who have not previously received PEP or PrEP

Human Rabies  
Immunoglobulin  
(RIG)



Rabies Vaccine

Rabies Vaccines

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Day 0

Days 3, 7, 14

# Features of an improved PEP schedule

- Effectiveness unchanged from currently recommended series
- Fewer doses than the current 4-dose schedule
- Completed sooner than the current schedule
  
- Intramuscular vaccine schedule
- Robust data supporting its use

# Updated WHO recommendations for PEP in healthy persons

**Table 1: PEP recommendations by category of exposure**

	Category I exposure	Category II exposure	Category III exposure
<b>Immunologically naive individuals of all age groups</b>	Wash exposed skin surfaces. No PEP required.	Wound washing and immediate vaccination: <ul style="list-style-type: none"> <li>- 2-sites ID on days 0, 3 and 7<sup>6</sup></li> <li style="text-align: center;">OR</li> <li>- 1-site IM on days 0, 3, 7 and between day 14-28<sup>7</sup></li> <li style="text-align: center;">OR</li> <li>- 2-sites IM on days 0 and 1-site IM on days 7, 21<sup>8</sup></li> </ul> RIG is not indicated.	Wound washing and immediate vaccination <ul style="list-style-type: none"> <li>- 2-sites ID on days 0, 3 and 7<sup>6</sup></li> <li style="text-align: center;">OR</li> <li>- 1-site IM on days 0, 3, 7 and between day 14-28<sup>7</sup></li> <li style="text-align: center;">OR</li> <li>- 2-sites IM on days 0 and 1-site IM on days 7, 21<sup>8</sup></li> </ul> RIG administration is recommended.
<b>Previously immunized individuals of all age groups</b>	Wash exposed skin surfaces No PEP required.	Wound washing and immediate vaccination*: <ul style="list-style-type: none"> <li>- 1-site ID on days 0 and 3;</li> <li style="text-align: center;">OR</li> <li>- at 4-sites ID on day 0;</li> <li style="text-align: center;">OR</li> <li>- at 1-site IM on days 0 and 3);</li> </ul> RIG is not indicated.	Wound washing and immediate vaccination*: <ul style="list-style-type: none"> <li>- 1-site ID on days 0 and 3;</li> <li style="text-align: center;">OR</li> <li>- at 4-sites ID on day 0;</li> <li style="text-align: center;">OR</li> <li>- at 1-site IM on days 0 and 3;</li> </ul> RIG is not indicated.

\* *except if complete PEP already received within <3 months previously*

# Question: What is the data for changing PEP schedule?

Vaccine 37 (2019) A107–A117

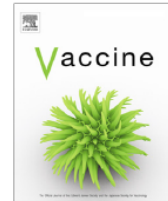


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## Vaccine

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Review

### Rabies post-exposure prophylaxis: A systematic review on abridged vaccination schedules and the effect of changing administration routes during a single course



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# Systematic review for Kessels et al

- Objective: Inform 2018 WHO update for rabies PEP schedules by evaluating
  - Immunogenicity and effectiveness of PEP schedules of reduced dose and duration
  - New evidence on effective PEP protocols for special populations
  - Effect of changing routes of administration (ID or IM) during a single course of PEP on the immunogenicity of PEP

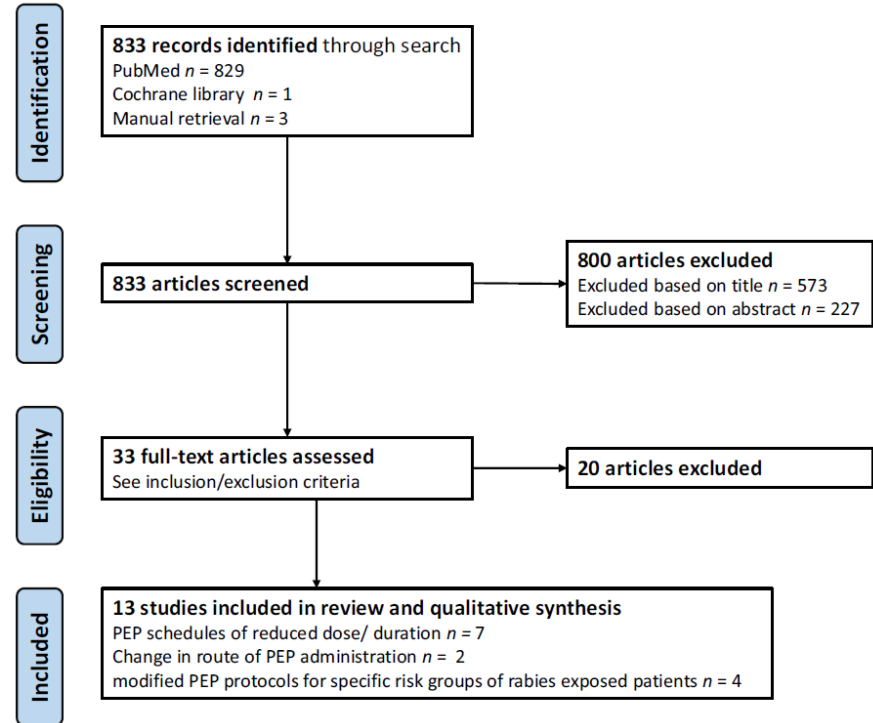


Fig. 1. PRISMA flow diagram showing the selection of studies on rabies post-exposure prophylaxis.

# WG considerations

- Current ACIP PEP schedules have not been problematic
- Cost considerations less critical
- Expectations for *ideal* data if changes proposed
  - High seroconversion rate (~100%)
  - Effectiveness for all population types
  - Large number of subjects
  - Impact of RIG on antibody levels considered
  - Vaccines used in the US
  - Route of administration can be converted to an intramuscular recommendation
  - If PEP was administered after an exposure, animal causing exposure was confirmed rabid

# Schedules reviewed

Author/Year	Schedule, vaccine, & participants	Results	Reported limitations
Shantavasinkul 2010	-ID [0, 3, 7 days] with and without eRIG+ TRC -4 site each day -PVRV* (3 arms) -N= 131	1) RVNA >0.5 IU/mL 2) Increased immunogenicity with 4-site than with TRC	1) Healthy subjects only 2) Rabies was not labconfirmed in biting animals
Sudarshan 2012	-ID [0, 3, 7 days] -4 site each day -PCEC* oPVRV(2 arms) -N= 80 (40 in each arm)	1) All with RVNA >0.5 IU/mL 2) 1 year after series, 79% of PCECV with RVNA >0.5 IU/mL and remainder boosted; 8 had inadequate	1) Healthy adult subjects only 2) Small sample size 3) Did not evaluate vaccine + RIG 4) Observational data re: PCEC
Naranya2015	-ID [0, 3, 7 days] -4-site each day -PCEC* oPVRV -N= 90 (45 in PCEC arm)	1) PCEC group with RVNA >0.5 IU/mL on days 14, 90, 365 2) With or without eRIGhad similar GMT	1) Not tested in children or pregnant / lactating persons 2) Rabies was not labconfirmed in biting animals 3) Observational data re: PCEC titers

\*PVRV: Purified Vero Cell Rabies Vaccine (cell culture vaccine believed to be equally efficacious to HDCV and PCECV)



# Main study that informed WHO recommendations

Author/Year	Schedule, vaccine, & participants	Results	Reported limitations
Tarantola 2019	-ID [0, 3, 7 days] -2 site each day -PVRV -N= 2,805 (1739 from confirmed rabid animals; of these, only 129 got 3 dose series)	1) No significant difference in deaths after 4-dose vs. 3-dose series but <u>low power</u> 2) Can be shortened with “no detectable added risk” with limitation in power	1) Low power for the outcome of importance 2) Vaccine used is not available in the U.S. but is believed to be equally efficacious 3) Study conducted in Cambodia, potentially not representative of U.S. population 4) Data is encouraging but more data is needed

\*PVRV: Purified Vero Cell Rabies Vaccine (cell culture vaccine believed to be equally efficacious to HDCV and PCECV)

## WG conclusions

- More studies are needed before a change can be proposed to the current 4-dose IM series
- Studies for consideration should involve
  - Large number of subject
  - Variety of populations (e.g., children of all ages)
  - Vaccines licensed in U.S.
  - Either IM schedule or ID that can be confidently extrapolated to a proposed IM schedule
  - Evaluation of the impact of RIG on antibody titers
  - Titers in human subjects after vaccination and confirmation of rabies in the offending animal

**Clinical guidance**

## Vaccine Recommendations and Guidelines of the ACIP

[ACIP Recs Home](#) > [Comprehensive Recommendations and Guidelines](#) > [General Best Practice Guidelines](#)



 [ACIP Recs Home](#)

Vaccine-Specific  
Recommendations +

Recs Listed by Date

**Comprehensive  
Recommendations and  
Guidelines** -

**General Best Practice Guidelines** -

Introduction

# Altered Immunocompetence

General Best Practice Guidelines for Immunization: Best Practices Guidance of the Advisory Committee on Immunization Practices (ACIP)

[Printer friendly version](#)  [27 pages]

## Updates

This section incorporates general content from the Infectious Diseases Society of America policy statement, 2013 IDSA Clinical Practice Guideline for Vaccination of the Immunocompromised Host ([1](#)), to which CDC provided input in November 2011. The evidence supporting this guidance is based on expert opinion and arrived at by consensus.

# Inactivated vaccines in immunocompromised persons

- No safety concerns
- Immune response may be inadequate
- Options for pre-exposure prophylaxis (PrEP)
  - Delay PrEP until no longer immunocompromised or consider avoiding activities for which rabies PrEP is indicated
  - Administer PrEP per recommendations for healthy persons but virus neutralizing antibody titers should be checked (and booster if lower than the minimum antibody titer threshold)

# 2008 rabies post-exposure prophylaxis for immunocompromised persons

- Avoid immunosuppressive agents during administration of PEP unless essential for the treatment of other conditions
- When PEP is administered to immunocompromised persons
  - One or more serum samples tested for rabies virus neutralizing antibody to ensure acceptable antibody response
  - Upon consultation with public health, booster doses typically given until adequate titers are reached

# 2008 ACIP recommendations versus 2010 Update

- 2008 ACIP recommendations
  - 5-dose series was recommended series
  - Same PEP series for healthy persons and immunocompromised
  - Titer check after completion of series was only recommended for immunocompromised persons (similar to previous ACIP recs)
- 2010 Update: Prompted by a shortage in rabies vaccines and provided updated recommendations for the PEP schedule
  - Data assessed and 4-dose PEP series found to be effective
  - 4-dose series replaced 5-dose series for healthy persons only

# WG considerations about immunocompromised

- For immunocompromised, ACIP recommends titer check after PEP series
- More vaccine doses (and more titer checks) may be indicated accordingly
- Since titer check is needed regardless of schedule, offering it with the fourth dose, i.e., sooner than current guidance, has advantages
  - Spare some persons unnecessary additional doses
  - Schedule recommendations for healthy and immunocompromised persons would be similar
    - Immunocompromised persons would still need titer to confirm adequate response
    - No negative impact on patient care



## Proposed clinical guidance (no vote needed)

- Titers for immunocompromised persons should still be checked after completion of PEP series (as has always been recommended)
- Titer should be checked with **fourth** dose and decisions about additional doses made accordingly
- Expedited titer checks occur when clinicians contact the lab where the titer check is occurring and indicate the importance for clinical decision-making
  - Titer check can often be completed within 48 hours
  - Clinician request is needed so that facility is aware

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## Questions?

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.