

WHO Guide for Rabies Pre and Post Exposure Prophylaxis in Humans

Updated 2013



World Health
Organization

General considerations in rabies Post-Exposure Prophylaxis (PEP)

- WHO recommends the use of purified rabies vaccines prepared on cell culture or embryonated eggs (referred to as CCEEVs) for PEP;
- These vaccines must comply with WHO criteria for potency, innocuity and have been assessed satisfactorily in humans in well-designed field trials;
- WHO strongly recommends discontinuation of production and use of nerve-tissue vaccines and their replacement with CCEEVs.



Top 10 general considerations in rabies PEP

1. Wounds must be immediately washed/flushed for 15 minutes and disinfected;
2. Rabies PEP is an emergency and as a general rule must not be delayed or deferred. Vaccine and in severe exposure immunoglobulin therapy must be instituted as soon as possible.

Top 10 general considerations in rabies PEP

3. PEP does not have contraindications if purified rabies immunoglobulin and vaccine are used. Pregnancy and infancy are no contraindications to PEP;
4. PEP must be applied using vaccine regimens and routes of administration that have been proven to be safe and effective;
5. If rabies immunoglobulin is not available on first visit its use can be delayed by a maximum of 7 days from date of first vaccine injection.

Top 10 general considerations in rabies PEP

6. Initiation of PEP should not await the results of laboratory diagnosis or be delayed by dog observation when rabies is suspected

7. When suspect rabid animal contacts (excluding bats) occur in an area free of carnivore rabies and where there is adequate rabies surveillance, PEP may not be required. The decision must be based on an expert risk assessment.

8. Persons who present for rabies PEP even months after having been bitten should be dealt with in the same manner as if the contact had occurred recently

Top 10 general considerations in rabies PEP

8. PEP should be initiated and completed if the suspect animal is not available for testing or observation. However Vaccine and immunoglobulin administration may be discontinued if:

- the animal involved is a properly vaccinated dog, a cat or ferret accessible for observation that remains healthy for 10 days after the exposure occurred or,
- the animal is humanely killed and proven to be negative for rabies by a WHO prescribed laboratory test;

9. In areas where canine or wildlife rabies is enzootic, PEP should be instituted immediately unless adequate laboratory surveillance is in place, and data from laboratory and field experience indicate that the species involved is not a vector of rabies.

10. When suspect rabid animal contacts (excluding bats) occur in an area free of carnivore rabies and where there is adequate rabies surveillance, PEP may not be required. The decision must be based on an expert risk assessment.

Rabies post-exposure Prophylaxis modalities

Wound treatment

- should be immediate
- is essential even if the person presents long after exposure
- consists of:
 - immediate washing and flushing for 15 minutes with soap and water, or water alone,
 - disinfection with detergent, ethanol (700ml/l), iodine (tincture or aqueous solution), or other substances with virucidal activity

Rabies post-exposure Prophylaxis modalities

Wound treatment

- Bleeding at any wound site indicates potentially severe exposure and must be infiltrated with either human or equine rabies immunoglobulin.
- Other treatments include
 - Administration of antibiotics and tetanus prophylaxis

Rabies PEP categories of exposure

Category III: single or multiple transdermal bites or scratches, licks on broken skin, contamination of mucous membrane with saliva (i.e. licks) and suspect contacts with bats:

use immunoglobulin plus vaccine

Category II: minor scratches or abrasions without bleeding and/or nibbling of uncovered skin

use vaccine alone

Category I : touching or feeding of animals, licks on intact skin, contact of intact skin with secretions or excretions of a rabid animal or human

no exposure therefore no prophylaxis if history reliable

Administration of rabies immunoglobulin (RIG) in wounds

Administration of rabies immunoglobulin (RIG) wounds infiltration with RIG is of upmost importance in category 3 exposure management. Bites especially on the head, neck, face hand and genitals are category 3 exposures.

Infiltrate into the depth of the wound and around the wound

- as much as anatomically feasible of the RIG should be infiltrated around the wound
- remainder if any should be injected at an intramuscular site distant from that of vaccine inoculation e.g. into the anterior thigh

Administration of rabies immunoglobulin (RIG) in wounds

- Quantities/volume of RIG: 20 IU/ kg for Human RIG (HRIG) or 40 IU/ kg of Equine RIG (ERIG)
 - the total recommended dose should not be exceeded
 - If RIG is unavailable on first visit and vaccine injection its administration can be delayed by a maximum of 7 days from date of that first injection if the calculated dose is insufficient to infiltrate all wounds, sterile saline may be used to dilute it 2 to 3 fold to permit thorough infiltration



Administration of rabies immunoglobulin (RIG) in wounds

There are no scientific grounds for performing a skin sensitivity test prior to administration of ERIG.

- The treating physician should be prepared to manage anaphylaxis which, however rare, could occur at any stage of the ERIG administration

Rabies PEP modalities

Non-specific care

- Postpone suturing if possible; if suturing is necessary ensure that RIG has been applied locally;
- Apply antimicrobials and tetanus toxoid if necessary



Intramuscular regimens for rabies PEP

Three intramuscular schedules for category 2 and 3 exposures:

- The 5 dose regimen
- The 2-1-1 regimen
- The 4 dose regimen with RIG in both categories 2 and 3

Vaccines should be injected into the deltoid muscle for adults and children aged 2 years and more. The anterolateral thigh is recommended for younger children.

Vaccines should not be injected into the gluteal region

Intramuscular regimens for rabies PEP

- The 5 dose intramuscular regime:
 - One dose of the vaccine should be administered on days 0, 3, 7, 14 and 28
 - Given in the deltoid region or, in small children, into the anterolateral area of the thigh muscle.

(1-1-1-1-1)

Intramuscular regimens for rabies PEP

- The 2-1-1 regimen may also be used:
 - Two doses are given on day 0 in the deltoid muscle, right and left arm.
 - In addition one dose in the deltoid muscle on day 7 and one on day 21.

(2-0-1-0-1)

Intradermal regimen for rabies PEP

The Intradermal (ID) method is particularly appropriate where vaccine or/and money are in short supply as the ID regimen requires considerably less vaccine than any of the intramuscular regimens.



Intradermal injections reduce the volume of vaccine required and vaccine cost by 60% to 80%

Intradermal PEP regimen

- The volume per intradermal (ID) site is 0,1 mL;
- PVRV (Verorab™) and PCECV (Rabipur™) have been proven to be safe and efficacious by the ID route using 0.1 mL per ID site according to WHO recommended ID regimen;
- Vaccine administered iD must raise a visible and palpable “bleb” in the skin. In the event that a dose of vaccine is inadvertently given subcutaneously or intramuscularly, a new dose should administered intradermally.

Intradermal PEP regimen for category 2 and 3 exposures

- One dose of vaccine, in a volume of 0.1 ml is given intradermally at two different lymphatic drainage sites
 - usually in the deltoid muscle on the left and right upper arm and suprascapular area
 - Given on days 0, 3, 7 and 28.

2-site intradermal method ('2-2-2-0-2')

Adopting the ID route for PEP:

- Any country willing to adopt the WHO recommended ID regimen need not repeat immunogenicity studies in their own population.
- WHO recommends use of the WHO prequalified rabies vaccines that can be used by the ID route.

Vaccine vial insert for intradermal use of rabies vaccines for PEP

In countries where relevant national authorities have approved the intradermal route for rabies PEP and for WHO pre-qualified vaccines recommended for intradermal use manufacturers are requested to add in the vaccine insert a statement saying:

“This vaccine is of sufficient potency to allow its safe use in one of the WHO recommended intradermal post-exposure regimens”

Intradermal route: requirements for new rabies vaccines

- To be approved for intradermal use:
 - Manufacturers should provide clinical evidence that new products are immunogenic, effective and safe when given intradermally; Administration should adhere to WHO guidance for that route and prior approval by relevant national authorities;
- In particular:
 - Any new candidate vaccine should be proven potent by the mouse protection potency test (NIH test) and have at least 2.5 IU per single immunizing (intramuscular) dose
 - its efficacy and/or immunogenicity and safety should be demonstrated with the volume of 0.1 ml per intradermal site using the WHO recommended PEP regimen.

Rabies PEP in immunosuppressed individuals

- Thorough wound treatment should be further stressed for immunosuppressed individuals;
- RIG should be administered deeply into the wound for both category 2 and 3 exposures;
- Vaccine should always be administered and no modification of the recommended number of doses is advisable.
- An infectious disease specialist with expert knowledge of rabies prevention should be consulted.
- When possible , the rabies virus neutralizing antibody response should be determined 2-4 weeks after vaccination to assess whether an additional dose of vaccine is required

Interchangeability of modern rabies vaccine types and routes for PEP

- When completion of PEP with the same modern rabies vaccine is not possible, the switch can be done provided that it is one of the WHO recommended cell culture or embryonated egg vaccine;
- No extensive study has been done yet on change of the route of vaccine administration and vaccine immunogenicity (from intradermal to intramuscular and vice versa) during PEP. Preliminary results indicate that this practice should remain the exception.

Short rabies PEP of previously vaccinated persons

- Local treatment of wound(s) should be ensured
- Two *active immunization* schedules are available
- No RIG should be applied

- However full PEP should be given to persons :
 - who received pre-or post-exposure prophylaxis with vaccines of unproven potency or
 - in patients in whom immunological memory is not longer assured as a result of HIV/AIDS or other immunosuppressive causes

Short rabies PEP of previously vaccinated persons

- **Schedule 1:**
 - One dose to be injected intramuscularly or intradermally on days 0 and 3;
 - The dose is either 1 single immunizing intra muscular (IM) dose (1 ml or 0.5 ml depending on vaccine type) or one intradermal (ID) dose of 0.1 ml per site;
- **Schedule 2:**
 - A “4-site” intradermal (ID) PEP can be used;
 - It consists of 4 injections of 0.1 mL equally distributed over the left and right deltoids, thigh or suprascapular areas at a single visit;
- Decision to use schedule 1 or 2 is left with the health care provider in consultation with the patient.

Pre-exposure rabies prophylaxis (PrEP)

PrEP is recommended for anyone who is at continual, frequent or increased risk for exposure to the rabies virus, as a result of their occupation or residence such as:

- Groups of persons at high risk of exposure to live rabies virus (laboratory staff, veterinarians, animal handlers and wildlife officers);
- Children living in or visiting rabies-affected areas may be immunized preventively on a voluntary individual basis or in mass campaigns when there are no economic, programmatic or logistical obstacles;
- Travellers to rabies-affected areas according to the level of risk in that area. (see 8.8 in TRS page 61 in TRS 982 WHO 2013)

Pre-exposure rabies prophylaxis regimens (PrEP) with vaccines fulfilling WHO requirements

- Intramuscular
 - One intramuscular dose is given on each of days 0, 7 and 21 or 28.
 - Site of injection: deltoid area of the arm for adults; anterolateral area of the thigh is recommended for children aged less than 2 years.
- Intradermal
 - One intradermal injection of 0.1 ml is given on each of days 0, 7, and 21 or 28.
 - If antimalarial chemoprophylaxis is applied concurrently, intramuscular injections must be used.
- As far as possible the vaccination series listed above must be completed in the stipulated time. However there is no need to restart the series if the doses are not given on the exact schedule.

Booster vaccination and monitoring of previously immunized persons

- Persons working with live rabies virus in diagnostic laboratories, research laboratories, vaccine production laboratories at permanent risk of exposure to rabies should have:
 - one serum sample taken every six months
 - a booster dose when the titre falls below 0.5 IU/ml
- Others professions (veterinarians, animal handlers, wildlife officers...) in rabies infected countries/areas should have:
 - one serum sample taken every two years
 - a booster dose when the titre falls below 0.5 IU/ml
- Routine booster vaccine doses after primary rabies vaccination are not required for the general public living in areas of risk.