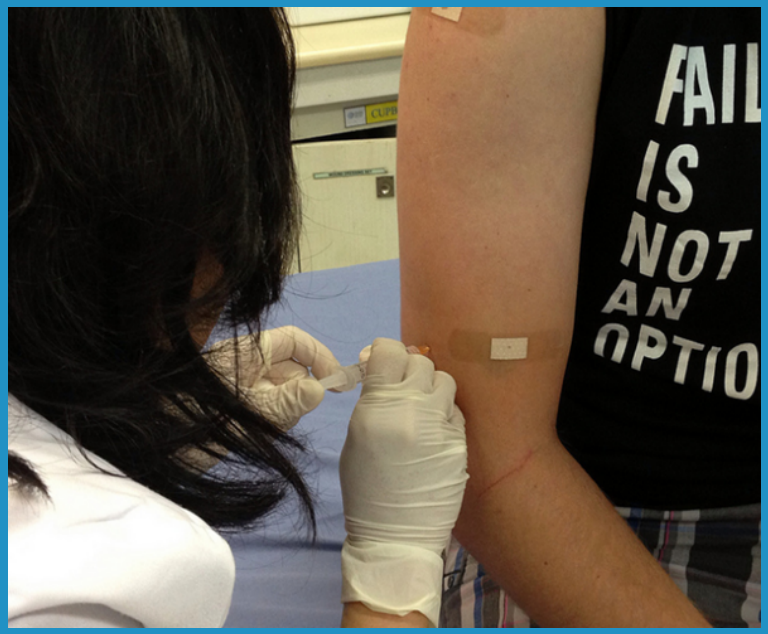
WHO Guide for Rabies Pre and Post Exposure Prophylaxis in Humans

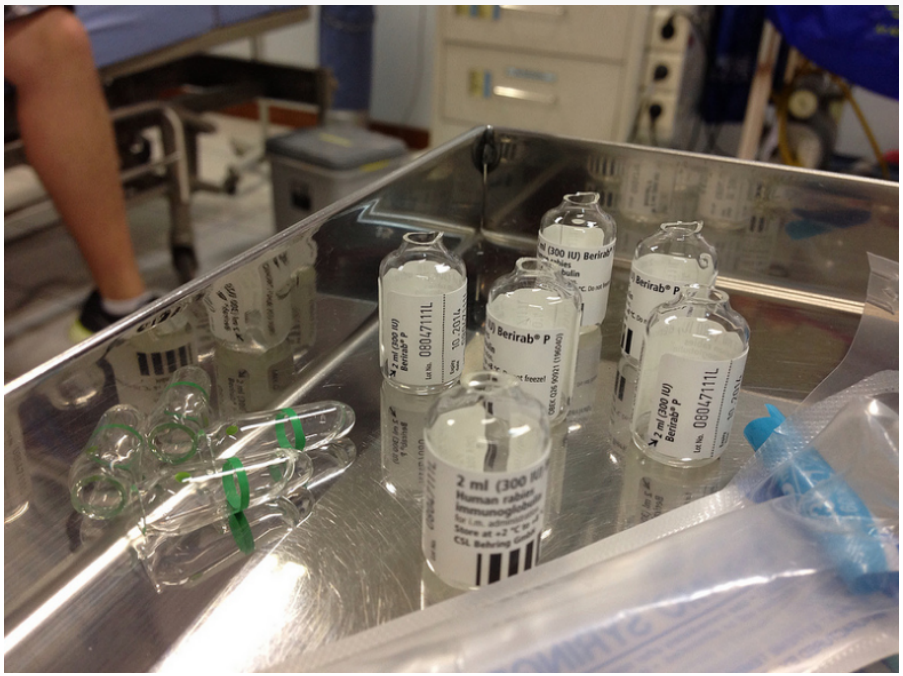
Updated 2014



World Health Organization

General considerations in rabies Post-Exposure Prophylaxis (PEP)

- WHO strongly recommends discontinuation of the nerve tissue vaccine, and replacement with modern concentrated and purified cell culture derived vaccines (CCDV) and embryonated egg-based rabies vaccines
- These vaccines must comply with WHO criteria for potency and innocuity following satisfactory assessment in humans during well-designed field trials



Top 10 General Considerations in Rabies PEP

1. Wounds must be immediately washed/flushed for 15 minutes and disinfected
2. Rabies PEP should be instituted immediately. PEP consists of a course of potent, effective rabies vaccine that meets WHO recommendations and administration of rabies immunoglobulin
3. PEP must be applied using vaccine regimens and administration routes that have been proven to be safe and effective
4. PEP does not have contraindications if purified rabies immunoglobulin and vaccine are used. Pregnancy and infancy are not contraindications to PEP

Top 10 General Considerations in Rabies PEP

5. If rabies immunoglobulin is not available on first visit, use can be delayed by up to 7 days from the date of the first vaccine dose

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 areas free of carnivore-mediated rabies and where there is adequate surveillance in place, PEP may not be required. The decision must be based on expert risk assessment

Top 10 General Considerations in Rabies PEP

8. Patients presenting for rabies PEP even months after having been bitten should be treated as if the contact had recently occurred

9. PEP should be administered even 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 vaccinated dog (cat or ferret) that following observation for 10 days, remains healthy *or* is humanely killed and declared negative for rabies by a WHO prescribed laboratory test

10. In areas enzootic for (canine and wildlife) rabies, PEP should be instituted immediately unless adequate laboratory surveillance and data indicates that the species involved is not a vector of rabies

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 wound 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
- 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 Post-Exposure Prophylaxis Modalities

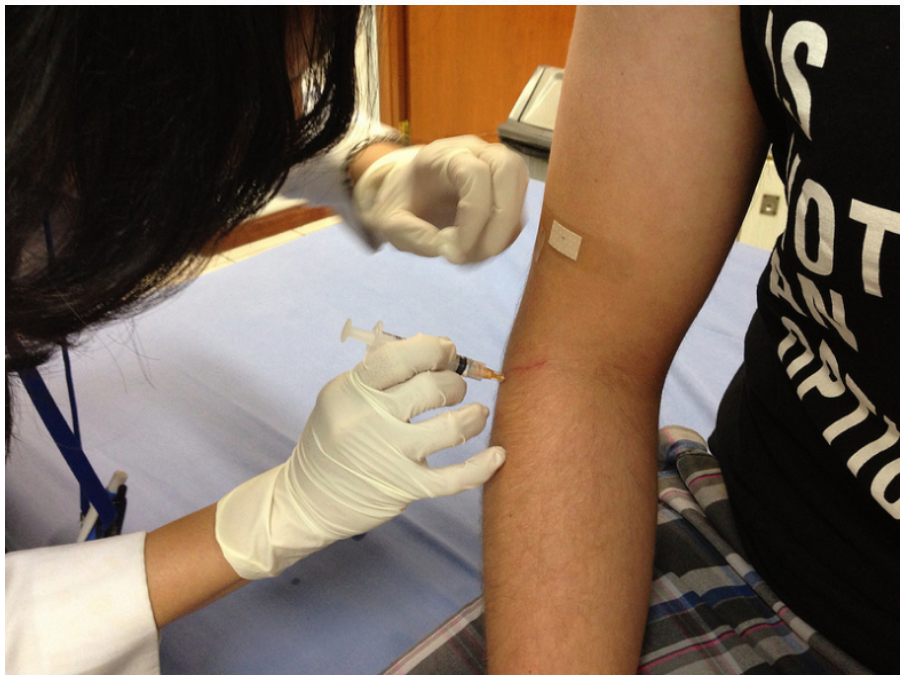
In countries or areas enzootic for rabies, exposure to suspected or confirmed rabid animals are categorised by WHO as follows:

Category of exposure	Description	Post-exposure prophylaxis
Category I	Touching or feeding animals, licks on intact skin, contact of intact skin with secretions or excretions of rabid animal or person	Not regarded as exposures, therefore no PEP required
Category II	Nibbling of uncovered skin, minor scratches or abrasions without bleeding	Vaccine should be injected as soon as possible
Category III	Single or multiple transdermal bites or scratches, licks on broken skin, contamination of mucous membrane with saliva from licks and exposure to bats.	Vaccine and rabies immunoglobulin should be administered at distant sites as soon as possible. Immunoglobulin can be administered up to 7 days after injection of the first dose of vaccine

Administration of Rabies Immunoglobulin (RIG)

- Administration of rabies immunoglobulin (RIG) to wounds classified as category III exposure, is of upmost importance in wound management.
  - Bites to the head, neck, face hand and genitals are category III exposures
- Infiltrate RIG into the depth of the wound and around the wound
  - RIG should be infiltrated around the wound as much as anatomically feasible
  - Remaining RIG should be injected at an intramuscular site distant from that of vaccine inoculation (e.g. into the anterior thigh)

Administration of Rabies Immunoglobulin (RIG)



Quantities/volume of RIG:

- 20 IU/ kg for Human RIG (HRIG) or 40 IU/ kg of Equine RIG (ERIG)
  - Total recommended dose should not be exceeded
  - If RIG is unavailable on first visit, its administration can be delayed by a maximum of 7 days from the date of first vaccine dose
  - If the calculated dose of RIG 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)

There are no scientific grounds for performing a skin sensitivity test prior to administration of equine rabies immunoglobulin (ERIG).

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

Rabies Post-Exposure Prophylaxis 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 Post-Exposure Prophylaxis

There are 3 intramuscular schedules for category II and III exposures:

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

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 Post-Exposure Prophylaxis

The 5 dose intramuscular regime: (1-1-1-1-1)

- One dose of the vaccine should be administered on days 0, 3, 7, 14 and 28
- Given in the deltoid region or, for young children, into the antero-lateral area of the thigh muscle

Intramuscular regimens for rabies Post-Exposure Prophylaxis

The 2-1-1 regimen:

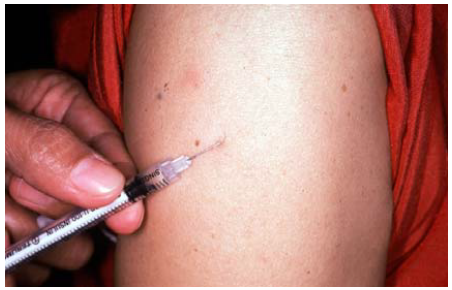
(2-0-1-0-1)

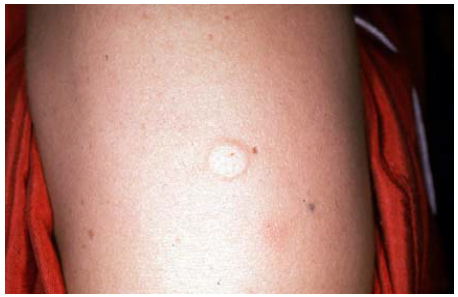
- Two doses are given on day 0 in the deltoid muscle, right and left arm
- An additional one dose is administered in the deltoid muscle on day 7 and day 21

Intradermal regimen for rabies Post-Exposure-Prophylaxis

- The intradermal (ID) regimen requires a reduced volume of vaccine to be utilised than any of the intramuscular regimens therefore, reducing vaccine cost by 60-80%

- This method is appropriate where vaccine or/and money are in short supply, particularly in rural areas with high-flow clinics





Intradermal regimen for rabies Post-Exposure-Prophylaxis

- The volume per intradermal (ID) site is 0.1 mL
- Using the ID route of administration, PVRV (Verorab™) and PCECV (Rabipur™) have been proven to be safe and efficacious
  - 0.1 mL per ID site is used, 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 II and III Exposures

The 2-site intradermal method: (2-2-2-0-2)

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

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, manufacturers are requested insert a statement for WHO pre-qualified vaccines recommended for intradermal use, 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
- The 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

PEP for immunosuppressed individuals

- Thorough wound treatment should be further stressed for immunosuppressed individuals
- RIG should be administered deeply into the wound for both category II and III 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 vaccines being used are 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 have received pre-or post-exposure prophylaxis with vaccines of unproven potency
  - Where immunological memory is no 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
- Consists of 4 injections of 0.1 mL equally distributed over left and right deltoids, thigh or suprascapular areas during 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

The vaccination series listed above must be completed at the stipulated times. 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 etc) working in rabies endemic 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.