2013

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Government of India

National Guidelines on Rabies Prophylaxis

National Centre for Disease Control
Directorate General of Health Services
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Contents

List of Abbreviations and Acronyms

AEFI	**Adverse events following immunization**
AIDS	Acquired Immunodeficiency Syndrome
ARC	Anti-Rabies Centre/Clinic
ARV	Anti-Rabies Vaccine
CCV	Cell Culture Vaccine
DCGI	Drug Controller General of India
ERIG	Equine Rabies Immunoglobulin
HDCV	Human Diploid Cell Vaccine
HIV	Human Immunodeficiency Virus
HRIG	Human Rabies Immunoglobulin
IAP	Indian Association of Pediatrics
ICMR	Indian Council of Medical Research
ID	Intradermal
IM	Intramuscular
IU	International Units
NCDC	National Centre for Disease Control
NICD	National Institute of Communicable Diseases
NSAID	Non-steroidal anti-inflammatory drug
NTV	Nerve Tissue Vaccine
PCEC	Purified Chick Embryo Vaccine
PDEV	Purified Duck Embryo Vaccine
PEP	Post-Exposure Prophylaxis
PrEP	Pre-Exposure Prophylaxis
PVRV	Purified Vero Cell Vaccine
RIG	Rabies Immunoglobulin
WHO	World Health Organization
ºC	Degree Centigrade

1. Introduction

Rabies is an acute viral disease that causes fatal encephalomyelitis in virtually all the warm-blooded animals including man. The virus is found in wild and some domestic animals, and is transmitted to other animals and to humans through their saliva (i.e. following bites, scratches, licks on broken skin and mucous membrane). In India, dogs are responsible for about 97% of human rabies, followed by cats (2%), jackals, mongoose and others (1%). The disease is mainly transmitted by the bite of a rabid dog.

Rabies has terrified man since antiquity. The fear is by no means unfounded since the disease is invariably fatal and perhaps the most painful and horrible of all communicable diseases in which the sick person is tormented at the same time with thirst and fear of water (hydrophobia). Fortunately, development of rabies can be prevented to a large extent if animal bites are managed appropriately and in time. In this regard the post-exposure treatment of animal bite cases is of prime importance.

National Centre for Disease Control (formerly National Institute of Communicable Diseases), Delhi, WHO Collaborating Centre for Rabies Epidemiology, organized an expert consultation in 2002 to formulate national guidelines for rabies prophylaxis to bring out uniformity in post-exposure prophylaxis practices. As per WHO recommendations, the production of the nervous tissue vaccine (NTV), which was the mainstay for post-exposure prophylaxis for a long time, has been stopped since December 2004 in the country. Modern cell culture vaccines (CCVs) are being used for post-exposure prophylaxis. Higher cost of intra-muscular administration of CCV is a limiting factor for its wider use. To overcome this problem, WHO recommended use of efficacious, safe and feasible intra-dermal (ID) route of administration of CCVs. Clinical trials conducted in India proved intra-dermal route to be safe, efficacious and feasible for use in the country. National authorities after expert consultations approved the use of ID route for administration of CCVs in the country in February 2006. The guidelines of animal bite management were revised with inclusion of ID administration of anti-rabies CCVs in 2007. In the last six years, there have been newer developments in rabies prophylaxis and a need was felt to review and revise the national guidelines to ensure uniformity in Post-Exposure Prophylaxis (PEP).

2. Post-Exposure Prophylaxis (PEP)

2.1 Decision to treat

In a rabies endemic country like India where there is sustained dog-to-dog transmission, every animal bite is suspected as a potentially rabid animal bite, and treatment should be started immediately after exposure. Bite by all warm blooded animals necessitates post-exposure prophylaxis. As rabies is practically 100% fatal, bites by dogs and cats in particular must be considered as a "medical emergency" and the "life-saving" post exposure prophylaxis must be provided immediately.

Observation of biting dog/cat: The PEP should be started immediately after the bite. The observation period of 10 days is valid for dogs and cats only. The natural history of rabies in mammals other than dogs and cats is not fully understood and therefore the 10-day observation period is not applicable.

The treatment may be modified if dog or cat involved remains healthy throughout the observation period of 10 days by converting post-exposure prophylaxis to pre-exposure vaccination by skipping the vaccine dose on day 14 and administering it on day 28 while using Essen Schedule. While using ID administration complete course of vaccination should be given irrespective of status of animal.

Vaccination status of the biting animal: Although unvaccinated animals are more likely to transmit rabies, vaccinated animals can also do so if the vaccination of the biting animal was ineffective for any reason. A history of rabies vaccination in an animal is not always a guarantee that the biting animal is not rabid. Animal vaccine failures may occur because of improper administration or poor quality of the vaccine, poor health status of the animal, and the fact that one vaccine dose does not always provide long-lasting protection against rabies infection in dogs. Hence, appropriate documentation of vaccination status of dog/cat and proper history should be elicited before deciding to defer post-exposure prophylaxis after bite by vaccinated dog/cat.

Provoked versus unprovoked bites: Whether a dog bite was provoked rather than unprovoked should not be considered a guarantee that the animal is not rabid as it can be difficult to understand what provokes a dog to attack. Hence, PEP should be immediately instituted irrespective of whether the bite was provoked or unprovoked.

Bite by wild animals: Bite by all wild animals should be treated as category III exposure. All animal bites in forest or in the wild should be treated as category III exposure.

Bite by rodents: Exposure to domestic rodents, squirrel, hare and rabbits do not routinely require PEP.

Bat rabies: Bat rabies has not been conclusively proved in India and hence exposure to bats does not warrant PEP.

Post-exposure prophylaxis of immune-compromised patients: Several studies of patients with HIV/AIDS have reported that those with low CD4 (<200 counts) will mount a significantly lower or no detectable neutralizing antibody response to rabies. In such patients and those in whom the presence of immunological memory is no longer assured as a result of other causes (patients on chemotherapy, steroid therapy, cancer patients, etc) proper and thorough wound management and antisepsis accompanied by local infiltration of rabies immunoglobulin followed by complete course of anti-rabies vaccination by intramuscular route in both category II and III exposures are of utmost importance. Preferably, if the facilities are available, anti-rabies antibody estimation should be done 14 days after the completion of course of vaccination to assess the need of additional doses of vaccine.

Human-to-human transmission: The risk of rabies transmission to other humans from a human rabies case is very minimal and there is no well-documented case of human-to-human transmission, other than the few cases resulting from organ transplant. However, people who have been exposed closely to the secretions of a patient with rabies may be offered PEP as a precautionary measure.

Contraindications and Precautions: As rabies is nearly 100% fatal disease, there is no contraindication to PEP. Pregnancy, lactation, infancy, old age and concurrent illness are no contra indications for rabies PEP in the event of an exposure. PEP against rabies takes preference over any other consideration as it is a lifesaving treatment. Moreover, rabies vaccine does not have any adverse effect on pregnant woman, course of pregnancy, fetus or lactating mother. Hence, complete PEP should be given depending on the category of the exposure.

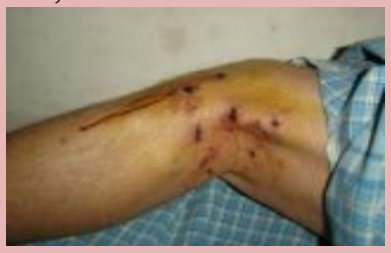
People taking chloroquine for malaria treatment or prophylaxis may have a reduced response to ID rabies vaccination. These patients should receive the rabies vaccine intramuscularly.
As with all other immunizations, vaccinated persons should be kept under medical supervision for at least 15–20 minutes following vaccination. Previous reaction to any component of a vaccine is a contraindication to the use of the same vaccine for PEP or PrEP.

Because of long and variable incubation period, which is typical of most cases of human rabies, it is possible to institute PEP to protect the individual. This must be started at the earliest to ensure that the individual is immunized or protected before the rabies virus reaches the nervous system. However, people who present for treatment even months or years after a possible rabies exposure should be evaluated and treated as if the event had occurred recently.

Risk assessment of potential rabies exposure can be complex and confusing. When in doubt post exposure prophylaxis should be initiated and the attending physician should consult specialist at Anti Rabies Centres.

To bring out uniformity globally, the classification of animal bite for post-exposure prophylaxis has been based on WHO recommendations (Table 1).

Table 1: Type of contact, exposure and recommended post-exposure prophylaxis

Category	Type of contact	Recommended post-exposure prophylaxis
I	• Touching or feeding of animals • Licks on intact skin • Contact of intact skin with secretions / excretions of rabid animal /human case	• None, if reliable case history is available
II	• Nibbling of uncovered skin • Minor scratches or abrasions without bleeding 	• Wound management • Anti-rabies vaccine
III	• Single or multiple transdermal bites or scratches, licks on broken skin  • Contamination of mucous membrane with saliva (i.e. licks) 	• Wound management • Rabies immunoglobulin • Anti-rabies vaccine

It is re-emphasized that PEP should be started as early as possible after exposure. However, PEP should not be denied to person reporting late for treatment as explained previously.

2.2. Approach to Post-Exposure Prophylaxis (PEP)

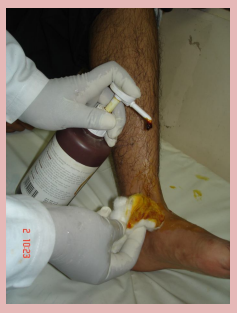
The post-exposure prophylaxis is a three-pronged approach. All three carry equal importance and should be done simultaneously as per the category of exposure

- Management of animal bite wound(s)
- Passive immunization with Rabies Immunoglobulin (RIG)
- Active immunization with Anti-Rabies Vaccines (ARV)

2.2.1 Management of animal bite wound(s)

Wound(s) toilet: Since the rabies virus enters the human body through a bite or scratch, it is imperative to remove as much saliva, and thereby the virus, from the wound(s) as is possible by an efficient wound(s) toilet that should not involve additional trauma. Since the rabies virus can persist and even multiply at the site of bite for a long time, wound(s) toilet must be performed even if the patient reports late. (Table 2)

Table 2: Wound(s) Management

<table>
<tr><th colspan="3">Do’s</th></tr>
<tr><td>Physical</td><td>Wash with running water</td><td>Mechanical removal of virus from the wound(s)</td></tr>
<tr><td>Chemical</td><td>Wash the wound(s) with soap and water
Apply disinfectant
   </td><td>Inactivation of the virus</td></tr>
<tr><td>Biological</td><td>Infiltrate immunoglobulin into the depth and around the wound(s) in Category III exposures
  </td><td>Neutralization of the virus</td></tr>
<tr><th colspan="3">Don’ts</th></tr>
<tr><td colspan="3">• Touch the wound(s) with bare hand
• Apply irritants like soil, chilies, oil, lime, herbs, chalk, betel leaves, etc.</td></tr>
</table>

Wound(s) toilet can be done by prompt and gentle thorough washing with soap or detergent and flushing the wound(s) with running water. If soap and detergent are not immediately available wash with running water. Avoid direct touching of wound(s) with bare hands. Considering the importance of this step the anti-rabies clinics should have wound washing facilities.

The application of irritants (like chilies, oil, turmeric, lime, salt, etc) is unnecessary and damaging. In case irritants have been applied on the wound(s), enough gentle washing with soap or detergent to remove the external applicant/s should be done followed by flushing with copious amount of water immediately.

It should be noted that the immediate washing of the wound(s) is a priority. However, the victim should not be deprived of the benefit of wound(s) toilet as long as there is an unhealed wound(s) which can be washed even if the patient reports late. The maximum benefit of the wound(s) washing is obtained when fresh wound(s) is cleaned immediately.

Application of antiseptics: After thorough washing and drying the wound(s), any one of the available chemical viricidal agents should be applied, such as povidone iodine, alcohol, etc.

Local infiltration of rabies immunoglobulin: In category III exposures rabies immunoglobulin should be infiltrated in the depth and around the wound(s) to neutralize the locally present virus as described in section 3.2.

Suturing of wound(s) should be avoided as far as possible. If surgically unavoidable, after adequate cleansing, rabies immunoglobulin should be infiltrated in the depth and around the wound(s) and suturing should be delayed by several hours. Minimum loose sutures should be applied. The delay in suturing allows diffusion of antibodies in the tissues.

Cauterization of wound(s) is no longer recommended as it leaves bad scar, and does not confer any additional advantage over washing the wound(s) with water and soap.

Tetanus prophylaxis should be given if required. To prevent sepsis in the wound(s), a suitable course of an antibioticmay be recommended.

2.2.2 Rabies Immunoglobulin (RIG)

The anti-rabies serum/Rabies Immunoglobulin (RIG) provides passive immunity in the form of ready-made anti-rabies antibodies, to tide over the initial phase of the infection before it is physiologically possible for the patient to begin producing his/her own antibodies following anti-rabies vaccination. Anti-rabies serum or RIG has the property of binding with the rabies virus, thereby resulting in neutralization and thus loss of infectivity of the virus and hence it is most logical to infiltrate RIG locally at the site of exposure.

Two types of RIGs are available:

Equine Rabies Immunoglobulin (ERIG): ERIG is of heterologous origin produced by hyper-immunisation of equines. Currently manufactured ERIGs are highly purified Fab 2' fragments and the occurrence of adverse events has been significantly reduced. These are produced in the country in public and private sectors. (Annexure 1: Table 1: Currently available ERIG in India)

Since, ERIG are of heterologous origin, they carry a small risk of anaphylactic reaction (1/150,000). However, literature supports that there is no scientific ground for performing a skin test prior to administering ERIG because testing does not predict reactions, and ERIG should be given irrespective of the result of the test. The treating physician should be prepared to manage anaphylaxis, which, although rare, could occur during any stage of administration, even when the skin test did not show any reaction. However, some manufacturers of ERIG still recommend performing a skin test.

Human Rabies Immunoglobulin (HRIG): HRIG are of homologous origin and are relatively free from the side effects encountered in a serum of heterologous origin. However, it is expensive and is imported from other countries. (Annexure 1: Table 2: Currently available HRIG in India). Because of their longer half-life, they are given at half the dose of equine anti-rabies serum.

Indication: RIG should be administered to all category III exposures. However, in immune compromised individuals, RIG should be administered in both category II and III exposures.

Dose of rabies immunoglobulin: The dose of ERIG is 40 IU per kg body weight of patient. The ERIG produced in India contains 300 IU per ml. The dose of the HRIG is 20 IU per kg body weight. HRIG preparation is available in concentration of 150 IU per ml.

Administration of rabies immunoglobulin: The RIG should be brought to room temperature (25ºC to 30ºC) before administration to the patient.

As much of the calculated dose of RIG as is anatomically feasible should be infiltrated into and around the wound/s. Multiple needle injections into the wound/s should be avoided. After all the wound/s has been infiltrated, if any volume of RIG is remaining, it should be administered by deep intramuscular injection at a site distant from the vaccine injection site.

Animal bite wounds inflicted can be severe and multiple, especially in small children. In such cases, the calculated dose of the rabies immunoglobulin may not be sufficient to infiltrate all wounds. In these circumstances, it is advisable to dilute the calculated volume of RIG in sterile normal saline to a volume sufficient to infiltrate all the wounds. However, the total recommended dose of RIG must not be exceeded as it may suppress the antibody production stimulated by the anti-rabies vaccine.

Rabies immunoglobulin for passive immunization is administered only once, preferably within 24 hours after the exposure i.e. on day 0 along with the first dose of anti-rabies vaccine. If RIG was not administered when ARV was begun, it can be administered up to the seventh day after the administration of the first dose of ARV. Beyond the seventh day, RIG is not indicated since

an antibody response to ARV would have occurred and administration of RIG at this stage can suppress the immune response of the patient to the ARV received.

Infected bite wound is no contraindication to infiltration of immunoglobulin. Tip of finger/s and toe/s, ear lobe/s or bites on nose or around the eye can be safely injected with RIG provided the injection is not done with excessive pressure, which can cause compression syndrome.

Rabies Immunoglobulin should never be administered in the same syringe or at the same anatomical site as vaccine.

Animal bite victim should be kept under observation for at least half–an–hour after administration of ERIG. There is no need to admit the patient.

Physicians administering ERIG should always be ready to treat anaphylactic reactions with adrenalin. The dose is 0.5 ml of 0.1 percent solution (1 in 1000, 1mg/ml) for adults and 0.01ml/kg body weight for children, injected subcutaneously or IM. Other emergency drugs and supportive therapy should also be available.

Administration of full dose of RIG intramuscularly into the gluteal region or infiltration of half the dose of RIG locally and half intramuscularly is not recommended.

Tolerance and side effects: There may be transient tenderness at the injection site and a brief rise in body temperature that does not require any treatment. Anaphylactic reactions are extremely rare. RIG must never be given intravenously.

Serum sickness is rare and occurs usually 7 to 10 days after injection of ERIG, but it has not been reported after treatment with HRIG.

A full course of ARV should follow thorough wound cleansing and passive immunization.

2.2.3 Anti-Rabies Vaccines

Active immunization is achieved by administration of safe and potent cell culture vaccines (CCVs) or purified duck embryo vaccine (PDEV). In India, NTV was used for post-exposure prophylaxis in public sector. However, as this vaccine was reactogenic and less immunogenic, the production was stopped in December, 2004. CCVs and PDEV are now used for active immunization. Currently available CCVs and PDEV could be administered by IM regimen andCCVs approved for ID use shall be administered by ID regimen.

Anti-rabies vaccines are produced as one single intramuscular dose with potency of $\geq$ 2.5IU per IM dose for post exposure and pre-exposure prophylaxis. It is absolutely essential that every batch of cell culture vaccine or purified duck embryo vaccine have minimum potency of 2.5IU per intramuscular dose.

Indications: All animal bite victims of Category II and III exposures irrespective of age and body weight require the same number of injections and dose per injection. All Category III

exposures and Category II exposures in immuno-compromised individuals, in addition, require administration of RIG as discussed previously in section 3.2.

Storage and transportation: Though most CCVs and PDEV are marketed in freeze dried (lyophilized) form, which is more tolerant to vagaries of temperature, yet it is recommended that these vaccines should be kept and transported at a temperature range of 2-8ºC and protected from sunlight. Freezing does not damage the lyophilized vaccine but there are chances of breakage of ampoule containing the diluent. Liquid (adsorbed) rabies vaccines should never be frozen.

Reconstitution and storage: The lyophilized rabies vaccine should be reconstituted with the diluent provided with the vaccine immediately prior to use. Some vaccines have 0.5ml diluent and others have 1ml diluent, as per the approval of the brand, which cannot be altered. It is imperative that the information literature accompanying the vaccine is carefully read and the instructions given are adhered to.

While using intramuscular administration the vaccine should be used immediately after reconstitution. However, in case of unforeseen delay it should not be used after 8 hours of reconstitution.

While using intradermal administration, the vaccine vial should be stored at 2-8ºC after reconstitution. The total content of the vial should be used as soon as possible, but at the maximum within 8 hours.

All vaccines which are reconstitutedand not used thereafter should be discarded after 8 hours of reconstitution.

Adverse effects following administration of CCVs and PDEV: The CCVs and PDEV are widely accepted as the least reactogenic rabies vaccines available today. However, few studies have now shown that adverse effects can be either general in nature or allergic in origin. Mild systemic adverse events following immunization (AEFI) include headache, malaise, nausea and fever. Symptomatic treatment may be needed.Minor and transient erythema, pain and/or swelling may occur at the site of injection, particularly following intradermal administration. Serious AEFIs mainly of allergic or neurological nature rarely occur.

Switch over from one brand/type of vaccine to the other: Shifting from one brand/type of CCV/PDEV to other brand/type should not be encouraged in routine practice. However, under unavoidable circumstances, available brand/type may be used to complete PEP.

Duration of immunity

The development of immunological memory after vaccination with CCVs and PDEV is critical for the establishment of long lasting immunity against rabies in humans. Individuals who had received their primary series 5–21 years previously showed good anamnestic responses after booster vaccination. Long-term immunity is also achieved with intradermal immunization, and may persist even when antibodies are no longer detectable. The ability to develop an anamnestic

response to a booster vaccination is related neither to the route of administration of the initial series (intramuscular or intradermal) nor to whether the patient completed a pre-exposure or post-exposure series.

Protective level of anti-rabies antibody: Humoral antibodies play an important role in protection against rabies. Anti-rabies neutralizing antibody titre of 0.5 IU/ml or more in serum is considered as protective. This level is achieved in most healthy individuals by day 14 of a post-exposure regimen, with or without simultaneous administration of rabies immunoglobulin.

2.2.3.1 Intra-muscular (IM) Regimen

The currently available vaccines and regimen in India for IM administration are described below.

Vaccines

1. Cell Culture Vaccines
   - Human Diploid Cell Vaccine (HDCV), Liquid (Adsorbed), 1ml: Produced locally in private sector
   - Purified Chick Embryo Cell Vaccine (PCECV), 1ml: Produced locally in private sector
   - Purified Vero Cell Rabies Vaccine (PVRV), 0.5ml and 1ml: Imported and also produced locally in public & private sectors

2. Purified Duck Embryo Vaccine (PDEV), 1ml: Produced locally in private sector

(Annexure 1: Table 3: Currently available ARVs in India)

Regimen

Essen regimen (1-1-1-1-1): Five dose intramuscular schedule - The course for post-exposure prophylaxis consists of intramuscular administration of five injections, one dose each given on days 0, 3, 7, 14 and 28. Day 0 indicates date of administration of first dose of vaccine. .

Site of injection: The deltoid region is ideal for the administration of these vaccines. Gluteal region is not recommended because the fat present in this region retards the absorption of antigen and hence impairs the generation of optimal immune response. In case of infants and young children antero-lateral part of the thigh is the preferred site.

2.2.3.2 Intra-dermal (ID) Regimen

Current anti-rabies vaccines are produced as one single intramuscular dose. Intradermal regimens consist of administration of a fraction of intramuscular dose of approved rabies vaccine on one or more than one site in the layers of the dermis of the skin. The vaccines used are same; however route, dose and site of administration differ.

The use of intra-dermal route leads to considerable savings in total amount of vaccine needed for full pre- or post- exposure vaccination, thereby reducing the cost of active immunization. Single dose (0.5ml or 1ml) of anti-rabies vaccine when given by IM route gets deposited in the muscle.

There after the antigen is absorbed by the blood vessels and is presented to antigen presenting cells which triggers the immune response. Whereas, while using ID route, small amount (0.1ml) of anti-rabies vaccine is deposited in the layers(dermis) of the skin at one or more than one site, the antigen is carried by antigen presenting cells via the lymphatics to the regional lymph nodes and reticulo-endothelial system eliciting a prompt and protective antibody response. Immunity is dependent mainly upon the CD 4 + T-cell dependent neutralizing antibody response to the G protein. The cell-mediated immunity is also an important part of the defense against rabies. Cells presenting the fragments of G protein are the targets of cytotoxic T- cells and the N protein induced T helper cells. The immune response induced by ID administration of anti-rabies vaccine is adequate and protective against rabies.

Use of intradermal route of administration of anti-rabies vaccine allows wider coverage of PEP in available quantity of vaccines and hence makes it cost effective. WHO recommended use of ID route for administration of anti-rabies vaccines in 1992.Based on WHO recommendation and results of various safety, efficacy studies and feasibility trial conducted by ICMR, Drug Controller General of India (DCGI) approved the use of intra-dermal vaccination regimen for rabies post-exposure prophylaxis.

Vaccines and regimen approved for ID use in the country

Currently, the following vaccines have been approved by DCGI for use by intra-dermal route.

PCECV - Rabipur, Chiron Behring, Vaccines Pvt. Ltd
– Vaxirab N, ZydusCadila

PVRV – Verorab, Aventis Pasteur (Sanofi Pasteur) India Pvt. Ltd
– Pasteur Institute of India, Coonoor
– Abhayrab, Human Biologicals Institute
– Indirab, Bharat BiotechInternational Ltd.

Only the anti-rabies vaccines approved by DCGI for ID administration should be used for ID route.The vaccine package leaflet should include a statement indicating that the potency as well as immunogenicity and safety allow safe use of vaccine by both the IM and ID routes for post-exposure and pre-exposure prophylaxis.

Potency of approved vaccines

The vaccines should have stated potency of ≥ 2.5 IU per IM dose, irrespective of reconstituted volume.
The same vaccine is used for ID administration as per stated schedule. A dose of 0.1ml of vaccine, irrespective of reconstituted volume (0.5ml or 1 ml for IM route), is administered per ID site as per the stated schedule.

Regimen

Post-exposure regimen

Updated Thai Red Cross Schedule (2-2-2-0-2).

This involves injection of 0.1ml of reconstituted vaccine per ID site and on two sites per visit (one on each deltoid area, an inch above the insertion of deltoid muscle) on days 0, 3, 7 and 28. The day 0 is the date of first dose administration of anti-rabies vaccine and may not be the date of rabies exposure/animal bite.

Maintenance of vaccine vial in use

- Use aseptic technique to withdraw the vaccine.
- Store in a refrigerator at 2ºC to 8ºC. Do not freeze the vaccine.
- Do not expose the vaccine to sunlight.
- Use reconstituted vaccine as soon as possible or within 8 hours if kept at 2ºC to 8ºC. Discard all unused reconstituted vaccine at the end of 8 hours.

Materials required

- A vial of anti-rabies vaccine along with its diluent that is approved by the DCGI for ID administration.
- 2 ml disposable syringe with 24 G needle for reconstitution of vaccine.
- **D**isposable 1 ml (insulin) syringe (with gradations upto 100 or 40 units) with a fixed (self-mounted) (28 G or more) needle (Fig-1), Syringes with detachable needles are not preferred as they contribute to wastage of vaccine.
- Disinfectant swabs (e.g. 70% ethanol, isopropyl alcohol) for cleaning the top of the vial and the patients' skin.

Fig-1: 1ml syringe with self-mounted needle (Insulin syringe)

ID injection technique

- Using aseptic technique, reconstitute the vial of lyophilized vaccine with the diluent supplied by the manufacturer.

- With 1 ml syringe draw 0.2 ml (up to 20 units if a 100 units syringe is used or up to 8 units if a 40 units syringe is used) of vaccine needed for one patient (i.e. 0.1 ml per ID site for 2 sites).
- Expel the air bubbles carefully from the syringe thereby removing any dead space in the syringe.
- Using the technique of BCG inoculation, stretch the surface of the skin and insert the tip of the needle with bevel upwards, almost parallel to the skin surface (Fig-2) and slowly inject half the volume of vaccine in the syringe (i.e. 0.1ml; either 10 or 4 units) into the uppermost dermal layer of skin, over the deltoid area an inch above the insertion of deltoid muscle. If the needle is correctly placed inside the dermis, resistance is felt while injecting the vaccine. A raised bleb should begin to appear immediately causing a peau d' orange (orange peel) appearance (Fig-3).
- Inject the remaining volume of vaccine (i.e. 0.1ml; either 10 or 4 units) on the opposite deltoid area.
- If the vaccine is injected too deeply into the skin (subcutaneous), bleb (Peau de orange) is not seen. Then the needle should be withdrawn and reinserted at an adjacent site and ID vaccine given once more.
- If for some reason the deltoid region cannot be used for injection, then the alternative sites are the suprascapular area or the anterolateral thigh.

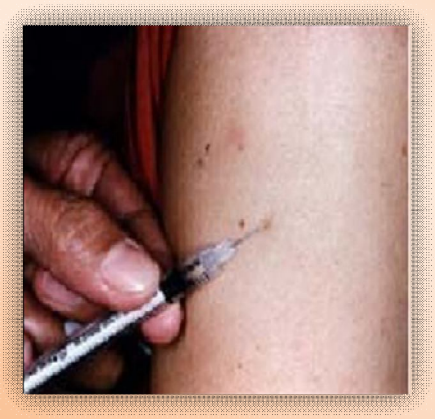


Fig-2: Insertion of needle for ID inoculation

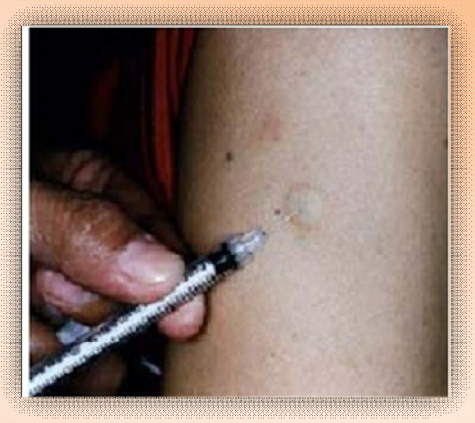


Fig-3: Bleb raised on ID inoculation

Advise to the vaccinated person:

- Do not rub the injection site
- Do not apply anything to the injection site
- Complete the course of vaccination

Adverse reactions following ID administration of anti-rabies vaccine:

Adverse events may include mild itching, erythema, rarely body ache and fever that are usually self-limiting. Sometimes symptomatic management using analgesics and antihistamines may be needed.

Anti-rabies treatment centres that meet the following criteria may use ID administration:

- Have adequately trained staff to give ID inoculation of anti-rabies vaccine.
- Have adequate cold chain facility for vaccine storage.
- Ensure adequate supply of suitable self-mounted syringes for ID administration.
- Are well versed in management of open vial and safe storage practices.
- Are familiar with safe disposal of clinic waste

Animal bite victims on chloroquine therapy should be given ARV by intramuscular route.

Switch over from IM to ID route of administration or vice versa during PEP: Shifting from one route to other i.e. IM to ID or vice-versa during post exposure prophylaxis is not recommended as there is no sufficient scientific evidence/study on vaccine immunogenicity following changes in the route of vaccine administration during PEP.

2.3 Management of re-exposure in previously vaccinated individuals

Priming of immune system and the development of immunological memory after complete pre-exposure vaccination or post-exposure vaccination with potent cell culture vaccines is an important factor in the establishment of long lasting immunity against rabies.
Several studies have indicated that persons who have previously received complete pre- or post-exposure prophylaxis will elicit an anamnestic response to one or more booster doses of rabies vaccine even if the initial series of vaccination was administered several years previously. This response will occur whether:

- the initial vaccination regimen was administered IM or ID;
- the booster dose is given IM or ID
- the previously vaccinated person has detectable rabies virus neutralizing antibodies or not.

Based on the above if re-exposed persons who have previously received and documented full pre- or post-exposure prophylaxis (either by IM or ID route) with a cell-culture vaccine or PDEV should now be given only two booster doses intramuscularly (0.5ml/1ml) or CCVs intra-dermally (0.1 ml at 1 site) on days 0 and 3. Proper wound toilet should be done. Treatment with RIG is not required.

Persons who have previously received full post-exposure treatment with NTV or vaccine of unproven potency or cannot document previous pre- or post-exposure treatment should be treated as fresh case and given treatment as per merits of the case.

3. Pre-Exposure Prophylaxis (PrEP)

Pre-exposure vaccination may be offered to high risk groups like laboratory staff handling the virus and infected material, clinicians and persons attending to human rabies cases, veterinarians, animal handlers and catchers, wildlife wardens, quarantine officers and travelers from rabies free areas to rabies endemic areas. The Indian Academy of Pediatrics (IAP) has recommended pre-exposure prophylaxis of children. This may be considered on voluntary basis.

Schedule of vaccination: Pre-exposure vaccination is administered as one full dose of vaccine intramuscularly or 0.1 ml intra-dermally on days 0, 7 and either day 21 or 28.

Laboratory staff and others at high continuing risk of exposure should have their neutralizing antibody titres checked every 6 months during the initial two years period after the primary vaccination. If it is less than 0.5 IU/ml a booster dose of vaccine should be given. Subsequently, sero-monitoring is recommended every two years. Because vaccine-induced immunological memory persists in most cases for years, a booster would be recommended only if rabies virus neutralizing antibody titers have dropped to less than 0.5IU/ml. Such individuals on getting exposed to rabies virus after successful pre-exposure immunization require only two booster injections of vaccine given on days 0 and 3 and no RIG

4. List of Experts

Dr. L.S. Chauhan **Director, NCDC, Delhi**	**Dr. Veena Mittal** **Additional Director & Head, Zoonosis Division, NCDC, Delhi**	**Dr. R.L. Ichhpujani** **Additional Director** **NCDC, Delhi**
Dr. Mala Chhabra **Joint Director** **NCDC, Delhi**	**Dr. M.K. Sudarshan** Principal &Dean, Kempegowda Institute of Medical Sciences Bangalore	**Dr. Prof. B.J. Mahendra** Mandya Institute of Medical Sciences Mandya
Dr. I. S. Hura **Technical Officer** **O/o DCG(I), New Delhi**	**Dr. Sandhya Kulshestra** Consultant & DDG, DGHS, NirmanBhavan, New Delhi	**Dr. Arvind Nath** Indian Council for Medical Research, New Delhi
Dr. Sunil Gupta **Director** **Central Research Institute** **Kasauli, Himachal Pradesh**	**Dr. B. Sekar** Director Pasteur Institute of India Coonoor, Tamil Nadu	**Dr. Madhusudan S.N.** Professor NIMHANS Bangalore
Dr. G Sampath **Medical Officer, Incharge** **Anti-Rabies Treatment Centre, Institute of Preventive Medicine, Hyderabad**	**Dr. AT Kanan** Prof & Head Dept of Community Hospital GTB hospital Delhi	**Dr. Anurag Agarwal** Maharishi Valmiki hospital Pooth Kurd, New Delhi
Dr. Veena Dobhal, **Hindu Rao Hospital** **New Delhi**	**Dr. D Bhattacharya** Additional Director NCDC, Delhi	**Dr. Shilpi Das** Deputy Assistant Director NCDC, Delhi
Dr. Sahoo **Human Biological Institute** **Hyderabad**	**Dr. B Kundu** RML hospital, New Delhi	**Dr. Khan Amir Maroof** UCMS & GTB Hospital Delhi
Ms. Lillian Orciari **CDC Rabies Programme** **Atlanta, GA**	**Dr. Gyanendra Gongal** WHO Regional Office for South-East Asia, New Delhi, India	**Dr. Sampath Krishnan** WR-India New Delhi
Mr. S. Balakrishanan **Novartis Vaccines, Mumbai**	**Mr. Roy Cherion** Aventis Pharma, New Delhi	**Dr. Sandeep Arora** Novartis Vaccines
Mr. O.P Singh **Zydus Fortis** **Ahmedabad**	**Dr. G.V.J.A. Harshavardhan** Bharat Biotech International Ltd, Hyderabad	**Dr. Aldon Fernandes** Bharat Serums & Vaccines Ltd, Mumbai
Dr. Bhuvneshwari Sharma **Serum Institute of India, Pune**	**Mr. Nikhil Sharma** Bharat Serums and Vaccines Ltd.	**Mr. P. Vinai Babu** Bharat Serums and Vaccines Ltd.
	Mr. Sameer Joshi Bharat Serums and Vaccines Ltd.	

Annexures

Annexure 1

Table1: Currently available equine rabies immunoglobulin in India

	Brand	Product	Pharmaceutical
1.	Anti-Rabies Serum (ARS)	Purified equine RIGs, 5 ml vial (300 IU/ml, 1500 IU potency)	Central Research Institute, Kasauli, Himachal Pradesh
2.	Equirab	Purified Equine RIGs, 5ml vial (300 IU/ml, 1500 IU potency)	Bharat Serums and Vaccines Limited, Mumbai
3.	Vinrig	Purified Equine RIGs, 5ml vial (300 IU/ml, 1500 IU potency)	VINS Biopharma, Hyderabad.
4.	Abhayrig	Purified Equine RIGs, 5 ml vial (300 IU/ml, 1500 IU potency)	Human Biologicals Institute, Hyderabad

Table 2: Currently available human rabies immunoglobulin in India

	Brand	Product	Pharmaceuticals
1.	Berirab-P	Human Rabies Immunoglobulin, 150IU/ml; 2 ml (300 IU) ampoule and 5 ml (750 IU) ampoule	ZLB Behring AG,Marburg, Germany/Bharat Serums and Vaccines Ltd., Mumbai.
2.	Imogamrab	Human Rabies Immunoglobulin, 150IU/ml; 2 ml (300 IU) ampoule and 5 ml (750 IU) ampoule	Sanofi Pasteur, France
3.	Kamrab	Human Rabies Immunoglobulin, 150 IU/ml; 2 ml (300 IU) vial and 5 ml (750 IU) vial	Kamada Ltd.,Beit-Kama, Israel /Synergy Diagnostics Pvt. Ltd.,Thane,Maharashtra

Table 3: Currently available anti-rabies vaccines in India#

	Brand	Product	Pharmaceutical
1.	Abhayrab	Purified Vero cell Rabies Vaccines (PVRV)	Human Biologicals Institute, Hyderabad
2.	Indirab	Chromatographically purified (PVRV)	Bharat Biotech International Ltd, Hyderabad
3.	PVRV*	Purified Vero cell Rabies Vaccine (PVRV)	Pasteur Institute of India, Coonoor, Tamilnadu
4.	Rabipur	Purified Chick Embryo Cell Vaccine (PCECV)	Novartis Vaccines, Mumbai
5	Rabivax	Human Diploid Cell Culture Vaccine (HDCV) (Liquid)	Serum Institute of India, Pune
6	Vaxirab	Purified Duck Embryo Vaccine (PDEV)	Zydus Health Care ltd., Ahmedabad
7	Vaxirab-N	Purified Chick Embryo Cell Vaccine (PCECV)	Zydus Health Care Ltd, Ahmedabad
8.	Verorab	Purified Vero cell Rabies Vaccines (PVRV)	Sanofi Pasteur/ Zuventus Health Care, Mumbai
* Limited production, since July 2001.			

A few other vaccines are being used in the country in limited quantities

Proforma for management of animal bite case at an antirabies centre/clinic(ARC) **Annexure 2**

Name: Age : Gender :
Residential address :
Telephone/Mobile Nos.:
Occupation: Monthly income (in Rupees)
Previous anti- rabies vaccination Status(with dates): Not vaccinated( ) Vaccinated ( ) : Record available ( ) Not available/Not applicable ( ) DD/MM/YY(doses)
Date of animal bite: Time of bite:
Address/ Place where bite took place:
Interval between bite and reporting to ARC (in hours/days) :
Site of bite/s: Number of wounds: Superficial …. Deep …. Total …….
Biting Animal- species: Dog/Cat/Monkey/Mongoose/Others (specify)
Type: Pet/Stray/Wild
Vaccination Status of Animal: Vaccinated/Not vaccinated /Not known If vaccinated: number of doses received: Vaccination card : not available( )available( )(show it)
Bite: Provoked/unprovoked
Type of provocation:
Fate of animal: Alive/Killed/Died/Unknown/Untraceable:
No. of other persons bitten by same animal within one week of the bite: Not known( )
Outcome in other persons bitten: Not Applicable ( )
Type of exposure: WHO category – Category I ( ) Category II ( ) Category III ( ) a) Licks on intact skin b) Nibbling of uncovered skin c) Minor scratches or abrasions without bleeding d) Licks on broken skin e) Single or multiple bites with bleeding f) Contamination of mucus membrane with saliva
Remedy taken before coming to anti-rabies centre/ clinic: a) None ( ) b) Washed with water…….. c) Washed with soap and water…….. d) Antiseptic application…… e) Any other specify: application of oil/salt/chilies/lime/herbs/any other (specify)……..
Duration between bite & Local treatment of wound:
Who advised you to come to anti-rabies clinic:
Treatment given at the anti-rabies clinic: a) Wound washed in the clinic…… b) RIG (Name) given…… Local (mL)……Systemic (mL)……..Total(mL)…… c) Wound suturing (if done, details). …… d) Vaccine (Name): IM/ID: on days 0/3/7/14/28 (as applicable) (dates)…… e) Injection TT…… f) Record/Report adverse events to vaccine or RIG: …….. g) Antibiotics…… h) Analgesics/NSAID/Antihistamines…… i) Other drugs/treatment given (if any)……

5. Decision Tree: Guide to Post-Exposure Prophylaxis