

RABIES IS 100 PERCENT FATAL BUT PREVENTABLE

Rabies can be caused by bite or scratch of rabid animal such as dogs, cats etc

Do not apply chillies, mustard oil or any other irritant on the bite wounds

Wash the wound immediately with plenty of soap & water

Do not apply dressing & Do not get the wound stitched

Consult your doctor immediately or rush to nearest antirabies clinic

Complete the course of antirabies vaccination, as advised by your doctor

In severe bites, combined antirabies serum and vaccine therapy is recommended

Vaccinate your pets against rabies every year

NATIONAL CENTRE FOR DISEASE CONTROL
(Directorate General of Health Services)
22-SHAM NATH MARG, DELHI - 110 054
<http://www.ncdc.gov.in>
2015



National Rabies Control Programme

National Guidelines on Rabies Prophylaxis



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Dr. Jagdish Prasad
M.S. M.Ch., FIACS
Director General of Health Services



भारत सरकार
स्वास्थ्य एवं परिवार कल्याण मंत्रालय
स्वास्थ्य सेवा महानिदेशालय
निर्माण भवन, नई दिल्ली-110 108
GOVERNMENT OF INDIA
MINISTRY OF HEALTH & FAMILY WELFARE
DIRECTORATE GENERAL OF HEALTH SERVICES
NIRMAN BHAWAN, NEW DELHI-110 108
Tel : 23061063, 23061438 (O), 23061924 (F)
E-mail : dghs@nic.in

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FOREWORD

Rabies continues to pose a major public health challenge in India. Although the exact magnitude of the disease is not reliably known, some studies estimate that 174 lakh persons are bitten and approximately 20,000 persons succumb to the disease annually.

In last two decades, India has made considerable strides in many aspects of preventing human deaths due to rabies. Reactogenic Nerve Tissue Vaccine has been phased out since December 2004. India has capability and infrastructure for producing modern rabies cell culture vaccines. The country is also producing equine rabies immunoglobulins indigenously. In addition, introduction of intradermal route of inoculation of cell culture vaccines has facilitated provision of wider coverage of post-exposure prophylaxis to animal bite victims within the available quantity of vaccines.

Since there was no comprehensive national programme, under 11th Five year plan a pilot project on prevention and control of human rabies was carried out in five cities. The strategy was found to be effective and implementable and hence, under 12th Plan a National Rabies Control Programme was approved and is being implemented. The programme has two components. The human health component is being rolled out throughout the country and the animal health component is being pilot tested in the State of Haryana and in Chennai Corporation.

One of the important strategies to prevent human deaths is to provide appropriate animal bite management to all animal bite victims. I congratulate Director, NCDC, Dr. Veena Mittal, Head (Zoonoses) and her team for bringing out these guidelines. I am confident that medical professionals all over India will find these guidelines useful for providing appropriate animal-bite management including effective administration of Anti-Rabies prophylaxis. This will ensure uniformity in provision of post-exposure prophylaxis to all those who are in need of it.

(Dr. Jagdish Prasad)



सत्यमेव जयते

भारत सरकार

राष्ट्रीय रोग नियंत्रण केन्द्र

स्वास्थ्य सेवा महानिदेशालय, स्वास्थ्य एवं परिवार कल्याण मंत्रालय

22, शामनाथ मार्ग, दिल्ली-110054

Government of India

Dr S. VENKATESH

DNB, MD, DPH, MPH (Harvard), FAMS, FIPHA
DIRECTOR

NATIONAL CENTRE FOR DISEASE CONTROL
[Formerly known as National Institute of Communicable Diseases (NICD)]

Directorate General of Health Services
Ministry of Health & Family Welfare, Govt. of India
22, Sham Nath Marg, Delhi-110054

Direct.: 011-23913148,
23922132, 23944035
Fax : 011-23922677
Email: dirnecd@nic.in;
dirnecd@gmail.com
Website: www.ncdc.gov.in
www.idsp.nic.in

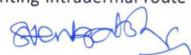
PREFACE

Rabies, a disease as old as our civilization, has terrified man since antiquity. The disease is practically cent percent fatal; however, it can certainly be prevented by providing timely and appropriate treatment. Till date no treatment has succeeded in curing hydrophobia and in spite of great strides in the prevention of rabies, with few exceptions, the disease is no less a global problem now than it was almost a century ago. In India the disease is reported throughout the year and in all parts of the country with the exception of water-locked islands of Lakshadweep and Andaman and Nicobar. Estimates suggest that 175 lakhs animal bites occur annually. Dogs inflict more than 95% of bites. Monkeys, cats, cattle, mongoose, are some of the other animals which bite human beings who would require post exposure prophylaxis.

Control of rabies involves two components, viz. elimination of human deaths due to rabies through timely and appropriate post-exposure prophylaxis to all exposed since rabies is endemic in the country and control of canine rabies through mass immunization to break the chain of transmission of the disease and animal birth control for dog population management. Multiple agencies/sectors are carrying out control activities. However no tangible results have been achieved so far as the efforts are patchy and have not been carried out in organized and coordinated manner.

Tools for prevention and control of rabies have expanded substantially in recent years. This provides a sound technical basis to launch an initiative to control rabies. Ministry of Health & Family Welfare, Government of India has initiated the National Rabies Control Programme (NRCP) under 12th Five Year Plan which has both human and animal health components. National Centre for Disease Control is the nodal agency for the human health component. The strategy of human health component i.e training of health professionals, implementing use of intradermal route of inoculation of cell culture vaccines and strengthening surveillance, is being rolled out throughout the country. The strategy of animal health component i.e population survey of dogs, mass vaccination of dogs, dog population management and strengthening surveillance and response is initially being pilot tested in Haryana and Chennai by Animal Welfare Board of India, Ministry of Environment & Forest, Government of India, and will subsequently be implemented in the country. In addition, IEC activities and laboratory strengthening of four regional laboratories will be carried out together in coordinated manner.

The national guidelines on rabies prophylaxis have been revised at NCDC in an expert consultation to bring out uniformity in post-exposure prophylaxis and implementation of NRCP. I sincerely hope that this publication will be of immense use for managing animal bites and implementing intradermal route of inoculation of cell culture vaccines.


(Dr. S. Venkatesh)

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
NRCP	National Rabies Control Programme
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
°C	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 (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 dreadful 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. These guidelines were revised in an expert consultation in 2007 and again in 2013, after (NTV) New Tissue Vaccine production was stopped (2004) in the country and modern cell culture vaccines (CCVs) were recommended for use for post exposure prophylaxis. Higher cost of intra-muscular administration of CCV is a limiting factor for its wider use. And hence, in February 2006, as per WHO recommendations, results of clinical trials on safety, efficacy and feasibility, Drug Controller General of India (DCGI) approved the use of safe, efficacious and economical Intra-dermal (ID) route of inoculation of CCVs.

Under the 12th five year plan National Rabies Control Programme (NRCP) has been approved. The NRCP has both human and animal health components. The human health component is being implemented throughout the country. The NCDC is the nodal centre for its implementation and the focus of human health component is on providing timely and appropriate animal bite management to all animal bite victims. This can be attained by creating awareness in general community to seek (PEP) Post-exposure prophylaxis, train doctors in appropriate animal bite management and implement ID route of inoculation of CCVs for wider coverage in available quantity of vaccines. Hence, need was felt to review national guidelines and disseminate them widely for uniformity in 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/cats. 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 bite: A provoked dog bite should also be managed as an exposure and PEP started immediately. A provoked bite does not mean that the biting animal is not rabid. It is difficult to understand what provokes a dog so it is prudent to start PEP at the earliest.

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 ordinarily require PEP.

Bat rabies: Bat rabies has not been conclusively proved in India and hence, at present, 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, long term 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/tissue (cornea) transplant. However, people who have been exposed closely to the secretions of a patient with rabies may be offered PEP as a precautionary measure. Organ/tissue (cornea) for transplantation, should never be collected from suspected/confirmed rabies or rabies like encephalitis cases.

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 contraindications 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) Pre-exposure prophylaxis.

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 (WHO TRS 2013) (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 	Wound management Rabies immunoglobulin Anti-rabies vaccine
	Contamination of mucous membrane with saliva (i.e. licks) 	

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. Washing of wound(s) should be carried out as soon as possible with soap and water. 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

Do's		
Physical	Wash with running water 	Mechanical removal of virus from the wound(s)
Chemical	Wash the wound(s) with soap and water Apply disinfectant 	Inactivation of the virus
Biological	Infiltrate immunoglobulin into the depth and around the wound(s) in Category III exposures 	Neutralization of the virus
Dont's		
Touch the wound(s) with bare hand Apply irritants like soil, chilies, oil, lime, herbs, chalk, betel leaves, etc.		

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. The maximum benefit of the wound(s) washing is obtained when fresh wound(s) is cleaned immediately. Considering the importance of this step all health facilities 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 victim 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 a few hours. The delay in suturing allows diffusion of antibodies in the tissues. Minimum loose sutures should be applied for arresting the bleeding in life threatening situations.

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 and antibiotic prophylaxis should be given if required. To prevent sepsis in the wound(s), a suitable course of an antibiotic may 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, before it is physiologically possible for the victim 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 horses. 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 currently manufactured 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 (WHO TRS 2013, pg 43). 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 (25°C to 30°C) 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 (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 (after 3 doses of vaccine have been administered), 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). Currently available CCVs could be administered by IM regimen and CCVs approved for ID use shall be administered by ID regimen.

Anti-rabies vaccines are produced as one single intramuscular dose with potency of > 2.5IU per IM dose for post exposure and pre-exposure prophylaxis. It is absolutely essential that every batch of CCVs have minimum potency of 2.5IU per IM dose, irrespective of whether the vaccine is administered by IM or ID route.

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 2.2.

Storage and transportation: Though most CCVs are marketed in freeze dried (lyophilized) form, it is recommended that these vaccines should be kept and transported at a temperature range of 2-8°C and protected from sunlight. Temperature monitoring device should be used while storage or transportation of vaccine. 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 diluents and others have 1ml diluents 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 ID administration, the vaccine vial should be stored at 2-8°C after

reconstitution. The total content of the vial should be used as soon as possible, but at the maximum, within 8 hours.

While using IM 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.

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

Adverse effects following administration of CCVs: The CCVs 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 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-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 rabies vaccines which is also approved for use by ID route 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 Biotech International Ltd.

Only the anti-rabies vaccines (lyophilized vaccine along with the diluent of specified volume) 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 volume of the diluent remains the same as that of the IM dose)

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 2°C to 8°C. 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 2°C to 8°C. 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.
- Disposable 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 in a 100 units syringe is) 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; 10 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; 10 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.

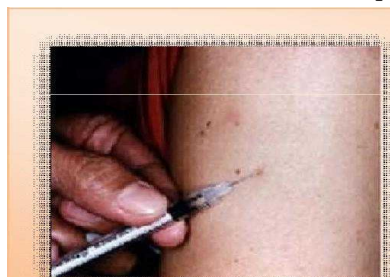


Fig-2: Insertion of needle for
ID inoculation



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.

Logistic requirements for giving antirabies vaccine at health facility:

- 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.

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.

2.2.3.2 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 and is currently being exported.

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.

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

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- Expert Consultation

Dr. N S Dharamshaktu Addl DGHS, Dte GHS New Delhi	Dr. S Venkatesh Director NCDC, Delhi	Dr. Veena Mittal Addl Director & Head, Zoonosis Division, NCDC, Delhi
Dr. B. J Mahendra Director & Dean Kodugu Institute of Medical Sciences Medikeri	Dr. G. Sampath Deputy Civil Surgeon Institute of Preventive Medicine Hyderabad	Dr. Indu Grewal Head, Health promotion and Education Division, CHEB
Dr. Gyanendra Gongal WHO Regional Office for Zoonosis Focal Point South East Asia, New Delhi	Dr. Manju Rahi Scientist-E Indian Council of Medical Research New Delhi	Mr. Rahul S Shakhapure Asst. Drug Controller India, DSCO, DCGI Office, New Delhi
Dr. Veena Dhobhal CMO Incharge, Anti-rabies clinic Hindu Rao Hospital, Delhi	Dr. HK Gohil CMO Incharge ARV Centre MVID Hospital Delhi	Dr. Naveen Gupta Joint Director CRI, Kasauli
Dr. Yogesh Gautam Medical Officer, Casualty VMMC & SJH, New Delhi	Dr. Shati Kolhapure Head Medical affairs Novartis Vaccines India	Dr. S Balakrishnan Head Institutional Business Novartis Vaccines, India
Dr. Dipesh Bhattacharya Addl Director, NCDC, Delhi	Dr. Simmi Tiwari Assistant Director, NCDC, Delhi	Dr. Monil Singhai Assistant Director, NCDC, Delhi
Dr. Mala Chhabra Joint Director NCDC, Delhi		

5. Annexures

Annexure 1

Table 1: Equine rabies immunoglobulin currently manufactured in India

	Pharmaceutical
1.	Central Research Institute, Kasauli, Himachal Pradesh
2.	Bharat Serums and Vaccines, Limited, Mumbai
3.	VINS Biopharma, Hyderabad.
4.	Human Biologicals Institute, Hyderabad
5.	Virchow Biotech Pvt Ltd, Qutubullapur, Telengana
6.	Haffkine Biopharmaceutical Corp Ltd, Pimpri
7.	Premium Serums & Vaccines Pvt Ltd, Pune
8.	Serum Institute of India, Pune

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	Plasmarab	Human Rabies Immunoglobulin, 150IU/ml; 2 ml (300 IU) vial and 5 ml (750 IU) vial	Kamada Ltd., Beit-Kama, Israel

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

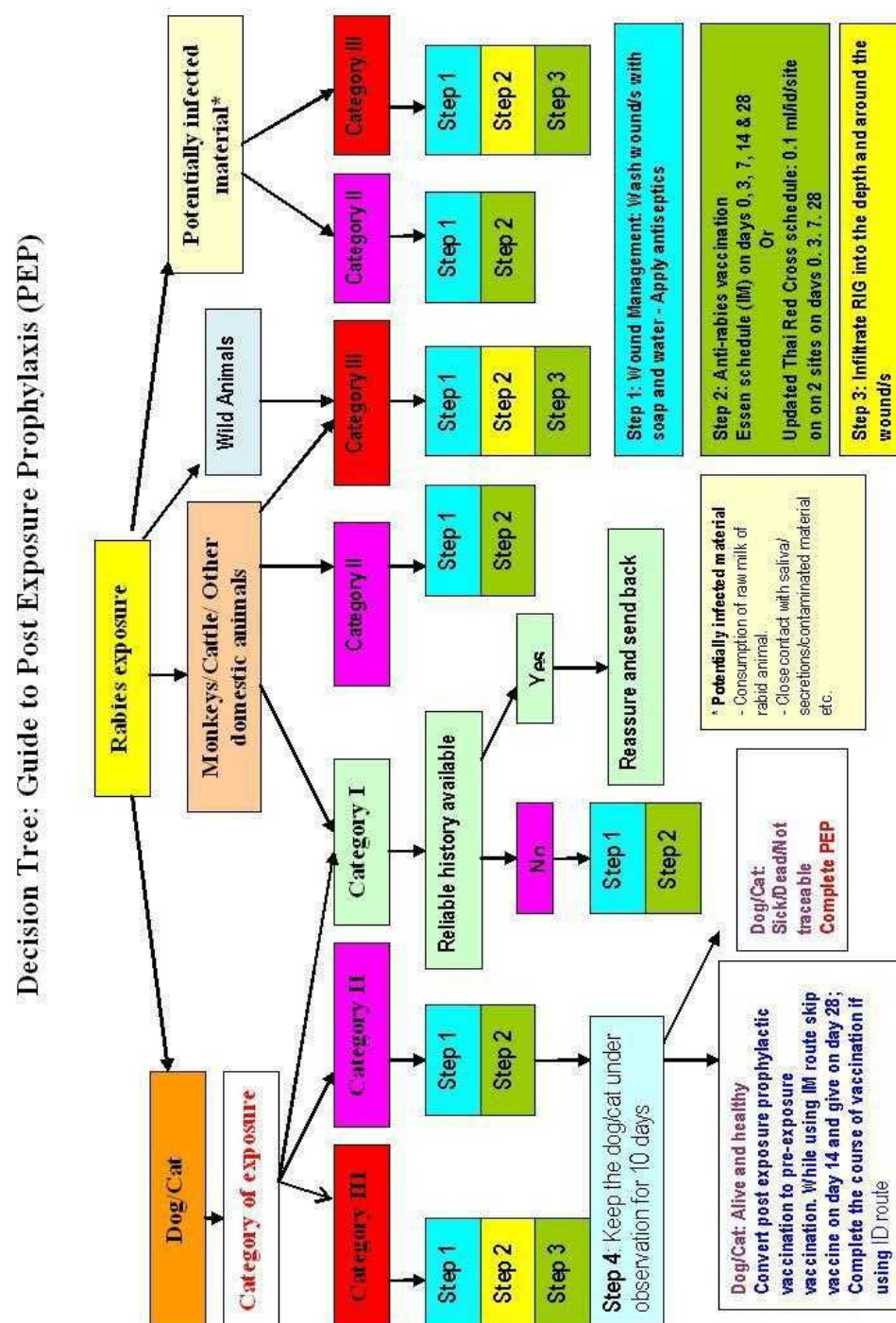
	Brand	Product	Pharmaceuticals
1	Abhayrab	Purified Vero cell Rabies Vaccines (PVRV)	Human Biologicals Institute, Hyderabad
2	Indirab	Chromatographically purified (PVRV)	Bharat Biotech International Ltd, Hyderabad
3	PVRV*	Purified Vero cell Rabies Vaccine(PVRV)	Pasteur Institute of India, Coonoor, Tamilnadu
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/ Zuentus Health Care, Mumbai
* Limited production, since July 2001.			

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

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

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: SuperficialDeep 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).....		

6. Decision Tree: Guide to Post-Exposure Prophylaxis (PEP)



7. Frequently Asked Questions

Question 1: Is there any vaccine which can protect against rabies with one or two doses?

Answer: No such vaccine exists in the world which can induce protective immunity against rabies with only 1 or 2 injections. A complete course comprises of administration of DCG (I) approved vaccine (Lyophilized vaccine with specified amount of diluent) as per recommended schedule i.e. 0.1 ml of vaccine on 2 sites on days 0, 3, 7 & 28.

Question 2: Application of chillies, lime, salt and mustard oil to animal bite wound is common practice. Does it confer any advantage over washing with soap and water?

Answer: Application of any of these does not confer any advantage. On the contrary, irritation produced by any of these may provide more avenues to the virus to gain entry into nerves and spread to brain. This also gives a false sense of security that some treatment has been administered.

Question 3: Are there any dietary restrictions for animal bite victims receiving anti-rabies vaccination?

Answer: No dietary restriction need be imposed on the vaccinee. However, excessive intake of alcohol should be discouraged.

Question 4: Can a vaccinated dog transmit rabies?

Answer: A dog effectively vaccinated against rabies cannot suffer and transmit the disease. However in the absence of laboratory documentation of protection, it cannot be presumed that a vaccinated dog is actually protected, given the variable efficacy of various anti-rabies vaccines in animals and/or health status of animals. Hence, irrespective of the vaccination status of the biting dog, the PEP is given.

Question 5: If I am bitten by a rat do I require post-exposure prophylaxis (PEP)?

Answer: Rat rabies has been reported from some Asian countries but is extremely rare. It is not necessary to take PEP in bite cases by house rats. However, it is prudent to take PEP in consultation with an infectious disease physician when bitten by wild rats/rodents.

Question 6: Can consumption of meat from an infected animal transmit rabies?

Answer: The consumption of raw meat from infected animals requires PEP. Cooking kills the virus and hence consumption of cooked meat does not transmit rabies. However, it is not advisable to consume meat from an infected animal.

Question 7: Do we need to consider specific vaccine potency for ID vaccination?

Answer: There has been concern as single IM doses are reconstituted in different volumes depending on manufacturers. The recommended minimum potency of all anti-rabies vaccine is > 2.5 IU per IM dose. The recommended volume of a single dose of rabies vaccine administered per ID site is 0.1 ml. The DCG(I) approved vaccine (pack containing i.e. lyophilized vaccine and specified amount of diluent) with a potency of > 2.5 IU/IM dose should be used for ID inoculation. The recommended dose is 0.1 ml at 2 sites on day 0, 3, 7 & 28.

Question 8: It is necessary to perform an antibody test following anti-rabies vaccination in all animal bite victims?

Answer: No, it is not required in all cases. When human rabies vaccines are given according to the approved schedule in a healthy individual it is not necessary to do antibody titre estimation. It is recommended only under special circumstances such as for immunocompromised patients, patients receiving immunosuppressive therapy or patients who have not taken vaccination as per recommended schedule.

Question 9: Is there any possibility of failure after PEP?

Answer: There are occasional human rabies cases reported despite PEP, due to various factors related to negligence and individual health status. Most cases have been reported due to delayed vaccination, or non-use of rabies immunoglobulin in category III exposure, or incomplete course of vaccination. Some cases are related to immunocompromised status such as HIV/AIDS, cirrhosis or use of chloroquine, long term steroids, or anti-cancer drugs. Unexplained failure in cases where everything was apparently done correctly have also been documented, however, are very rare.

Question 10: DCG (I) approved vaccine is being used in anti-rabies centre which reconstitutes to 0.5ml volume. Is it advisable to add extra diluent to this and use it for ID inoculation using 0.1 ml per site at 2 sites on days 0,3,7 & 28.

Answer: No, this should never be done.