ASSOCIATION FOR PREVENTION AND CONTROL OF RABIES IN INDIA (APCRI)

REPORT

EXPERT CONSULTATION ON USE OF RABIES IMMUNOGLOBULINS AND RABIES MONOCLONAL ANTIBODIES FOR POST EXPOSURE PROPHYLAXIS IN HUMANS

JUNE, 2022

Registered office
Department of Community Medicine
Kempegowda Institute of Medical Sciences (KIMS)
Bangalore -560070, INDIA; Website:www.apcri.in

About APCRI

APCRI was founded in the year 1998 with a vision to make: India Rabies Free by 2020. Since then, it has evolved into a national organization that is one of the most vibrant scientific societies in the field with strength of 950 life members.

APCRI serves as a platform that brings together the best minds in the country comprising of medical professionals, public health personnel, veterinary doctors and others for Advocacy, Research & Information dissemination about prevention & control of Rabies.

APCRI led by an excellent team of experts and dedicated people is actively involved in organizing conferences, continuing medical education (CME), symposia, lectures, trainings, scientific publications, book releases, etc. and has a pan India representation.

APCRI has its own official indexed and peer reviewed journal on prevention and control of rabies that is published biannually.

APCRI, with the technical and financial assistance from World Health Organization (WHO) undertook the landmark National multi-centric rabies survey India during 2002 – 2004 and in 2017-18, it conducted yet another Indian multi-centric rabies survey with financial assistance from WHO.

Now, the goal is to “Eliminate dog mediated human rabies by 2030” in line with the global WHO mandate.

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This is issued in public interest for use primarily by medical professionals and others.

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Foreword

Dr. Gyanendra Gongal
Senior Public Health Officer;
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It is my great pleasure to go through guidelines on administration of rabies immunoglobulins (RIGs) and rabies monoclonal antibodies (RMAbs) in humans to be published and disseminated by the Association for Prevention and Control Rabies in India (APCRI). Although rabies is one of the oldest human diseases, postexposure prophylaxis (PEP) is often confusing and continuous medical education (CME) should incorporate application of new immunobiological products. This guidebook is comprehensive, updated with new World Health Organization (WHO) recommendations on cost-effective, innovative PEP including administration of RMAbs.

It is a fact that less than 10% of patients with category III exposures receive passive immunization due to economic and technical reasons. Presently RIGs of human and equine origin are being used in most parts of the world for passive immunization. Although plasma derived RIGs have proven to be highly efficient in conferring protection after rabies exposure, the limited access, high cost and often short supply of RIGs in rabies endemic low and middle-income countries have hampered efforts to reduce the rabies death toll. Therefore, a search for a replacement to plasma derived RIGs has been strongly encouraged by the WHO since 1990. The

development and availability of RMAbs in recent years in India is a paradigm shift in passive immunization addressing shortcomings of plasma derived RIGs and animal welfare issues. The Indian pharmaceutical industries are at the forefront of innovation, technology transfer and commercially viable for economical production including RMAbs.

Non-discriminatory, universal and equitable access to quality assured rabies MAb for passive immunization is need of the time. The post-marketing surveillance data on use of RMAbs in India will be valuable to make policy informed decision. There is an urgent need to scale up the availability, accessibility and affordability of these essential, lifesaving immunobiological products to achieve universal health coverage (UHC). It will definitely contribute to achieve universal target of zero human death due to rabies by 2030.

4th June, 2022 **Dr. Gyanendra Gongal**

Preface

Dr. M.K. Sudarshan
Founder President & Mentor, APCRI
Ex. Director, Retired Dean & Principal
KIMS, Bangalore, India

Rabies is a practically 100% fatal disease, but is preventable through timely and effective post-exposure prophylaxis (PEP) and pre-exposure vaccination / prophylaxis (PrEP) of at-risk population in humans. India is known to contribute nearly one-third of the global burden of human rabies. The Association for Prevention and Control Rabies in India (APCRI) founded in 1998 is the first scientific society that has been at the forefront of activities for rabies elimination in the country. The APCRI is playing an active supportive role with Government of India (GoI) and World Health Organization (WHO).

With the recent addition of rabies monoclonal antibodies in the arsenal of passive immunization against rabies, there is a need to provide an update and guidelines on administration of RIG and RMAb in humans. It is sincerely hoped that this guidebook is a first step in that direction. This shall be not only being available on the website of APCRI, but also widely circulated on the social media. Also a video link demonstrating the use of passive immunization in rabies prophylaxis is provided in this manual. Lastly, there is need for regular hands-on training of medical and nursing professionals in the speciality anti-rabies clinics (ARCs) in the country. I recommend to APCRI to soon fulfil this need through its regional representatives and other office bearers.

4th June, 2022

Dr. M.K. Sudarshan

List of Abbreviations

ACIP	Advisory Committee on Immunization Practices
ADE	Adverse Drug Event
APCRI	Association for Prevention and Control of Rabies in India
ARC	Anti-Rabies Clinic
ARS	Anti-Rabies Serum
ARV	Anti-Rabies Vaccine
CCV	Cell Culture Vaccine
DCGI	Drug Controller General of India
ELISA	Enzyme-linked Immunosorbent assay
ERIG	Equine Rabies Immunoglobulin
HRIG	Human Rabies Immunoglobulin
ID	Intra Dermal
IDRV	Intra Dermal Rabies Vaccination
IM	Intra Muscular
IMRV	Intra Muscular Rabies Vaccination
IU	International Units
mL	Millilitre
MTA	Material transport agreement
NIMHANS	National Institute of Mental Health & Neurosciences
NRCP	National Rabies Control Programme
NSAIDs	Non-steroidal anti-inflammatory drugs
PCECV	Purified Chick Embryo Cell Culture Vaccine
PEP	Post Exposure Prophylaxis
PMS	Post Marketing Surveillance
PrEP	Pre exposure Prophylaxis
PVRV	Purified Vero cell Rabies Vaccine
RABV	Rabies virus
RFFIT	Rapid Fluorescent Focus Inhibition Test
RIG	Rabies Immunoglobulin
RMAb	Rabies Monoclonal Antibodies
RVNA	Rabies Virus Neutralizing Antibody
SAGE	Strategic Advisory Group of Experts on Immunization
SDG	Sustainable Development Goal
SST	Skin Sensitivity Test
TRC	Thai Red Cross
UIP	Universal Immunization Programme
VPD	Vaccine Preventable Diseases
WHO	World Health Organization

1. Introduction

Rabies is a neglected zoonotic viral disease that is practically 100% fatal, yet 100% preventable by timely and correct rabies prophylaxis. The rabies virus is present in the saliva of rabid animals, and is transmitted to other animals and humans following bites, scratches, licks on broken skin and mucous membrane.

Rabies continues to be a major public health problem throughout mainland India; and the islands of Andaman & Nicobar and Lakshadweep are rabies free. The presence of unvaccinated free roaming dogs amidst human settlements is a major contributor to the high incidence of rabies in India. An estimated 20,000 human rabies deaths and 17.4 million animal bites are known to occur annually as reported from WHO-APCRI National Multicentric Rabies Survey 2004(1). The disease is transmitted largely by dogs and cats (>97%), followed by wild animals (2%) such as mongoose, foxes, jackals, wild dogs, wild rodents and occasionally by monkeys, horses, donkeys and others. Domestic rats, squirrels, rabbits and birds are ordinarily not known to transmit rabies.

In an rabies endemic country like India, where every animal bite is potentially suspected as rabid exposure, the exposed individuals should seek early medical care; and post exposure prophylaxis (PEP) should be started immediately at the health care facility.

1. WHO-APCRI National multicentric rabies survey, 2004.
www. http://apcri.in/pdf/WHO-APCRI%20%202003%20-04%20%20Survey%20Report.pdf

Therefore, to achieve the elimination of dog mediated human rabies by 2030, all animal bite cases should have ready access to life saving rabies biologicals i.e., anti-rabies vaccines (ARV) and rabies immunoglobulin (RIG) or rabies monoclonal antibodies (RMAb) at all levels of health facilities, both in government and private sectors in the entire country.

2. Post Exposure Prophylaxis (PEP)

Early and complete PEP will prevent rabies, even after high-risk exposure to potentially rabid animals. The comparatively long incubation period gives an opportunity for providing highly effective PEP. It consists of -

- Washing of all wound/s with soap/detergent and water, followed by application of virucidal agents to reduce the viral inoculum at the wound site
- Complete course of rabies vaccination to induce antibodies which prevents the virus entering peripheral nerves
- Infiltration of rabies immunoglobulin (RIG) or rabies monoclonal antibody (RMAb) in all Category III exposures to neutralize the virus at the wound site.
- Depending on the type of wound; antibiotics, analgesics and tetanus vaccination may be provided.

Points to note:

- PEP is lifesaving and it is not contraindicated even during pregnancy & lactation.
- PEP may be provided along with any other vaccination like Covid vaccination or others, as it will not interfere with the production of antibodies.
- Although unvaccinated animals are more likely to transmit rabies; vaccinated animals can also transmit the virus, following ineffectiveness of vaccination for any reason. Therefore, history of rabies vaccination in an animal does not guarantee that the biting animal is not rabid.

- Animal vaccine failure 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 protection against rabies infection in dogs/cats.
- Likewise, a bite by a unprovoked animal does not mean that the animal is not rabid. Therefore, an unprovoked dog bite should also be managed as an exposure; thus PEP should be started immediately.

2.1 Indications for PEP

Common and frequent exposures

- Bites, scratches and licks by dogs and cats; others like monkeys, horses, and donkeys
- Exposure to wild animals like mongoose, foxes, jackals and other biting animals(not in snake bite)

Atypical and rare exposures

- Recipients of organ transplant from rabies-infected organ donors
- Bites from, or mucosal exposure following medical or dental procedures, kissing, intimate touching by a rabies-infected person
- Individuals with exposures to rabies-infected animals during butchering or processing of its meat including eating meat of rabid animals
- Healthcare workers or caregivers of rabies patients who were exposed to saliva, tears, urine of the patient
- Individuals co-exposed to an animal which caused a rabies case
- Persons exposed to aerosols in a cave infested with bats

PEP is not ordinarily indicated in:

- Individuals bitten by rodents unless the rodent shows abnormal behavior/activity or has tested positive. However, whenever in doubt, it is always safer to provide PEP.
- Drinking milk from a rabies infected animal
- Breast fed baby of a rabies-infected mother
- Exposure to bats in India (since there is no sufficient evidence to suggest transmission of rabies to humans from bats in India).

3. Categorization of animal bite wound(s)

In countries or areas enzootic for rabies, exposure to suspected, probably or confirmed rabid domestic or wild animals, the wound/s is/are categorized to provide PEP.

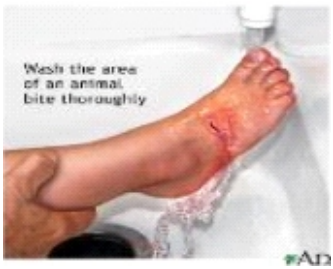
Category	Type of contact	Type of Exposure	Recommended PEP
I	➢ Touching/feeding of animals ➢ Licks on intact skin	None#	No PEP, if case history is reliable.
II	➢ Nibbling of uncovered skin ➢ Minor scratches or abrasions without bleeding	Minor 	✓ Local treatment of all wounds ✓ Administer full course of anti - rabies vaccine ✓ No RIG is needed
III	➢ Single/multiple transdermal bites/scratches ➢ Licks on broken skin ➢ Contamination of mucous membrane with saliva (licks)	**Severe** 	✓ Local treatment of all wounds ✓ Infiltrate RIG or RMAb into all wounds as anatomically feasible ✓ Administer full course of anti-rabies vaccine

#Note: If no wound is seen, to check for breach in dermis that exposes the cut end of the nerve/s, surgical/ medicinal spirit or after shave lotion may be applied to the exposed area. If there is burning sensation, it shows there is breach in dermis and it shall be treated as category II.

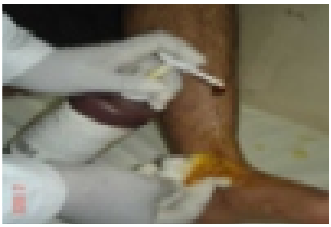
4. Wound/s management

Early and prompt local treatment of all bite wounds and scratches is an important step in PEP. Since the rabies virus present in the saliva of the rabid animal enters the human body through a bite or scratch, it is imperative to remove as much saliva as possible by efficient wound/s management that should not cause additional trauma/ injury to the tissues.

- The recommended first-aid procedures include immediate, thorough flushing and washing of all wounds with soap (any) and water and application of povidone iodine/ surgical spirit or any other antiseptic with virucidal activity.



- If soap or a virucidal agent is not available, the wound(s) should be thoroughly and extensively washed/flushed with water.



Properties	Steps in wound management	Rationale
Physical	Ideally wash all wounds with running water for15 mins	Mechanical removal of virus from wounds.
Chemical	Clean the wounds with soap and water & apply antiseptics.	Inactivation of the virus.
Biological	Infiltrate with RIG or RMAb into and around all the wound/s in Category III exposures, and also in category II exposures in immuno-compromised individuals	Neutralization of the virus

Points to note:

- If eyes and mucous membranes are exposed, these should be thoroughly rinsed with sterile normal saline or at least clean water.
- If irritants like lime, turmeric, oil, chili, tea or coffee powder, etc. have been applied on the wound/s; then such applicants shall be removed by gently washing with soap/detergent and water
- Since the rabies virus can persist and even multiply at the site of bite for a long time, wound(s) management must be performed even if the patient report late. The exposed/ bitten area shall be cleansed and antiseptic applied even if there are no visible marks.
- In case of need for suturing; like for stopping bleeding (to achieve haemostasis), then firstly all wound(s) shall be cleaned with soap and water, antiseptic applied; and then soon thoroughly infiltrated with RIG or RMAb. Then suturing shall be delayed as far as possible for several hours to allow diffusion of the RIG or RMAb through the tissues before minimal sutures are done.
- If the suturing is already done, then without disturbing the sutures wound/s shall be infiltrated with RIG or RMAb.
- Secondary sutures are less likely to become infected and present better cosmetic results if done under optimal conditions. This is ideally done after day 14 of vaccination, as protective level of rabies virus neutralizing antibody (RVNA) would have appeared i.e., $\geqslant$0.5 IU/ml
- An infected bite wound is not a contraindication to inject RIG or RMAb.
- Chemical or thermal cauterization of wound(s) is strictly prohibited.

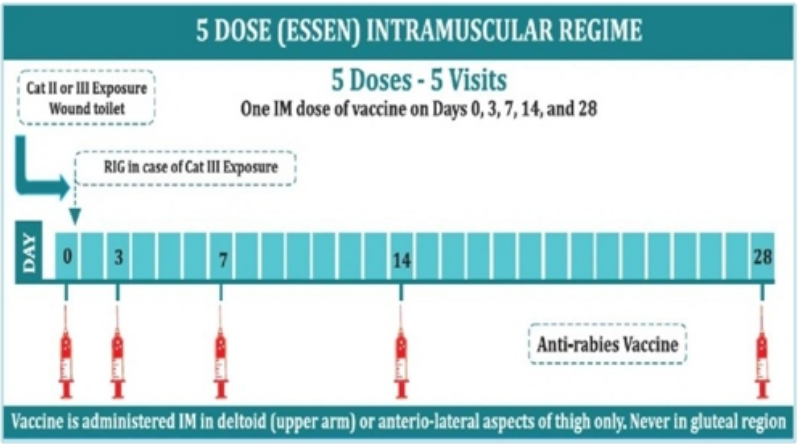
5. Anti-rabies vaccination (ARV)

Rabies is a vaccine preventable disease (VPD). The vaccination must be started immediately in cases of category II & III exposures irrespective of the status of the biting animal. Any modern anti-rabies vaccines like purified chick embryo cell vaccine (PCECV), purified verocell rabies vaccine (PVRV) or recombinant Nano-particle rabies G protein vaccine must be administered as per Government of India schedule/ package insert of the vaccine.

5.1. Vaccination Schedules

In those who have previously not taken any rabies vaccine (unvaccinated) :

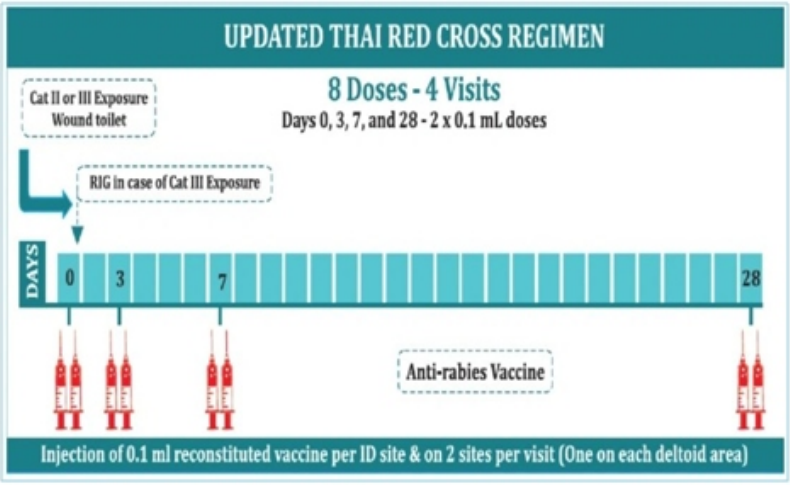
Intramuscular(IM) schedule (Essen Regimen): 1 dose of vaccine on Days 0, 3, 7, 14 & 28. (Day 0 is the date of administration of the first dose of vaccine and may not be the day/date of bite)



- All modern anti rabies vaccines are equally effective and safe with a potency of ⩾2.5 IU/ intramuscular dose for PEP.
- For adults, vaccine should always be administered in the deltoid area of the arm; for young children (aged < 2 years), the anterolateral area of the thigh is recommended.

- Vaccines should not be injected into the gluteal area/buttocks region as due to presence of fat locally, there will be variable absorption of the vaccine and its subsequent poor sero-response that may result in vaccine failure increasing the risk of rabies and death.

Intradermal (ID) schedule (Updated Thai Red Cross Regimen):
0.1ml X 2 sites on Days 0, 3, 7 & 28.



Points to note:

- WHO recognizes the equivalent clinical effectiveness of intradermal route vis-a-vis IM route; and hence, ID route is preferred and considered cost–effective in clinics where several new animal bite cases are seen per day. Ideally a minimum of 4 cases per day would be cost-effective.
- Rabies vaccines labeled for intramuscular use may be used by intradermal route. However, the package/ product insert that accompanies the vaccine shall be referred to before administration of vaccine by ID route. In many government hospitals, separate circulars are issued to the medical officers to use certain vaccines by ID route and in such instances that direction shall be followed.

- One intradermal dose corresponds to 0.1 mL of vaccine, irrespective of the volume of the vial.
- The dose of 0.1mL X 2 sites is injected in the right and left deltoids intradermally
- Health care personnel should be careful not to inject less than the full 0.1 mL ID dose due to the dead space in the syringe and needle mount. Alternatively, insulin syringes may be used.
- A papule of minimum 4-5 mm should be visible with ID administration or else vaccine should be given again in the adjoining area.

In those who have previously taken full course of either pre-exposure (PrEP) or post exposure prophylaxis (PEP) vaccination, any time in the past (Vaccinated):

Such persons are given -

- Only 2 doses of vaccine on days 0 & 3 either by IM/ ID route (one site ID or one site IM on Days 0 and 3
- No RIG or RMAb is necessary.

5.2. Immune response to anti rabies vaccination

- Rabies virus neutralizing antibodies (RVNA) titre of $\geqslant$ 0.5 IU/ mL in serum is considered to be protective/ adequate seroconversion post vaccination. This level is achieved in most healthy individuals by Day 14.
- The immune response of a person undergoing PEP can be measured through rapid fluorescent focus inhibition test (RFFIT) after 2-4 weeks of completion of a rabies vaccination series. The RFFIT takes about 48-72 hours.

The RFFIT is the current gold standard serological assay recommended by the Advisory Committee on Immunization Practices (ACIP) and the World Health Organization (WHO). RFFIT is done at the WHO Collaborating centre for reference and research on Rabies, Department of Neurovirology,

NIMHANS, Bangalore. Alternatively, an adequately validated ELISA test may be used for this purpose.

For most persons who are healthy and completing pre-exposure or post exposure prophylaxis, routine serological testing is not necessary to check for seroconversion, unless the:

- person is immuno suppressed
- significant deviations of the prophylaxis schedule have occurred
- patient started vaccination overseas with a product of questionable quality
- An individual's antirabies antibody status is being monitored routinely due to occupational exposure to rabies virus.

6. Passive immunization in rabies PEP

The rabies immunoglobulin (RIG) and the recently introduced rabies monoclonal antibodies (RMAb) form the arsenal of passive immunization in rabies PEP.

RIG and RMAb are ready made anti-rabies antibodies, which provide passive immunity by neutralizing the virus at the site of deposition, and thus give immediate protection that is lifesaving in all Category III exposures, i.e.

- Single/ multiple transdermal bites
- Scratches/ licks on broken skin
- Contamination of mucous membrane with saliva following lick/s
- Wild animal exposures

Any wound that is bleeding, even if tiny and at any site indicates potentially severe exposure i.e. category III and such wound/s should be infiltrated with RIG/ RMAb immediately or as soon as possible.

Genesis and rationale of passive immunization

The administration of passive immunization was first advocated by WHO in 1973; at that time only unpurified antirabies serum (ARS) of equine origin was available and because it was a heterologous protein and the dose was calculated depending on the weight of the patient giving due consideration to body surface and biological half-life of the protein. As evidence mounted that systemically administered immunoglobulins may not reach adequate concentrations in the blood and body fluids, WHO in 1982 advocated, that half the calculated dose of immunoglobulin to be infiltrated locally into and around the wound(s) and rest to be administered by intramuscular route. In 1992, WHO revised its recommendation and advocated that as much as possible of RIG should be infiltrated locally and rest, if any, should be administered systemically. WHO in its revised guidelines 2018 emphasises the value of only wound infiltration of RIG; as IM injection of remaining RIG is of little or no use except in conditions of aerosol exposure or where wounds are not visible. Further, it was recommended that considering the unusual and prolonged incubation period of the disease, local wound infiltration should be considered even in cases who report weeks or months after the exposure even though the local wound had healed. This clearly indicates that local infiltration of RIG/ RMAb is crucial for effective neutralization of the virus to prevent its access to CNS (2). RIG/ RMAbs have proved their efficiency when administered at the site of virus entry i.e. wound/ exposed areas, in association with rabies vaccine.

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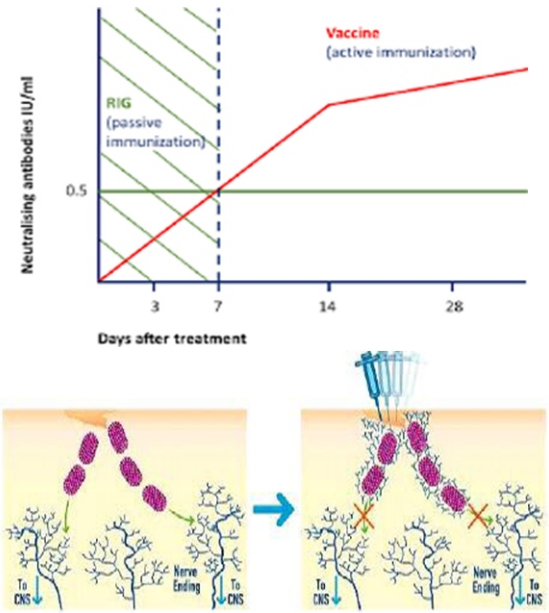
2. Bharti O.K., Madhusudana S.N., Gaunta P.L., Belludi A.Y. Local infiltration of rabies immunoglobulins without systemic intramuscular administration: an alternative cost effective approach for passive immunization against rabies. Hum VaccinImmunother 2016; 12(3):837–42.

https://www.tandfonline.com/doi/full/10.1080/21645515.2015.1085142

Need for Passive immunization in rabies PEP

The modern anti rabies vaccine, if given immediately after the bite, are capable of producing the rabies virus neutralizing antibodies (RVNA) with sero-positive titre of ⩾ 0.5 IU/ml in the bitten person only after 7 - 14 days from the first dose of vaccine, thus leaving the person vulnerable to rabies during this window period. Therefore, infiltration of RIG/ RMAb into and around all the bite wounds as early as possible; after thorough washing of all wounds will neutralize the virus at the site of bite and thus, saves the life of bite victim (see figures below)



- RIG shall always be used along with rabies vaccine & never to be used alone to treat animal bite victims.
- RIG is more effective if infiltrated immediately or at the earliest i.e. before day 7 after the first dose of vaccine, because circulating virus neutralizing antibodies will begin to appear thereafter. However, it can be administered anytime if the person has not received any vaccine.

6.1. Types of Passive immunization agents

There are two classes of biological products available for passive immunization viz.

1. **Rabies immunoglobulin (RIG)**
   - Human rabies immunoglobulin (HRIG)
   - Equine rabies immunoglobulin (ERIG)
2. **Rabies monoclonal antibodies (RMAb)**
   - Single rabies monoclonal antibody
   - Cocktail of 2 rabies monoclonal antibodies

6.2. Human rabies immunoglobulin (HRIG)

HRIG is safe and highly effective, as it is prepared from pooled plasma of human donors who are hyper-immunized with rabies vaccine. Since HRIG is of homologous origin, it is relatively free from the side effects encountered in a serum of heterologous origin like ERIG, and thus provides passive immune protection with a half-life of 21 days.

HRIG can be infiltrated directly into all category III exposures as anatomically feasible without the need for test dose just like any injection. HRIG should be given at a maximum dose of 20 IU/kg of body weight. It is available as 2ml vial of 300 IU, having a potency of 150 IU per mL

Presently, there are 2 products available in India viz. Berirab P and Plasmarab. Both are imported and thus may have fluctuations in their availability.

- The HRIG (Berirab P) is manufactured by CSL Behring, Germany. This has been used for rabies PEP in many countries across the globe since 1992. Since more than 30 years of its licensure, more than 15,00,000 vials of Berirab P have been distributed in the market and no safety concerns have been reported nor have cases of PEP failure been reported in the post marketing experience.

- Plasmarab is manufactured by Kamada Ltd, Israel.

  However, HRIG is expensive.

6.3. Equine rabies immunoglobulin (ERIG)

Equine rabies immunoglobulins (ERIG) are clinically equivalent to human rabies immunoglobulins (HRIG) and are considered safe and efficacious; life and cost-saving biologics. Both neutralize the rabies virus at the wound site within a few hours. For all RIG products meeting quality standards, the safety and efficacy profiles are similar for both ERIG and HRIG.

Equine Rabies Immunoglobulin (ERIG) is of heterologous origin produced by hyper-immunization of horses. Currently manufactured ERIGs are highly purified Fab 2' fragments and consequently the adverse events have been significantly reduced. These are produced in the country both in public and private sectors. For optimal effectiveness, the maximum dose calculation is 40 IU/kg body weight for equine derived RIG (ERIG).

Presently available ERIGs viz. Equirab, Premirab and Vinrig are from private pharmaceutical companies. The production and availability of anti-rabies serum (ARS) from Central Research Institute, Kasauli, Himachal Pradesh, a central government institution is limited.

Precautions to be taken while administering ERIG

- Carefully elicit the history of any previous administration of horse sera viz. anti-tetanus, anti-diphtheria, anti-gas gangrene or even anti-rabies sera (ERIG).
- Also elicit any adverse reactions to other drugs like penicillin, sulphonamides and others
- The patient should not be on empty stomach, more so in case of women and children.
- All emergency drugs and facilities for managing any adverse reactions must be available.

- The RIG once taken out from refrigerator should always be kept for few minutes at room temperature before injecting.
- While infiltrating ERIGs into bite wounds, care must be taken to avoid injecting into blood vessels, nerves and other sensitive organs like eyes, etc. Always keep in mind the anatomical feasibility, while injecting RIGs.
- While injecting into finger tips, care must be taken to avoid compartment syndrome.
- Keep the patient under observation for at least one hour after ERIG administration and then send home.

Points to Note:

- WHO no longer recommends skin sensitivity test (SST) prior to administering ERIG; because skin sensitivity testing does not accurately predict adverse reactions, and ERIG should be given irrespective of the result of the test.
- Any severe adverse events or any indication of varying quality of RIG should be monitored and reported.
- The treating physician should be prepared to manage any adverse events / anaphylaxis which is rare, could occur during any stage of administration, even when the skin sensitivity test is negative.
- However, manufacturers of ERIG still recommend performing a skin test and some have left to the discretion of the treating physician.

Skin Sensitivity Testing (SST) & Interpretation

The national drug law mandates a compulsory skin test to check for hypersensitivity before the full dose administration of ERIG.

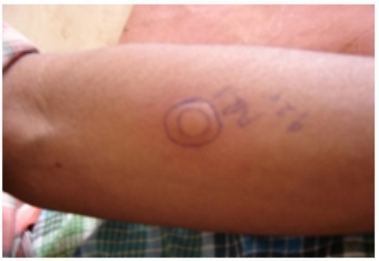
The skin test acts as a window, which helps us to identify the possible immunological response that will be mounted by the immune system of an individual to an allergen. But the skin testing may detect the rare case of IgE mediated (type I) hypersensitivity to equine serum protein. However, majority of reactions to ERIG results from complement activation and are not IgE mediated and hence, will not be predicted by skin testing.

RIGs should be given in a hospital facility under competent hands and close medical supervision. Normally, one should follow the guidelines given in the package insert, which accompanies every vial of ERIG in the box. However, the general guidelines are as follows:

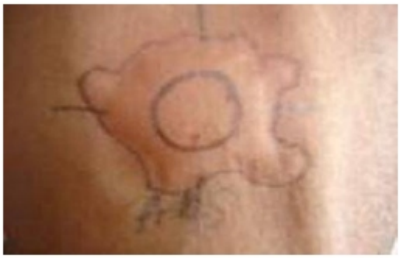
- Let the patient be in a sitting position.
- Record baseline pulse, blood pressure and respiratory rate of the patient.
- Draw 0.1 ml (4 units) of sterile normal saline into an insulin syringe (26 G needle) and inject it intradermally into flexor aspect of right forearm. This will raise a bleb/swelling of about 4-5 mm (control injection).
- Take 0.1 ml of ERIG in another insulin syringe (26 G needle) and draw 0.9 ml of sterile normal saline into the same syringe and gently rotate and mix it in syringe. Inject 0.1 ml of this 1:10 dilution of ERIG intradermally into the flexor aspect of left forearm raising a bleb/swelling of about 4-5 mm size (ERIG test dose).
- Keep a constant watch on the pulse, blood pressure and respiratory rate of the patient for the next 30 minutes and observe for any local or systemic reactions.

Interpretation

- The skin sensitivity test (SST) is considered positive, if there is erythema & induration of >10 mm in the left forearm (ERIG test dose) with or without any systemic reaction (any increase or abrupt fall in blood pressure, syncope, hurried/ difficult breathing, palpitation, etc) and the control right forearm showing no such local dermal reaction.



Induration & erythema



Induration, erythema with pseudopodia

- The skin sensitivity test (SST) is considered negative, when there is no reaction in both the forearms. A negative SST must never be considered as a guarantee that anaphylactic reaction will not occur subsequently.

How to manage cases that are SST positive

Generally, if there is reaction and the skin test is positive, we have to switch over to either HRIG or RMAb depending on their availability and affordability. This may not be possible in all situations.

Therefore, in mild reaction with erythema and induration, Inj. Pheneramine Maleate (0.8 mg/kg) and Inj. Ranitidine (1-2 mg/kg) can be given as pre-medication and later full dose of ERIG can be infiltrated into and around the wounds. In cases of skin test positivity with erythema and induration with pseudopodia, Inj. Hydrocortisone hemisuccinate (1-2 mg/kg) has to be administered along with the above drugs as pre-

medication, Inj. Deriphyllin (0.5 mg/kg), oxygen cylinder and intra venous fluids should be kept ready & used if needed.

In general, those administering ERIG should always be ready to treat anaphylactic reactions early with Inj. Adrenaline with the dose of 0.5 mL of 0.1 % solution (1 in 1000, 1mg/mL) for adults and 0.05 ml/kg body weight for children injected subcutaneous.

Adverse reactions to ERIG

Unlike the rabies sera used previously, the currently available ERIGs are highly purified products. Hence, incidence of anaphylactic reaction is rare and none has died of anaphylaxis following ERIG. The common adverse events are pain & swelling at the site of injection, erythema and serum sickness like reactions may occur in about 1 to 2 % subjects after six days of full dose ERIG administration. The clinical manifestations of serum sickness are fever, pruritus, rash, urticaria, erythema, lymphadenopathy and arthralgia. This can be treated with non-steroidal anti-inflammatory drugs (NSAIDS) and antihistamines.

Limitations of RIGs

HRIG

- Supply and use of HRIG is limited to high income countries
- Imported and high cost, limited production
- Finding human donors is becoming difficult.

ERIG

- Supply and use of ERIG is limited to low income rabies endemic countries.
- Production is also fraught with many difficulties including animal welfare issues.
- There is general reluctance on the part of the medical professionals citing unfoundedsafety concerns; and to inject locally into wounds, that is cumbersome and time consuming.

APCRI recommends establishing specialty antirabies clinics (ARCs) in government facilities and provide free of cost equine rabies immunoglobulin along with intradermal rabies vaccination. This meets the need of the poor who constitute the majority of rabies exposed individuals in the country. This will go a long way in achieving the goal of dog mediated human rabies free India by 2030.

6.4 Rabies monoclonal antibodies (RMAb)

A monoclonal antibody (MAb) is made by cloning a unique white blood cell. All subsequent antibodies derived this way trace back to a unique parent cell. Monoclonal antibodies can have monovalent affinity, binding only to the same epitope i.e. the part of an antigen that is recognized by the antibody.

Rabies monoclonal antibodies (RMAbs) capable of neutralizing a diverse range of rabies isolates offer a solution to address the cost, supply and safety issues associated with blood derived RIGs consisting of both ERIG and HRIG. The ultimate goal is to make a safe and effective product which can be used broadly and should be available at the lowest possible and reasonable price to the public sector of developing countries. RMAb has also been shown to have neutralization ability to a broad panel of globally prevalent rabies virus isolates. Clearly, they have major advantages over RIG in that, they can be produced using large-scale molecular technology and eliminate the use of animals for production purposes as well as can reduce the inadvertent risk of transferring viruses and other infections in the plasma from human donors.

WHO has recommended the use of RMAb cocktails containing at least two antibodies against RABV, as alternatives to RIGs in PEP. It should be recommended for use in public health programmes, depending on the epidemiological and geographical setting, with monitoring of its safety and efficacy

(clinical outcomes) during post-marketing use. WHO recommends that a registry be maintained to monitor clinical use and outcomes of RMAb products.

Advantages of RMAbs

- Rapid industrial production capability with consistent quality of RMAb is a greater advantage to meet a global demand.
- As monoclonal antibodies come in the form of a concentrated product, they can be more useful and effective than RIGs for infiltration into and around the wounds
- RMAb is much cheaper than HRIG.
- If the production of RMAb is scaled up, based on the demand, it may be available at a much lesser price
- Development of RMAb in lyophilized forms will allow long term storage as well as convenience of supply to rural areas
- RMAb could offer an equally efficacious, affordable, accessible, more standardized and safer alternative to plasma derived RIGs

Several RMAbs have been tested against rabies; presently two of them are available in the market and both are manufactured in India.

6.4.1. Single rabies monoclonal antibody (RMAb)

The first rabies monoclonal antibody was manufactured by Serum Institute of India, Pune; licensed and marketed from 2017 as 'Rabishield'.

The pre-clinical and clinical data was reviewed by independent experts and shows that, this RMAb neutralizes a broad panel of globally prevalent rabies virus isolates and has shown equivalent response to HRIG in a hamster challenge

model and the PEP regimen consisting of this RMAb, mounts rabies neutralizing activity to a level that is similar with PEP containing HRIG in patients with Category III exposure. Studies so far show the equivalence of its performance to HRIG.

Rabishield

- Broadly neutralizing monoclonal antibody 17C7 was generated by transgenic mice that express human immunoglobulin genes
- Single human IgG1 type RMAb that binds to a conformational epitope of rabies glycoprotein
- Product was found to be safe and demonstrated non-inferiority to HRIG
- The WHO - SAGE also noted that this product would serve as an important learning process for future RMAb products
- WHO formal position paper on rabies vaccines now includes recommendations for the use of monoclonal antibody products in PEP
- The recommended dose of Single rabies monoclonal antibody is 3.33 IU/kg.
- When compared to HRIG, for a person weighing 75 kg, the cost of Rabishield is about 20% of the cost of HRIG
- Available in the form of 2 preparations: 2.5 ml vial (100 IU) and 1.25 ml vial (50 IU).
- Production capacity: 5 million vials per year.
- Since licensure (> 4 years) more than 400,000 vials of Rabishield have been distributed in the market and no safety concerns have been reported. No cases of PEP failure have been reported in the PMS, Phase IV study or during the post marketing experience.

6.4.2 Cocktail rabies monoclonal antibodies (RMAbs)

'Twinrab' is the first 'cocktail' RMAb containing Docaravimab and Miromavimab that is produced by Zydus Cadila. It was licensed in 2019 and marketed from 2020 in India. It combines two murine MAbs which bind to different epitopes on the rabies glycoprotein. Because G protein of rabies virus (RABV) is prone to high level of diversity in nature, cocktail of MAb can broadly neutralise the virus. WHO has recommended use of RMAb cocktails containing at least two antibodies against RABV, as alternatives for RIGs in PEP.

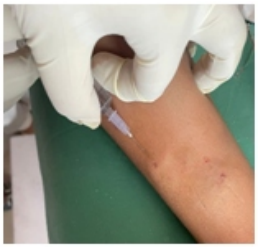
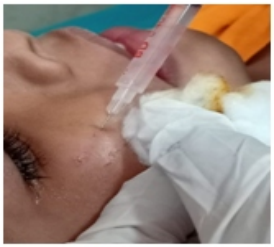
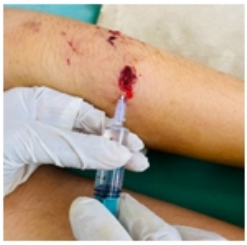
The RMAbs were donated from two WHO Collaborating Centres for Rabies, i.e., Animal Diseases Research Institute, Canada (RMAb: M777-16-3) and the Centres of Disease Control and Prevention, USA (RMAb:62-71-3). WHO transferred the technology to Zydus Cadila under a material transport agreement (MTA) which includes a commitment from the manufacturer to sell any resulting product at affordable prices to the public sector of developing countries.

Twinrab

- Twinrab was found to be a safe and effective alternative to HRIG.
- The recommended dose of 'Twinrab' is 40 IU/kg
- When compared to HRIG, for a person weighing 75 kg, the cost of Twinrab is about 20% of the cost of HRIG
- Available in the form of 2 preparations: 2.5 ml vial (1500 IU) and 1 ml vial (600 IU).
- Production capacity: 1 million vials per year.
- The post marketing surveillance (PMS) to monitor clinical use and outcomes of Twinrab is planned in the country.
- Since licensure (>1½ years) more than 25,000 vials of Twinrab have been distributed in the market and no safety concerns have been reported. No cases of PEP failure have been reported in the post marketing experience.

6. 5. Mode of administration of full dose of RIG/ RMAb

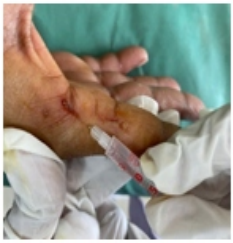
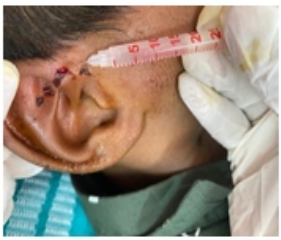
The entire dose of RIG/RMAb, or as much as anatomically possible should be infiltrated carefully into or as close as possible to the wound(s) or exposure sites.

WHO no longer recommends injecting the remainder of the calculated RIG/RMAb dose intramuscularly at a distance from the wound. Evidence suggests that injecting the remaining RIG volume intramuscularly at a distance from the wound provides no or little additional protection against rabies as compared with infiltration of the wound alone.

All wounds, however small, should be identified and infiltrated with RIG/RMAb, so as to neutralize the virus locally. This is particularly important in small children who may not show all the exposed / scratched/ bite marks on their body surface. No wound should be missed for RIG/RMAb administration. The maximum volume to be infiltrated is calculated for the body weight of the exposed victim. The RIG/ RMAb shall be injected into the edges and base of the wound/s till traces of RIG/ RMAb oozes out.

In small wounds, the maximal quantity that is anatomically feasible should be injected. It is important to avoid the compartment syndrome which occurs if large volumes of RIG are injected into a small body area with limited tissue. Bites on the tips of the fingers or toes, ear lobes, nasal area, lips or external genitalia can be safely injected with RIG, provided excessive pressure is avoided, as this can cause compression or compartment syndrome.


For large and multiple wounds, RIG can be diluted if necessary, with sterile normal saline to ensure thorough infiltration of all wounds and not exceeding the maximum permissible dose.

This Video link provides a guide to infiltration of RIG/ RMAb: https://www.youtube.com/watch?v=BZKVAn_0Yew

Points to Note:

- RIG/ RMAb should never be administered in the same syringe or at the same anatomical site where vaccine was administered.
- RIG/ RMAb after removing from the refrigerator should be brought to room temperature before injecting it
- In case of likelihood of additional small wounds (e.g. if a child does not report all wounds), injection of the remaining RIG/ RMAb volume intramuscularly as close as possible to the presumed exposure site, to the degree that is anatomically feasible, is indicated.
- The same applies to mucosal exposure with no wound, and rinsing with RIG/ RMAb is recommended.
- In case of contamination of eyes with saliva as aerosol or otherwise of a rabid animal, RIG /RMAb shall be applied as drops into the eyes in quantity that is just sufficient to flush the eyes.
- In the case of suspected exposure to RABV via aerosols like following exposure to bats in caves, the intramuscular injection of RIG/RMAb is still recommended

- It is strongly recommended that private institutions and physicians who provide services for a fee shall strictly comply with the guideline that is provided in the package / product–insert/leaflet as the information contained therein has the approval of the regulatory authority i.e. Drugs Controller General of India (DCGI). Following any deviation and resultant adverse event may invite litigation and demand for compensation under consumer protection act.

7. Managing special situations of rabies exposures

Pregnancy & lactating women: Vaccines and RIGs are safe & efficacious (The safety and efficacy of RMAbs has to be studied in due course). The dosage & schedule remain same.

Interchangeability: In unavoidable/exceptional circumstances, change in route of administration or in vaccine product during a PEP/ PrEP course is safe and immunogenic. In such cases vaccination schedule need not be restarted & regimen to be continued as per the new route.

Irregular vaccination: In general, 3 doses of ARV have to be administered by 7-10 Days and 4 or 5 doses (by ID/ IM route) by day 28. There is no need to restart the vaccine, if there is delay of few days.

Late reporting (even by few weeks or months): PEP should be given as rabies has a prolonged incubation period. If patient has not taken any dose of ARV, even RIG/ RMAb should be injected to the site of bite, even though there are no bite marks seen.

Anti rabies vaccine with other COVID 19/ UIP vaccines: It can be given at a site different from COVID 19/ UIP vaccines; it is safe & will not interfere with the antibody production.

Persons consuming raw milk of rabid animals: There are no documented cases of transmission of rabies after drinking milk of rabid animal. Rabies PEP is not required.

HIV/AIDS with low CD4 count <200: Thorough wound treatment + RIG/ RMAb (Category II & III exposures) + 5 doses of vaccine by IM only. If feasible RVNA response should be determined 2-4 weeks after completion of 5 doses to assess whether additional dose of vaccine is required.

Chloroquine treatment: There is no contraindication for individuals receiving chloroquine. However, if possible, PEP/ PrEP should be completed before chloroquine is initiated.

Lastly, there is no contraindication to rabies PEP as it is lifesaving in rabies that is practically 100% fatal.

8. Conclusion

Rabies is 100% fatal once symptoms appear. Hence, early and complete PEP that includes administration of RIG or RMAb in high risk/category III exposures will prevent the disease, even after exposure to suspect or confirmed rabid animals. RIGs and RMAbs are certainly lifesaving immune-biological in all category III rabies exposures. It provides rabies virus neutralizing antibodies, i.e., passive immunity at the site of exposure that neutralizes/inactivates the rabies virus present locally and thus offers immediate protection before the patient starts producing his/her own protective levels of neutralizing antibodies following anti rabies vaccination.

9. References, suggested further readings and useful web links.

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Annexure- I

Availability of different brands for passive immunization in India

Product	Brand name	Company	Dose	Formulation	Approx. cost (INR)
HRIG	**Berirab-P**	Manufactured by CSL Behring,Germany& Marketed by BSV	20 IU/Kg body weight	2 mL pre-filled syringe containing 300 IU	6080/- per vial
	Plasmarab	Manufactured by Kamada Ltd., Israel and marketed by Plasmagen	20 IU/ Kg body weight	2 mL containing 300 IU	5750/- per vial
ERIG	**Equirab**	Bharat Serums & Vaccines Ltd. (BSV)	40 IU/Kg body weight	5 mL vial containing 1500 IU	515/- per vial
	Premirab	Premium Serums & Vaccines Ltd.	40 IU/Kg body weight	5 mL vials containing 1500 IU	550/- per vial
	VINRIG	VINS Biopharma	40 IU/Kg body weight	5 mL vial containing 1500 IU	500/- per vial
RMAb	**Rabishield**	Serum Institute of India	3.33 IU/Kg body weight	1.25 mL containing 50 IU & 2.5 mL containing 100 IU	1.25 mL 960/- ; 2.5 mL 2100/-
	Twinrab	ZydusVaxxicare	40 IU/Kg body weight	1 mL containing 600 IU & 2.5 containing 1500 IU	1 mL 1700/- ; 2.5 mL 3085/-

Annexure- II

Dosage chart for passive immunization

Body weight (in Kgs)	ERIG (Volume in mL)	HRIG (Volume in mL)	Single RMAb (Volume in mL)	Cocktail RMAb Volume in mL	*Body weight (in Kgs)*	ERIG (Volume in mL)	HRIG (Volume in mL)	Single RMAb (Volume in mL)	Cocktail RMAb (Volume in mL)
2	0.3	0.3	0.2	0.1	***51***	6.8	6.8	4.2	3.4
3	0.4	0.4	0.2	0.2	***52***	6.9	6.9	4.3	3.5
4	0.5	0.5	0.3	0.3	***53***	7.1	7.1	4.4	3.5
5	0.7	0.7	0.4	0.3	***54***	7.2	7.2	4.5	3.6
6	0.8	0.8	0.5	0.4	***55***	7.3	7.3	4.6	3.7
7	0.9	0.9	0.6	0.5	***56***	7.5	7.5	4.7	3.7
8	1.1	1.1	0.7	0.5	***57***	7.6	7.6	4.7	3.8
9	1.2	1.2	0.7	0.6	***58***	7.7	7.7	4.8	3.9
10	1.3	1.3	0.8	0.7	***59***	7.9	7.9	4.9	3.9
11	1.5	1.5	0.9	0.7	***60***	8.0	8.0	5.0	4.0
12	1.6	1.6	1.0	0.8	***61***	8.1	8.1	5.1	4.1
13	1.7	1.7	1.1	0.9	***62***	8.3	8.3	5.2	4.1
14	1.9	1.9	1.2	0.9	***63***	8.4	8.4	5.2	4.2
15	2.0	2.0	1.2	1.0	***64***	8.5	8.5	5.3	4.3
16	2.1	2.1	1.3	1.1	***65***	8.7	8.7	5.4	4.3
17	2.3	2.3	1.4	1.1	***66***	8.8	8.8	5.5	4.4
18	2.4	2.4	1.5	1.2	***67***	8.9	8.9	5.6	4.5
19	2.5	2.5	1.6	1.3	***68***	9.1	9.1	5.7	4.5
20	2.7	2.7	1.7	1.3	***69***	9.2	9.2	5.7	4.6
21	2.8	2.8	1.7	1.4	***70***	9.3	9.3	5.8	4.7
22	2.9	2.9	1.8	1.5	***71***	9.5	9.5	5.9	4.7
23	3.1	3.1	1.9	1.5	***72***	9.6	9.6	6.0	4.8
24	3.2	3.2	2.0	1.6	***73***	9.7	9.7	6.1	4.9
25	3.3	3.3	2.1	1.7	***74***	9.9	9.9	6.2	4.9
26	3.5	3.5	2.2	1.7	***75***	10.0	10.0	6.2	5.0
27	3.6	3.6	2.2	1.8	***76***	10.1	10.1	6.3	5.1
28	3.7	3.7	2.3	1.9	***77***	10.3	10.3	6.4	5.1
29	3.9	3.9	2.4	1.9	***78***	10.4	10.4	6.5	5.2
30	4.0	4.0	2.5	2.0	***79***	10.5	10.5	6.6	5.3
31	4.1	4.1	2.6	2.1	***80***	10.6	10.6	6.7	5.3
32	4.3	4.3	2.7	2.1	***81***	10.8	10.8	6.7	5.4
33	4.4	4.4	2.7	2.2	***82***	10.9	10.9	6.8	5.5
34	4.5	4.5	2.8	2.3	***83***	11.0	11.0	6.9	5.5
35	4.7	4.7	2.9	2.3	***84***	11.2	11.2	7.0	5.6
36	4.8	4.8	3.0	2.4	***85***	11.3	11.3	7.1	5.7
37	4.9	4.9	3.1	2.5	***86***	11.5	11.5	7.2	5.7
38	5.1	5.1	3.2	2.5	***87***	11.6	11.6	7.2	5.8
39	5.2	5.2	3.2	2.6	***88***	11.7	11.7	7.3	5.9
40	5.3	5.3	3.3	2.7	***89***	11.9	11.9	7.4	5.9
41	5.5	5.5	3.4	2.7	***90***	12.0	12.0	7.5	6.0
42	5.6	5.6	3.5	2.8	***91***	12.1	12.1	7.6	6.0
43	5.7	5.7	3.6	2.9	***92***	12.3	12.3	7.7	6.1
44	5.9	5.9	3.7	2.9	***93***	12.4	12.4	7.7	6.2
45	6.0	6.0	3.7	3.0	***94***	12.5	12.5	7.8	6.3
46	6.1	6.1	3.8	3.1	***95***	12.7	12.7	7.9	6.3
47	6.3	6.3	3.9	3.1	***96***	12.8	12.8	8.0	6.4
48	6.4	6.4	4.0	3.2	***97***	13.0	13.0	8.1	6.5
49	6.5	6.5	4.1	3.3	***98***	13.1	13.1	8.2	6.5
50	6.7	6.7	4.2	3.3	***99***	13.2	13.2	8.2	6.6
					100	13.3	13.3	8.3	6.7

Annexure- III

List of participants in Expert Consultation meeting held at Nagpur, Maharashtra on 27th March, 2022

1 Dr. M. K. Sudarshan, Founder President & Mentor, APCRI, Bangalore: Chairperson

2 Dr.(Mrs) Simmi Tiwari, Joint Director & Head, Division of Zoonotic Diseases Programme (DZDP), NCDC, Delhi: Co-Chairperson

3 Dr. (Mrs) Monil Singhai, Joint Director & Section In charge, Center for Arboviral & Zoonotic Diseases, National Center for Disease Control (NCDC), Delhi

4 Dr. Tushar N. Nale, Deputy Director, Division of Zoonotic Diseases Programme (DZDP), NCDC, Delhi.

5 Dr. Reeta S. Mani, Professor, Department of Neurovirology, NIMHANS, Bengaluru

6 Dr. Ashwin Belludi, Assistant Professor, Department of Neurovirology, NIMHANS, Bengaluru

7 Dr. (Mrs) Ashwini, Senior Scientific Officer, Dept. of Neurovirology, NIMHANS, Bengaluru

8 Dr. Navaneeth S Krishna, Scientist-B, National Institute of Epidemiology (NIE), Indian Council of Medial Research (ICMR), Chennai

9 Dr. Jugal Kishore, Director, Professor & Head of Department of Community Medicine, VMMC & Safdarjung Hospital (Ministry of Health & Family Welfare), New Delhi

10 Dr. Muralidhar Thambe, Deputy Dean & Professor of Community Medicine, B.J.Government Medical College, Pune

11 Dr. Thomas Mathew, Joint Director (Medical), Directorate of Medical Education, Thiruvananthapuram, Kerala

12 Dr. D. H. Ashwath Narayana, President, APCRI, Bengaluru

13 Dr. Durga Madhab Satapathy, Vice-President, APCRI, Berhampur, Odisha
14 Dr. Sumit Poddar, Secretary General, APCRI, Kolkata
15 Dr. H. S. Ravish, Treasurer, APCRI, Bengaluru
16 Dr. K. K Singh, Joint Secretary, APCRI, Ranchi
17 Dr. Omesh Kumar Bharti, North Zone Representative, APCRI, Shimla
18 Dr. Hemanth Gohil, North Zone Representative, APCRI, New Delhi
19 Dr. Govardhan Meena, West Zone Representative, Jaipur
20 Dr. M. N. Siddiqui, Central Zone Representative, Lucknow
21 Dr Ashok Jadhao, Professor and Head, Dept. of Community Medicine, Indira Gandhi Government Medical College, Nagpur
22 Dr Prashant Bagdey, Associate Professor of Community Medicine, Indira Gandhi Government Medical College, Nagpur
23 Dr. Narendra Patil, CSL Behring, Singapore
24 Dr. Anand Lakhkar, Serum Institute of India, Pvt.Ltd.
25 Dr. Anirudha Potey, Serum Institute of India, Pvt.Ltd.
26 Mr. Nitin Jain, Zydus Vaxxicare
27 Mr. Anand Verma, Zydus Vaxxicare
28 Mr. Snehit Joshi, Zydus Vaxxicare
29 Ms. Neeta Joshi, Zydus Vaxxicare
30 Dr. Saswata Banerjee, Bharat Serums and Vaccines Ltd.
31 Dr. Badal Suthar, Bharat Serums and Vaccines Ltd.
32 Dr. M.V. Khadilkar, Premium Serums and Vaccines Pvt. Ltd.
33 Dr. V.B. Sovani, Premium Serums and Vaccines Pvt. Ltd.
34 Mr. Ravindra Tripathi, Premium Serums and Vaccines Pvt. Ltd.
36 Mr. Nikhil Sharma, VINS Bioproducts
37 Dr. Ashok Agarwal, Cadila Pharmaceuticals
38 Mr. Amit Jain, Vice President, Cadila Pharmaceuticals

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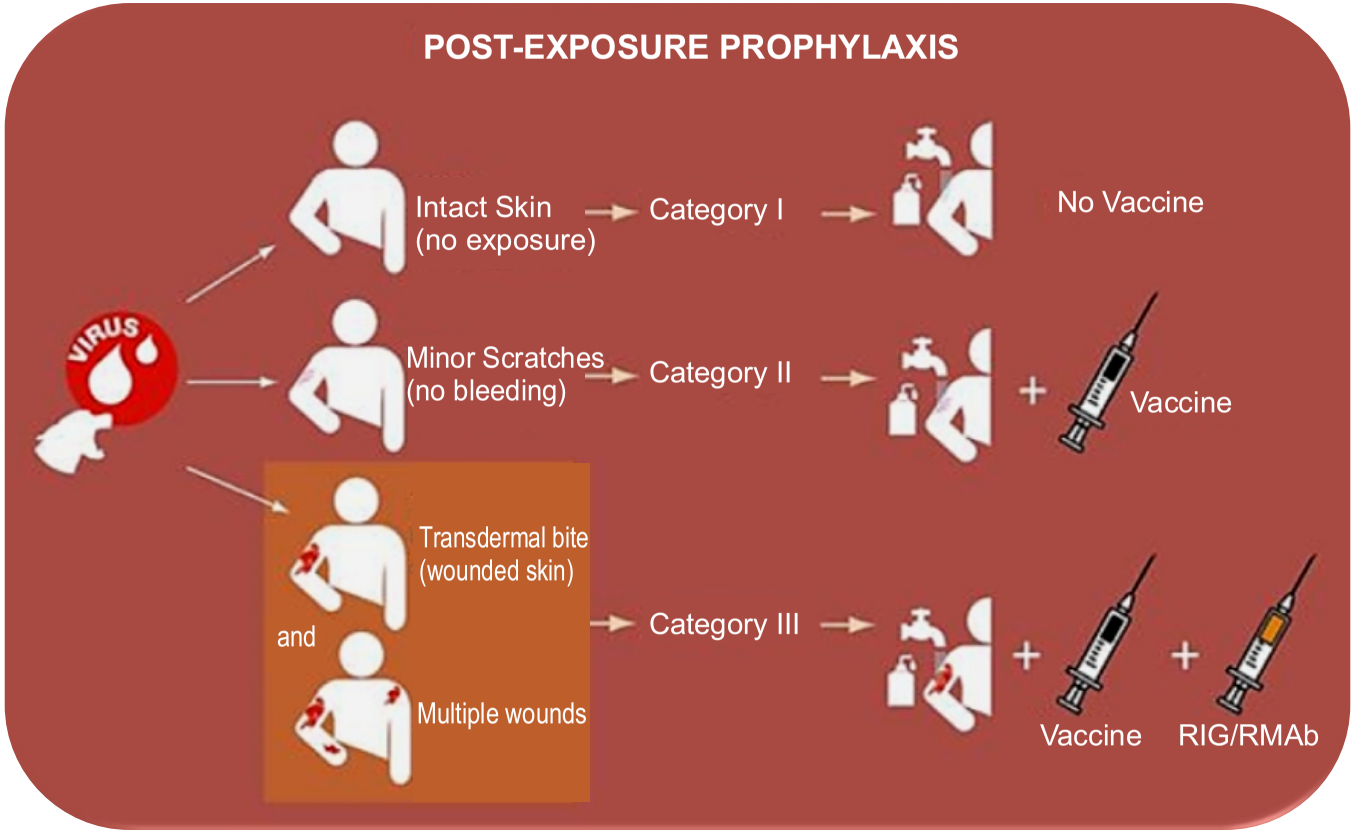
POST-EXPOSURE PROPHYLAXIS
VIRUS
Intact Skin
(no exposure)
Category I
No Vaccine
Minor Scratches
(no bleeding)
Category II
Vaccine
Transdermal bite
(wounded skin)
and
Multiple wounds
Category III
Vaccine
RIG/RMAb

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