

National Guideline of Rabies Prophylaxis-2010

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Introduction:

Rabies, a dreadful zoonotic disease caused by bullet shaped lyssa (rabies virus) with horrifying symptoms which is 100% fatal but 100% preventable¹. The disease is transmitted from animal to animal or from animal to human. Human infection by rabies virus usually occurs as a result of a transdermal bite or scratch from an infected wild or domestic animal.^{2,3} Other modes of transmission from animals to humans are possible, for example, when infectious material such as saliva from a rabid animal comes into contact with a victim's mucous membranes (mouth, nose, eyes) or fresh skin lesions. Transmission has also been reported to have occurred through inhalation of virus-containing aerosols. In addition, man-to-man transmission through transplantation of tissue and transmission through a bite or kiss have also been reported.² Worldwide the number of deaths annually, due to rabies, is estimated to be between 35,000 to 50,000 approximately³. It is estimated more than 2000 people die of Rabies in Bangladesh and more than 100,000 persons take post-exposure treatment⁴. But the exact magnitude of problem is much more as the surveillance system is not standard in our country. According to WHO, 1550 people die of rabies and about 100,000 people is getting post-exposure treatment (PET) each year, more than thirty thousand animals are given post exposure anti rabies vaccine (According to vaccine supply^{5,6}). The number of post exposure treatment with vaccine is increasing in human and animal every year. The Nervous Tissue Vaccine (NTV) was the mainstay for post-exposure prophylaxis in Bangladesh. The country is producing phenolised sheep brain vaccine (NTV) and consuming a large amount of vaccine. As per WHO recommendations, the production and use of this reactogenic vaccine should be gradually phased out from our country. Most of the countries have already discontinued to use NTV⁶. But in Bangladesh no attempt has yet been taken previously to discontinue this unsafe and low potent vaccine. NTV is supply with subsidized rate but yet it is not sufficiently available. So, the poorest of the poor sometimes failed to get that treatment also. Modern, safe and effective anti-rabies Cell Culture Vaccines (CCVs) is recommended by WHO to be used in most of the countries in the world having rabies as endemic disease. Communicable disease control(CDC) of, Directorate General of Health Services (DGHS) took the noble initiative to establish the national rabies elimination programme 2010 with a comprehensive approach of care for human and control of rabid animal. An expert group was formed to prepare the national guideline

for post exposure prophylaxis for rabies for uniform and effective treatment protocol. It is sincerely hoped that the guideline will be of immense use for better management of animal bite cases and availability and affordability of modern rabies vaccine for all through introduction of cost-effective multisite Intradermal (ID) schedule for post-exposure rabies prophylaxis.

Materials and Methods:

An expert group was formed by CDC of DGHS, Mohakhali, Dhaka to formulate the guideline. The participants in the group included expertise on rabies management, practitioners managing anti-rabies clinic, laboratory medicine practitioners, policy makers, public health experts from both public and private sector. Repeated brainstorming meetings were done by the expert groups. Extensive literature was searched through Pubmed and Other search engine (e.g-google) to accommodate the materials. The expertise from different countries (Thailand, Srilanka, India, philipines etc) were also helped through online for formulating the nation based papers. All WHO papers on rabies were critically appraised and recent recommendation from international seminar, symposium (e.g-Bali Recommendation, Jan 2010) were also keep before making final recommendation for national guideline. Extended meeting in abroad (In Thailand) with expertise were also done before drafting the national guideline. Considering the recommendations of experts, results of clinical trials and international experience, experts of Bangladesh recommends this national guideline. The draft paper was critically appraised in different meeting and also presented in front of the National Technical Working Group(NTWG) of Rabies control programme,2010. The final recommendation was done in final meeting of Rabies control programme in IEDCR, Dhaka in June,2010. The final copy is endorsed by the Ministry of Health, Bangladesh to be used for Health care providers of Bangladesh.

Results and Discussion:

In rabies endemic country like Bangladesh, where animal rabies control programme is non-existent, every animal bite is potentially suspected as a rabid animal bite. Hence the management should be immediate, complete and comprehensive. Because of long incubation period, it is possible to institute post-exposure prophylaxis (PEP).WHO has given guide to PEP management for endemic countries⁸. To bring out uniformity globally, the classification of animal bite for post-exposure prophylaxis has been based on WHO recommendations(Table 1).

Table-I
Type of contact, exposure and recommended post-exposure prophylaxis⁸

Category	Type of contact	Recommended treatment
I	Touching or feeding of animals Licks on intact skin	None, if reliable case history is available
II	Nibbling of uncovered skin Minor scratches or abrasions without bleeding.	Anti-Rabies vaccine Wound Management
III (Fig 1)	Single or multiple transdermal bites Or scratches, licks or broken skin Contamination of mucous membrane with saliva (i.e. licks). Exposure to bats **	Administer rabies immunoglobulin and Administer Anti-Rabies vaccine immediately Wound Management

Source: WHO.Department of Neglected Tropical Diseases – Neglected Zoonotic Diseases team (revised 30 June 2009)

* Stop treatment if dogs or cats remain healthy throughout an observation period of 10 days or if animal is euthanized and found to be negative for rabies by appropriate laboratory techniques.

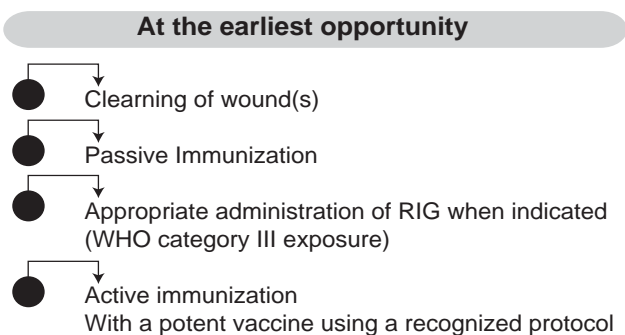
** Post exposure prophylaxis should be considered when contact between a human and a bat occurred unless the exposed person can rule out a bite or scratch, or exposure to mucous membrane.

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



Fig 1: CAT III injury at different region with variability

Management of Animal bite: 3 major steps in PEP



Management of animal bite wound (Table-II):

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 as is possible by an efficient wound toilet that should not involve additional trauma. Since the rabies virus can persist and even multiply at the site of bite for a long time, wound toilet must be performed even if the patient reports late^{9,10}.

Table-II
Wound Management

Do's		
Physical	Wash with running tap water or speedy running water	Mechanical removal of virus from the wound
Chemical	Wash the wound with soap and water. Apply disinfectant	Inactivation of the virus
Biological	Infiltrate immunoglobulins (HRIG/ ERIG) in the depth and around the wound in Category III exposures	Neutralization of the virus
Don'ts		
<ul style="list-style-type: none"> • Touch the wound with bare hand • Apply irritants like soil, chillies, oil, herbs, chalk, betel leaves etc. 		

Rabies Immunoglobulins (RIG):

The anti-rabies serum/rabies immunoglobulin provides passive immunity in the form of ready-made anti-rabies antibody to tide over the initial phase of the infection. Anti-rabies serum or RIG has the property of binding with the rabies virus, thereby resulting in the loss of infectivity of the virus. Two types of RIGs are available and recommended to use: a. Equine Rabies Immunoglobulins (ERIG) and b. Human Rabies Immunoglobulins (HRIG).

Dose of rabies immunoglobulins:

Equine rabies immunoglobulins(ERIG):**40 IU per kg** body weight upto a maximum of 3000 IU. Human rabies immunoglobulins (HRIG): **20 IU per kg** body weight (maximum 1500IU).

Indication of RIG and importance:¹¹

- All category III exposures, irrespective of status of biting animal.
- Administer even when treatment is delayed but RIGs should not be given after 7 days of start of vaccination (3rd dose ARV administered)
- Immunoglobulins (HRIG /ERIG) are life saving when timely used.
- There is no substitute for RIG and all other options are inferior.

Administration of RIG:

As much of the calculated dose of RIG as is anatomically feasible should be infiltrated into and around the wounds (site of bite). Multiple needle injections into the wound should be avoided. Remaining, if any, after all wounds have been infiltrated, should be administered by deep intramuscular injection at an injection site distant from the vaccine injection site. Immunoglobulin should never be administered in the same syringe or at the same anatomical site. All emergency drugs and facilities for managing any adverse reactions must be available. RIG should be administered before starting anti-rabies vaccination. RIG should not be administered in the same syringe(**fig 3**) as the vaccine or at the same site as vaccine. While infiltrating RIG into bite wounds, care must be taken to avoid injecting into blood vessels and nerves. Anatomical feasibility must always be kept in mind while injecting RIG. While injecting into finger tips, care must be taken to avoid compartment syndrome. In small children with multiple bites, if the volume is insufficient for infiltration in and around all wounds, dilute RIG with sterile N. saline up to double or 3 times. Pregnancy is not a contra-indicated for RIG and anti-rabies vaccination when indicated. Keep the patient under observation for at least one hour after ERIG administration and send home. The treating physician should

be prepared to manage anaphylaxis which could occur at any stage of administration of ERIG irrespective of the outcome of the skin sensitivity test.

Sensitivity test before administration of ERIG^{11,12}:

ERIG must be administered only after the Test dose.

Test dose (ERIG) : Follow the Manufacturer Guidelines or Inject 0.1 ml of 1:10 dilution of the ERIG in normal saline, Intra Dermally over flexor aspect of forearm. A negative skin test must never reassure the physician that no anaphylactic reaction will occur.

Observe for : Wheal, Erythema, Induration, Itching, Tachycardia, Fall in Blood Pressure, Feeble Pulse.

Positive test reaction (Fig 2)

- Ø Induration >10mm with or without constitutional symptoms.
- Ø If skin test is positive – HRIG is preferred (affordability, availability)
- Ø If ERIG has to be administered then pre treat with Adrenaline / Epinephrine and with Antihistamine before administering full dose.



Fig.-2: Positive reaction of RIG test dose.

Management if anaphylactic reaction occurs:

1. Adrenaline: The dose is 0.5 ml of 0.1 percent solution (1 in 1000, 1mg/ml) for adults and 0.01 ml/kg body weight for children, injected intramuscularly(IM).
2. Inj Hydrocortisone: 100 mg stat and 6 hourly
3. Inj Chlorpheniramine :
4. Inj Ranitidine

RIG Infiltration:**Fig.-3:** RIG Infiltration around wound**Active Immunization:****Rabies Biologicals:**

Rabies vaccines induce an active immune response that includes the production of virus neutralizing antibodies. The active antibody response requires approximately 7—10 days to develop, and detectable rabies virus neutralizing antibodies generally persist for several years.

- Two types of vaccines to protect against rabies in humans exist –

Nerve Tissue Vaccine (NTV): are prepared from rabid sheep, goat (Semple vaccines in Asia) or suckling mouse brains (Fuenzalida Palacios vaccine in South America) by phenol-inactivation. It is to be phased out gradually from Bangladesh and there is no recommendation by WHO to use it due to its low efficacy and high side effects.

Cell Culture Vaccines (CCV) : is made of inactivated virus grown in cell cultures, human diploid fibroblasts (HDCV, fetal rhesus cells (Bioport), primary Syrian hamster kidney cells (PHKCV), chick embryo cells (PCECV) and Vero cells (PVRV)

Anti-Rabies Vaccines:^{8,9,11,12}

Active immunization is achieved by administration of safe and potent CCVs. In Bangladesh, NTV is still used for post-exposure treatment in public sector. However, as this vaccine is reactogenic, the production will be stopped soon. Privately, CCVs are now used for active immunization. Very soon CCV will be available in public sector too.

Indications: All age groups of animal bite victims of Category II and III require the same number of injections and dose per injection. The Category III exposures, in addition require administration of rabies immunoglobulins as discussed earlier.

Storage and transportation: Though most Cell Culture Vaccines are marketed in freeze dried (lyophilised) form which is more tolerant of vagaries of temperature, yet it is recommended that these vaccines should be kept and

transported at a temperature range of 2-8°C. Freezing does not damage the lyophilised vaccine but there are chances of breakage of ampoule containing the diluent.

Liquid vaccines of nerve tissue or cell culture origin should never be frozen. Reconstitution and storage: The lyophilised vaccine should be reconstituted with the diluent provided with the vaccine immediately prior to use. However, in case of unforeseen delay it should not be used after 6-8 hours of reconstitution.

Precaution: Immunosuppression like Corticosteroids, other immunosuppressive agents, antimalarials, and immunosuppressive illnesses can interfere with the development of active immunity after vaccination. immunosuppressed persons who are at risk for rabies should have their virus neutralizing antibody titers checked after completing the pre-exposure. Pregnancy is not considered a contraindication to postexposure prophylaxis. If the risk for exposure to rabies is substantial, pre-exposure prophylaxis also might be indicated during pregnancy. Persons who have a history of serious hypersensitivity to components of rabies vaccine or to other vaccines with components that are also present in rabies vaccine should be revaccinated with caution

Protective level of anti-rabies antibody:

Humoral antibodies play important role in protection against rabies and a titre of 0.5 IU/ml or more in serum as tested by Rapid Fluorescent Focus Inhibition Test (RFFIT) is considered as protective. Currently available CCVs could be administered by IM regimen or approved CCVs could be administered by ID regimen

Intra-muscular (IM) Regimen

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

Vaccines: Cell Culture Vaccines

- Purified Vero Cell Rabies Vaccine (PVRV)
- Purified Chick Embryo Cell Vaccine (PCEC)

Regimen (fig 4)Zagreb schedule:

Four doses/Three visits (2-1-1) intramuscular regimen (D0, D7, D21)

In the abbreviated multisite schedule, the 2-1-1 regimen, one dose is given in the right arm and one dose in the left arm at day 0, and one dose applied in the deltoid muscle on days 7 and 21. The 2-1-1 schedule induces an early antibody response and may be particularly effective when post-exposure treatment does not include administration of rabies immunoglobulin.

Because of the less doses to be used in 3 visits with similar efficacy, Government of Bangladesh has chosen the Zagreb schedule (2-1-1) for post-exposure rabies prophylaxis in Bangladesh

Essen schedule:

Five doses/ Five visits (1-1-1-1-1) intramuscular regimen (D0, D3, D7, D14, D28)

Five doses/ Five Visits intramuscular regimen - The course for post-exposure prophylaxis should consist of intramuscular administration of five doses of CCV on days 0, 3, 7, 14 and 28 (D0, D3, D7, D14 and D28). The sixth injection (D90) should be considered as optional and should be given to those individuals who are immunologically deficient, are at the extremes of age and on steroid therapy. Day 0 (D0) indicates date of first injection not necessarily day of bite. In Bangladesh Essen schedule is recommended only for those who are immunosuppressed (including pregnancy) with Category II and III injury.

Intramuscular (IM) schedules (WHO Recommendations):

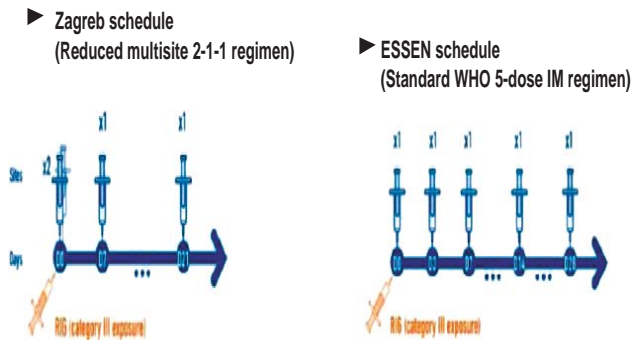


Fig.-4: Intramuscular Zagreb and Essen schedule

Intra-dermal (ID) Regimens:^{12,13}

Intradermal regimens consist of administration of a fraction of intramuscular dose of certain Cell

Culture rabies vaccine on multiple sites in the layers of dermis of 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 terms of total amount of vaccine needed for full pre- or post- exposure vaccination, thereby reducing the cost of active immunisation. While using ID route, small amount (0.1ml) of rabies vaccines/antigen is deposited in the layers of the skin at multiple sites. The antigen is directly presented to the antigen presenting cells (with out circulation/dilution in blood) at multiple sites triggering a stronger immune response. Intra-dermal injections must be administered by staff trained in this technique. Vaccine vials must be stored at 2° to 8°C after reconstitution. The total content of reconstituted vial should

be used as soon as possible, but within 6 hours. All the reconstituted vaccines should be discarded after 6 hours of reconstitution and at the end of the day. Rabies vaccines formulated with an adjuvant should not be administered intra-dermally. Vaccine when given intra-dermally should raise a visible and palpable bleb in the skin. In the event that the dose is inadvertently given subcutaneously or intramuscularly or in the event of spillage, a new dose should be given intra-dermally in near by site. Only medical practitioners and health professionals who have completed short training course on application of ID schedule for rabies prophylaxis are permitted to use ID schedule.

I/D schedule is not recommended for immunocompromised patients (patients on cytotoxic drugs, on long term steroids, positive for HIV/AIDS, on anti-malarial and biologics).

Vaccines :

- Purified Vero Cell Rabies Vaccine (PVRV)
- Purified Chick Embryo Cell Vaccine (PCEC)

Potency of approved vaccines: The vaccines should have stated potency of > 2.5 IU per IM dose, irrespective of reconstituted volume. The same vaccine is used for ID administration as per stated schedule. 0.1 ml of vaccine, irrespective of reconstituted volume, is administered per ID site as per schedule below.

Regimen

Intra-dermal Rabies Vaccines, Updated Thai Red Cross Schedule (2-2-2-0-2). (Fig 5)

This involves injection of 0.1ml of reconstituted vaccine per ID site and on two such ID 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 day of first dose administration of ID RV and may not be the day of rabies exposure/animal bite.

WHO approved ID regimens for Post-Exposure Prophylaxis

Day	0	3	7	14	28
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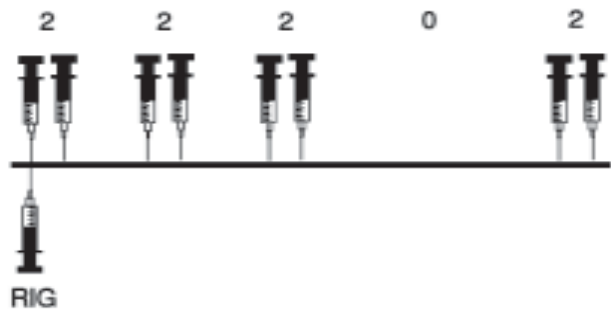


Fig.-5 – ID schedule of ARV..... Source: Thailand National Guidelines of Rabies for Year 2004. By Thai CDC Ministry of Public Health

The ID route is used in limited countries. (Only 0.1ml/injection is administered when PVRV is used)

WHO approved rabies vaccines for ID RV regimen

Only the cell-derived vaccines (PVRV, PCECV, HDCV) that meet the WHO requirements (0.5 to 0.7 IU /0.1ml ID RV) regarding safety, potency and efficacy for this application may be considered for ID (intra-dermal) use

ID injection technique (Fig 6)

Using aseptic technique, reconstitute the vial of freeze-dried vaccine with the diluent supplied by the manufacturer. With 1 ml syringe draw 0.2 ml (up to 20 units if a 100 units syringe is used or upto 8 units if a 40 units syringe is used) of vaccine needed for one patient (i.e. 0.1 ml per ID site X 2 sites. A raised papule should begin to appear immediately causing a peau d' orange (orange peel) appearance. Inject the remaining half the volume of vaccine (i.e. 0.1ml; either 10 or 4 units) on the opposite deltoid area. If the vaccine is injected too deeply into the skin (subcutaneous), papule is not seen. Then the

needle should be withdrawn and reinserted at an adjacent site and the ID vaccine given then at an appropriate intradermal site.

Post-Exposure Prophylaxis for previously vaccinated persons

a. Managing re-exposure following post-exposure treatment with TCV: (D0, D3)

If re-exposed, persons who have previously received full post-exposure prophylaxis (either by IM or ID route) with a potent cell-culture vaccine within last five years should now be given only two booster doses, intramuscularly (0.5ml/1ml)/intra-dermally (0.1 ml at 1 site) on days 0 and 3¹⁴. Proper wound toilet should be done. RIG application is not necessary. In re-exposed case where person who have not received complete course of PEP by IM/ID route within 5 yrs or not sure about the number of doses, a complete PEP courses should be applied. After five years animal bite case will be treated as a fresh case.



Fig.-6: Insertion of needle for ID inoculation



Bleb raised on ID inoculation

Summary Regimens (Table-III)

Table-III
Antirabies vaccine schedule for Bangladesh(IM and ID)

Regimen	DO*	D3	D7	D14	D21	D28	Total
ESSEN-IM	1	1	1	1	0	1	5 Visits – 5 IM doses
ZAGEB-IM	2	0	1	0	1	0	3 Visits – 4 IM doses
TRC-ID updated	2	2	2	0	0	2	4 visits – 8 IM doses

b. Managing exposure following pre-exposure prophylaxis with TCV: (D0,D3)¹⁴

If after recommended pre-exposure prophylaxis within last five years, a vaccinated person is exposed to rabies, a proper wound toileting should be done and two IM/ID (0.1 ml at 1 site) doses of Cell Culture Vaccine be given on days 0 and 3. RIG application is not necessary.

c. Managing re-exposure following post-exposure treatment with NTV¹⁴.

Persons who have previously received full post-exposure treatment with NTV should be treated as fresh case and may be given treatment as per merits of the case.

Pre-exposure Vaccination

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. 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. If it is less than 0.5 IU/ml a booster dose of vaccine should be given. 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 without any anti-rabies serum/RIGs. If possible, a pre-plan should be developed to use reconstituted vaccine for school children in local area but primo-vaccinates should be convinced to take two extra doses on D7 and D21 or 28. A reminder can be sent one day prior to vaccination schedule

Conclusion:

To operationalise the use of cost-effective intradermal (ID) route there is an urgent need to follow national guidelines

for ID application of human rabies vaccine. This guideline will be extremely useful for the country to make rational use of modern rabies vaccine and phase out NTV by 2011.

Conflict of Interest : None

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