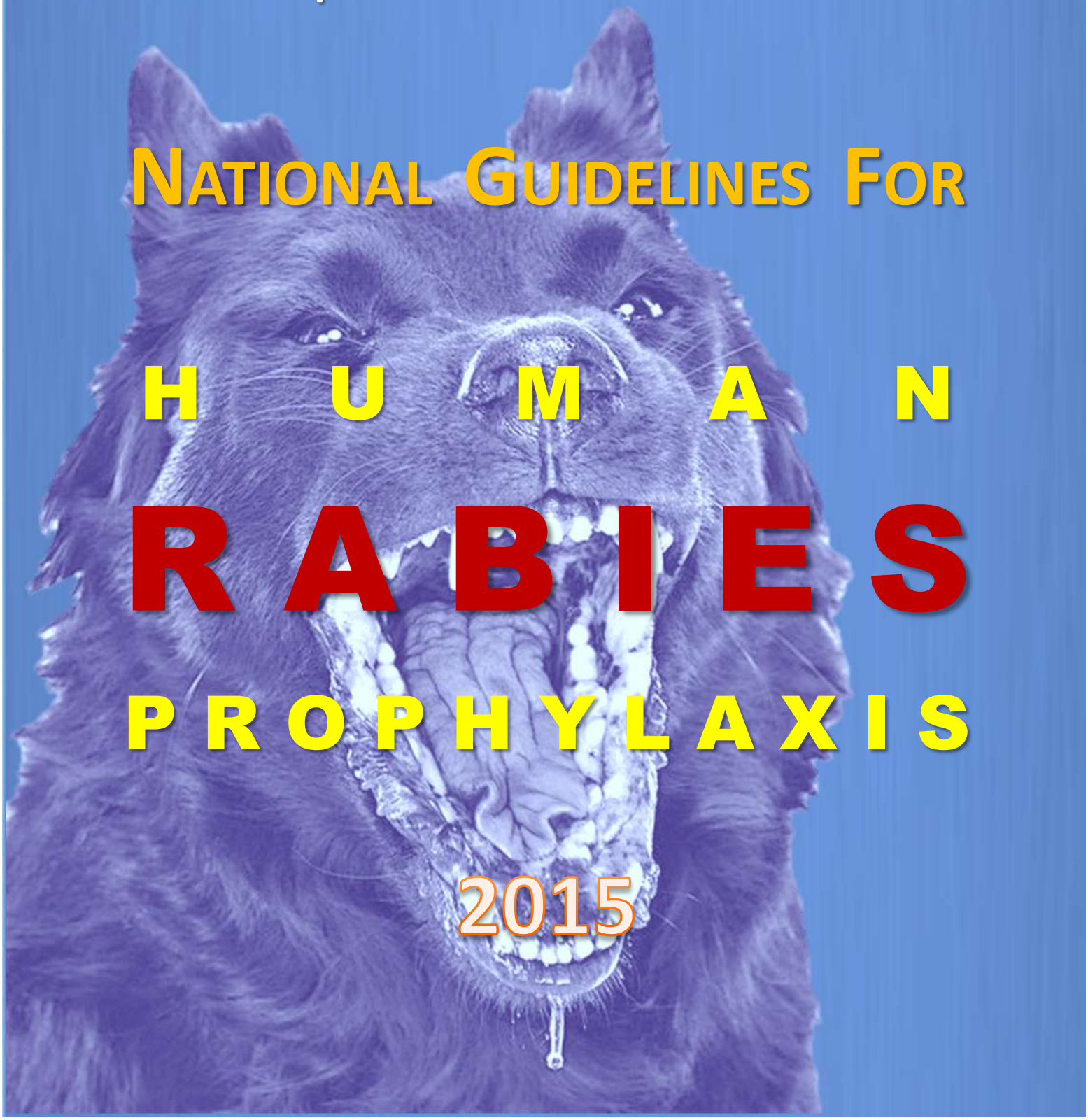
The Republic of the Union of Myanmar

Ministry of Health

Department of Public Health

National Guidelines For

HUMAN RABIES PROPHYLAXIS



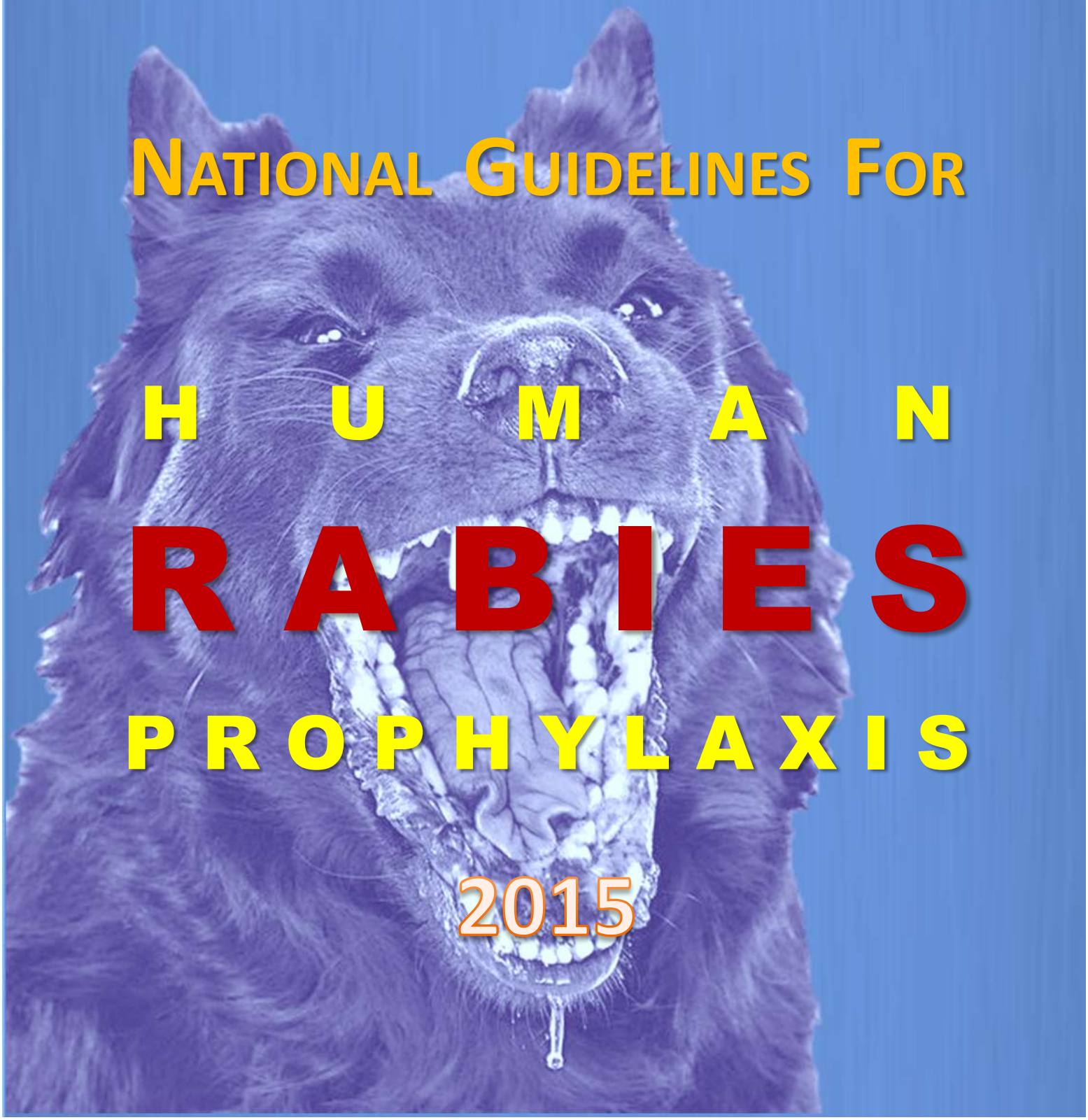
2015

World Health Organization
Country Office for Myanmar

EUROPEAN COMMISSION

National Guidelines For

HUMAN RABIES PROPHYLAXIS



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CONTENTS

ACKNOWLEDGEMENT

This National Guidelines for Human Rabies Prophylaxis for clinicians and health professionals is developed by the Department of Public Health to guide the best practice in human rabies prophylaxis and the efficient utilization of rabies vaccines and immunoglobulin. This guideline has been resourced from the discussions during the "National Workshop on Development of Guidelines for Clinical Management of Human Rabies" conducted in June 2014 and the "Dissemination Workshop on National Guidelines for Human Rabies Prophylaxis" in October 2015, feedback of the experts and other relevant reference materials.

Foremost, the Department of Public Health would like to express our sincere gratitude to the participants of the Workshops: Professor Dr Aung Gyi, Retired Professor from University of Medicine (Mandalay), Professor Dr Chit Soe, Professor and Head of Department of Medicine from University of Medicine (2), Professor Dr Nang Phyu Phyu Aung, Professor and Head of Department of Medicine from University of Medicine (Magway), Dr Tint Tint Kyi, Senior Consultant Physician from Insein General Hospital, Lecturers from the Universities of Medicine, Consultant Physicians and Paediatricians from Hospitals, Epidemiologists from Livestock Breeding and Veterinary Department, Senior Officials from Department of Medical Services, Virologists from the National Health Laboratory and experts from the WHO SEARO, WHO Country office of Myanmar and World Organization for Animal Health (OIE) for providing their valuable technical inputs, insightful comments and suggestions for finalization of the Guidelines.

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ABBREVIATIONS

AEFI	Adverse Events Following Immunization
AIDS	Acquired Immune Deficiency Syndrome
ARV	Anti-Rabies Vaccine
BCG	Bacillus Calmette-Guerin
EEO	Embryonated Egg Origin
ERIG	Equine Rabies Immunoglobulin
FAVN	Fluorescent Antibody Virus Neutralization Test
HIV	Human Immunodeficiency Virus
HRIG	Human Rabies Immunoglobulin
ID	Intradermal
IDRV	Intradermal Rabies Vaccine
IEC	Information, Education and Communication
IM	Intramuscular
IU	International Unit
NTO	Nerve Tissue Origin
OIE	World Organization for Animal Health
PCECV	Purified Chick Embryo Cell-culture Vaccine
PDEV	Purified Duck Embryo Vaccine
PVRV	Purified Verocell Rabies Vaccine
PEP	Post-Exposure Prophylaxis
PrEP	Pre-Exposure Prophylaxis
RFFIT	Rapid Fluorescent Focus Inhibition Test
RIG	Rabies Immunoglobulin
SEARO	South-East Asia Regional Office
TCO	Tissue Culture Origin
TRC	Thai Red Cross
WHO	World Health Organization

OBJECTIVES OF THE GUIDELINES

Rabies is a zoonotic disease of public health importance in Myanmar and dog bite is primary cause for seeking post exposure rabies prophylaxis. It will remain as a public health problem unless there will be significant progress in controlling rabies at the source, i.e. dogs. Rabies Vaccine of Nervous Tissue Origin (NTO) was the sole human rabies vaccine available for post-exposure rabies vaccination in the public sector till 2012. Although modern rabies vaccines have been marketed in Myanmar and recommended by private medical practitioners, high cost is a limiting factor for most victims of animal bite although they are safe and highly potent modern rabies vaccine. WHO Expert Consultation on Rabies recommends the use of cost-effective vaccination schedules such as abbreviated multisite Zagreb protocol (4 doses, 3 visits) and updated Thai Red Cross (TRC) intradermal regimen to phase out NTO in order to improve accessibility, availability and affordability of modern rabies vaccines in the public sector. The Strategic Framework for Elimination of Human Rabies transmitted by Dogs in the South East Asia has set 2014 as a deadline for phasing out production and use of rabies vaccine of NTO and encouraged Member States to introduce cost-effective intradermal rabies vaccination as an alternative.

To operationalize the introduction of abbreviated multisite Zagreb protocol and cost-effective intradermal (ID) route, there is an urgent need to develop National Guidelines for Human Rabies Prophylaxis with modern rabies vaccines and rabies immunoglobulin considering latest WHO recommendations on post-exposure rabies prophylaxis. This National Guidelines has been developed to provide guidance to clinicians and health professionals to conduct the best practice in human rabies prophylaxis and make cost effective use of modern rabies vaccines in public as well as in private sectors.

1 BACKGROUND

1.1 Introduction

Rabies is a neglected zoonotic disease (a disease that is transmitted from animals to humans), caused by the rabies virus of the genus *Lyssavirus*, and It is almost always fatal following the onset of clinical signs.

In more than 99% of human cases, the rabies virus is transmitted by domestic dogs. Rabies affects domestic and wild animals, and is spread to people through bites or scratches, usually via saliva.

With the exception of Antarctica, the disease is endemic on all continents. The highest case incidence occurs in Asia and Africa, where rabies potentially threatens over 3 billion people. More than 95% of human deaths occur in Asia and Africa.

Rabies is a 100% vaccine-preventable disease. However, despite the availability of tools to manage the disease, rabies prevails to cause tens of thousands of deaths every year. The disease disproportionately affects poor, low-resource communities, particularly children with 4 out of every 10 human deaths by rabies occurring in children younger than 15 years.

Rabies is a neglected disease of poor and vulnerable populations whose deaths are rarely reported and where human vaccines and immunoglobulin are not readily available or accessible.

1.2 Transmission

People are usually infected following a deep bite or scratch by an infected animal. Dogs are the main host and transmitter of rabies. They are the cause of human rabies deaths in Asia and Africa.

Bats are the source of most human rabies deaths in the Americas. Bat rabies has also recently emerged as a public health threat in Australia and western Europe. Human deaths following exposure to foxes, raccoons, skunks, jackals, mongooses and other wild carnivore host species are very rare.

Transmission can also occur when infectious material – usually saliva – comes into direct contact with human mucosa or fresh skin wounds. Human-to-human transmission by bite is theoretically possible but has never been confirmed. There has never been a documented case of human-to-human transmission in hospital settings.

However, human-to-human transmissions through corneal tissue/ organ transplantation have been reported. Such transmission has occurred among recipients of transplanted corneas and recently among recipients of solid organs and one vascular tissue. Investigations revealed each of the donors had died of an illness compatible with or proven to be rabies. Therefore corneas or organs should not be collected from a patient who died

due to rabies encephalitis or undiagnosed neurological disease.

Rarely, rabies may be contracted by inhalation of virus-containing aerosol. Ingestion of raw meat or other tissues from animals infected with rabies is not a source of human infection.

There is no viremia in rabies infection and therefore it is not transmitted through blood and blood products. There are no evidence-based reports of human rabies due to consumption of milk. Individuals or professionals who slaughter rabies-infected animals and handle brain and other infected material may be at risk but there are no human cases due to consumption of cooked meat.

1.3 Symptoms

The incubation period for rabies is typically 1–3 months, but may vary from <1 week to >1 year. The initial symptoms of rabies are fever and often pain or an unusual or unexplained tingling, severe itching, pricking or burning sensation (paraesthesia) at the wound site. As the virus spreads through the central nervous system, progressive, fatal inflammation of the brain and spinal cord develops.

Two forms of the disease can follow. People with furious rabies exhibit signs of hyperactivity, excited behaviour, hydrophobia and sometimes aerophobia. After a few days, death occurs by cardiorespiratory arrest.

Paralytic rabies accounts for about 30% of the total number of human cases. This form of rabies runs a less dramatic and usually longer course than the furious form. The muscles gradually become paralyzed, starting at the site of the bite or scratch. A coma slowly develops, and eventually death occurs. The paralytic form of rabies is often misdiagnosed, contributing to the under-reporting of the disease.

1.4 Diagnosis

No tests are available to diagnose rabies infection in humans before the onset of clinical disease, and unless the rabies-specific signs of hydrophobia or aerophobia are present, the clinical diagnosis may be difficult. Human rabies can be confirmed *intra-vitam* and post mortem by various diagnostic techniques aimed at detecting whole virus, viral antigens or nucleic acids in infected tissues (brain, skin, urine or saliva).

1.5 Prevention and Control

Post-exposure prophylaxis (PEP)

Post-exposure prophylaxis (PEP) means the treatment of a bite victim that is started immediately after exposure to rabies in order to prevent rabies infection. This consists of:

- local treatment of the wound, initiated as soon as possible after exposure;
- a course of potent and effective rabies vaccine that meets WHO standards; and
- the administration of rabies immunoglobulin, if indicated.

Immediate wound cleansing with soap and water after contact with a suspect rabid animal can be life-saving.

Effective treatment soon after exposure to rabies can prevent the onset of symptoms and death.

In developing countries, the vaccination status of the suspected animal alone should not be considered when deciding whether to initiate prophylaxis or not.

Human rabies prevention is promoted through the elimination of rabies in dogs as well as a wider use of the intradermal route for PEP which reduces volume and thereby the cost of cell-cultured vaccine by 60% to 80%.

Every year, more than 15 million people worldwide receive a post-bite vaccination to prevent the disease; this is estimated to prevent hundreds of thousands of rabies deaths annually.

Eliminating rabies in dogs

Rabies is a vaccine-preventable disease. Vaccinating dogs is the most cost-effective strategy for preventing rabies in people. Dog vaccination will drive down not only the deaths attributable to rabies but also the need for PEP as a part of dog bite patient care.

Preventive immunization in people

Pre-exposure vaccination/ prophylaxis (PrEP) is recommended for anyone who is at continual, frequent or increased risk of exposure to the rabies virus, either as a result of their residence or occupation.

Rabies Elimination

Stockpiles of dog and human rabies vaccine have had a catalytic effect on rabies elimination efforts in countries.

Rabies transmitted by dogs has been eliminated in many Latin American countries, including Chile, Costa Rica, Panama, Uruguay, most of Argentina, the states of São Paulo and Rio de Janeiro in Brazil, and large parts of Mexico and Peru.

Many countries in the WHO South-East Asia Region have embarked on elimination campaigns in line with the target of regional elimination by 2020. Bangladesh launched an elimination programme in 2010 and, through the management of dog bites, mass dog vaccination and increased availability of vaccines free of charge, human rabies deaths decreased by 50% during 2010–2014

2 DEALING WITH AN ANIMAL BITE CASE

Rabies is almost always a fatal disease but it is preventable disease. Thus it is important to prevent occurrence by active and passive immunization after exposure to rabies virus. The vaccines and rabies immunoglobulin (RIG) used for rabies prophylaxis should comply with the WHO recommendations for production and control as well as immunogenicity and safety.

Exposure to a biting dog is a frightening experience in itself; hence all dog bite victims are anxious and should be handled gently. Reassurance and counselling by a physician is invaluable in this scenario. Children should be handled with particular care.

3 POST-EXPOSURE PROPHYLAXIS

Post-exposure prophylaxis (PEP) against rabies takes preference over any other consideration since it is a life-saving procedure. Moreover, rabies vaccine of TCO or EEO does not have any adverse effect on fetus, mother-to-be and the course of pregnancy, and lactating mothers.

PEP consists of three activities:

1. Risk assessment and categorization of exposure
2. Management of a patient following an animal bite
3. Application of rabies vaccine and/or immunoglobulin

3.1 Risk Assessment and Categorization of Exposure

3.1.1 Risk assessment

Observation of biting dog or cat

The PEP should be started immediately after the bite. However **if the animal remains healthy throughout the observation period of 10 days, post-exposure prophylaxis may be modified to pre-exposure vaccination. The observation period is valid for dogs and cats only.** The natural history of rabies in mammals other than dogs or cats is not fully understood and therefore the 10-day observation period may not be applicable.

Unvaccinated dogs are more likely to transmit rabies, but one must be absolutely certain of a dog vaccination status before making a decision. Vaccination cards recording previous immunizations are valuable for making correct decisions. Dog vaccine failures may occur because of improper administration or poor quality vaccine.

Bite by wild animals or rodents

Bite by all wild animals should be treated as category III exposure. It should be noted that bites by domestic rats, mice, squirrel, hare and rabbits does not routinely require PEP except proper wound care.

Human-to-human transmission

The risk of rabies transmission to other humans from a human rabies case is minimal. However, people who have been exposed closely to the secretions of a patient with rabies may be offered PEP as a precautionary measure.

3.1.2 Categorization of exposure

Risk assessment leads to the categorization of wound according to category of exposure developed by WHO as shown in Table 1.

Table 1: WHO guidelines for risk assessment of rabies exposure

Category	Severity and Site of the Wound	Action
Category I: No Risk	• Touching or feeding of animals • Lick on intact skin	• Reassurance only • No vaccine needed
Category II: Moderate Risk	• Nibbling of uncovered skin • Minor scratches or abrasion without bleeding	• Wound management • Start Vaccination Day 0*
Category III: High Risk	• Single or multiple wounds on head and neck • Single or multiple transdermal bites/ scratches/ laceration with bleeding • Scratches with bleeding • Licks on broken skin • Contamination of mucous membrane of eyes, mouth, nose or wounds with saliva or discharges from rabid animals	• Wound management • Infiltrate RIG into wound • Start Vaccination at same time: Day 0*
Day 0* denotes day of first vaccination, not necessarily day of bite. Note: Administer RIG along with vaccine in all category II bites and category III bites in case of immune-compromised / immune-suppressed patients (persons on steroids, chloroquine and chemotherapy for malignant diseases, and HIV/AIDS patients).		

3.2 Management of a Patient Following an Animal Bite

Human rabies caused by classical rabies virus continues to be a 100% fatal disease with no specific treatment available anywhere in the world. Fortunately, if a person is bitten or scratched by a suspected rabid animal, immediate thorough cleansing of the wound, multiple rabies vaccine injections and, in severe exposures, administration of rabies immunoglobulin can save precious life.

3.2.1 Local treatment of wound

Since the rabies virus enters the human body through a bite or scratch, it is vital to remove as much saliva, as is possible. **Prompt local treatment of all bite wounds and scratches that might be contaminated with rabies virus is a very important step of PEP.** Recommended first-aid procedures include immediate and thorough flushing and washing of the wound with soap and water, detergent, povidone iodine or other substances with virucidal activity on rabies virus. If soap or an antiviral agent is not available, the wound should be thoroughly and extensively washed with plain water.

Early wound washing can reduce chances of developing rabies at least by 50% as it reduces viral load. **Wound washing should be taught in the community to save time and improve outcome before the victim reaches a health care facility.** Home remedies like chewed rice, salt, chillies, oil, etc. should not be used on the wound, as these substances push the virus deeper into the tissues. Touching of wounds with bare hands should be avoided. Wound washing should include the following steps:

- Thorough but gentle washing with soap or detergent and flushing the wound with running water for a minimum of 15 minutes. **Rabies virus is a fragile virus and any soap will denature the virus protein and destroy the virus.** If soap and detergent are not immediately available, wash with clean running water for at least 15 minutes.
- If the wound is deep or in absence of running water, flush with a saline filled syringe to remove dirt and saliva. After thorough washing and drying of the wound, any one of the available antiseptics should be applied.

3.2.2 Suturing of wounds

Wounds should not be sutured as surgical manipulation can further traumatize the tissues and push the virus deeper. Occasionally, as in the case of severe facial bite, e.g. a torn pinna, nose or eyelid, RIG should be infiltrated and loose sutures may be applied.

Most severe bite wounds are best treated by daily dressing followed by secondary suturing where necessary. If suturing after wound cleansing cannot be avoided, the wound should first be infiltrated with human or equine rabies immunoglobulin and suturing delayed for several hours. This will allow diffusion of the rabies immunoglobulin to occur through the tissues before minimal sutures are applied. Proper suturing may be done after 2-3 days.

3.2.3 Injection of tetanus toxoid

Injection of Tetanus toxoid should be given to the un-immunized individual. Give tetanus toxoid series at the same time according to national immunization schedule.

3.2.4 Additional care

To prevent sepsis in the wound, a suitable course of antibiotic (amoxicillin or doxycycline) should be given for at least 5 days.

In a rabies endemic country, every dog bite should be suspected as a rabies exposure, and PEP should be started immediately. However, people who present for PEP even months after a possible rabies exposure should be treated as if the event has occurred today; this is because of the long incubation period of the disease that may extend to six months or more.

3.3 Application of Rabies Vaccine and Immunoglobulin

After completing wound cleansing to all injuries, active with/ without passive immunization is given according to the category of the wound.

Category		Action
Category I:	No Risk	No Vaccine/ Immunoglobulin
Category II:	Moderate Risk	Vaccine only
Category III:	High Risk	Immunoglobulin + Vaccine

Pregnancy, lactation, infancy, old age and concurrent illness are no contraindications for rabies post-exposure prophylaxis in the event of an exposure.

For Category III Exposure, RIG should be administered before starting anti-rabies vaccination or at the same time. If RIG was not administered when vaccination was begun, **it can be administered up to the seventh day after the administration of the first dose of vaccine**. **Beyond the seventh day, RIG must not be given** since an antibody response to vaccine is presumed to have occurred and further response would be stunted. RIG should never be administered in the same syringe or at the same anatomical site as vaccine.

As with all other immunizations, person vaccinated with rabies vaccine should be kept under medical supervision for at least 15–20 minutes following vaccination. Previous severe reaction to any component of a vaccine is a contraindication to the use of the same vaccine for PEP or PrEP.

3.3.1 Application of Rabies Immunoglobulin

3.3.1.1 Rabies Immunoglobulin

Rabies immunoglobulin (RIG) should be administered in all patients with category III exposure. The rabies immunoglobulin provides passive immunity in the form of ready-made anti-rabies antibody to tide over the initial phase of the infection. **The RIG has the property of binding with the rabies virus, thereby resulting in the loss of infectivity of the virus.**

RIG should always be brought to room temperature (20 – 25ºC) before use.

Types of Rabies Immunoglobulin

Two types of RIGs are available:

1. Human Rabies Immunoglobulin (HRIG):

Human rabies immunoglobulin has a relatively slow clearance (the half-life is about 21 days), so it is the preferred product, particularly in cases of multiple severe exposures and bites on the head, face and hands. HRIG are free from the side effects encountered in a serum of heterologous origin, and because of their longer half-life, are given in half the dose of ERIG.

However, owing to its short supply and high price, equine immunoglobulin should be used.

2. Equine Rabies Immunoglobulin (ERIG):

Most of the new equine immunoglobulin preparations are potent, highly purified, safe and considerably less expensive than human rabies immunoglobulin. However they are of heterologous origin raised by hyper-immunization of horses, and carry a small risk of anaphylactic reaction (1/45,000 cases).

Since the serum for ERIG is prepared from horses there are chances (although rare) of anaphylactic reaction. There are no scientific grounds for performing a skin test prior to administering equine immunoglobulin because testing does not predict reactions, and it should be given irrespective of the test result. WHO does not recommend skin sensitivity test. It is therefore important that medicines are readily available to treat an anaphylactic shock. The treating physician should be prepared to manage anaphylaxis which, although rare, could occur during any stage of administration.

Anaphylactic reactions should be treated promptly with adrenaline. The dose is 0.5 ml (1:1000, 1mg/ml) for adults and 0.01 ml/kg body weight for children, injected subcutaneously or intramuscularly.

Dosage Calculation

Both HRIG and ERIG are equally effective. The HRIG is being more expensive. The doses are calculated according to the body weight.

Table 2: HRIG calculated as per body weight

Weight in Kg	IU	ml	No. of vials of HRIG
15	300	2	1
30	600	4	2
45	900	6	3
60	1200	8	4 (maximum)
A 2 ml vial of HRIG contains 300 IU. Dose is 20 IU/kg. (maximum dose is 1200 IU or 4 vials)			

Table 3: ERIG calculated as per body weight

Weight in Kg	IU	ml	No. of vials of ERIG
25	1000	5	1
50	2000	10	2
75	3000	15	3
100	4000*	20	4 (maximum)*
A 5 ml vial of ERIG contains 1000 IU. Dose is 40 IU/kg. (*Maximum dose varies from 3000 to 4000 IU, depending on the preparation. Check the prescriber's leaflet.)			

3.3.1.2 Administration of Rabies Immunoglobulin

Infiltrate the calculated dose of RIG (whether HRIG or ERIG) into and around the wounds. Multiple needle injections into the wound should be avoided. After all wounds have been infiltrated, remaining RIG, if any, should be administered by deep intramuscular injection at an injection site distant /away from the vaccine injection site.

Animal bite wounds 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 ***(Figure. 1)***. In these circumstances, it is advisable to dilute the immunoglobulin in sterile normal saline 2 to 3 fold to be able to permit infiltration of all wounds. The total recommended dose of immunoglobulin must not be exceeded as it may suppress the antibody production by the vaccine.

Figure 1: Administering RIG into the wound

Precautions to be taken while administering RIGs

- All emergency drugs and facilities for managing any adverse reactions must be available.
- The RIG vial(s) taken out from refrigerator should be kept outside for a few minutes before administration to the patient (to warm it to room/body temperature).
- **RIG should be administered before starting anti-rabies vaccination or at the same time.**
- RIG should not be administered in the same syringe 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.

3.3.2 Application of Rabies Vaccine

3.3.2.1 Rabies Vaccine

Active immunization is achieved by administration of safe and potent rabies vaccine of tissue-culture origin (TCO) or embryonated egg origin (EEO). Currently available rabies vaccines of TCO or EEO could be administered by Intramuscular (IM) or Intradermal (ID) regimen.

Since their development over four decades ago, rabies vaccines of TCO or EEO have proved to be highly effective in preventing human rabies, both when administered as pre-exposure prophylaxis (PrEP) and when used in association with RIG for post-exposure prophylaxis (PEP).

Rabies vaccine of TCO or EEO consists of inactivated rabies virus that has been propagated in cell substrates such as Vero cells (kidney cells from the African green monkey), primary Syrian hamster kidney cells, and primary chick embryo cells or in embryonated duck eggs. The vaccines based on chick embryo cells and Vero cells have safety and efficacy records comparable to those of the human diploid cell vaccines and are less expensive.

Rabies vaccines are not supplied in multi dose vials for intramuscular injection. Rabies vaccines prequalified by WHO do not contain preservatives such as thiomerosal. The shelf-life of these vaccines is ≥2 years, provided they are **stored at +2°C to +8°C and protected from sunlight. Following reconstitution with the accompanying sterile diluents, the vaccines should be used immediately, or within 6 hours** because of contamination not coaxing efficacy if kept at the correct temperature. All rabies vaccines of TCO or EEO should comply with the WHO recommended potency of ≥2.5 IU per single intramuscular dose (0.5 ml or 1.0 ml volume after reconstitution, depending on the type of vaccine).

Storage and transportation

Although most Rabies Vaccine of TCO or EEO are marketed in freeze dried (lyophilized) form, yet it is recommended that these **vaccines should be kept and transported at a temperature range of + 2 to + 8ºC.**

Reconstitution and storage

The lyophilized vaccine should be reconstituted with the diluents provided with the vaccine immediately prior to use. However, in case of unforeseen delay it **should not be used after 6 hours of reconstitution.**

Site of inoculation

Intramuscular vaccine should be injected only in the deltoid area. Gluteal region is not recommended because the presence of fat decreases the absorption of antigen leading to impaired immune response. Antero-lateral part of the thigh is the preferred site in infants and young children.

Limitations and interchangeability

Currently available rabies vaccines of TCO or EEO are to be administered through IM or ID route. In patients on chloroquine, vaccine should be given by the intra muscular route only.

Interchangeability of modern rabies vaccine is not recommended. When completion of PEP with the same modern rabies vaccine is not possible, the switch can be done provided that it is one of the WHO recommended cell culture vaccine. This practice should be the exception.

No study has been done yet on vaccine immunogenicity and change of the route of vaccine administration (e.g. from intramuscular to intradermal) during PEP. It is not recommended during the course of vaccination.

Vaccine efficacy and immunogenicity

All rabies vaccines of TCO or EEO induce a prompt and high rabies-virus neutralizing antibody response to the viral G protein. WHO's specified minimum titre of 0.5 IU/ml of serum, measured by the rapid fluorescent focus inhibition test (RFFIT) or the fluorescent antibody virus neutralization test (FAVN) is a widely used reference. In healthy people, this level should be achieved in most individuals by day 14 of a post-exposure regimen, with or without simultaneous administration of rabies immunoglobulin and irrespective of age. When new rabies vaccines are introduced, their immunogenicity is evaluated by comparing the rabies-virus neutralizing antibody titres induced by the vaccine being tested with those induced by a vaccine of demonstrated efficacy.

Studies from Thailand and other countries in South-East Asia have established the immunogenicity and effectiveness of rabies vaccines of TCO or EEO for both pre-exposure and post-exposure prophylaxis. The feasibility of using PVRV and PCECV either intramuscularly or intradermal in all age groups, including infants, has been clearly demonstrated. In both pre-exposure and post-exposure use, these vaccines induce an adequate antibody response in almost all individuals. Prompt post-exposure use of rabies vaccines of TCO or EEO combined with proper wound management and simultaneous administration of rabies immunoglobulin is almost invariably effective in preventing rabies, even following high-risk exposure. However, delays in starting or failure to complete correct prophylaxis may result in death, particularly following bites in highly innervated regions, such as the head, neck, finger tips or genitals, or following multiple bites.

3.3.2.2 Administration of Rabies Vaccine

The cost of rabies vaccines of TCO or EEO for intramuscular administration limits their widespread use in many countries where dog rabies is endemic. **Intradermal administration of rabies vaccine of TCO or EEO (PCECV only) offers an equally safe and immunogenic alternative that requires only 1–2 vials of vaccine to complete a full course of post-exposure prophylaxis, thereby reducing the volume used and the direct cost of vaccine by 60–80% compared with standard intramuscular schedule.** There is no evidence that intradermal administration requires vaccines with potency higher

than that recommended for intramuscularly administered rabies vaccines. Intradermal regimens have been successfully introduced for post-exposure prophylaxis in countries such as Bangladesh, India, Philippines, Sri Lanka and Thailand. However, in addition to using vaccines explicitly authorized for the intradermal route, proper delivery of the vaccine requires sufficient staff training to ensure correct storage, reconstitution and injection.

Intramuscular regimen (Zagreb regimen) and intradermal regimen (Thai Red Cross Schedule) are cost-effective way of using rabies vaccines of TCO or EEO and both regimens have been successfully used in rabies endemic countries of Asia.

The decision on using these regimens depends on numbers of patients and availability of trained health professionals for ID regimen**. If the number of patients per day is less than 3, then Zagreb regimen is the preferred choice** because of cost effectiveness and lesser number of visits. **If the daily turn-out of dog bite victims is 3-5, Thai Red Cross intradermal regimen is preferred** because it is safe, effective and economical.

Intramuscular Regimen

All age groups of dog bite victims of Category II and III require the same number of injections and dose per injection.

Zagreb Regimen (2-1-1)

The four dose Zagreb regimen is administered as two doses on day 0 (one dose in the right and one in the left deltoid), and then one dose on each of days 7 and 21 into the deltoid muscle ***(Figure. 2)***.

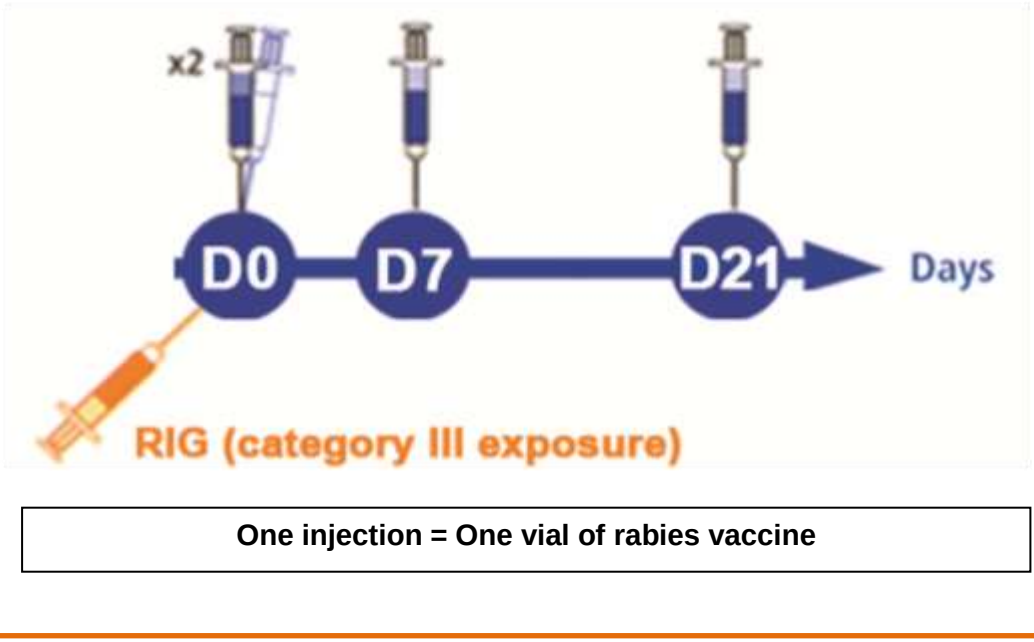

Figure 2: Zagreb Schedule

Intradermal regimen

In this regimen, (0.1ml) of rabies vaccine is administered on multiple sites in the dermis of skin. Until ID injection devices become available proper administration of a fraction of the vaccine contained in the vial requires knowledge and skill of the technique of intradermal injection. Not all WHO prequalified rabies vaccines can be used by the intradermal route. **PCECV and PVRV as mentioned in Annex (2) are recommended for ID route.**

Thai Red Cross Regimen (2-2-2-0-2)

Injection of 0.1 ml of reconstituted vaccine is given per ID site one on each deltoid area (left and right arms), one inch above the insertion of deltoid muscle on days 0, 3, 7 and 28 ***(Figure.3)***. Day 0 is the day of first dose administration of IDRV and may not be the day of rabies exposure/dog bite.

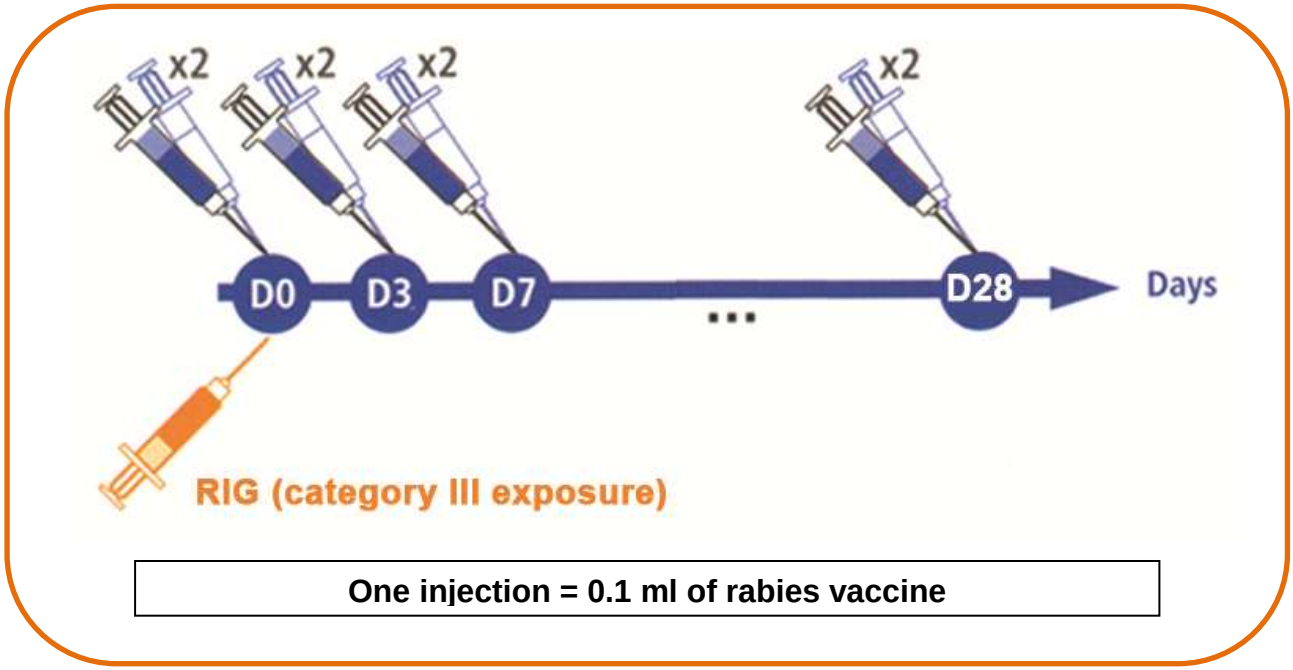

Figure 3: Thai Red Cross Regimen

General guidelines for use of intradermal vaccination

- Intradermal injections must be administered by trained staff.
- 1ml syringe with hypodermic needle (e.g. Insulin Syringe) should be used for intra-dermal administration.
- Always use a new syringe for each patient.
- Reconstituted vaccines must be used as soon as possible or within 6 hours if kept at +2 to + 8ºC. Vaccine when given intradermal should raise a visible and palpable bleb in the skin. If a bleb is not raised, repeat the injection slightly away from the first one. (The technique is similar to BCG inoculation).
- If the dose is inadvertently given subcutaneously or intra-muscularly or in the event of spillage, a new dose should be given intradermal in nearby site.

- Dog bite victims who are immune-compromised or immune-suppressed (patients on chloroquine, steroids and chemotherapy for malignant diseases, and HIV/AIDS patients) should not be given vaccine by ID route. They should be given rabies vaccine of TCO or EEO by intramuscular route.
- A timetable for return visits should be given to the patient for better compliance.

Intradermal injection technique

- Using aseptic technique, reconstitute the vial of freeze-dried vaccine with the diluents supplied by the manufacturer. With 1 ml syringe draw 0.2 ml (i.e. 0.1 ml per ID site X 2 sites).
- Using the technique of BCG inoculation, stretch the surface of the skin and insert the tip of the needle with bevel upwards, parallel to the skin surface ***(Figure. 4)***. Slowly inject half the volume of vaccine (i.e. 0.1 ml) into the intradermal layer of skin, over the deltoid area. A raised bleb ***(Figure. 5)*** should begin to appear causing an orange peel appearance (peau d' orange). Similarly inject 0.1ml intradermally on the other deltoid area.

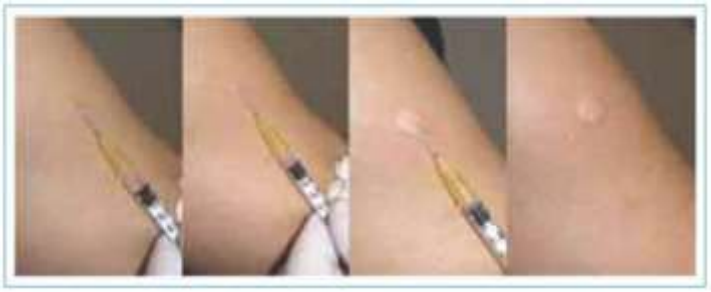

Figure 4: Intradermal injection technique

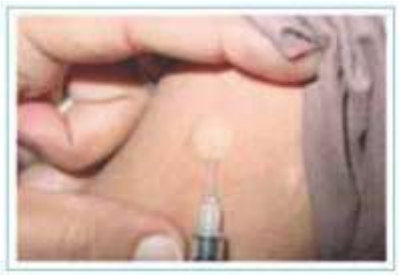

Figure 5: Raised bleb on intradermal inoculation

4 POST - EXPOSURE PROPHYLAXIS FOR PREVIOUSLY VACCINATED PERSONS

4.1 Managing Re-Exposure Following PrEP or PEP with Rabies Vaccine of TCO or EEO

In case of re-exposure, for persons who have previously received full post-exposure prophylaxis (either by IM or ID route) with a potent rabies vaccine of TCO or EEO, perform wound cleansing and give rabies vaccine (TCO or EEO) boosters on Day 0 and Day 3 intra muscularly or intradermally.

4.2 Managing Re-Exposure Following PEP with Rabies Vaccine of NTO

Personal who have previously received full post- exposure treatment with rabies vaccine of NTO, should be treated as fresh case and may be given PEP as per merits of the case.

5 PRE-EXPOSURE PROPHYLAXIS

Pre-exposure vaccination/ prophylaxis (PrEP) is recommended for anyone who is at continual, frequent or increased risk of exposure to the rabies virus, either as a result of their residence or occupation.

The same safe and effective vaccines can be used for pre-exposure immunization. This is recommended for travellers spending a lot of time outdoors, especially in rural areas, involved in activities such as bicycling, camping, or hiking as well as for long-term travellers living in areas with a significant risk of exposure.

Pre-exposure immunization is also recommended for people in certain high-risk occupations such as laboratory workers dealing with live rabies virus and other rabies-related viruses (lyssaviruses), and people involved in any activities that might bring them professionally or otherwise into direct contact with bats, carnivores, and other mammals in rabies-affected areas. As children are considered at higher risk because they tend to play with animals, may receive more severe bites, or may not report bites, their immunization could be considered if living in or visiting high-risk areas.

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

PrEP is especially recommended for the following:

- Laboratory staff handling the rabies virus and infected material
- Clinicians and nurses attending to human rabies cases
- Veterinarians
- Dog catchers
- Wildlife wardens

6 DOG BITE MANAGEMENT IN IMMUNO-COMPROMISED PATIENTS

Rabies Post-Exposure Prophylaxis for Immuno-compromised Persons

In patients with compromised immune status, care of the wound is the same as with the immuno-competent individuals but there are some variations with regard to vaccination and administration of RIG.

Vaccination of these individuals should be done by IM route. In an unvaccinated person a full course of Essen Regimen (Day 0, 3, 7, 14, 28) should be used. In previously vaccinated persons, vaccination regimen is the same as with the immuno-competent persons.

Regarding RIG, it should be given to all patients with category II & III exposure if they are not vaccinated previously. HRIG should preferably be used.

It is essential to check whether these patients achieve protective level of rabies antibody after the completed course of prophylaxis.

Table 4: Rabies Post-Exposure Prophylaxis for Immuno-compromised Persons

Vaccination Status	Treatment/ Testing	Dosage/ Administration Guidelines for all Ages	Day of Regimen
Immuno-compromised, Unvaccinated Persons	• Wound cleaning		
	• Tetanus toxoid booster	• Indicated if last tetanus vaccine was more than 5 years prior to exposure	
	• Human rabies immune globulin (HRIG)	• 20 IU/kg body weight • Infiltrate HRIG into and around wound • Remaining HRIG given IM at a site distant from the vaccination site	**Day 0** (can be given up to day 7)
	• Rabies vaccine	• **Five** 1 vial doses, IM ▪ Adults/ older children: deltoid area ▪ Young children: anterolateral thigh ▪ Never in gluteals	**Day 0, 3, 7, 14, 28**
Immuno-compromised, Previously Vaccinated Persons	• Wound cleaning		
	• Tetanus toxoid booster	• Indicated if last tetanus vaccine was more than 5 years prior to exposure	
	• **DO NOT give HRIG**		
	• Rabies vaccine	• **Two** 1 vial doses, IM • Adults/ older children: deltoid area • Young children: anterolateral thigh • Never in gluteals	**Day 0, 3**

7 MANAGEMENT OF ADVERSE EFFECTS FOLLOWING IMMUNIZATION (AEFI)

Once initiated, rabies prophylaxis should not be interrupted or discontinued because of local or mild systemic adverse reactions to rabies vaccine. Mild systemic adverse events, such as transient fever, headache, dizziness and gastrointestinal symptoms, have been observed in 5–15% of vaccinated people, usually such reactions can be successfully managed with anti-inflammatory and antipyretic agents, such as ibuprofen or acetaminophen.

When a person with a history of serious hypersensitivity to rabies vaccine must be revaccinated, antihistamines can be administered. Adrenaline and other lifesaving drugs should be readily available to counteract anaphylactic reactions, and the person should be observed carefully immediately after vaccination. Such persons should preferably be vaccinated under medical supervision.

8 REFERENCES

- http://www.who.int/rabies/human/postexp/en/index.html
- http://www.who.int/mediacentre/factsheets/fs099/en/
- http://www.searo.who.int
- WHO Expert Consultation on Rabies. Second Report 2012 Geneva
- National Guidelines for Rabies Prophylaxis and Intradermal Administration of Cell Culture Rabies Vaccines 2007. National Institute of Communicable Diseases. Government of India
- National Guideline for Rabies Prophylaxis and Intra-dermal Application of Cell Culture Rabies Vaccines. June 2010. Disease Control Unit. Ministry of Health & Family Welfare Bangladesh.

Annex (1): The modern rabies vaccines of TCO or EEO

Generic	Brand Name	Volume after reconstitution	Approved route of administration	WHO Pre-qualified
Purified Vero Cell Rabies Vaccine (PVRV)	Verorab®	0.5 ml	IM or ID	Yes
	Speeda®	0.5 ml	IM	No
	Indirab®	0.5 ml	IM	No
Purified Chick Embryo Cell Vaccine (PCECV)	Rabipur®	1.0 ml	IM or ID	Yes

Annex (2): Proforma for Post-exposure management of animal bite cases

Section I – History Taking

Referred by: _____

Date: _____ Registration Number: _____

Name: _____ Age: _____

Sex: Male ☐ Female ☐ Occupation _____

Complete home address: _____

_____

Phone Number: _____

Date of bite: _____ Time lapse: _____

Locality of biting episode: _____

Biting animal: Dog ☐ Cat ☐ Monkeys ☐ Others ☐

Animal Status: Pet ☐ Stray ☐

If pet, Vaccinated ☐ Non Vaccinated ☐

Outcome of the biting animals: Under observation ☐ Observed for 10 Days ☐

Killed ☐ Escaped ☐ Healthy ☐

Section II – Physical Examination

Category	Severity and Site of the Wound
Category I: No Risk	• Touching or feeding of animals • Lick on intact skin
Category II: Moderate Risk	• Nibbling of uncovered skin • Minor scratches or abrasion without bleeding
Category III: High Risk	• Single or multiple wounds on head and neck • Single or multiple transdermal bites/ scratches/ laceration with bleeding • Scratches with bleeding • Licks on broken skin • Contamination of mucous membrane of eyes, mouth, nose or wounds with saliva or discharges from rabid animals

Wound Category: Category I ☐ Category II ☐ Category III ☐

Sites of Wounds: _____

Section III – Management

Previous history of animal bite/ exposure: Yes ☐ No ☐

If yes, When: _____ Place: _____

PEP given: Yes ☐ No ☐

Past and present medical history: Immuno-compromised Yes ☐ No ☐

Currently taking chloroquine therapy Yes ☐ No ☐

Patient's Weight: _____ kg

Thorough washing of bite wound: Yes ☐ No ☐

Rabies Immunoglobulin (RIG) for category III bite: Human RIG: ☐ Equine RIG: ☐

Number of vials administered: _____ Date administered: _____

Brand Name of Rabies Vaccine: _____

Intradermal (Thai Red Cross Regimen)			
Day	Doses	Site	Date
Day 0	2		
Day 3	2		
Day 7	2		
Day 28	2		
OR			
Intramuscular (Zagreb Regimen)			
Day	Doses	Site	Date
Day 0	2		
Day 7	1		
Day 21	1		

Any side effects of vaccine if reported: _____

_____

Remarks: _____

_____

Annex (3): Requirements for a dog bite treatment centre

The following are the recommended guidelines for physical facilities and staff requirements for a dog bite treatment centre

I. Accommodation

- Treatment room 20’ X 15’ (minimum) and waiting hall
- Wound washing area with running tap water
- Small Water Tank (In case of shortage of water in the Centre)

II. Staff

- Medical Officer – 1
- Staff Nurses – 3
- Attendant – 1

III. Furniture

- Office Table – 1 (Medical Officer)
- Arm chairs – 2
- Revolving stools – 3
- Bed for examining the patient -1

IV. Equipment and Instruments

- Refrigerator
- Weighing machine – 1
- BP apparatus
- Washing Area
- Safety Box to dispose of used syringes

V. IEC materials

- National Guidelines for Human Rabies Prophylaxis Book
- Standard Operating Procedures for Human Rabies Prophylaxis Book
- Information booklet
- Vaccination Cards
- Sign Board
- Treatment Proforma
- Entry Register
- Schedule Calendar

VI. Drugs (Injectable and Applicants)

- Rabies vaccine
- Rabies immunoglobulin
- Injection Adrenaline
- Injection Antihistamine
- Injection Steroid
- Povidone Iodine
- Normal Saline
- Anti Tetanus toxoid
- Emergency Kit

VII. Other Supplies and Consumables

- Cotton
- Adhesive plaster
- Dressing material
- Liquid Soap
- Surgical gloves
- Insulin syringes with 26G needles
- 20 mL and 50mL syringes for wound toilet in absence of running water
- Kidney tray
- Dressing bin
- Covered waste bin