



**OPERATIONAL GUIDELINES FOR RABIES PROPHYLAXIS -
INTRA DERMAL RABIES VACCINATION AND
RIGs ADMINISTRATION IN KERALA**



4th Edition

**Department of Health and Family Welfare
Government of Kerala**



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MESSAGE


Rabies continues to be a major public health problem claiming an estimated 20,000 lives in India annually. 50-60 deaths due to rabies are reported from Kerala every year. We are spending a sizeable sum of 25 crores, exerting a dual burden on the Government as well as on the bite victim. It is at this juncture, that the State Government has decided to take a role in the fight against rabies and introduced the strategy of Intra Dermal Rabies Vaccination.

The National Workshop held at Thiruvananthapuram in September 2008 resulted in formulation of operational guidelines. In November 2008, the G.O for implementation of IDRV in Kerala was released. The implementation of IDRV is to be done in a systematic and phased manner. NRHM, DHS, DME, KMSCL have all played important roles in scripting the success story. Within a year's effort and into the second phase of implementation, IDRV

is being made available in the entire district and taluk hospitals. I am proud that we were able to make IDRV free of cost to all regardless of APL or BPL status. Administration of Rabies immunoglobulins (RIGs) is the other major area which has to be enhanced as it is a life saving measure in severe bite cases.

I want to reiterate that we will not leave a single stone unturned in our pursuit to make the treatment available to every bite victim in the state. But let me remind you all that IDRV is not our ultimate aim. It is one of the means to reach the ultimate goal of a rabies free Kerala by 2015. For this, we should have a broader spectrum of action in mind. What we need is an integrated approach involving the department of Health, Animal Husbandry and the Local Self Government. It is encouraging to realize that the World Health Organization itself has taken note of our humble efforts.

I thank all those who have contributed to make IDRV a reality in Kerala and wish success to each step in reaching the vision of rabies-free Kerala by 2015.


P. K. Sreemathi Teacher



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Secretary (Health)

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FOREWORD

Rabies in India has been a disease of low public health priority both in the medical and veterinary sectors. With almost 20000 deaths annually, more people die of rabies than yellow fever, dengue and Japanese encephalitis combined. The dog population is swelling over 22 million in India and in Kerala it is over 14 lakhs. It is estimated that India spends about 1500 crores for rabies vaccines.

Kerala was the first state in the country to start using modern CCV's. Higher cost of intra-muscular administration of CCV's was a limiting factor for its wider use. The launch of IDRV in the state in 2009 is a remarkable step towards rabies control. Administration of vaccine through the intra dermal route will lead to about one-fifth reduction in cost and volume of vaccine. In other words, the vaccination can be provided to five times more patients with the same amount of vaccine. The number of visits of the patients is also reduced.

IDRV is a major step in the direction of the State's vision of a Rabies Free Kerala by 2015. Realizing the significance of implementing IDRV in the State, the Government has decided to provide IDRV free of cost to all, irrespective of their APL or BPL status. As of today there are 21 centres providing this service in the state and the government is planning to scale it to all hospitals in the state which caters to more than 5 bite victims per day.

I take this opportunity to appreciate each and every one of you who have contributed to make IDRV a success in Kerala.

Shri. Manoj Joshi I.A.S.



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PREFACE

Rabies is virtually a 100% fatal disease, but preventable by timely and appropriate post- exposure treatment.

The administration of Post Exposure prophylaxis (PEP) for rabies in Kerala, rose from 5785 PEP/year in 2003-04 to 10311 PEP/year in 2006-07 compared to 18 lakhs PEP/year in India. Implementation of the more cost effective Intra Dermal Rabies Vaccination, introduced by the WHO in 1992, has brought a solution to the dilemma faced by the government in rabies control and prevention. IDRV has been approved by the Drug Controller General of India (DCGI) in 2006 and has already been implemented in various states.

Kerala, though a forerunner in the field of health was left behind in the launching of IDRV regimen. The efforts towards rabies control in the state took a new direction with the introduction

of the IDRV regimen in Kerala in 2009. Following the Government order for implementation of the same, vaccines were procured through Kerala Medical Services Corporation Limited (KMSCL). Selected antirabies clinics from across the state were converted into Model Antirabies Clinics, where stakeholders for IDRV implementation were trained.

IDRV programme has been a great success in Kerala. There are 21 IDRV centers now, covering the 5 Medical Colleges, the major District hospitals, General hospitals and Taluk Head Quarters Hospitals. The government is planning to scale it up to all hospitals in the State which caters to more than 5 bite victims per day. The strategy of implementation of IDRV in the State was appreciated by Dr.FX Meslin from World Health Organisation during his visit to Kerala in November 2009.

The Government of Kerala has set a vision of Rabies Free Kerala by 2015 and the strategies include control of animal rabies, free post exposure treatment for bite victims and control of animal rabies through increasing community awareness. IDRV is a major step in that direction, which ensures free treatment to a larger population.

I wish everyone working in the implementation of IDRV success.

Dr. Dinesh Arora I.A.S



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MESSAGE

Rabies is perhaps one of the most dreadful diseases, with huge public health impact which results in approximately, 3 million people receiving post exposure prophylaxis in our country annually. The financial burden of the disease is unaffordable to common man. WHO estimates that an average Asian citizen has to spend nearly a month's wages on a full course of antirabies vaccination. As an alternative the new IDRV regimen has been approved by WHO and Govt. of India. State level inauguration of IDRV in Kerala was done by Hon'ble minister for Health and Social Welfare Smt.P.K.Sreemathi Teacher at General Hospital, Trivandrum on 27th February 2009. At present there are 21 IDRV centres across the state. I take this opportunity to congratulate all those who have worked to make IDRV a reality in the state.

Dr. M.K. Jeevan



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Director, Medical Education



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MESSAGE

Rabies being a disease with 100% mortality, timely and proper Antirabies vaccination is the most important step in saving the lives of bite victims. Govt. spends crores on the procurement of vaccine, yet there is a shortage of vaccine at times putting additional financial burden on patients. Intradermal rabies vaccination is the solution for this dilemma. IDRV which will reduce cost of Antirabies vaccination by 60-70% has already been approved by WHO and DCGI. IDRV has been successfully implemented in the State in 2009 with 21 IDRV centres covering the 5 Medical colleges, General hospital, major District and Taluk hospitals. The State Government has decided to provide IDRV free of cost to all, irrespective of their APL or BPL status. I wish this venture all success and thereby hope that the vision of Rabies Free Kerala by 2015 could be achieved.

Dr. V. Geetha



GOVERNMENT OF KERALA

Abstract

Health & Family Welfare Department - IDRV Vaccines - free of cost to all patients
-Sanction accorded - Orders issued.

HEALTH & FAMILY WELFARE (J) DEPARTMENT

G.O.(Rt)No. 3357/2009/H&FWD Dated, Thiruvananthapuram, 18/11/2009.

- Read:-
1. G.O (Ms), No, 557/2008/H&FWD dated 31/10/08.
 2. Note No. NRHM/SDCMC/035/09 dated 16/3/09 and 18/7/09 from National Rural Health Mission, Thiruvananthapuram.
 3. Letter No. 3787/2009/PUR/KMSCL dated 20/6/2009 from the Managing Director, Kerala Medical Services Corporation Limited.
 4. Letter No. PH2 - 32337/08/DHS dated 27/10/09 from the Director of Health Services, Thiruvananthapuram.
 5. Letter dated 3.11.09 from Dr. Thomas Mathew, Nodal Officer, SDCMC and Nodal Officer IDRV, Kerala.

ORDER

As per the G.O read as 1st paper above, Government ordered to implement Intra dermal rabies vaccination (IDRV) in the State in a phased manner through the Anti Rabies Clinics (ARCs) attached to the Community Medicine Department of all the 5 Medical college Hospitals and the Anti Rabies Clinics identified in District and General Hospitals in the State from 1st January 2009 as per the operational guidelines appended to the Government Order.

2. In the note read as 2nd paper above it is requested to issue orders for implementing Intra dermal rabies vaccination free of cost to all patients.

3. Government have examined the matter in detail and are pleased to accord sanction to implement Intra dermal rabies vaccination at free of cost to all patients (BPL & APL) subject to the following conditions:-

1. IDRV should be given through casualties/OP/Anti Rabies Clinics of Government Medical Colleges/District Hospitals/General Hospitals/ Taluk Head Quarters Hospitals, CHCs and PHCs where a minimum of 5 patients will come for ARV daily. ARV through intra-muscular route may be continued in the institutions where less than 5 patients are coming for vaccination.


2. Since administration of Rabies immunoglobulin (Equine/human) is a life saving emergency service, facilities for administration of this should be provided in at least one institution in each district, preferably, the District Hospital. ,
3. IDRV should be given on all days including Sundays and holidays.
4. The full course of IDRV should be given free of cost to all patients irrespective of their APL/BPL status.
5. The details of animal bites treated daily and deaths occurring due to rabies should be collected by the head of the institution and reported to the district authorities and the State Disease Control & Monitoring Cell, Thiruvananthapuram in the prescribed format.

By Order of the Governor,
MANOJ JOSHI
Secretary to Government.

To

The Director of Health Services, Thiruvananthapuram.
The Director of Medical Education, Thiruvananthapuram,
The Managing Director, Kerala Medical Services Corporation Limited
The Principal, Government Medical College, Thiruvananthapuram/
Alappuzha/ Kottayam / Thrissur / Kozhikode.
All District Medical Officers (Health)
The Principal Accountant General (Audit), Kerala, Thiruvananthapuram.
The Accountant General (A&E), Kerala, Thiruvananthapuram, SF/OC.

Copy to: PS Minister (H&SW)
PA to Secretary (Health)

Forwarded/By order,

Section Officer.



GOVERNMENT OF KERALA

Abstract

Health & Family Welfare Department- Implementation of Intra Dermal Rabies Vaccination (IDRV) in Kerala- Orders issued

HEALTH & FAMILY WELFARE (J) DEPARTMENT

GO(MS) No.557/2008/H&FWD dated Thiruvananthapuram, 31st October, 08

Read: 1. DCGI Order no: 11026/23/05D dtd 03.07.2007

-
2. National Guidelines for Rabies Prophylaxis and Intra dermal Administration of Cell Culture Rabies Vaccines, NICD, 2007.
 3. Guidelines for Rabies Prophylaxis and Intradermal Rabies Vaccination in Kerala, 2008

ORDER

1. Realising the importance of implementing Intra-Dermal Rabies Vaccination (IDRV) in Kerala, Government of Kerala organized a workshop on developing guidelines for the implementation of IDRV in Kerala. Government is now pleased to adopt “Guidelines for Rabies Prophylaxis and Intradermal Rabies Vaccination in Kerala, 2008” which has been prepared on the basis of deliberations of the workshop (Annexure - I).

2. Government have decided to implement intradermal rabies vaccination in a phased manner in the state. In the first phase, it will be implemented in the Anti Rabies Clinics (ARCs) attached to the Community Medicine Departments of all the 5 Govt. Medical Colleges and ARCs identified in District and General Hospitals in the state, from 1st January 2009. These centres shall follow the operational guidelines prepared by the expert committee (Annexure – II).

3. Dr Thomas Mathew, Prof. & HOD, Community Medicine, TDMC, Alappuzha and Nodal Officer, State Disease Control and Monitoring Cell (SDCMC) is appointed as State Level Nodal Officer to coordinate the activities related to the implementation of IDRV in Kerala.

4. Training will be imparted to key stakeholders from the State in IDRV technique at the Institute of Preventive Medicine, Hyderabad, Andhra Pradesh.

5. The State PEID Cell, Medical College, Thiruvananthapuram will coordinate the training to the key stakeholders in ARCs including Medical Officers, Health Inspectors and Nursing staff.

6. The centres converted as model ARCs for IDRV will function as training centres for IDRV.

7. The drugs for IDRV implementation will be procured and distributed through Kerala Medical Service Corporation Ltd, Kerala.

(By Order of the Governor)

Dr. Vishwas Mehta

Secretary to Government

The Director of Health Services, Thiruvananthapuram
The Director of Medical Education, Thiruvananthapuram
The Managing Director, Kerala Medical Services Corporation Ltd
The Principal, Govt Medical College, Trivandrum/Alappuzha/ Kottayam/
Thrissur/Kozhikode
The Director, Information and Public Relations Department
All District Medical Officers (Health)
SF/OC

Forwarded/ By Order

PS to Minister (Health & Social Welfare)
PA to Secretary (Health)

Section Officer



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IDRV - THE KERALA EXPERIENCE

Rabies is a 100% fatal disease but is totally preventable by timely and appropriate post-exposure treatment. Kerala was the first state to start exclusive use of modern CCVs way back in 1993. The high cost of vaccine was the major limiting factor in the fight against the disease when Intra Muscular Rabies Vaccination was in use. The IDRV regimen on the other hand has a reduced dosage (1/5th) and at a 68% reduced cost. Realizing the significance of this, the Govt. of Kerala decided to implement IDRV and took progressive steps towards the implementation of the same.

A two day workshop on developing guidelines for the implementation of IDRV in Kerala was organized by the Govt. of Kerala along with Kerala Medical Services Corporation Ltd (KMSCL) and the State Disease Control & Monitoring Cell (SDCMC), NRHM in September 2008. The workshop was enriched by the presence of experts of national and international repute. On the basis of deliberations of the workshop, "Guidelines for Rabies Prophylaxis and Intra dermal Rabies Vaccination in Kerala, 2008" was framed with the Guidelines put forward by the National Institute of Communicable Diseases in 2007 as the base document.

This was followed with a visit by a core team of policy makers and practitioners from Kerala led by Smt. P. K. Sreemathi Teacher, Hon. Minister for Health & Social Welfare, to the Institute of Preventive Medicine, Hyderabad, to get a hands-on experience. The implementation of IDRV was in a phased manner in the State with a Govt. order issued in November 2008. The first IDRV clinic was inaugurated by Smt. P. K. Sreemathi Teacher at General Hospital, Trivandrum on 27th February 2009. The first phase was initiated at Anti Rabies Clinics (ARCs) attached to Community Medicine Departments of all the 5 Govt. Medical Colleges and ARCs identified in District and General Hospitals in the State. The second phase initiated with the launch of IDRV at the District Hospital Kannur on May 23rd 2009 and is expected to cover 235 centers including District Hospitals/General Hospitals and Taluk Head Quarters Hospitals in the State by December 31st 2010. In the third phase it is to be established in Community Health centres and Primary Health Centres.

Eight model IDRV centres has been set in the State that include the 5 Medical colleges, General Hospital, Trivandrum; District Hospital, Palakkad and Taluk Head Quarters Hospital, Ottapalam. The systematic and scientific implementation of IDRV in the State was appreciated at the national and international level leading to the 11th National Conference of Association for Prevention and Control of Rabies in India(APCRI) being held at Trivandrum on the 4th and 5th of July 2009. It was inaugurated by the Hon Health Minister and the theme was 'IDRV: The challenges ahead'. The State level World Rabies Day was inaugurated by

Sri.C.Divakaran, Honorable Minister for Animal Husbandry, Food and Civil Supplies on 28 September 2009. As part of the World Rabies Day Observance, an awareness rally was flagged off by Sri.C.Jayan Babu, Mayor, Thiruvananthapuram from Raktha Sakshi Mandapam to Press Club.

The vision *Rabies Free Kerala by 2015* set by the Government is on track with the implementation of IDRV. The strategy developed in implementation of IDRV in Kerala is unique and is a model which can be replicated. Dr. F. X. Meslin, Team leader, Neglected Zoonotic Diseases, WHO was invited to review the implementation of IDRV in Kerala. 'IDRV-The Kerala experience', was organized on 18th Nov. 2009 to welcome Dr.F.X.Meslin. Contributors to the implementation of IDRV in the State were honoured at the event. Inaugurated by Smt.P. K. Sreemathi Teacher, the event was significant with the release of the order to provide IDRV free of cost to the public, a major achievement in the fight against rabies. Dr.F.X.Meslin visited various clinics set in Kerala during 18th to 22nd November and was inspired by the political and administrative support of the State in the implementation of IDRV. In accordance to his visit a recommendation towards implementation of RIG in Kerala has been put forward.RIG should be administered to all WHO Cat III (severe) exposures.

All the landmarks made in the implementation of IDRV are by team effort and the support provided by the State Government. Let us work together to achieve our vision and make rabies a history!

ACKNOWLEDGEMENT

The implementation of IDRV in Kerala has been made possible, due to the efforts of many distinguished personalities. I am deeply indebted to:

Smt P.K Sreemathi Teacher, Hon'ble Minister for Health & Social Welfare, Kerala

Shri Manoj Joshi I.A.S, Secretary, Health & F.W, Govt. of Kerala

Dr. Usha Titus I.A.S, Secretary, Health & S.W, Govt. of Kerala

Dr. Dinesh Arora I.A.S, Jt. Secretary, H & F.W & SMD , NRHM & MD KMSCL

Dr. M. K Jeevan, Director of Health Services (i/c), Kerala

Dr. V. Geetha, Director of Medical Education, Kerala

Dr. M.K. Sudarshan, Principal & Prof. of Comm. Medicine, KIMS, Bangalore

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Dr. G. Sampath, Deputy Civil Surgeon, IPM, Hyderabad & President APCRI

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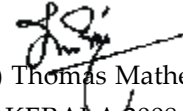
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Dr. Anuja U, Asst. Prof. of Com. Medicine, MC, Thiruvananthapuram.

I am thankful to the Association for Prevention and Control of Rabies in India (APCRI) for using the source material from their Manual on Rabies Immunoglobulins (RIGs) Administration, (February 2009).

I place on record my sincere gratitude to SPEID Cell team (Dr.Khuraisha Beevi. P, Mr. Sivankutty Nair.M), HLFPT team (Mr. Baby Prabhakaran, Mrs. Sandhya Haridas, Mr. Firoz Khan, Ms. Arya Chandran, Mr. Anuraj. T) SDCMC team (Dr. Mohammed Asheel, Mr. Venu Kumar. S, Ms. Preethi. K, Mr. Abhilash. R for layout & cover design) and all others who have worked for the successful implementation of IDRV in the state.



Prof. (Dr) Thomas Mathew
Nodal Officer, IDRV KERALA 2008-09

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ABBREVIATIONS

ARV	: Anti Rabies Vaccine
ARS	: Antirabies Serum
BCG	: Bacillus Calmette Guerin
CCV	: Cell Culture Vaccine
DCGI	: Drug Controller General Of India
ERIG	: Equine Rabies Immunoglobulin
HRIG	: Human Rabies Immunoglobulin
HDCV	: Human Diploid Cell Vaccine
ID	: Intradermal
IM	: Intramuscular
IDRV	: Intradermal Rabies Vaccination
NICD	: National Institute of Communicable Diseases
NTV	: Nervous Tissue Vaccine
PCEC	: Purified Chick Embryo Cell Vaccine
PVRV	: Purified Vero Cell Rabies Vaccine
PMS	: Post Marketing Surveillance
PEP	: Post Exposure Prophylaxis
RIG	: Rabies Immunoglobulin
RFFIT	: Rapid Fluorescent Focus Inhibition Test
TRC	: Thai Red Cross
WHO	: World Health Organisation
KMSCL	: Kerala Medical Services Corporation Ltd
TNMSC	: Tamil Nadu Medical Services Corporation

1. INTRODUCTION

Rabies is an acute viral disease which causes fatal encephalomyelitis in virtually all the warm blooded animals including man. The virus is found in wild and some domestic animals, and is transmitted to other animals and human beings through their saliva (i.e. bites, scratches, licks on broken skin and mucous membrane). In urban areas, the disease is mainly transmitted by dogs; being responsible for about 96% of animal bite cases.

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

There are two types of vaccines, nervous tissue vaccines (NTVs) and cell culture vaccines (CCVs) available for rabies prophylaxis. Until recently NTV was the main stay of treatment for prevention of rabies. In our country, the production and use of this reactogenic vaccine was stopped in December 2004 based on WHO recommendations. Kerala had stopped the production of NTVs way back in 1993 and was the first state to start exclusive use of CCVs. Higher cost of intra-muscular administration of CCV is a limiting factor for its wider use. To overcome this problem,

WHO has recommended use of efficacious, safe and feasible intra-dermal (ID) route of inoculation of CCVs. Sri Lanka, Thailand and Philippines have successfully adopted ID route of administration of CCV against rabies as part of their policies. Clinical trials conducted in India have proved intra-dermal route to be safe, efficacious and feasible for use in the country. National authorities after expert consultation have approved the use of ID route for administration of CCVs in the country in a phased manner. Drug Controller General of India (DCGI) has approved the Intra dermal administration of cell culture vaccine in February & June 2006 (Annexure I) and has been implemented in states like Uttar Pradesh, Orissa, Andhra Pradesh, Karnataka, West Bengal, Tamilnadu and Himachal Pradesh.

A workshop on developing guidelines for IDR (Intra Dermal Rabies Vaccine) in Kerala was held at Thiruvananthapuram on 20th and 21st September 2008. The workshop was enriched by the presence of experts of international and national repute from within and outside the state. Faculties from seven states, who had already implemented the IDR regimen in their states, shared their experiences. The workshop was attended by key stakeholders from all over the state. National Guidelines put forward by NICD in 2007¹ was used as the basic document to formulate guidelines for implementing IDR in Kerala.

¹ "National Institute of Communicable Diseases, National guidelines for rabies prophylaxis and intra-dermal administration of cell culture rabies vaccines", 2007, New Delhi. Published by the Govt. Of India

2. POST-EXPOSURE PROPHYLAXIS

2.1 Decision to treat

In a rabies endemic country like India, where every animal bite is potentially suspected as a rabid animal bite, the post exposure prophylaxis (PEP) should be started immediately. Because of long and variable incubation period, which is typical of most cases of human rabies, it is possible to institute PEP. This must be started at the earliest to ensure that the individual will be immunized before the rabies virus reaches the nervous system. However, **people who present for PEP even months after a possible rabies exposure should be evaluated and prophylaxis given according to the type of exposure as if the event had occurred recently.**

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

Vaccination status of the biting animal:

Although unvaccinated animals are more likely to transmit rabies, vaccinated animals can also do so if the vaccination of the biting animal was ineffective for any reason. A history of rabies vaccination in an animal is not always a guarantee that the biting animal is not rabid. Animal vaccine failures may occur because of improper administration or poor quality of the vaccine, poor health status of the animal, and the fact that one dose of vaccine does not always provide long-lasting protection against infection in dogs.

Provoked versus unprovoked bites:

Whether a dog bite was provoked rather than unprovoked should not be considered a guarantee that the animal is not rabid as it can be difficult to understand what a dog considers provocation for an attack.

Observation of biting animal:

PEP should be started immediately after the bite. The PEP may be modified if animal involved (dog or cat) remains healthy throughout the observation period of 10 days by converting post-exposure prophylaxis to pre-exposure vaccination by skipping the vaccine dose on day 14 and administering it on day 28 while using Essen IM Schedule. Complete the course of treatment while using ID route.

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.

Bite by wild animals:

Bite by all wild animals should be treated as category III exposure.

Bite by rodents:

It should be noted that bites by domestic rats, mice, squirrel, hare and rabbits seldom require PEP. However, following exposure to bandicoots and mongoose, PEP is recommended.

Consumption of raw milk of rabid animals:

Following history of consumption of raw milk from a rabid animal, the person may be given rabies PEP.

Bat rabies:

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

Human-to-human transmission:

The risk of rabies transmission to other humans from a human rabies case is very minimal and there has never been a well documented case of human-to-human transmission, other than the few cases resulting from organ transplant. However, people who have been exposed closely to the secretions of a patient with rabies may be offered PEP as a precautionary measure.

2.2 Special circumstances**Physiological states**

Pregnancy, lactation, infancy, old age and concurrent illness are no contra indications for rabies post-exposure prophylaxis in the event of an exposure. PEP against rabies takes preference over any other consideration since it is a life saving treatment. Moreover, rabies vaccine does not have any adverse effect on fetus, mother-to-be and the course of pregnancy. Hence, complete PEP should be given depending on the category of the exposure.

Post-exposure prophylaxis of immuno compromised patients:

Severely immuno compromised (HIV/AIDS patients with CD4count<200, patients with chronic renal failure, those on

immuno suppressive drugs or anticancer drugs) **with category II exposures should receive category III PEP. Vaccine should be given by IM route only_(Essen schedule).** Preferably, if the facilities are available, antirabies antibody estimation should be done 10 days after the completion of course of vaccination.

Concurrent drug use:

Concurrent drug use is not a contraindication for PEP. But animal bite victims on Chloroquine therapy (anti-malarial therapy) should be given ARV by intramuscular route.

It is reemphasised that PEP should be started as early as possible after exposure. However, it should not be denied to persons reporting late for PEP as explained previously.

2.3 Approach to Post-Exposure Prophylaxis (PEP)

The post-exposure prophylaxis is a three pronged approach. All three carry equal importance and should be done simultaneously as per the category of the bite (refer Decision tree, Annexure VI).

- Management of animal bite wound
- Passive immunisation: Rabies Immunoglobulins (RIG)
- Active immunisation: Anti-Rabies Vaccines (ARV)

2.3.1 Management of animal bite wound

Wound toilet:

Since 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 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. (Table 2, Annexure VII)

This can be done by prompt and gentle thorough washing with soap and flushing the wound with running water for 15 minutes. Avoid direct touching of wounds with bare hands. Considering the importance of this step the anti-rabies clinics should have wound washing facilities.

The application of irritants (chillies, oil, turmeric, lime, salt, plant sap etc) is unnecessary and damaging. In case irritants have been applied on the wound, enough gentle washing with soap to remove the extraneous material especially oil, should be done; followed by flushing with copious amount of water for 10 minutes immediately.

It should be noted that the immediate washing of the wound is a priority. However, **the victim should not be deprived of the benefit of wound toilet as long as there is an unhealed wound which can be washed even if the patient reports late.** Care must be taken not to disturb scabs, if formed. The maximum benefit of the wound washing is obtained when fresh wound is cleaned immediately.

Application of antiseptics: After thorough washing and drying the wound, any one of the available chemical agents should be applied viz Povidone iodine (Betadine), Alcohol, Chlorhexidine Gluconate and Cetrimide solution (Savlon - in the appropriate recommended dilution), etc.

Local infiltration of rabies immunoglobulins: In category III bites rabies immunoglobulin should be infiltrated in the depth and around the wound to inactivate the locally present virus as described in Table 2 (Annexure - VII)

Suturing of wound should be avoided as far as possible. If surgically unavoidable, minimum loose sutures should be applied after adequate local treatment along with proper infiltration of rabies immunoglobulins (RIGs). RIG should be infiltrated into already sutured wound without disturbing the sutures.

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

Occlusive dressing to be avoided as far as possible.

Injection tetanus toxoid should be given to the un-immunised individual.

Antibiotic / Analgesics: Depending on the severity of the wound an appropriate antibiotic may be given.

2.3.2 Rabies Immunoglobulins (RIGs)

The anti-rabies serum/rabies immunoglobulin provides passive immunity in the form of ready-made anti-rabies antibodies to tide over the initial phase of the infection. 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:

Equine Rabies Immunoglobulins (ERIG):

ERIG/ anti rabies serum (ARS) is of heterologous origin raised by hyper-immunisation of horses. However, currently manufactured ERIGs are highly purified and the occurrence of adverse events has been significantly reduced. Still these should be administered after obtaining *informed consent and performing sensitivity test.*

Human Rabies Immunoglobulins (HRIG):

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 equine anti-rabies serum.

The RIGs should always be brought to room temperature (20 – 25°C) before use.

Dose of rabies immunoglobulins:

The dose of equine rabies immunoglobulin is 40 IU per kg body weight of patient (up to a maximum of 3000 IU) and is given after testing for sensitivity. The ERIG produced in India contains 300 IU per ml. The dose of the human rabies immunoglobulin (HRIG) is 20 IU per kg body weight (maximum 1500 IU). HRIG does not require any prior sensitivity testing. HRIG preparation is available in concentration of 150 IU per ml.

Administration of immunoglobulins:

As much of the calculated dose of RIG as is anatomically feasible should be infiltrated into and around the wounds.

Remaining, if any, after all wounds have been infiltrated, should be administered by deep intramuscular injection in the gluteal region. Multiple needle injections into the wound should be avoided. If the calculated dose of the rabies immunoglobulin is not sufficient to infiltrate all wounds, it is advisable to dilute the immunoglobulin in sterile normal saline to a volume sufficient to infiltrate all wounds.

Technique of administration

As the RIG is being injected the needle should be slowly withdrawn while the piston of the syringe is pushed so that entire wound is infiltrated. The RIG shall be injected into the edges & base of the wound(s) till traces of RIG oozes out. It is preferable to use separate needles for infiltrating different wounds. Multiple needle injections into the wound should be avoided as far as possible. If significant quantity of RIG may ooze out of the wounds, the quantity of RIG should be replaced by fresh infiltration using an equivalent volume of RIGs. Before administering RIG, confirm that needle is not in blood vessels.

In situations where immunoglobulin was not administered with the first dose of vaccine; it can be given upto the seventh day. Beyond the seventh day in a person who has received three doses of vaccine on days 0, 3 & 7, Rabies Immunoglobulin (RIG) is not indicated since an antibody response to anti-rabies vaccine is presumed to have occurred. Immunoglobulin should never be administered in the same syringe or at the same anatomical site as vaccine.

Sensitivity test before administration of ERIG:

With antisera of equine origin, anaphylactic shock may occur and thus sensitivity testing is mandatory before giving ERIG. Skin test may be performed as per the manufacturer's instructions given in the product insert. Otherwise general guidelines are described in Table 3.

Table 3: Skin testing prior to administration of ERIG

- Inject 0.1 ml ERIG diluted 1:10 in physiological saline intra-dermally into the flexor surface of the forearm to raise a bleb of about 3-4 mm diameter.
- Inject an equal amount of normal saline as a negative control on the flexor surface of the other forearm.
- After 15 minutes an increase in diameter to > 10 mm of induration surrounded by flare is taken as positive skin test, provided the reaction on the saline test was negative.
- An increase or abrupt fall in blood pressure, syncope, hurried breathing, palpitations and any other systemic manifestations should be taken as positive test.

Precautions to be taken while administering RIGs

- The patient should not be on an empty stomach.
- 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).
- While infiltrating RIG into bite wounds, care must be taken to avoid injecting into blood vessels and nerves. Sufficient

care must also be taken while infiltrating RIG into bit wounds near the eyes and genital region. Anatomical feasibility must always be kept in mind while injecting RIG.

- All emergency drugs and facilities for managing any adverse reactions must be available.
- If ERIG is being administered: Carefully elicit the history of any previous administration of horse sera viz. anti tetanus, anti-diphtheria, anti-gas gangrene, anti snake venom serum & even anti-rabies sera(ERIG).
- Keep the patient under observation for at least one hour after ERIG administration and then send home.
- RIG should never be administered in the same syringe or at the same anatomical site as vaccine administration.
- RIG should be infiltrated into already sutured wounds without disturbing the sutures.
- RIG can be safely injected into already infected animal bite wounds following proper wound cleansing and administration of appropriate antibodies

A negative skin test must never reassure the physician that no anaphylactic reaction will occur. Those administering ERIG should always be ready to treat early anaphylactic reactions with adrenalin. 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 subcutaneously or IM. If patient is sensitive to ERIG, HRIG should be preferred. However, if HRIG is not available, ERIG can still be considered after taking due precautions and obtaining an informed high risk consent.

Approach to a patient requiring rabies immunoglobulin when none is available:

In circumstances where no immunoglobulin is available, greater emphasis should be given to proper wound toileting followed by Intra muscular Essen Regimen of CCV with double dose on day 0 at 2 different sites intramuscularly (0 day – 2 doses on left and right deltoid) and then by single dose each on 3, 7, 14 and 28 days. This emphasise that doubling the first dose of CCV is not a replacement to RIG.

Tolerance and side effects:

With RIG, there may be transient tenderness at the injection site and a brief rise in body temperature which do not require any treatment. Skin reactions are extremely rare. RIG must never be given intravenously since this could produce symptoms of shock, especially in patients with antibody deficiency syndromes. Serum sickness occurs in 1% to 6% of patients usually 7 to 10 days after injection of ERIG, but it has not been reported after treatment with HRIG.

Note

1. RIG should never be administered in the same syringe or at the same anatomical site as vaccine administration.
2. RIG should be infiltrated into already sutured wounds without disturbing the sutures.
3. RIG can be safely injected into already infected animal bite wounds following proper wound cleansing and administration of appropriate antibodies.

RIGs in re exposure cases

- In persons who have received previously (anytime in the past) either pre exposure vaccination (3 doses on day 0,7 & 21/28) or post exposure prophylaxis (5doses), there is no need for RIG administration because their immune system has already been primed and once they receive a booster dose of vaccine, their immune system will initiate an immediate anamnestic response which is adequate to neutralize the virus. Hence, re-exposure cases need only two doses of modern anti rabies vaccine on days 0 & 3.
- Persons who have received sheep brain vaccine (NTV) previously or persons who cannot remember the type & dose of rabies vaccine that they received previously, have to receive complete PEP including RIG.

2.3.3 Anti-Rabies Vaccines

Active immunisation is achieved by administration of safe and potent CCVs. In Kerala, NTV was used for PEP in the public sector. However as this vaccine was reactogenic, the production was stopped in the state in 1993 whereas in India the production of NTVs was stopped in December 2004. CCVs are now used for active immunisation.

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, it is recommended that these vaccines should be kept and transported at a temperature range of 2-8°C. Liquid vaccines should never be frozen.

Reconstitution and storage:

The lyophilised vaccine should be reconstituted with the diluent provided with the vaccine immediately prior to use. The remaining vaccine after reconstitution should be stored at 2-8°C. However, in case of unforeseen delay it should not be used after 6-8 hours of reconstitution.

Adverse effects with Cell Culture Vaccines:

The Cell Culture Vaccines are widely accepted as the least reactogenic rabies vaccines available today. However, few studies have now shown that adverse effects can be either general in nature or allergic in origin. The general adverse reactions include sore arm, headache, malaise, nausea, fever and localised oedema at the site of injection. Symptomatic treatment may be needed.

Switch over from one brand/type of vaccine to the other:

Shifting from one brand/type of CCV to other brand/type should not be encouraged as literature supports that good immunity is best achieved with same brand. However, under unavoidable circumstances, available brand/type may be used to complete PEP.

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.

2.3.3.1 Intra Muscular (IM) regimen(Essen Schedule)

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

Vaccines

1. Cell Culture Vaccines

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

2. Purified Duck Embryo Vaccine (PDEV)

Regimen

Five dose intramuscular regimen - The course for post-exposure prophylaxis should consist of intramuscular administration of one injection each on days 0, 3, 7, 14 and 28. The sixth injection (Day 90) 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 indicates date of first injection and not necessarily the day of bite/exposure.

Site of inoculation:

The deltoid region is ideal for the inoculation of these vaccines. Gluteal region is not recommended because the fat

present in this region retards the absorption of antigen and hence impairs the generation of optimal immune response. In case of infants and young children, antero-lateral part of the thigh is the preferred site.

2.3.3.2 Intra - Dermal (ID) Regimen

Concept of intra-dermal inoculation of anti-rabies vaccines (IDRV):

Intra-dermal regimens consist of administration of a fraction of intramuscular dose of approved cell culture 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. Single dose (0.5ml/1ml) of rabies vaccine/antigen when given by IM route gets deposited in the muscles. Thereafter the antigen is absorbed by the blood vessels and is presented to antigen presenting cells which trigger immune response. Whereas, while using ID route, small amount (0.1ml) of rabies vaccine/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.

Mechanism of action of IDRV:

Intra-dermal inoculation is deposition of approved rabies vaccine (or antigen) in the layers of dermis of skin. Subsequently the antigen is carried by antigen presenting cells via the lymphatic

drainage to the regional lymph nodes and later to the reticulo-endothelial system eliciting a prompt and highly protective antibody response. Immunity is believed to depend mainly upon the CD 4 +T-cell dependent neutralising antibody response to the G protein. In addition, cell-mediated immunity has long been reported as an important part of the defense against rabies. Cells presenting the fragments of G protein are the targets of cytotoxic T-cells and the N protein induced T helper cells. The immune response induced by IDRV is adequate and protective against rabies.

Vaccines and regimen approved for IDRV by DCGI in India

Considering the recommendations on intra-dermal rabies vaccination by WHO and results of safety, efficacy and feasibility trials conducted in India, Drug Controller General of India (DCGI) approved the use of reduced dosage intra-dermal vaccination regimen for pre and post exposure prophylaxis¹. The use of this route leads to considerable savings in terms of the total amount of vaccine needed for a full post-exposure vaccination, thereby reducing the cost of active immunisation.

The following vaccines have been approved by DCGI for use by intra-dermal route:-(Annexure II)

1. PCECV – Rabipur - vial of 1ml, Chiron Behring Vaccines Pvt. Ltd.
2. PVRV – Verorab – vial of 0.5ml, Aventis Pasteur (Sanofi Pasteur) India Pvt.Ltd.

¹ GOI (DCGI) ORDER NO: X-11026/23/05-D dtd 28th February 2006

3. PVRV – Pasteur Institute of India, Coonoor
4. PVRV – Abhayrab – vial of 0.5ml, Human Biologicals Institute
5. PVRV – Indirab, vial of 0.5 ml/ 1ml Bharath Biotech, Hyderabad (2008)

PDEV (Vaxirab) and Liquid HDCV (Rabivax) are not approved for IDRV by DCGI.

Precautions:

- A sterile needle and syringe must be used to draw up vaccine for each patient, to prevent cross-infection of hepatitis, HIV and other infections.
- A separate syringe and needle should be used for each site of intradermal injection in each patient.
- Intradermal injections must be administered strictly by staff trained in this technique.
- Rabies vaccines formulated with an adjuvant should not be administered intradermally.

Potency of Vaccines:

The vaccines should have a stated potency of ≥ 2.5 I.U. per IM dose, irrespective of reconstituted volume. The same vaccine which is used for intramuscular administration is used for ID administration after amendment of label and package insert. The amended label along with the package insert should be approved by Drug Controller General of India (DCGI). Post marketing surveillance (PMS) data should be maintained for minimum of two years by vaccine manufacturers on a pre designed and

approved protocol. The vaccine package leaflet should include a statement indicating that the potency as well as immunogenicity and safety allow safe use of vaccine by ID pre and post exposure.

Approved IDRV Regimen

As per DCGI recommendations, the schedule approved for IDRV is the Updated Thai Red Cross regimen (2-2-2-0-2). In this regimen 0.1 ml of reconstituted vaccine is given per ID site and on two such ID sites per visit on days 0, 3, 7 and 28. Day 0 is the date administration of first dose of vaccine.

UPDATED TRC REGIMEN

Day	Dose	Total Volume
0	0.1ml on each arm	0.2ml
3	0.1ml on each arm	0.2ml
7	0.1ml on each arm	0.2ml
28	0.1ml on each arm	0.2ml
	Total	0.8ml

Thus the total volume of vaccine used in this regimen is 0.8 ml, whereas it will be 2.5 ml or 5ml, depending on the vaccine used, if vaccine is administered by intramuscular route.

COMPARISON OF INTRAMUSCULAR AND INTRADEMAL REGIMENS

Intra muscular(Essen) regimen(in deltoid region)			Intradermal (Updated Thai regimen) 0.1 ml per site(in deltoid region)
Day	0	one injection	2 Sites
Day	3	one injection	2 Sites
Day	7	one injection	2 Sites
Day	14	one injection	<i>No Injection</i>
Day	28	one injection	2 Sites

TECHNIQUE

Preparation of a Patient for IDRV:

The patient must be made to sit comfortably and adequate privacy should be ensured especially for female patients. Both the sites of vaccination (deltoid) must be adequately exposed.

Equipments required:

- A vial of freeze dried rabies vaccine and diluents.
- 2 ml. disposable syringe with needle for reconstitution of vaccine
- A disposable 1 ml syringe. *Preferably an insulin syringe with a fixed needle (28 or more gauge) should be used.*
- Antiseptic swabs (e.g.70% ethanol) for cleaning the top of the vial and the patient's skin.

Procedure:

Reconstitute the vial of freeze-dried vaccine with diluent supplied by the manufacturer, using aseptic technique.

With the 1 ml syringe, draw up the volume of vaccine needed to inject at one site, i.e. 0.1ml, allowing for any dead space in the syringe. Expel any air bubbles carefully.

If a 40 unit Insulin syringe is used, draw upto 4 units.

If a 100 unit Insulin syringe is used draw upto 10 units.

(Do not use a 1ml syringe with a detachable needle for administering IDRV, as nearly one-third of the volume of the vaccine remains in the nozzle of the syringe after injecting the vaccine).

With the antiseptic swabs clean the patient's skin on both the sites. Allow the disinfectant to dry before administering the vaccine.

Stretch the surface of the skin and insert the tip of the needle bevel upwards, almost parallel to the skin surface and slowly inject the vaccine into the uppermost layer of skin over the deltoid area (similar to the technique for BCG inoculations).

If the needle is correctly placed, considerable resistance is felt while injecting the vaccine. A raised papule should begin to appear immediately resulting in a visible & palpable bleb in the skin. Finally a "peau d'orange" (orange peel) appearance is seen. In a similar way inject 0.1 ml of vaccine on the opposite deltoid area.

If the vaccine is injected too deeply into the skin, and a papule is not seen, the needle should be withdrawn and reinserted nearby.

If there is complete failure to inject intradermally at one site, an extra intradermal dose should be given at a nearby site.

Those inexperienced with the technique should practice using 0.1 ml of isotonic saline until they can reliably produce a peau d'orange (orange peel) papule.

Some difficulty may arise with elderly patients who have thin, inelastic skin, and with infants who are crying.

Storage of reconstituted vaccines:

If great care is taken with aseptic technique, an appropriate dose of vaccine may be withdrawn from a vial and the remainder used for another patient, provided that the vial is stored in a refrigerator at 2° to 8°C.

Although the vaccine antigen is very stable at 4°C, there is a high risk of contamination of multidose vials by microorganisms, especially if the vaccine does not contain a preservative. Reconstituted vaccines should be used as soon as possible but at least within 8 hours if kept at 2° to 8°C.

Advice to patients

- Patients should be advised not to rub at the site of intradermal injection after administration of vaccine.
- Patients should be made aware about the common side effects, i.e., itching and pain at the site of injection.
- They must be advised to complete the full course of vaccine as per the advised schedule.
- No dietary restrictions
- No restriction of physical exercise.
- Best to avoid consumption of alcohol during the course of treatment.

Side effects of ID vaccine treatment:

Throughout 25 years of use, cell culture vaccines have proved remarkably safe and free of significant complications.

Mild symptoms of pain, erythema, irritation, (itching) or swelling at the intradermal injection sites occur in some of the patients. The most frequent symptom is local irritation. Generalized symptoms reported by 3% to 14% of recipients include headache, fever and influenza-like illness. Transient maculopapular and urticarial rashes are occasionally seen.

2.4 Post-exposure prophylaxis for previously vaccinated persons

Managing re-exposure following post-exposure prophylaxis with CCV:

If re-exposed, persons who have previously received full post-exposure prophylaxis (either by IM or ID route) with a potent cell-culture vaccine should now be given only two booster doses, intramuscularly (0.5ml or 1ml as relevant to the type of vaccine)/ intradermally (0.1 ml at 1 site) on days 0 and 3. Proper wound toilet should be done. Treatment with RIG is not necessary.

Managing exposure following pre-exposure prophylaxis with CCV:

If after recommended pre-exposure vaccination, a vaccinated person is exposed to rabies, 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. Treatment with RIG is not necessary

Managing re-exposure following post-exposure prophylaxis with NTV:

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

3. 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 travellers 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 at one site on days 0, 7 and either day 21 or 28.

Laboratory staff and others at high continuing risk of exposure should have their neutralising 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 immunisation require only two booster injections of vaccine given on days 0 and 3 without any anti-rabies serum/RIGs.

Record of Treatment

Hospital records should include the vaccine type, batch number and treatment regimen.

The timing of future injections must be emphasized by means of an appointment card given to each patient.
(Annexure VIII)

4. SELECTION OF CENTRES FOR IDR V

- Centre should have adequately trained staff and proper cold chain facilities.
- Staff should be well versed in open vial and safe storage practices.
- Adequate supply of syringes and needles should be available.
- Attendance of adequate number of patients every day.

Training of Health personnel in IDR V Technique

To ensure that IDR V is effective, training should be imparted to those involved in its implementation.

Training of trainers (TOT) to be conducted at Institute of Preventive Medicine, Hyderabad.

The centres converted to Model ARCs with IDR V facility shall function as nodal centres for further training in the state.

5. POINTS TO REMEMBER FOR IDR V.

1. Vaccines given by intra-dermal route should be approved and licensed by DCGI.
2. The vaccine package leaflet should include a statement indicating that the potency as well as immunogenicity and safety, allow the safe use of vaccine by ID for pre-and post-exposure prophylaxis.
3. Post Marketing Surveillance (PMS) data should be maintained for minimum of two years by vaccine manufacturers on a pre-designed and approved protocol.

4. The pack labels on the vials should clearly indicate that it is meant for ID route of administration.
5. Intra-dermal injections must be administered by staff trained in this technique.
6. Vaccine vials must be stored at 2° to 8°C after reconstitution.
7. The total content of the reconstituted vial should be used as soon as possible, but at least within 8 hours.
8. All the reconstituted vaccines should be discarded after 8 hours of reconstitution or at the end of the day, whichever is earlier.
9. PDEV (Vaxirab) and rabies vaccines formulated with an adjuvant (rabivax) should not be administered intradermally.
10. Vaccine when given intradermally should raise a visible and palpable bleb in the skin.
11. In the event that the dose is inadvertently given subcutaneously or intramuscularly or in the event of spillage, a new dose should be given intradermally in near by site.
12. Animal bite victims on chloroquine therapy (anti-malarial therapy) should be given ARV by intramuscular route.
13. Immuno compromised patients with category II exposures should receive category III PEP. Vaccine should be given by IM route only.

6. PROCUREMENT OF VACCINE

The following special clauses under eligibility criteria may appear in the Bid Document of KMSCL :

- Vaccines procured for administration by intradermal route should be approved and licenced by DCGI.
- For vaccines recommended by WHO to be used intradermally, the vaccine insert should contain a statement saying:
“This vaccine is of sufficient potency to allow its safe use in one of the WHO recommended intradermal post exposure regimens in countries where relevant national authorities have approved the intradermal route for rabies PEP.” (WHO, Department of communicable disease surveillance and response)
- The pack labels on the vials should clearly indicate that it is meant for ID route of administration.

Nomenclature of the Vaccine as appeared in 2008-09 TNMSC Tender 001/M(P)/TENDER/DRUGS/TNMSC/2008 dated 26-03-08 :

“Rabies Vaccine Human (Cell Culture) I.P (Intradermal) 2.5 IU 1ml vial with diluent”

ANNEXURE -I

GOI (DCGI) order

X-11026/23/05-D
Directorate General Of Health Services
(Drugs Section)

Nirman Bhawan, New Delhi
Dated, 28th February, 2006.

To

1. M/S Aventis Pasteur (Sanofi Pasteur) India Pvt. Limited
Chaitanya-1, Chaman Farm Village, Bundh Road
Gadaipur, New Delhi-110 030.
2. M/S Chiron Behring Vaccines Private Limited
Plot No. 3501/A, 3502 & 3503/A
Post Box No. 136, GIDC Estate, Ankleshwar-393 002.
Distt- Bharuch, Gujarat.

Sub: Use of Intradermal,(I.D) route for administration of Tissue Culture Anti Rabies Vaccine- regarding.

Sir ,

Based on the recommendation of the expert group as well as WHO, it has now been decided to allow I.D. route of administration for Tissue Culture based Anti Rabies Vaccine, in post-exposure treatment of patients in a phased manner.

In the first phase, the Schedules and vaccines endorsed by WHO (WHO TRS 931, year 2005) for i.d. route and the schedule recommended by ICMR Study may be permitted, which are as follows:

- 2-site schedule,
- updated Thai Red Cross Regimens i.e 2-2-2-0-2,
- Thai Red Cross Regimen i.e 2-2-20-1-1 (WHO/EMC/Zoo/96.6 and ICMR study)
- Vaccines recommended in the first phase for i.d route are;
- (i) Purified vero cell Rabies Vaccines produced by Aventis Pasteur(Sanofi Pasteur) (ii) Purified Chick Embryo Cell Vaccine produced by Chiron Behring Vaccine Pvt. Ltd.

The unit dose of 0.1 ml of these vaccine having potency of at least 2.5 IU per single intramuscular immunizing dose should be applied as per recommended regimens.

Further the use of intradermal route may be approved initially for use in selected anti-rabies clinics which meet the following criteria:

- Attendance of minimum of 50 patients/day for Post – Exposure Treatment
- Have adequately trained staff to give i.d. inoculation;
- Can maintain cold chain for vaccine storage and ensure adequate supply of suitable syringes and needles for i.e. administration.
- Are adequately well versed in management of open vial and safe storage practices.

In view of above, you are allowed to market your licensed ARV through ID route, having the stated potency. And in the manner as recommended above. A copy of PMS Protocol and amended label along with its package insert for marketing of ARV through i.d. route may also be furnished to this Directorate.

While marketing you are advised to generate PMS data for two years. A copy of PMS protocol may also be furnished to this Directorate.

Yours faithfully,


(Ashwini Kumar)
Drugs Controller General (I)

Copy to:

1. PS to DGHS.
2. Director, NICD, Delhi. With reference to the recommendations of expert committee met on 15th Feb, 2006 at NICD, in the subject matter.

Nirman Bhawan, New Delhi
Dated:2/05/06

To

1. Pasteur Institute of India,
Coonoor TamilNadu
2. Human Biological Institute
Ooty, Chennai

Subject: Use of Intradermal,(I.D) route for administration of Tissue Culture Anti Rabies Vaccine – regarding

Sir,

Based on the recommendation of the expert group as well as WHO, it has now been decided to allow I.D route of administration for Tissue Culture based Anti Rabies Vaccine, in post exposure treatment of patients.

The recommendation were based on bridging study for immunogenicity by ID route which had been designed to conform the immunogenicity by approved vaccine when given in much smaller doses by ID route as compare to IM injections.

The schedules and vaccines endorsed by WHO (WHO TRS 931, year 2005) for I.d route and the schedule recommended by ICMR study may be permitted, which are as follows:

- 2-Site Schedule, updated Thai Red cross Regimens i.e 2-2-2-0-2.
- Vaccines recommended for I.d route are:
(i) Purified vero cell Rabies Vaccines produced by Human Biological Institute Ooty Chennai (ii) Purified vero cell Rabies Vaccines produced by Pasteur Institute of India Coonoor Tamil Nadu

The unit dose of 0.1 ml of these vaccine having potency of at least 2.5 IU per single intramuscular immunizing dose should be applies as per recommended regimens.

Further the use of intradermal route may be approved initially for use in selected anti-rabies clinics which meet the following criteria

- Attendance of minimum of 50 patients/day for post -Exposure Treatment.
- Have adequately trained staff to give i.d inoculation;
- Can maintain cold chain for vaccine storage and ensure adequate supply of suitable syringes and needles for i.c administration.
- Are adequately well versed in management of open vial and safe storage practices.

In view of above, you are allowed to market your licensed ARV through ID route, having the stated potency, and in the manner as recommended above. While marketing, you are also require to generate. Safety and efficacy data of your licenced vaccine along with data on post-marketing surveillance A copy of PMS protocol and amended label along with its package insert for marketing of ARV through i.d route may also be furnished to this Directorate.

Yours Faithfully



(A.B. Ramteke)

Drugs Controller General(I)

Copy to :

1. PS to DGHIS
2. DDG(JS)
3. Directorate., NICD, Delhi . with reference to the recommendation of expert committee met on 3rd April, 2006 at NICO, in the subject matter.

(Note: A DCGI order dated 9th August 2006, has revised the eligibility criteria for intradermal administration of tissue culture rabies vaccines at anti- rabies clinics (ARC) in India from those with a minimum attendance of 50 patients per day to those with a minimum of 10 patients per day)

ANNEXURE -II

No. 11026/23/05D
Directorate General of Health Services
(Drugs Section)

To,

All the concerned vaccine manufacturers

Subject: Use of Intradermal (I.D.) route for administration of Anti Rabies Cell Culture Vaccines – regarding

References: 1. No. X – 11026/23/05 – D, DGHS, (Drug Section) dated 28th Feb 06.
2. No. X – 11026/23/05 – D, DGHS, (Drug Section) dated 2/05/06
3. No. X – 11026/23/05 – D, DGHS, (Drug Section) dated 09th Aug 2006
4. No. X – 11026/23/05 – D, DGHS, (Drug Section) dated 23rd Oct 2006

In super session of all the previous letters vide references above, it is stated that based on the recommendations of the expert group as well as WHO and ICMR feasibility study, this office permits the use of administration of anti-rabies Cell Culture Vaccines by intra-dermal (ID) route for pre – and post-exposure prophylaxis.

The vaccines and schedules approved for ID route are as under:

Vaccines

PVRV – Verorab, Aventis Pasteur (Sanofi Pasteur) India Pvt. Ltd.

PCEC – Rabipur, Chiron Behring Vaccines Pvt. Ltd.

PVRV – Pasteur Institute of India, Coonoor

PVRV – Abhayrab, Human Biologicals Institute.

Schedule for post exposure prophylaxis

2-site schedule: (Updated Thai Red Cross Regimen i.e. 2-2-2-0-2)

0.1 ml of reconstituted vaccine, irrespective of total reconstituted volume, should be administered per id site at 2 sites on both deltoid regions on days 0, 3, 7 and 28.

Schedule for Pre-exposure vaccination

0.1 ml of reconstituted vaccine, irrespective of total reconstituted volume, on deltoid region on days 0, 7 and 21 or 28.

Potency of vaccine

The vaccines should have stated potency of ≥ 2.5 IU per intramuscular dose(IM), irrespective of total reconstituted volume. The same vaccine which is used for intramuscular administration, is used for ID administration after amendment of label and package insert as under:


Label and package inserts

The vaccine which is being used for IM administration can be used for ID administration after the vaccine manufacturers amend the label and package insert to indicate that the vaccine is fit for use by IM and ID route in anti-rabies treatment centres. PMS data should be generated for a period of two years. The manufacturers should submit the PMS protocol and amended label along with the package insert, at the earliest, for approval by this Directorate.

The use of intra-dermal route is approved in anti-rabies treatment centres which meet the following criteria:

- Have trained staff to give anti-rabies vaccination by ID route.
- Have cold chain facilities for vaccine storage and supply of syringes and needles.
- Are well versed in management of open vial and safe storage practices.

Yours faithfully,


(Dr. M. Venkateswarlu
Drugs Controller General of India)

Copy to:

1. Addl. DG & Director, NICD and Head, WHO Collaborating Centre for Rabies Epidemiology, NICD, Delhi
2. ADG (EPI), Directorate of Health Services, Nirman Bhavan, New Delhi

ANNEXURE -III

751

F.No 04/BBL-40/PVRV/07-DC
Directorate General of Health Services
Office of Drugs Controller General (India)
(Biological Division)

08 OCT 2008
FDA Bhawan,
Kotla Road, New Delhi

Dated 08 OCT 2008

To,

M/s. Bharat Biotech International Ltd.
Genome Valley Turkapally,
Shameerpet (Mandal), Hyderabad-500 078

Subject: Application for manufacturing & marketing licence of "INDIRAB" for intradermal injection with 1ml diluent- regarding.

Reference: Your letter no. BBL/CRA/III/886 dated 12.09.08

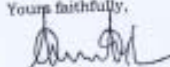
Sir,

This Directorate has no objection to recommend the use of intradermal route of administration to your licensed anti rabies vaccine to be reconstituted with 1ml diluent for use in selected anti rabies clinic which has attendance of 10 patients per day for post-exposure treatment. Further it is stated that each dose of 0.1ml of anti Rabies Vaccine (Vern Cell) having potency of 2.5 IU per single intramuscular dose as per the Thai CDC dosage regimen.

While manufacturing & marketing ID TCARV, you are also advised to supply syringes & hypodermic needles in addition to diluents to avoid use of other needles. You are required to conduct Post Marketing Surveillance Study after getting the Protocol duly approved by this Directorate.

~~Submit the package insert, labels before marketing the product.~~

Other terms & condition of this Directorate letter of even no. 04-37/03-DC (Pt. Vne-BB) dated 14.12.06 shall remain unchanged.

Yours faithfully,

(Dr. Surinder Singh)
Drugs Controller General (India)

Copy to
The Director,
Drugs Control Administration,
Drugs Control Bhawan,
Vengal Rao Nagar (Hyderabad) - 500038 (A.P.)



ANNEXURE -IV

List of experts

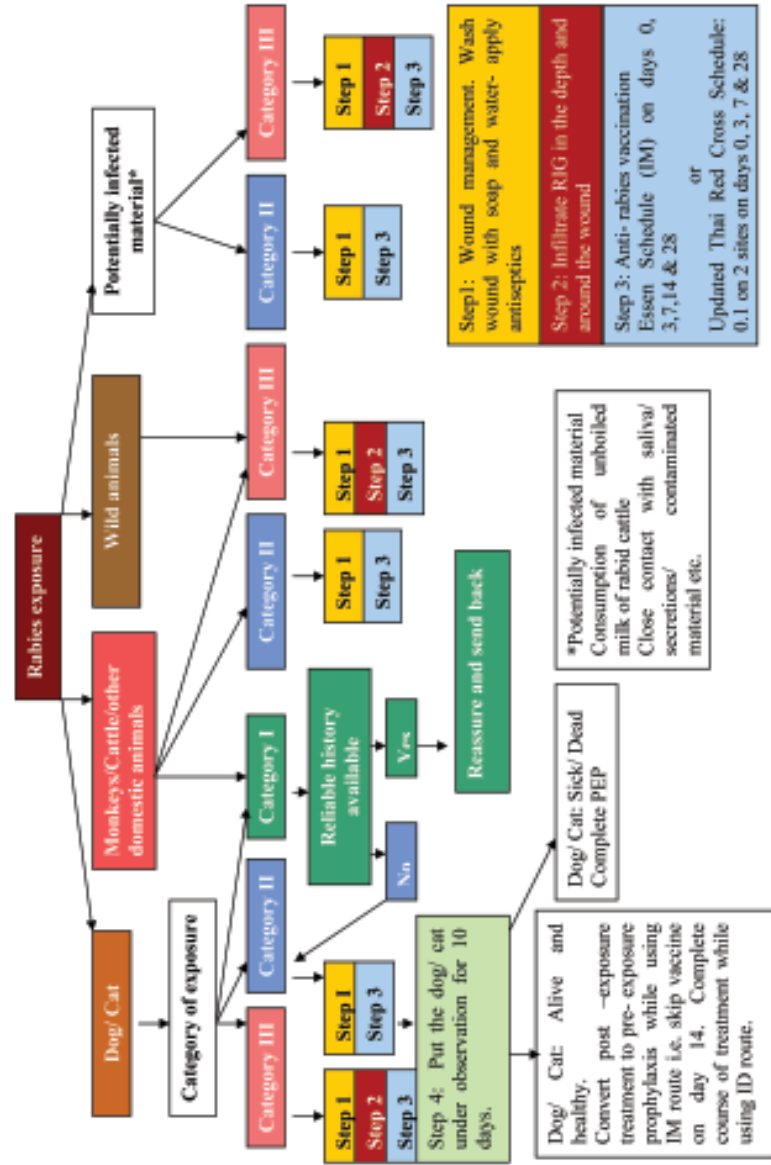
1. **Dr.S.N. Madhusudana**, Additional Professor of Neurovirology & Head, WHO Collaborating Centre on rabies research, National Institute of Mental Health and Neurosciences, Bangalore.
2. **Dr.M.K.Sudarshan**, Principal and Professor of Community Medicine & President, Rabies in Asia Foundation, Kempegowda Institute of Medical Sciences, Bangalore.
3. **Dr.G.Sampath**, Deputy Civil Surgeon, Institute of Preventive Medicine, Narayanaguda, Hyderabad. & President, Association for Prevention and Control of Rabies in India (APCRI)
4. **Dr.Thomas Mathew**, Professor of Community Medicine, Medical College, Thiruvananthapuram, Kerala & Secretary General , Association for Prevention and Control of Rabies in India (APCRI)
5. **Dr.D.H. Ashwath Narayana**, Associate Professor of Community Medicine, Kempegowda Institute of Medical Sciences, Bangalore.
6. **Dr Sara Varghese**, Professor of Community Medicine &Coordinator State PEID cell, Thiruvananthapuram
7. **Dr Sairu Philip**, Asso. Professor of Community Medicine & Coordinator Regional PEID cell, TD Medical College, Alappuzha
8. **Dr.Indu PS** Asso. Professor of Community Medicine, Govt. Medical College, Thiruvananthapuram
9. **Dr Anuja U**, Asst. Professor of Community Medicine, Medical College, Thiruvananthapuram
10. **Dr Regi Jose**, Asst. Professor of Community Medicine, Dr.Somervell Memorial CSI Medical College, Karakonam, Thiruvananthapuram.

ANNEXURE -V

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

Category	Type of contact	Type of exposure	Recommended PEP
I	<ul style="list-style-type: none"> • Touching or feeding of animals • Licks on intact skin 	None	None if reliable case history is available
II	<ul style="list-style-type: none"> • Nibbling of uncovered skin • Minor scratches or abrasions without bleeding 	Minor	<ul style="list-style-type: none"> • Wound Management • Anti rabies vaccine
III	<ul style="list-style-type: none"> • Single or multiple transdermal bites or scratches with oozing of blood, licks on broken skin • Contamination of mucous membrane with saliva (i.e. licks) 	Severe	<ul style="list-style-type: none"> • Wound management • Rabies immunoglobulin/ antirabies serum • Anti rabies vaccine

ANNEXURE -VI DECISION TREE: GUIDE TO POST EXPOSURE PROPHYLAXIS (PEP)



ANNEXURE -VII

Table 2: Wound management




Steps in wound management		
Physical	Wash with running tap water 	Mechanical removal of virus from the wound.
Chemical	Wash the wound with soap and water Apply antiseptics 	Inactivation of the virus
Biological	Infiltrate immunoglobulin/antirabies serum in the depth and around the wound in Category III exposure 	Neutrilisation of the viral antigen

Fig 1 & 2



FIG.1: Insertion of needle in the deltoid region for ID inoculation



FIG.2: Bleb raised on ID inoculation

ANNEXURE - VIII

Daily Reporting Format for IDRV & RIGs

IDRV Kerala 2010												
Name of centre :												
Date:	Male	Female	Animal bite (New)			Number of Patients (New)			Total Patients (Old&New)	VIALS	Drop Out Rate	ERIG / HRIG
			DOG	CAT	Others	Cat II	Cat III	Total				

PATIENT CARD

Hospital / ARC: _____

O.P. No. _____ Date: _____

Name: _____ Age (yrs): _____ Sex: M () F ()

1. Biting animal: Dog () Cat ()
Others (Specify) _____

2. Wound treatment: _____

3. Tetanus toxoid: _____

4. Antibiotics/ others: _____

5. Vaccine:

ID Vaccination

Days	Date Due	Date Given	Adverse Reactions	Treatment Given
D 0				
D 3				
D 7				
D 28				

6. RIGs: ERIGs / HRIGs _____

GENERAL INSTRUCTIONS

1. Observe the Dog/Cat for 10 Days for signs of rabies.
2. Complete the course of vaccination.
3. There are no dietary restrictions.
4. Daily bath can be taken.
5. Intake of alcoholic drinks should be avoided.