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Association for Prevention and Control of Rabies in India (APCRI) Regd.

RABIES PROPHYLAXIS

APCRI GUIDELINES



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Association for Prevention and Control of Rabies in India (APCRI) Regd.

Genesis of the current set of slides

- March 2001: 1st National workshop at Bangalore, 1st set of slides developed and hosted on association website.
- May 2004: WHO – APCRI National multi centric survey.
- October 2004: WHO Expert consultation meeting – TRS 931
- February 2006: 2nd National workshop at Hyderabad.
- Inputs from National and International experts
- Review of literature
- Expert consultations (NICD, NIE, CRI, MOH, NIMHANS, IPM, PII)

The Slide series intends to focus on – Disease, Agent, Prevention, Control



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DEFINITION

- Rabies is an acute fatal viral encephalitis caused by a single stranded RNA virus belonging to the genus *Lyssa* Virus of the family *Rhabdoviridae*.
- Rabies is a Zoonotic disease which is virtually 100% fatal but 100% preventable.



Ancient Disease, Still Prevails

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- Rabies is an ancient disease mentioned in the Vedas and other ancient scripts.
- The name Rabies is derived from the Sanskrit word 'Rabhas' which means "to do violence".
- Louis Pasteur developed the 1st vaccine (neural tissue) against Rabies in 1885.
- First cell culture vaccine was developed by T J Wiktor and H Koprowsky in 1965.
- 6th July is celebrated as 'WORLD ZONNOSES DAY'



Rabies in India

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Magnitude of the Problem:

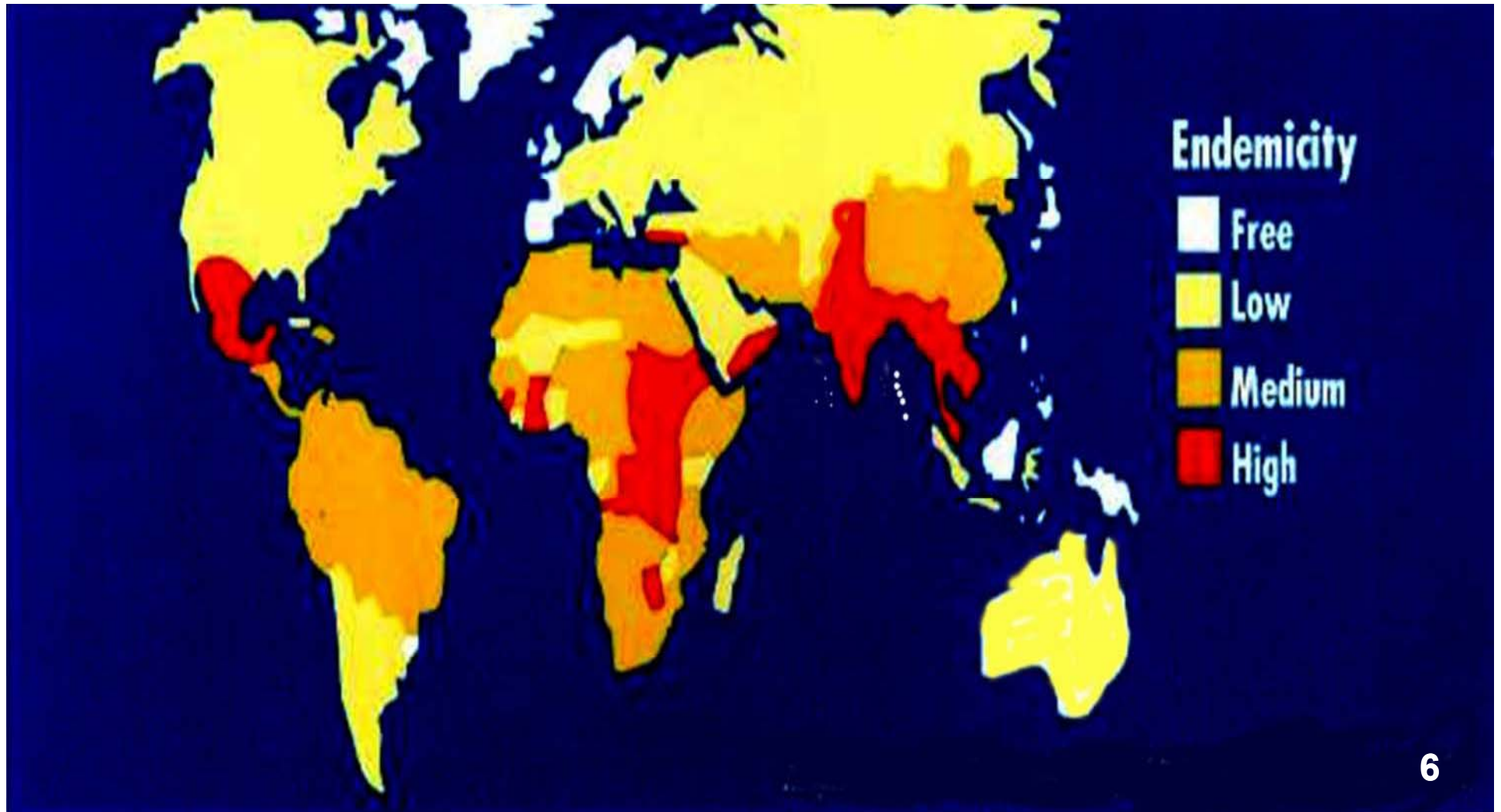
- 20,000 Deaths, 17.4 million animal bite cases annually.
- India accounts for 36% of the Global and 65% of the Asian human rabies deaths.
- In India rabies is reported from all states except Lakshadweep and the Andaman & Nicobar Islands.
- No age or sex predilections (higher incidence of animal bites and rabies deaths among children and adult males).
- 96 % of human rabies cases are due to bites from Rabid dogs.



Rabies: World wide incidence

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Highest incidence is in the Indian Subcontinent.

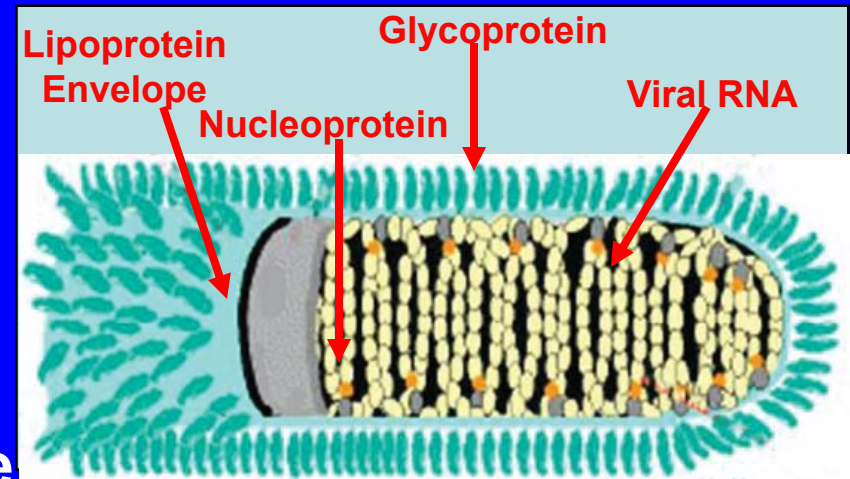




STRUCTURE OF RABIES VIRUS

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- Single Stranded RNA Virus
- Bullet Shaped.
- Size 75 nm x 180 nm.
- Enveloped Virus - Lipoprotein
- Numerous spikes present on the envelope, made up of glycoprotein.
- Glycoprotein necessary for viral attachment & induces protective antibodies.
- Nucleoprotein is also important and known to offer protection.





Properties of Rabies Virus

- **Thermo labile- sensitive to pasteurization and boiling.**
- **Inactivated by detergents (soap), alcohol, iodine, formaldehyde, phenol and betapropiolactone (BPL).**
- **Preserved by freeze drying, at ultra low temperatures (\leq minus 20°C) and glycerin.**



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ANIMALS TRANSMITTING RABIES IN INDIA

Domestic

Dogs & Cats

Peridomestic

Cows & Buffaloes

Sheep & Goats

Pigs

Donkeys

Horses

Camels

Wild

Foxes & Jackals

Monkeys

Mongoose

Bears

Not reported

Bats *

Rodents *

Birds

Squirrel

Note:

All exposures in wild are considered as category III exposures.

* Bite by Bats or Rodents do not ordinarily necessitate rabies vaccination.

However, bites by Bats or rodents in unusual circumstances may be considered for vaccination in consultation with an expert in the field of rabies.



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MODES OF TRANSMISSION

Bites from infected animals

Licks on Broken Skin or Mucous Membrane

Scratches

Inhalation

Organ transplantation



INCUBATION PERIOD (IN MAN)

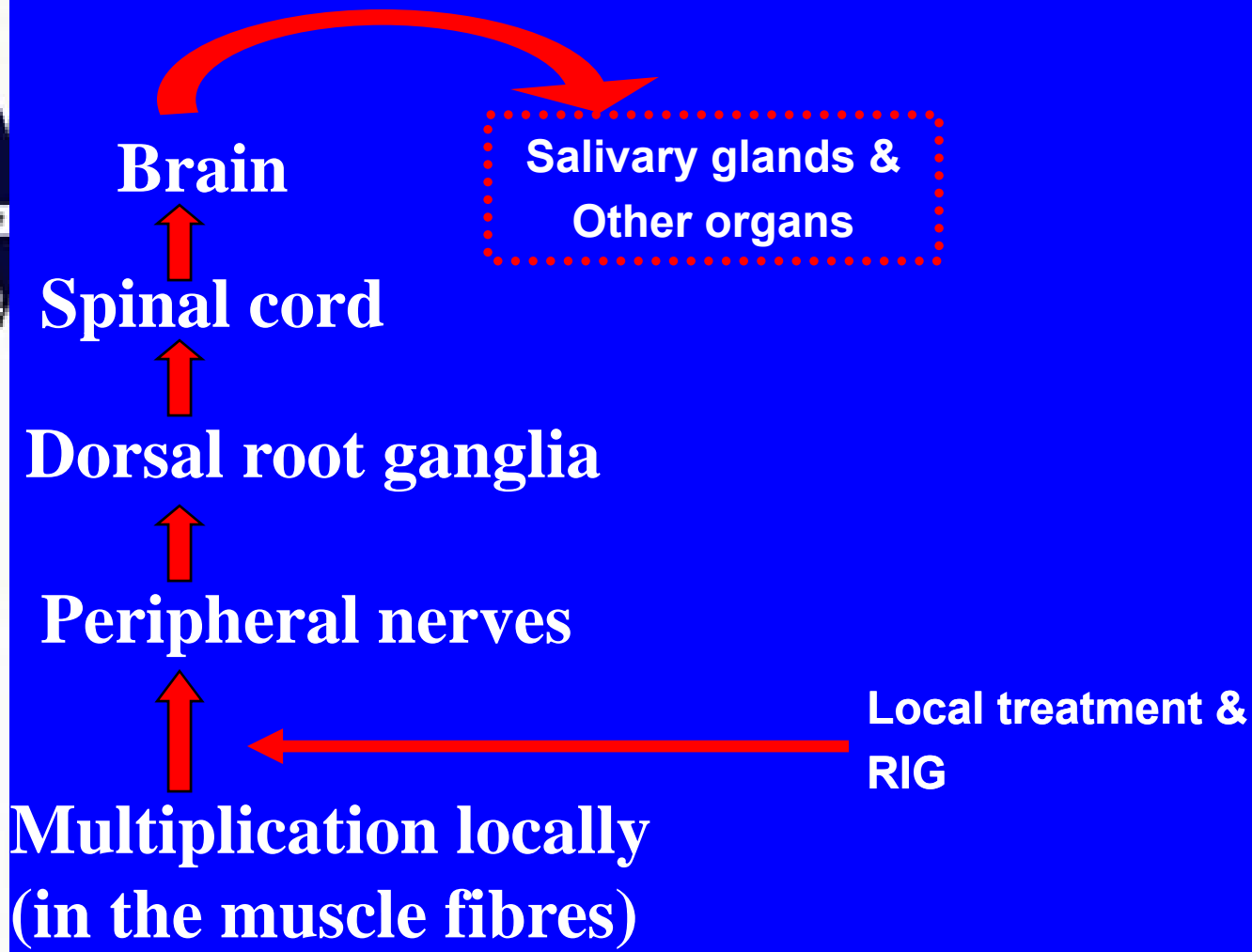
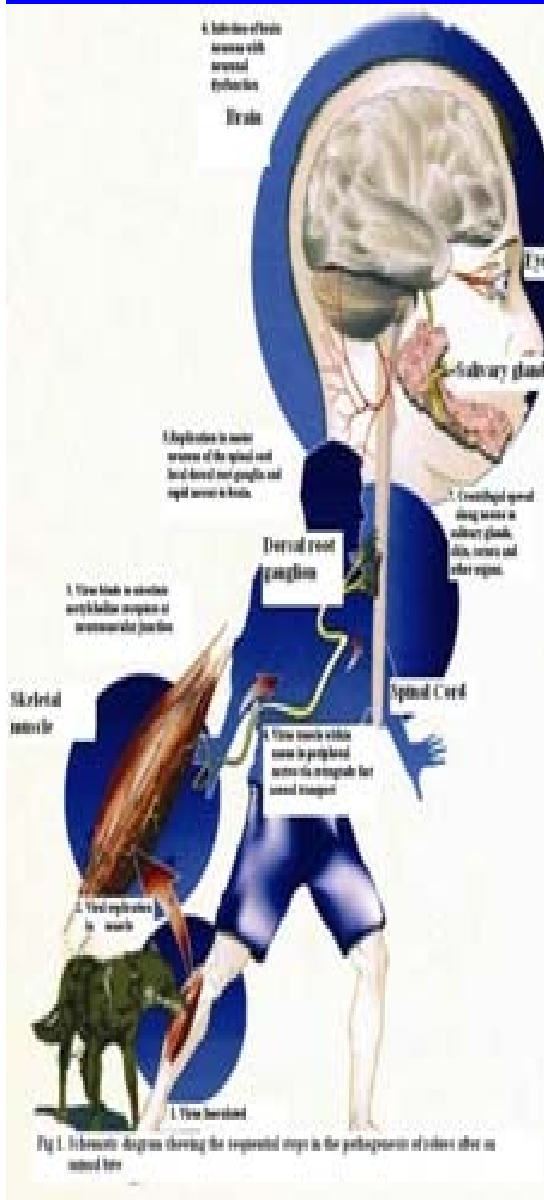
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- **2 weeks – 6 months (in > 85% cases).**
- **Ranges between 4 days to 6 years.**
- **Shorter in children (vulnerable group).**



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PATHOGENESIS



Note: The virus is neurotropic and there is no viremia in rabies.



PATHOLOGY

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- **Despite 100% fatal nature of the disease there are only Minimal Pathological changes**
- **Grossly - Brain is oedematous, congested**
- **Histopathologically-Perivascular cuffing, Gliosis**
- **Minimal Neuronal Damage – necrosis**
- **Presence of Negri bodies is Pathognomonic**





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Laboratory Diagnosis

Laboratory diagnosis is
not mandatory
for managing animal bite cases.



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Laboratory Diagnosis

Collection, Storage & Transportation of Samples

- **Brain Sample-Fresh Samples to be transported to laboratory within 2 - 3 hrs.**
- **If delay is expected samples should be put in 50% glycerol saline and transported to laboratory as soon as possible.**
- **CSF, Saliva in cold chain for antigen detection, PCR and virus isolation.**
- **CSF and sera in cold chain for antibody detection.**
- **Skin Biopsy - Frozen sections sent on dry ice.**



Laboratory diagnosis in Humans and animals

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- **Post-mortem - Confirmatory**
- **Sample – Brain**
- **Tests**
 - **Seller's Stain - Negri bodies**
 - **FAT - Antigen Detection**
 - **Mice / Cell Culture - Virus Isolation**
 - **RT- PCR - Nucleic Acid detection**



Laboratory Diagnosis... Contd.

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Antemortem diagnosis:

- Difficult
- Battery of tests are required
- No single test has 100% sensitivity
- Positive test by any one of the standardized procedure over rides negative reaction in others
- Negative tests do not rule out the possibility of rabies

Samples and tests:

- **Saliva** - Virus isolation / RNA detection
- **Skin** - Antigen detection
- **CSF** - Virus isolation / RNA detection and antigen detection



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PRINCIPLES OF POST EXPOSURE PROPHYLAXIS (PEP)

- Local treatment of Wounds
- Immunoglobulins
- Vaccination
- Advice and counseling



Local Treatment of Wounds

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Do's

- Gently wash under running water with soap for 5 times over a period of 15 minutes
- Disinfectants - Povidone Iodine, Spirit, etc.
- Suturing (1 - 2 loose sutures) only if required and only after administration of RIG.
- Simple, non occlusive dressing can be done if required
- Tetanus toxoid and antibiotics to be given as appropriate.

Don'ts

- Apply Irritants like chilli powder, plant sap, lime, atta, etc.
- Cauterize



CLASSIFICATION OF EXPOSURE

Based on WHO categorization.

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Category	Type of contact with a suspect or confirmed rabid domestic or wild animal, or animal unavailable for observation	Type of Exposure	Recommended Treatment
I	Touching or feeding of animals Licks on intact skin	None	None, if reliable case history is available.
II	Nibbling of uncovered skin Minor scratches or abrasions without bleeding.	Minor	Administer vaccine immediately Stop treatment if animal remains healthy throughout an observation period of 10 days or if animal is euthanized and found to be negative for Rabies by appropriate laboratory techniques.



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WHO CLASSIFICATION OF EXPOSURE

Guide for Post-Exposure Treatment

Category	Type of contact with a suspect or confirmed rabid domestic or wild animal, or animal unavailable for observation	Type of Exposure	Recommended Treatment
III	Single or multiple trans dermal Bites or Scratches. Contamination of mucous membrane with Saliva (i.e. licks)	Severe	Administer rabies Immunoglobulin and vaccine immediately. Stop treatment if animal remains healthy throughout an observation period of 10 days or is killed humanely and is found to be negative for rabies by appropriate laboratory techniques.

Note: exposure to Bats are categorized as Category III

Treatment may be considered in unusual circumstances in consultation with experts.



VACCINES - HISTORY

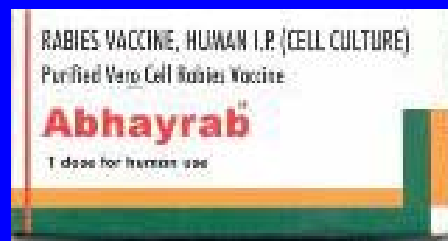
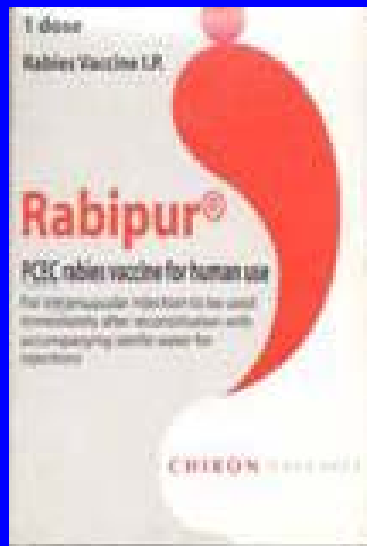
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- | | |
|------------------------------------|--|
| 1885 Louis Pasteur | - 1st Human Antirabies vaccine, France. |
| 1911 Sir David Semple | - Sheep Brain Vaccine, CRI Kasauli, India. |
| 1955 Fuenzalida et al | - Suckling Mouse Brain vaccine, Chile. |
| 1958 Peck et al | - Duck Embryo Vaccine, USA. |
| 1960 CRI Kasauli | - Introduction of BPL inactivated NTV |
| 1965 Wiktor & Koprowsky | - Human Diploid Cell Vaccine, USA. |
| 1985 Gluk et al | - Purified Duck Embryo Vaccine, Switzerland. |
| 1985 Barth et al | - Purified Chick Embryo Cell Vaccine, Germany. |
| 1988 Montegnan et al | - Purified Vero Cell Rabies Vaccine, France. |
| 2004 December | - Neural Tissue Vaccine (NTV) Production stopped in India |



Modern vaccines available in India (March 2006)

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POST EXPOSURE VACCINATION SCHEDULE

Vaccines : HDCV, PCEC, PVRV, PDEV.

Dose : HDCV, PCEC & PDEV - 1 ml

PVRV - 0.5 ml (PII, Coonor vaccine is 1 ml)

Route : Intra Muscular

**Site : Deltoid or anterolateral aspect of thigh (in
children)**

Never inject into the gluteal region.



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POST EXPOSURE VACCINATION SCHEDULE

Essen Regimen – Intra Muscular

Day 0 : 1st dose

Day 3 : 2nd dose

Day 7 : 3rd dose

Day 14 : 4th dose

Day 28 : 5th dose

Note: Zagreb regimen (2 – 1 – 1) is not approved for use in India.



POST EXPOSURE VACCINATION

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Points to remember

- Day 0 - Day of 1st dose of vaccine given, not the day of bite.
- All modern rabies vaccines approved by National Regulatory Authorities are effective and safe.
- Never inject the vaccines into the gluteal region.
- Interchange of vaccines acceptable in special circumstances, but not to be done routinely.
- Reconstituted vaccine to be used immediately.
- Vaccine dosage is same for all age groups.



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INDICATIONS FOR PASSIVE IMMUNIZATION

- **All category III exposures, irrespective of status of biting animal.**
- **Administer even when treatment is delayed but RIGs should not be given after 7 days of start of vaccination (3 doses administered)**
- **In re-exposure cases (completed post exposure prophylaxis previously) RIGs are not indicated.**
- **Immunoglobulins are life saving.**



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WHO CATEGORY III EXPOSURES





Immunoglobulins – History

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- 1890 Babes & Cerchez** – Whole blood of vaccinated humans used for treating people severely bitten by rabid wolf.
- 1945 Habel et al** – usefulness of RIGs clearly demonstrated by animal experiments.
- 1954 Habel & Koprowsky** – RIGs and vaccine was used as PEP in Wolf bite cases in Iran.
- 1959 Hosty et al** – production of ERIGs.
- 1963 Atanasiu** – clinical trials with ERIG & optimal dose was determined.
- 1966 WHO** – guidelines on standard guidelines on the combined use of RIGs & Vaccine for PEP
- 1971 Cabasso et al** – Standardized production of HRIG, determined the optimal dosage.
- 1972 CRI (Kasauli)** - Purified ERIG production.



PASSIVE IMMUNIZATION

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Human Rabies Immunoglobulin (HRIG) : 20 IU/kg body wt.
Maximum of 1500 IU

Equine Rabies Immunoglobulin (ERIG) : 40 IU/kg body wt.
Maximum of 3000 IU

ERIG must be administered only after the Test dose.

Test dose (ERIG)

Follow the Manufacturer Guidelines or Inject 0.1 ml of 1:10 dilution of the ERIG in normal saline, Intra Dermally over flexor aspect of forearm.

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

Positive test reaction: Induration >10mm with or without constitutional symptoms.



RIG Infiltration

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Positive test reaction: Induration $>10\text{mm}$ with or without constitutional symptoms.

- If skin test is positive – HRIG is preferred (affordability, availability)
- If ERIG has to be administered then pre treat with Adrenaline / Epinephrine and with Antihistamine before administering full dose.



Note:

A negative test is not a guarantee that Anaphylaxis will not occur.



PASSIVE IMMUNIZATION

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- RIG is most effective when administered locally and early.
- Infiltrate as much as possible into and around the wounds; remaining **if any** to be given Intra Muscularly at a site away from the site where vaccine has been administered.
- Inject RIG **into all wounds** (anatomically feasible).
- If RIG is insufficient (by volume) to infiltrate all the wounds, dilute it with sterile normal saline sufficient to infiltrate all wounds.
- Equine rabies immunoglobulin must be administered with full precautions.



RIG Infiltration

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SPECIAL CIRCUMSTANCES

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Post exposure treatment should be given to

- Immune compromised patients (AIDS, long term Steroid therapy, Chloroquine treatment, anti cancer therapy, immune suppressive therapy, etc.)
- Persons consuming raw milk of rabid animals.
- Pregnant and Lactating mothers.

Note: There is no absolute contraindication for Post Exposure Prophylaxis



SPECIAL CIRCUMSTANCES

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If RIGs are not available:

- 1. Proper local wound treatment**
- 2. Double the first dose of vaccine (D₀).**

Note: There is no substitute for RIG and all other options are inferior.

“When in doubt an infectious disease specialist with expert knowledge on rabies should be consulted”



INTRA DERMAL RABIES VACCINATION

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- **Approved by the WHO & DCGI (Feb 2006).**
- **Cost effective.**
- **Studies in India & abroad have confirmed safety and efficacy.**
- **Implementation in phased manner in centers with large attendance of animal bite victims.**



Note: DCGI presently has approved only PCEC (Rabipur) and PVRV (Verorab) for ID administration in India by the Thai Red Cross (TRC) regimen and updated TRC regimen.



PRE-REQUISITES FOR IDRV USAGE

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- Trained staff for ID technique.
- Vaccine vials should be stored between +2° C to +8° C.
- After reconstitution the total content should be used as soon as possible or at least within 6 - 8 hours.
- Rabies vaccine formulated with an adjuvant should not be administered intradermally

Note: IM route is preferred for immune compromised persons, persons on immunosuppressant drugs or therapy and on chloroquine therapy.



Thai Red Cross (TRC) regimen

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Dose : 0.1 ml / ID site

Site : Upper arm over each deltoid

Schedule : 2- 2- 2- 0- 1-1

Day 0 - 2 doses

Day 3 - 2 doses

Day 7 - 2 doses

Day 14 - No Dose

Day 28 - 1 dose

Day 90 - 1 dose



2 SITE REGIMEN (Updated TRC)

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Dose : 0.1 ml / ID site

Site : Upper arm over each deltoid

Schedule : 2- 2- 2- 0- 2

Day 0 - 2 doses

Day 3 - 2 doses

Day 7 - 2 doses

Day 14 - No Dose

Day 28 - 2 doses



8 SITE REGIMEN

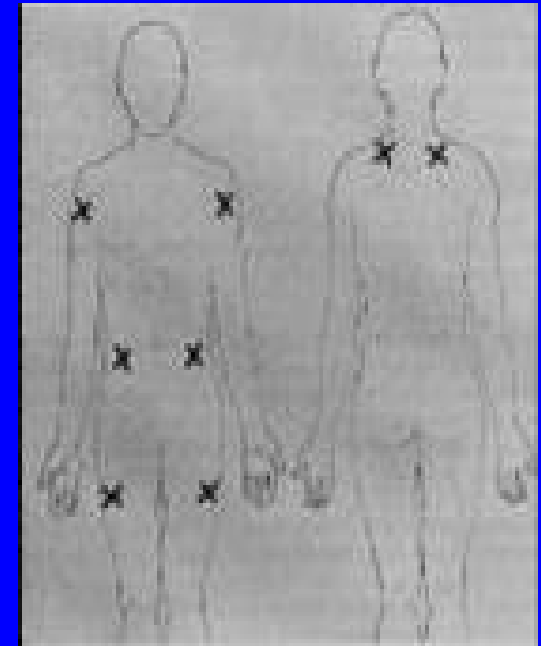
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Dose : 0.1 ml / ID site (subject to DCGI approval)

Schedule : 8- 0- 4- 0- 1-1

Day 0 - 8 doses
Day 3 - No Dose
Day 7 - 4 doses
Day 14 - No Dose
Day 28 - 1 dose
Day 90 - 1 dose

Sites





PRE - EXPOSURE PROPHYLAXIS

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Recommended for risk groups like

- Veterinarians, Laboratory personnel working with rabies virus, medical and paramedical personnel treating Rabies patients.
- Dog catchers/Dog pound workers, Forest staff, Zoo keepers.
- Postmen, Policemen, Courier Boys.
- Children in Canine rabies endemic countries.



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PRE-EXPOSURE PROPHYLAXIS (Contd.)

Intra Muscular Schedule

Dose : HDCV, PCEC & PDEV - 1 ml

PVRV - 0.5ml & 1ml (PIL Coonor)

Site : Deltoid or anterolateral thigh **Route** : Intra Muscular

Schedule : Day 0 - 1st dose

Day 7 - 2nd dose

Day 21 or 28 - 3rd dose

Note: Estimate antibody titres annually for all risk groups & every 6 months in lab personnel & if titres are < 0.5 IU/ml, give booster.



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PRE-EXPOSURE PROPHYLAXIS (Contd.)

Intradermal Schedule

Dose : 0.1 ml (for all vaccines)

Site : Deltoid **Route** : Intradermal

Schedule : Day 0 - 1st dose

Day 7 - 2nd dose

Day 21 or 28 - 3rd dose

Note: Estimate antibody titres annually (every 6 months in lab personnel) and if titres are <0.5 IU/ml, give booster.



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VACCINATION AFTER RE-EXPOSURE

- Re exposure after a full course of documented Pre / Post - exposure vaccination with modern vaccines;

2 boosters (Day 0 & Day 3) **No RIG.**

- All incomplete vaccinations, partial vaccinations or doubtful vaccination need to be treated as fresh cases.

Note:

In case of severe exposure anti rabies antibody titres may be done if possible. Otherwise consult an infectious diseases expert with knowledge in field of rabies prevention.



MEDICAL ADVICE TO PATIENTS

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- **No dietary restrictions.**
- **No restriction of physical exercise.**
- **Report adverse effects (if any) to the physician without fail.**
- **Best to avoid consumption of alcohol during the course of treatment.**
- **Complete the course of vaccination.**



CLINICAL MANIFESTATION IN HUMANS

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Furious Type (80%)

Tingling / numbness at bite site

Non specific symptoms
(Fever, malaise, headache, etc.)

Hydrophobia, Aerophobia

Photophobia

Death (cardio - respiratory failure)

Survival : 3 – 5 Days

Paralytic Type (20%)

Tingling / numbness at bite site

Non specific symptoms
(Fever, malaise, headache, etc.)

Ascending Paralysis

Coma

Death (cardio - respiratory failure)

Survival : 7 – 21 Days



Management of Human Rabies

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- **Admit in a separate, quiet & breeze free area.**
- **Barrier nursing and universal precautions.**
- **Invasive procedures should be avoided.**
- **Sedation with Morphine / Barbiturates.**
- **Emotional support and physical comfort.**



Management of Human Rabies

- **Necropsies should be performed with adequate personal protection.**
- **Early disposal of body by cremation or deep burial is recommended.**
- **All disposables contaminated with secretions or excretions and patient tissue or body fluids should be managed as infected.**



Advice to the attendants

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- Post-exposure vaccination for close contacts initiated with modern vaccines, where barrier nursing is not followed.

The **advice to attendants** should include the following;

- To avoid contact with secretions and excretions of the rabies patient.
- To wash hands and exposed areas thoroughly with soap and water.



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PERSONAL SAFETY AGAINST RABIES

- Do not touch animal bite wounds with bare hands.
- Do not touch fomites (Chain, food plate etc.) of an animal suspect or proven rabid.
- Keep away from stray / sick animals.
- Do not stare at or provoke any animal.
- Take pre-exposure vaccination if you are in constant touch with animals.
- Avoid contact with saliva, urine, tears, semen, vaginal secretions and other body secretions of a rabies patient.



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SIGNS OF RABIES IN DOGS / CATS DURING 10 DAY OBSERVATION PERIOD

Any of the following signs must evoke suspicion of rabies

- **Change in behaviour - undue aggression/depression.**
- **Running aimlessly and attacking others without any provocation.**
- **Becomes too drowsy and withdraws itself to a corner.**
- **Excessive Salivation.**
- **Change in voice.**
- **Refusal to feed or eating unusual objects like stones, papers, wood, metal pieces etc.**
- **Death of animal due to unknown cause.**



EDUCATION OF PET OWNERS

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- Get your pet regularly and periodically examined by a qualified veterinarian.
- Get your pet vaccinated at three months of age and again 1 month later; boosters must be given every year subsequently.
- Obtain a Municipal License, put a collar and keep your pet under leash in public places.
- Do not allow your pet to come in contact with community / street dogs / cats or other animals.
- Inform the Municipal authorities about sick / mad dogs.
- Take treatment even after pet dog bite including pups.



Rabies in animals

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Incubation period:

Dog / cat:	3 – 8 weeks
Cow:	3 – 15 weeks
Horse:	3 – 6 weeks
Fox:	3 – 10 weeks

Prodromal Phase

- Aggressive animal may become calm
- Friendly animal may become withdrawn
- Wildlife may lose fear of humans

Excitative Type or “Furious” rabies:

Agitated, restless, excitable, Indiscriminant biting, Profuse salivation, Vocal cords affected, Convulsions, paralysis, and death

Paralytic Type or “Dumb” rabies:

Muscles of head and neck affected, Difficulty in swallowing, Paralysis spreads to extremities, coma, death.

Unexplained sudden deaths in dogs should be viewed as suspected rabies,
hence handlers should be treated by PEP



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Reservoir Control

Domestic animals

- Vaccination programs for all dogs and cats.
- Removal of strays and unwanted animals.
- Animal Birth Control (ABC) for stray dogs is to be encouraged.
- New biological tools like specific contraceptive vaccines for dog population control to be introduced.
- **To create rabies free areas and maintain them by adequate Monitoring and surveillance**



National Rabies Control Programme

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APCRI recommends launching of “**National Rabies Control Programme**” by Govt. of India using the following approaches:

- **Prevention of Human Rabies:**
 1. Post exposure prophylaxis
 2. Pre exposure prophylaxis
 3. Diagnostics
- **Rabies free areas:**
 1. To keep rabies free areas free
 2. Monitoring and surveillance
- **Control of Animal reservoir:**
 1. Control of community dog population.
 2. Compulsory vaccination and licensing of pet dogs.
 3. Mass parenteral annual vaccination of community dogs.



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THANK



YOU

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