RABIES

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Specific Learning Objectives

- At the end of session, the learner shall be able to describe:

- Epidemiology of Rabies
- Diagnosis and treatment
- Prevention and control

Introduction

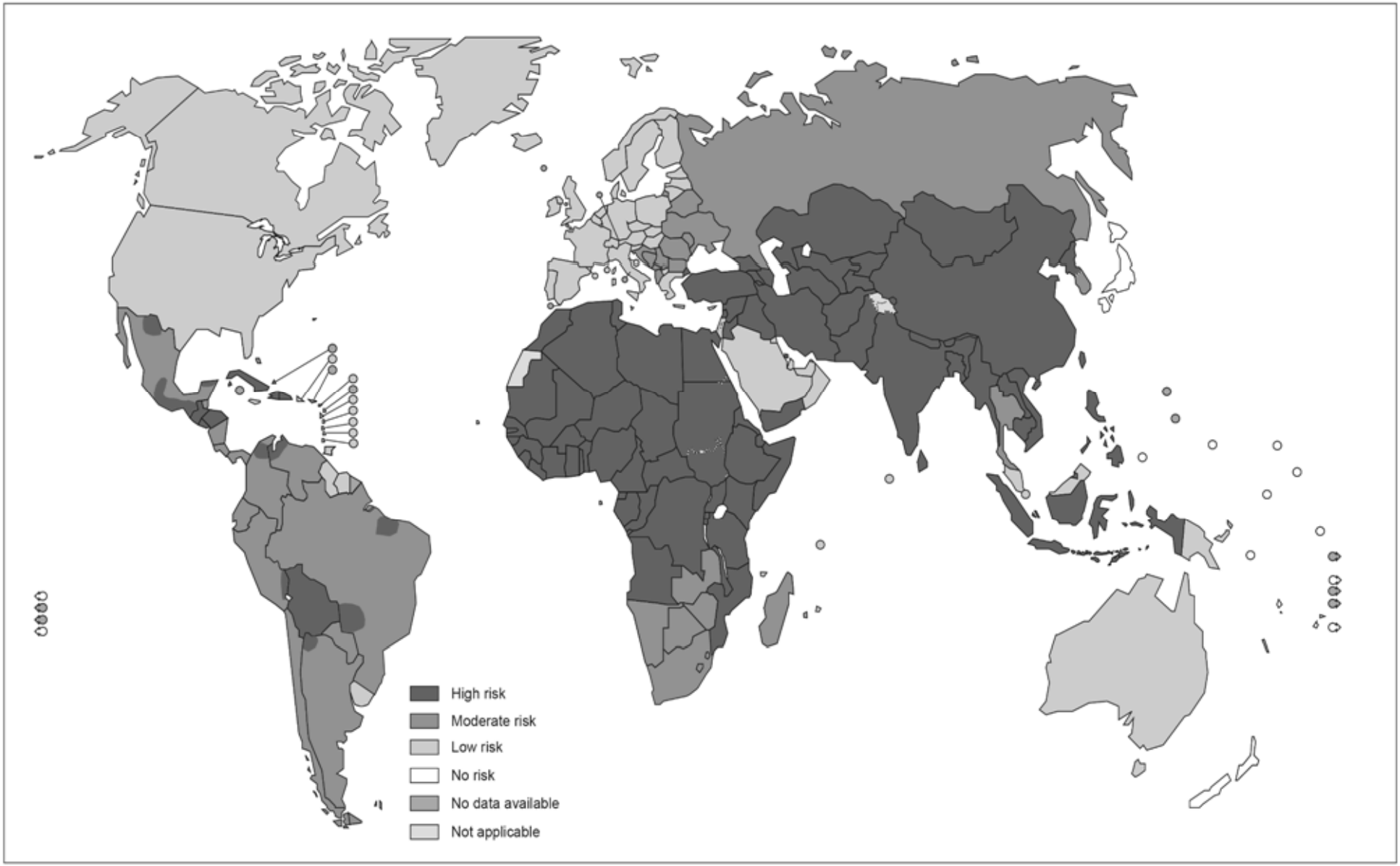
- Zoonotic disease
- Rabies virus
- The virus is found in wild and some domestic animals
- Causes *fatal encephalomyelitis* in virtually all the warm blooded animals including man.
- Transmitted to other animals and to humans ***through saliva*** (i.e. following bites, scratches, licks on broken skin and mucous membrane).

- Rabies is present on all continents with the exception of Antarctica.
- More than 95% of human deaths occur in Asia and Africa.
- ***A neglected disease of poor and vulnerable populations whose deaths are rarely reported***.
- Under-reporting of rabies also prevents mobilization of resources from the international community for the elimination of human dog-mediated rabies.

- Estimated 55,000 deaths caused by rabies each year occur in rural areas of Africa and Asia.
  - Africa: 24,000 deaths
  - India: 20,000 deaths

- "**Rabies free**" area: in which no case of indigenously acquired rabies has occurred in man or any animal species for 2 years.
  - Australia
  - Taiwan
  - Cyprus
  - Iceland
  - Ireland
  - Japan
  - Malta
  - New Zealand
  - The Islands of Western Pacific
  - ***Lakshadweep and Andaman & Nicobar Islands (India)***

Distribution of risk levels for human rabies (Year 2013)



- In India, *dogs are responsible for about 97%* of human rabies, followed by cats (2%), jackals, mongoose and others (1%).

- The disease is mainly transmitted by the bite of a rabid dog.

Agent

- Lyssavirus type 1
- RNA, family rhabdoviridae
- Serotype 2, 3 & 4: Rabies-related virus

- Street virus vs. Fixed virus.

Host factors

- All the warm blooded animals including man are susceptible.
- In man: dead-end infection.
- Age:
  - More common in Children < 15 years
- Risk group:
  - Lab staff
  - Veterinarians
  - Dog handlers
  - Hunters.

Source of infection

- ***Saliva of rabid animals***
  - Virus may be present *in saliva for 3-4 days* before onset of clinical symptoms and during course of illness till death.

Mode of transmission

- Following bites and scratches
- Can also occur when licks on broken skin and mucous membrane.
- Rarely, via *inhalation of virus-containing aerosol or via transplantation of organ.*

- Ingestion of raw meat or other tissues from animals infected with rabies -- **not** a source of human infection.

Incubation period

- Highly variable in man
- Commonly 1-3 months
  - may vary from 7 days to many years

- **Depends upon**:
  - Site of the bite
  - Severity of the bite
  - Number of wounds
  - Amount of virus injected
  - Species of the biting animal
  - Protection provided by the clothing
  - Treatment undertaken

Clinical features

- Fever
- Pain or an unusual or unexplained tingling, pricking or burning sensation at the wound site.

As the virus spreads through the central nervous system, progressive, fatal inflammation of the brain and spinal cord develops.

- Two forms of the disease can follow.
  - Furious rabies
  - Paralytic rabies

- **Furious rabies:**
  - signs of hyperactivity, excited behaviour, hydrophobia and sometimes aerophobia.
  - After a few days, death occurs by cardio-respiratory arrest.

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

Diagnosis

- Difficult to diagnose before the onset of clinical disease
  - unless the rabies-specific signs of hydrophobia or aerophobia are present.

- Human rabies can be confirmed *intra-vitam* and post mortem by various diagnostic techniques
  - aimed at detecting whole virus, viral antigens or nucleic acids in infected tissues (brain, skin, urine or saliva).

Rabies Prophylaxis

- National Centre for Disease Control, Delhi,
  - WHO Collaborating Centre for Rabies Epidemiology,
  - organized an expert consultation in 2002 to formulate national guidelines for rabies prophylaxis to bring out uniformity in postexposure prophylaxis practices.

- As per WHO recommendations, the production of the nervous tissue vaccine (NTV), which was the mainstay for post-exposure prophylaxis for a long time, has been stopped since December 2004 in the country.

- Modern ***cell culture vaccines (CCVs***) are being used for post-exposure prophylaxis.
  - Higher cost of intra-muscular administration of CCV is a limiting factor for its wider use.
- To overcome this problem, WHO recommended use of ***efficacious, safe and feasible intra-dermal (ID) route*** of administration of CCVs.
  - Clinical trials conducted in India proved intra-dermal route to be safe, efficacious and feasible for use in the country.
  - National authorities after expert consultations approved the use of ID route for administration of CCVs in the country in February 2006.

- The guidelines of animal bite management were revised with inclusion of ID administration of anti-rabies CCVs in 2007.

- In the last six years, there have been newer developments in rabies prophylaxis and a need was felt to review and revise the national guidelines to ensure uniformity in Post-Exposure Prophylaxis (PEP).

Post-Exposure Prophylaxis

Decision to treat

- In a rabies endemic country like India where there is sustained dog-to-dog transmission, every animal bite is suspected as a potentially rabid animal bite.
  - Treatment should be started immediately after exposure.
  - As rabies is practically 100% fatal, **bites by dogs and cats in particular must be considered as a "medical emergency"** and the "life-saving" post exposure prophylaxis must be provided immediately.

Observation of biting dog/cat:

- The PEP should be started immediately after the bite.
- The observation period of 10 days is valid for dogs and cats only.
- The natural history of rabies in mammals other than dogs and cats is not fully understood and therefore the 10-day observation period is not applicable.

- The treatment may be modified if dog or cat involved 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 Schedule.
  - While using ID administration complete course of vaccination should be given irrespective of status of animal.

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.

- Hence, appropriate documentation of vaccination status of dog/cat and proper history should be elicited before deciding to defer post-exposure prophylaxis after bite by vaccinated dog/cat.

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 provokes a dog to attack.

- Hence, PEP should be immediately instituted irrespective of whether the bite was provoked or unprovoked.

Bite by wild animals:

- Bite by all wild animals should be treated as category III exposure.
- All animal bites in forest or in the wild should be treated as category III exposure.

Bite by rodents:

- Exposure to domestic rodents, squirrel, hare and rabbits do not routinely require PEP.

Bat rabies:

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

Immune-compromised patients:

- proper and thorough wound management and antisepsis accompanied by local infiltration of rabies immunoglobulin followed by complete course of anti-rabies vaccination by intramuscular route in both category II and III exposures are of utmost importance.
- Preferably, if the facilities are available, anti-rabies antibody estimation should be done 14 days after the completion of course of vaccination to assess the need of additional doses of vaccine.

Human-to-human transmission:

- from organ transplant.

- People who have been exposed closely to the secretions of a patient with rabies may be offered PEP as a precautionary measure.

Contraindications and Precautions:

- As rabies is nearly 100% fatal disease, there is no contraindication to PEP.
  - Pregnancy, lactation, infancy, old age and concurrent illness are no contra indications for rabies PEP in the event of an exposure.

- Because of long and variable incubation period, which is typical of most cases of human rabies, it is possible to institute PEP to protect the individual.
- This must be started at the earliest to ensure that the individual is immunized or protected before the rabies virus reaches the nervous system.
- However, people who present for treatment even months or years after a possible rabies exposure should be evaluated and treated as if the event had occurred recently.

Type of contact, exposure and recommended post-exposure prophylaxis

Cat.	Type of contact	Recommended PEP
I	•Touching or feeding of animals •Licks on intact skin •Contact of intact skin with secretions /excretions of rabid animal /human case	•None, if reliable case history is available.
II	•Nibbling of uncovered skin •Minor scratches or abrasions without bleeding	•Wound management •Anti-rabies vaccine •RIG in immuno-compromised cases.
III	•Single or multiple transdermal bites or scratches, licks on broken skin. •Contamination of mucous	•Wound management •Rabies Ig (RIG) •Anti-rabies vaccine

Wound Management

DO		
Physical	Wash under running water.	Removal of virus from the wound.
Chemical	Wash with soap and water. Apply disinfectant/antiseptics.	Inactivation of the virus.
Biological	Infiltrate RIG into the depth and around (Cat III).	Neutralization of the virus.

- **Do not** touch the wound with bare hand.
- **Do not** apply irritants like soil, chilies, oil, lime, herbs, chalk, betel leaves, etc.
- Suturing of wound(s) should be avoided as far as possible.
- Cauterization of wound(s) is no longer recommended.

Anti-Rabies Vaccines

- Active immunization is achieved by administration of ARV.

- Nerve tissue vaccines (NTVs)
  - Reactogenic and less immunogenic,
  - The production was stopped in December, 2004.

- Currently available safe and potent
  - Cell culture vaccines (CCVs)
  - Purified duck embryo vaccine (PDEV)

Storage and transportation:

- 2-8^{o} Celsius

Reconstitution and storage:

- The lyophilized rabies vaccine should be reconstituted with the diluent provided with the vaccine immediately prior to use.
- All vaccines which are reconstituted and not used thereafter should be discarded after 8 hours of reconstitution.

Intra-muscular (IM) Regimen

- **Vaccines**

1. Cell Culture Vaccines
   - Human Diploid Cell Vaccine (HDCV), Liquid (Adsorbed), 1ml
   - Purified Chick Embryo Cell Vaccine (PCECV), 1ml
   - Purified Vero Cell Rabies Vaccine (PVRV), 0.5ml and 1ml

2. Purified Duck Embryo Vaccine (PDEV), 1ml

- **Essen Regimen (1-1-1-1-1)**
  - Days 0, 3, 7, 14 and 28.
  - Deltoid region.

Intra-dermal (ID) Regimen

- Currently, the following vaccines have been approved by DCGI for use by intra-dermal route:
- **PCECV**
  - Rabipur, Chiron Behring, Vaccines Pvt. Ltd
  - Vaxirab N, ZydusCadila
- **PVRV**
  - Verorab, Aventis Pasteur (Sanofi Pasteur) India Pvt. Ltd
  - Pasteur Institute of India, Coonoor
  - Abhayrab, Human Biologicals Institute
  - Indirab, Bharat BiotechInternational Ltd.

Only the anti-rabies vaccines approved by Drug Control General of India (DCGI) for ID administration should be used for ID route

- **Updated Thai Red Cross Schedule (2-2-2-0-2)**
  - 0.1 ml on days 0, 3, 7 and 28.
  - Deltoid area.

Anti-rabies treatment centres that meet the following criteria may use ID administration:

- Have adequately trained staff to give ID inoculation of anti-rabies vaccine.
- Have adequate cold chain facility for vaccine storage.
- Ensure adequate supply of suitable self-mounted syringes for ID administration.
- Are well versed in management of open vial and safe storage practices.
- Are familiar with safe disposal of clinic waste

Management of re-exposure in previously vaccinated individuals

- Only two booster doses on days 0 and 3
  - intramuscularly (0.5ml/1ml) or
  - CCVs intradermally (0.1 ml)
- Proper wound toilet should be done.

Pre-Exposure Prophylaxis (PrEP)

- High risk groups:
  - laboratory staff handling the virus and infected material,
  - clinicians and persons attending to human rabies cases,
  - veterinarians, animal handlers and catchers, wildlife wardens, quarantine officers and
  - travelers from rabies free areas to rabies endemic areas.

- The Indian Academy of Pediatrics (IAP) has recommended preexposure prophylaxis of children.

- **Schedule of vaccination:**
  - Days 0, 7 and either day 21 or 28.
  - One full dose of vaccine intramuscularly or 0.1 ml intra-dermally.

- Such individuals on getting exposed to rabies virus after successful PrEP require only two booster injections of vaccine given on days 0 and 3 and no RIG.

Rabies Immunoglobulin (RIG)

- Provides passive immunity.

- Has the property of binding with the rabies virus
  - thereby resulting in neutralization and thus loss of infectivity of the virus and hence it is most logical to infiltrate RIG locally at the site of exposure.

Two types of RIG

- Equine Rabies Immunoglobulin (ERIG)
- Human Rabies Immunoglobulin (HRIG)

Indication:

- All category III exposures.
- Both category II and III exposures In immune compromised individuals.

Dose of RIG:

- ERIG: 40 IU per kg body weight of patient.
  - The ERIG produced in India contains 300 IU per ml.
- HRIG: 20 IU per kg body weight.
  - HRIG preparation is available in concentration of 150 IU per ml.

Administration of RIG

- As much of the calculated dose of RIG as is anatomically feasible should be infiltrated into and around the wound/s.

- After all the wound/s has been infiltrated, if any volume of RIG is remaining, it should be administered by deep intramuscular injection at a site distant from the vaccine injection site.

Administration of full dose of RIG intramuscularly into the gluteal region or infiltration
of half the dose of RIG locally and half intramuscularly is not recommended.

- RIG is administered only once, preferably within 24 hours after the exposure along with the first dose of anti-rabies vaccine.
  - If RIG was not administered when ARV was begun, it can be administered up to the seventh day after the administration of the first dose of ARV.

- Rabies Immunoglobulin should never be administered in the same syringe or at the same anatomical site as vaccine.

- **Administration of rabies immunoglobulin:** The RIG should be brought to room temperature (25°C to 30°C) before administration to the patient.

THANKS