International Journal of Pharmacology and Clinical Research (IJPCR)

IJPCR |Volume 6 | Issue 2 | Apr - June- 2022
www.ijpcr.net

Research article *Clinical research*

ISSN: 2521-2206

NATIONAL RABIES CONTROL PROGRAMME; A National programme for development of appropriate health education strategies on rabies prevention and control.

Govind Shukla, Sangeeta Kumari[1], Dr. vinod yadav[2] Dr.Anil kumar[3], Dr. Vijaishree shukla[4], Akash S Mali [5], Shivani Prashar [6], Dr.O P Rathore [7], Dr. S.K Pandey[8] , Marlon O. Perez [9], Mercedita H. Perez [10] Dr. N Sriram[11]

1.Research Scholar, JNTU, Hyderabad, Telangana, India.
2.Ex Joint Director, Directorate of Medical health services, Jhansi, Uttar Pradesh, India
3.Chief Medical officer, Jhansi, Uttar Pradesh, India
4.Health Education Officer, Jhansi, Uttar Pradesh, India
5.Researcher, Department of Physiology, Charles University Czech Republic
6.Asst. General Manager, Zenta Healthcare Pvt. Ltd, Newdelhi India
7.Medical Superintendent, CHC Gursarai, Jhansi, Uttar Pradesh, India.
8.Medical officer in charge NPHC, Rampura, Jhansi, Uttar Pradesh, India.
9.Associate Professor, Department of Radiodiagnostics, Iloilo Doctors college, Iloilo City, Philippines.
10.RT II Ultrasound Section Head, Diagnostic Imaging Department &Radiological Sciences, Corazon Locsin Montelibano Memorial Regional Hospital Lacson St., Bacolod City, Philippines.
11.Associate Professor, Smt SarojiniRamulamma College of pharmacy Mahabub Nagar Telangana, India

Corresponding Author: Govind Shukla

ABSTRACT

Rabies is endemic throughout the country and human cases of Rabies are reported from all over throughout the year except for Andaman & Nicobar and Lakshadweep Islands. In India, about 96% of the mortality and morbidity due to Rabies is associated with dog bites. Although Rabies affects people of all age groups, children are the most vulnerable which constitutes 40% of people exposed to dog bites in Rabies-endemic areas. Different studies quote different figures of Animal Bites incidence and deaths due to Rabies in humans. As per WHO estimates, India accounts for 36% of the global and 65% of the human Rabies deaths in the South East Asia region. The World Health Organization (WHO) in 1992 had recommended the administration of Rabies vaccines by intradermal (ID) route in those countries and areas where there is a resource crunch. The ID Rabies vaccination was effectively used in *Thailand, Philippines* and *Srilanka* to successfully reduce the burden of human Rabies in those countries. The higher cost of intramuscular administration of CCV is a limiting factor for its wider use in India and hence, in February 2006, as per WHO recommendations, results of clinical trials on safety, efficacy and feasibility, the Drugs Controller General of India (DCGI) approved the use of safe, efficacious, and economical Intra-dermal (ID) route of inoculation of CCVs. National Centre for Disease Control (formerly known as National Institute of Communicable Diseases), Delhi, a WHO Collaborating Centre for Rabies Epidemiology, organized an expert consultation in 2002 to formulate "National Guidelines for Rabies Prophylaxis" to bring out uniformity in pre- and post-exposure prophylaxis (PEP) practices. These guidelines were revised through an expert consultation in 2007, 2013 and 2019.

Keywords: rabies control programme

INTRODUCTION

Rabies is a zoonotic disease and human infection caused by Lyssavirus, usually occurring after a transdermal bite or scratch by an infected animal. Transmission may also occur when infectious material, usually the saliva, comes into direct contact with the victim's mucosa or fresh skin lesions. Very rarely, rabies may occur through inhalation of virus-containing aerosol or via infected organ transplants. It is a highly fatal disease characterized by fluctuations in consciousness, phobic or inspiratory spasms and autonomic instability.

Rabies is estimated to cause 55,000 deaths every year worldwide, with about 56% of the cases occurring in Asia and 43.6% in Africa, mostly in rural areas. Rabies is present on all continents with the exception of Antartica. Once symptoms of the disease develop, rabies is nearly always fatal.

Rabies is a neglected disease of poor and vulnerable populations whose deaths are rarely reported. It occurs mainly in remote rural communities where measures to prevent dog to human transmission have not been implemented. Under-reporting of rabies also prevents mobilization of resources from the international community for the elimination of human dog-mediated rabies. Rabies remains to be a public health problem in the India. It is the most acutely fatal infectious disease responsible for the death of thousands of Indians every year.

At least one-third of human rabies deaths are among children less than15 years of age. Two thirds of human rabies cases are males. Dogs are the source of the vast majority of human rabies deaths. Several initiatives at the local level should be undertaken to minimize death due to rabies, such as the following: the provision of pre-exposure treatment to high risk personnel and post exposure prophylaxis to animal bite victims; provision of free routine immunization or pre-exposure prophylaxis; mass vaccination of dogs, establishment of a central base system for registered and vaccinated dogs; impounding, field control and disposition of unregistered, stray and unvaccinated dogs; and conduct of information and education campaign on the prevention and control of Rabies.

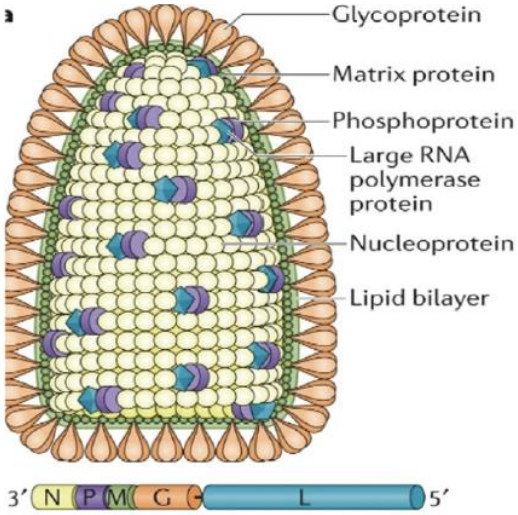

Fig 1: Structure of Rabies virus

Modes of Transmission

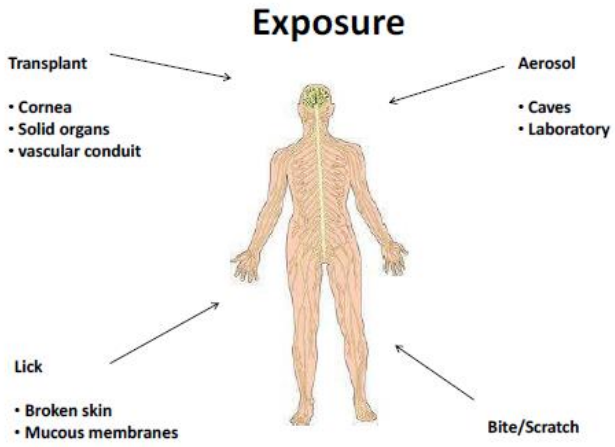

Fig 2: Bites from infected animals are the most common mode of transmission of rabies to humans.

Exposure to rabies may come from bites of infected dogs, cats, otherdomestic and wild animals including bats. However, bites from rats, rabbits, other rodents, reptiles and birds do not pose a risk for rabies infection.

Fig 3: Non-bite exposures are less important and are infrequent modes of transmission.

However**,** scratches, open wounds or mucous membranes that are licked by an infected animal, can be points of entry of the rabies virus and these may be in the form of the following:

- Contamination of intact mucosa (eyes, nose, mouth, genitalia) with saliva of infected animal;
- Licks on broken skin; and
- Inhalation of aerosolized virus in closed areas (e.g. caves with rabid bats, laboratories for rabies diagnosis).

Incubation period

Incubation period is the period from the time of exposure up to the appearance of first clinical signs and symptoms of rabies.

The average incubation period of human rabies is between one to three (1-3) months. In 90-95 % of cases, incubation period is less than one year but may be longer in 5-10 % cases. The duration of the incubation period depends on certain factors:

- The amount of the virus inoculated into the wound or mucosa.
- Severity of exposure - Patients with multiple and/or deep penetrating bite wounds may have shorter incubation period.
- Location of exposure - Patients with bite wounds in highly innervated areas and/or close to the central nervous system may have shorter incubation period.

Pathogenesis

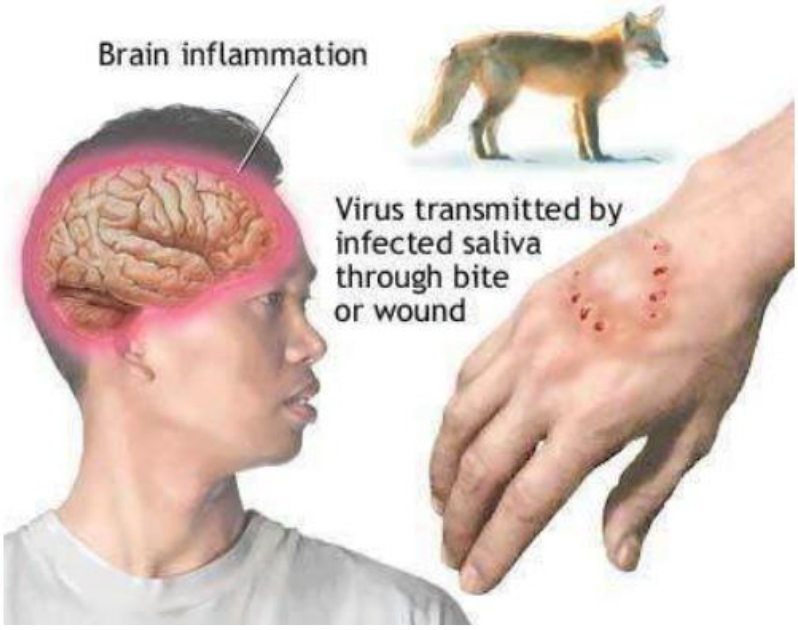

Fig 4: pathogenesis of Rabies Transmission

After inoculation, the rabies virus multiplies in the muscle cells (myocytes or may invade the nerve directly without prior multiplication in the myocytes. It is possible that the rabies virus may persist locally at the site of inoculation for

an unspecified period of time. This could explain the long incubation period for some rabies infections.

The virus then penetrates the peripheral nerve cells via viral uptake at neuronal endings. The virus is transported through both the sensory and motor nerve fibers to the central nervous system (CNS). In vitro studies show that velocity of axonal transport of the virus ranges from 25 to 50 mm per day. The spread of the rabies virus in the coulometer and optic nerves could be as fast as 12 mm/day.

Once the virus reaches the CNS, rabies replication occurs primarily in the neurons or brain cells through viral budding and the virus spreads and infects the nearby brain cells. Dissemination through the cerebrospinal fluid (CSF) occurs in the late stages of infection.

While viral dissemination occurs in the central nervous system, the rabies virus spreads into the peripheral tissues such as muscle fibers, salivary glands, corneas, adrenal medullae, lacrimal glands, myocardium, kidneys, lungs, pancreas and epidermis. Infection of salivary glands allows further transmission of the disease to other mammals.

Clinical Stages

Prodromal

The prodromal stage occurs when there is initial viral replication at the striated muscle cells at the site of inoculation *just before it enters the brain.* The virus then spreads centripetally up the nerve to the central nervous system through the peripheral nerve axoplasm. This stage lasts for 0-10 days with non-specific manifestations, which include fever, sore throat, anorexia, nausea, vomiting, generalized body malaise, headache and abdominal pain. Paresthesia or pain at the site of bite is due to viral multiplication at the spinal ganglion just before it enters the brain.

Acute Neurologic

The acute neurologic stage is the stage when the virus reaches the CNS andreplicates most exclusively within the gray matter. This stage has two types of presentation: encephalitic or furious type, which is present in 80% of rabies cases, and paralytic or dumb type, which is seen in 20 %. Autonomic manifestations such as hypersalivation appear during this stage. The virus passes centrifugally among autonomic nerves to reach other tissues- the salivary gland, adrenal medulla, kidney, lung, liver, skeletal muscle, skin and heart. Passage into the salivary gland facilitates further transmission of the disease through infected saliva. This stage lasts for 2-7 days, characterized by hyperactivity, hypersalivation, disorientation, hallucination, bizarre behavior interspersed with lucid intervals, seizures, nuchal rigidity or paralysis.

Coma: begins within 10 days of onset, and the duration varies.

Death: without intensive supportive care, respiratory depression, cardio respiratory arrest, and death occur in almost 100% of cases.

Laboratory Diagnosis

Often the diagnosis of rabies is based on the clinical manifestations and a history of exposure to a rabid animal. In cases where the pathognomonic hydrophobia and/or aerophobia are present, the diagnosis is straight forward. However, clinical diagnosis may be difficult in cases of paralytic rabies and atypical presentations. Thus, rabies laboratory confirmation is necessary. Rabies diagnosis can be performed on fresh tissue specimens stored at appropriate temperatures, preferably refrigerated. The specimens to be collected depend on the test to be performed.

In transporting specimen glycerine preservative (temperature:+40Cor-200C) or dried smears of brain tissue on filter paper (temperature:+300C) enables safe transport.

Ante-Mortem

Samples for Laboratory diagnosis of rabies during life secretions and biologicalfluids (saliva, spinal fluid, tears, etc.) can be used to diagnose rabies during life (intra vitam). They should be stored at -200C or below. Serum should be collected from blood samples prior to freezing and stored at -200C.

The following laboratory tests can be done to confirm rabies in humans:

Fluorescent Antibody Testing (FA)

The Fluorescent Antibody (FA) technique is the gold standard for rabies diagnosis. It is a rapid and sensitive test based on microscopic examination under ultraviolet light. Tissue samples from brainstem, thalamus, cerebellum and the hippocampus (Ammon's horn) are recommended for increased sensitivity of the test. Viral antigen may be detected by using the FA test on skin biopsies taken from the nuchal area of the neck, with hair follicles containing nerve endings.

Polymerase Chain Reaction (PCR)

The Polymerase Chain Reaction (PCR) is a laboratory technique for "amplifying" a specific DNA sequence. PCR is extremely efficient and sensitive; it can make millions or billions of copies of any specific sequence of DNA, even when the sequence is in a complex mixture

Serology

Serum Rapid Fluorescent Focus Inhibition Test (RFFIT). Serum neutralization assays ar used to determine the potency of rabies serum and immunoglobulins used for PEP, and to evaluate the immunogenicity of human and, to a lesser degree, animal rabies vaccines.

RABIES INFECTION IN DOGS

Animal Reservoirs of Rabies

Dogs are the principal reservoir of rabies in india. Rabies in domestic animals like cattle, pigs goats and horses has been reported since the 1930's but were all traced to bite of rabid dogs.

Incubation Period of Rabies in Dogs

Incubation period of rabies in dogs vary from 10-80 days after exposure. The incubation period varies from a few days to several months, and the virus can be shed in the saliva a few days prior to the appearance of any clinical neurological manifestations. In majority of dogs, virus excretion begins at the earliest 2-7 days shortly before or after the appearance of the clinical signs and symptoms of rabies.

Mode of Transmission

Rabies is transmitted among animals and from animals to man through excretion of rabies virus via saliva and is

transmitted to a new victim through a bite or through penetration of infected saliva into broken skin or mucosa.

Clinical Signs of Rabies In Other Domestic Animals

In cats, the incubation periods ranged from 2-12 weeks with a median of 4-6 weeks. Major signs of rabies in cats include behaviour change, gait abnormality, strange or unusual look in the eyes, increased frequency of vocalization and a reported wound within the preceding 6 months. In horses the incubation period averages 2-4 weeks (range of 2 weeks to 3 months. Clinical signs of disease at the time of initial examination usually include weakness of the hind quarter (ataxia and paresis) lameness and colic. After excitation period, paralytic signs occur that cause the difficulty in swallowing, followed by the in coordination of the extremities. Rabies in cattle and small ruminants is characterized by long incubation period of 14-26 days. Clinical signs include behavioural change, anorexia, hypersalivation, aggressiveness, hyperexcitability and hyperesthesia. The animal dies within one week.

Laboratory Diagnosis

The diagnosis of animal rabies is based on laboratory confirmation. The gold standard for laboratory diagnosis for animal rabies is Fluorescent Antibody Test (FAT). In the absence of FAT, other examinations are Direct Microscopic Examination (DME) and Mouse Inoculation Test (MIT).

Fluorescent Antibody Test (FAT)

The gold standard for laboratory diagnosis for animal rabies is Fluorescent Antibody Test (FAT). An immunoassay using monoclonal antibodies specific for rabies in an impression smear of the hippocampus (Ammon's horns) and brain stem treated with fluorescent in isothiocyanate-labeled anti-rabies globulin. It needs a fluorescent microscope to determine the staining reaction and the result may be obtained within 24 hours.

- ***Reverse Transcriptase-Polymerase Chain Reaction (RT-PCR)***

PCR is molecular detection or rabies nucleoprotein in a sample using rabiesspecific primers. Results should correlate clinically with other diagnostic tools.

- ***Rabies Fluorescent Focus Inhibition Test (RFFIT)***

A serologic assay uses a cell culture technology to determine the rabies virus neutralizing antibody (VNA) in an immunized or sick individual.

- ***Seller's Test or Negri Body Detection in Direct Microscopic Examination (DME)***

Technique using impression smear for the detection of rabies inclusion bodies known as Negri bodies, through direct microscopic examination. Demonstration of typical Negri bodies with Direct Microscopic Examination (DME) is considered diagnostic: however, the brains of as many as 15% of the infected animals may not contain demonstrable Negri bodies. In cases in which Negri bodies cannot be demonstrated, Mouse Inoculation Test (MIT) should be done.

- ***Mouse Inoculation Test (MIT)***

The MIT is an in vivo test to confirm the infectivity of the rabies virus through virus isolation. It is also conducted on specimens that are unsuitable for histopathologic or Fluorescent Antibody Test (FAT) of cases where additional verification is desired. Suckling mice (less than 3 days old) are more susceptible to rabies than weaning and adult mice and should be used whenever possible. The long post-inoculation observation period of 21 days limits its clinical usefulness in the management of animal bite cases.

GUIDELINES IN THE PREVENTION AND CONTROL OF RABIES

Fig 5: National Rabies Prevention and Control Program Manual of Operations

Local Wound Care

i. Wash wounds immediately and vigorously with soap/ detergent, and water, preferably for 10 minutes. If soap is not available, the wound should be thoroughly and extensively washed with water.
ii. Apply alcohol, povidone iodine or any antiseptic.
iii. Mucous membranes such as eyes, nose or mouth shall be flushed well with water.
iv. Suturing of wounds should be avoided since it may inoculate the virus deeper into the wounds. Wounds may be coaptated using sterile adhesive strips. If suturing is unavoidable, it should be delayed for at least 2 hours after administration of RIG to allow diffusion of the antibody to the tissues.
v. Do not apply any ointment, cream or wound dressing to the bite wound.

vi. The public should be educated in simple local wound treatment and warned not to use procedures that may further contaminate the wounds (e.g. tandok, bato, rubbing garlic on the wounds and other nontraditional practices.
vii. Antimicrobials are recommended for the following conditions:
a. All frankly infected wound
b. All category III cat bites
c. All other category III bites that are either deep, penetrating, multiple or extensive or located on the hand, face and genital area.
viii. Anti- tetanus immunization may be given if indicated. History of tetanus immunization (TT/DPT/Td) should be reviewed. Animal bites are considered tetanus prone wounds. Completion of the primary series of tetanus immunization is required

Immunization

Active Immunization

Active immunization refers to the administration of vaccine to induceprotective immune response through antibody and T-cell production in order to neutralize the rabies virus in the body. It induces an active immune response in seven – ten (7-10) days after vaccination which persists for many years providedthat primary immunization is completed.The program requires that all ABTCs should use WHO prequalified vaccines.

General Principles

a. Storage
a.1. Vaccines should be stored at +2 to + 8 °C in a refrigerator, not freezer
a.2. Once reconstituted, vaccines should be kept in the refrigerator and used within 8 hours
b. Administration Area
b.1. Injections should be given on the deltoid area of each arm in adults or at the anterolateral aspect of the thigh in infants.
b.2. Vaccine should never be injected in the gluteal area as absorption is unpredictable

Recommended PEP Regimens for ABTCs/ABCs

a. Intradermal Regimen

To maximize the limited resources of the NRPCP, all Animal Bite Treatment
Centers (ABTCs) are required to use only the recommended ID regimen in managing rabies exposures/animal bites. According to WHO, the ID use of Tissue Culure Vaccines can decrease the cost of PEP by as much as 60-80%. ABTCs are also required to administer only vaccines approved by WHO for ID use
Patients with with hematologic conditions where IM injection is contraindicated should receive rabies vaccine by ID route
Immunocompromised patients such as those with HIV infection, cancer/etc and patients with chronic liver disease and those taking chloroquine and systemic steroids should be given standard IM regimen as the response to ID regimen is not optimum for these conditions.

Updated 2-site Intradermal Regimen

This regimen is a modification of the original Red Cross regimen 2- site ID regimen where the Day 90 dose has been transferred to Day 28.
One dose for ID administration is equivalent to 0.1 ml both for PVRV and

PCECV

One dose should be given on each deltoid (or at the anterolateral aspect of both thighs in infants) on Days 0, 3, 7 and 28.

Principles of Management of Human Rabies

Considering the fatal outcome and absence of cure for human rabies once signs and symptoms commence, management should center on ensuring comfort for the patient, using sedation, avoidance of intubation and life support measures.

Medications

Any of the following medications may be given:
o Diazepam
o Midazolam
o Haloperidol plus Diphenhydramine

Supportive care

Patients with confirmed rabies should receive adequate sedation and comfort care in an appropriate medical facility.
 Avoid invasive procedures.
 Provide suitable emotional and physical care.
 Provide and discuss with relatives important information concerning transmission of the disease, and indications for PEP of contacts.
 Communicate gently and compassionately with relatives regarding the patient's prognosis.

INFECTION CONTROL

 The virus is not carried in blood and is only intermittently shed in saliva, CNS fluid, urine and within some tissues.
 Patients should be admitted in a quiet, draft-free isolation room.
 Staff taking care of a rabies patient should strictly adhere to proper barrier nursing methods for patient care, as is recommended for all infectious diseases.
 Health care workers and relatives coming in contact with the patient should wear proper personal protective equipment (PPE), including gown, gloves, mask and goggles.
 Staff should wear sufficient protection such as gowns, goggles, masks and thick gloves.
 Pre-exposure immunization against rabies of nursing staff and health-care personnel in hospitals may be considered for those who, after careful investigation, are considered most at risk.

POSTMORTEM MANAGEMENT OF BODIES OF PATIENTS WHO DIED OF RABIES

 Humans who died of rabies generally present a small risk of transmission to others. Blood does not contain the rabies virus. However, rabies virus may be present In many tissues, such as the central nervous system, salivary glands and muscle and in saliva and urine.
 Procedures in handling of brain or spinal cord, such as using electric saws and drills during necropsies, if done carelessly, can lead to mucous membrane and inhalation exposures. If extremely necessary, perform necropsies with strict infection control measures using proper personal protective equipment (PPE), including gown, gloves, mask and goggles.

 Tissues and body fluids should be disposed of in the same manner as practiced for other infectious diseases such as tuberculosis and hepatitis.
 Disinfect instruments by autoclave or boiling after use.
 Discourage embalming. Early disposal of the human remains by burial or cremation is highly recommended.

CONCLUSION

National Centre for Disease Control (formerly known as National Institute of Communicable Diseases), Delhi, a WHO Collaborating Centre for Rabies Epidemiology, organized an expert consultation in 2002 to formulate "National Guidelines for Rabies Prophylaxis" to bring out uniformity in pre-and post-exposure prophylaxis (PEP) practices. These guidelines were revised through an expert consultation in 2007, 2013 and 2019.

REFERENCES

1. Rabid by Bill Wasik, Monica Murphy: 9780143123576 | PenguinRandomHouse.com: Books. PenguinRandomhouse.com. Accessed January 19, 2021.
2. Radhakrishnan S, Vanak AT, Nouvellet P, Donnelly CA. Rabies as a Public Health Concern in India-A Historical Perspective. Trop Med Infect Dis. 2020;5(4). doi:10.3390/tropicalmed5040162.
3. Rose G, Barker DJ. What is epidemiology? Br Med J. 1978;2(6140):803-804. doi:10.1136/bmj.2.6140.803
4. WHO | Epidemiology and burden of disease. WHO. Published 2020. Accessed January 14, 2021.
5. Gongal G, Wright AE. Human Rabies in the WHO Southeast Asia Region: Forward Steps for Elimination. Adv Prev Med. 2011;2011:383870. doi:10.4061/2011/383870
6. WHO Expert Consultation on Rabies, Weltgesundheitsorganisation, eds. WHO Expert Consultation on Rabies: Third Report, Bangkok, Thailand on 26-28 April 2017. WHO; 2018.
7. Encyclopedia of Microbiology | ScienceDirect. Accessed September 2, 2021. https://www.sciencedirect.com/referencework/9780123739445/encyclopedia-of-microbiology
8. Anna Rovid Spickler. Rabies. Published online 2012. http://www.cfsph.iastate.edu/DiseaseInfo/factsheets.
9. Reddy GBM, Singh R, Singh KP, et al. Molecular epidemiological analysis of wild animal rabies isolates from India. Vet World. 2019;12(3):352-357. doi:10.14202/vetworld.2019.352-357
10. Madhusudana SN, Mani R, Ashwin YB, Desai A. Rabid fox bites and human rabies in a village community in southern India: epidemiological and laboratory investigations, management and follow-up. Vector Borne Zoonotic Dis. 2013;13(5):324-329. doi:10.1089/vbz.2012.1146
11. N Veeraraghavan. A case of hydrophobia following bat bite. Published online 1954.
12. Childs JE, Colby L, Krebs JW, et al. Surveillance and spatiotemporal associations of rabies in rodents and lagomorphs in the United States, 1985-1994. J Wildl Dis. 1997;33(1):20-27. doi:10.7589/0090-3558-33.1.20
13. Fitzpatrick JL, Dyer JL, Blanton JD, Kuzmin IV, Rupprecht CE. Rabies in rodents and lagomorphs in the United States, 1995–2010. J Am Vet Med Assoc. 2014;245(3):333-337. doi:10.2460/javma.245.3.333
14. THE PREVENTION AND CONTROL OF INFECTIOUS AND CONTAGIOUS DISEASES IN ANIMALS ACT, 2009.
15. The Delhi Municipal Corporation Act, 1957.
16. Government of India. The Epidemic Diseases Act, 1897. Published online 1897.
17. Government of India. The Public Liability Insurance Act, 1991. Published online 1991.
18. Central Pollution Control Board Guidelines. guidlines for carcass disposal. Published online 2020.
19. Section 393, Disposal of Dead Animals., Indian Penal Code.
20. Chao A, Colwell RK, Chiu C-H, Townsend D. Seen once or more than once: applying Good–Turing theory to estimate species richness using only unique observations and a species list. Methods in Ecology and Evolution. 2017;8(10):1221-1232.