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Rabies in the 21st century

M. Bindu Pushpa*[1], M. Prasanth Kumar[2], P. Nikhitha Sree[3]

[1]*Department of Veterinary Public Health & Epidemiology, Institute of Veterinary Sciences and Animal Husbandry, Siksha O Anusandhan University, Bhubaneswar, Odisha-751003 India*

[2]*Post Graduate Scholar, Department of Veterinary Gynaecology and Obstetrics, Rajiv Gandhi Institute of Veterinary Education and Research (RIVER), Kurumbapet, Puducherry -605 009 India*

[3]*Graduate Research Assistant, Comparative Biomedical Sciences, Oklahoma University, United States of America (USA)*

***Corresponding Author:** bindupushpa1221@gmail.com

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Introduction:

Rabies is a preventable yet neglected tropical disease (NTD) and is the deadliest viral zoonosis in history, with a fatality rate of 100% once symptoms manifest. Over 99% of human rabies cases are caused by dog bites, spreads through the saliva of infected dogs, often through bites, scratches, or contact with mucous membranes like the eyes, mouth, or open wounds. This fatal disease can be effectively prevented through strong political commitment, mass vaccination of dogs, improved access to pre-exposure prophylaxis (PrE) and post-exposure prophylaxis (PEP), and education on responsible dog ownership and bite prevention. Enhanced surveillance systems are also crucial for early detection and response.

Etiology:

Rabies is caused by viruses from the genus *Lyssavirus*, part of the family *Rhabdoviridae*. These viruses are rod-shaped, with rabies virus (RABV) being the primary cause of rabies in humans and animals. The rabies virus is a single-stranded, negative-sense, non-segmented RNA virus that belongs to the order *Mononegavirales*. This order includes viruses with specific characteristics such as their type of nucleic acid, replication strategy, genomic organization, size, and morphology. The rabies virus, for example, measures about 75 nm by 200 nm and has a helical nucleocapsid surrounded by a protein-studded membrane. Rabies virus uses specific cell surface components like nicotinic acetylcholine receptors, low-affinity nerve-growth factor receptors, and gangliosides to enter cells. These viruses are neurotropic, primarily targeting the mammalian central nervous system, though they can be adapted in lab settings to propagate in various cell cultures.

Global Burden of Rabies:

Rabies is found worldwide, except in Australia and Antarctica, where no dog-mediated rabies cases have been reported. Dog-mediated rabies has been eliminated in parts of the world, including western Europe, Canada, the

USA, Japan, and some Latin American countries. However, it remains a serious public health challenge in many Asian and African countries, where tens of thousands of human deaths occur annually. The disease disproportionately affects poor and marginalized populations, particularly children under the age of 15, with an estimated 50,000–60,000 deaths per year, 95% of which occur in Asia and Africa.

The economic burden of rabies is significant, costing an estimated US$8.6 billion annually. In Africa and Asia, where rabies is most prevalent, the cost of prevention and control exceeds US$500 million, mostly for providing PEP. In rural areas of Tanzania, for instance, a person earning less than US$1 a day would need to spend over US$100 to complete the WHO-recommended PEP treatment. The high cost and lack of access to healthcare contribute to the high death rates in Africa.

As interactions between humans, animals, and their environments increase, so does the risk of zoonotic diseases like rabies emerging and spreading. To combat these challenges, there is a growing recognition of the need for a holistic approach to health that addresses the interconnectedness of human, animal, and environmental health. This integrated strategy aims to enhance rabies prevention, particularly in Africa, and aligns with the WHO's vision of eradicating dog-mediated rabies and preventing human deaths by 2023.

Diagnosis:

Rabies diagnosis has advanced significantly, employing various laboratory techniques to ensure accurate detection of the virus. The diagnosis primarily relies on identifying the rabies virus or its components in brain tissues. The fluorescent antibody test (FAT) is the most commonly used and recommended by WHO and OIE. It involves adding a drop of conjugated antibody to a brain tissue smear and observing fluorescence to detect viral antigens. FAT provides reliable results in 95-99% of cases.

Other diagnostic methods include:

- **Histological identification:** This method detects Negri bodies (viral aggregates in neurons), but it is less sensitive and has largely been replaced by immunological techniques.
- **Mouse inoculation test:** This involves inoculating mice with brain tissue samples and observing for symptoms of rabies. While effective, it is slow, costly, and increasingly replaced by cell culture tests.
- **Cell culture test:** Neuroblastoma cell lines are used to culture the virus, providing faster results and avoiding the use of live animals.
- **Polymerase chain reaction (PCR):** Used in specialized laboratories, PCR can detect viral nucleic acids and differentiate between vaccine and field strains.

Advanced techniques like ELISA, monoclonal antibodies, and nucleic acid probes are also used for specific virus identification and to distinguish between different rabies-related viruses.

Public Awareness and Global Efforts to Control Rabies:

The risk of rabies exists globally, whether through dog bites in developing countries or wildlife in developed countries. Communicating the risks and preventive measures effectively is crucial. The World Rabies Day initiative has helped highlight the need for global action, and successful control measures in the U.S. provide a model for other countries.

The global rabies burden remains alarmingly high, with an estimated 50,000–55,000 people dying annually, and around half of these deaths occurring in India alone. This staggering toll is primarily the result of rabid dog bites, particularly in regions like Asia and Africa, where rabies control efforts have lagged. Despite the existence of

effective prevention strategies, over 3 billion people across 100 countries remain at risk of infection. Children make up a significant proportion of rabies victims, highlighting the need for urgent action.

The persistence of canine rabies in many developing countries is a key driver of human rabies deaths. More than 95% of these deaths occur in Asia and Africa, areas where rabies control programs are insufficiently implemented. In contrast, developed countries have successfully eliminated canine rabies, offering models for other regions to follow. These successes demonstrate that mass vaccination of domestic dogs is a cost-effective and practical approach to eliminating rabies, reducing human deaths significantly. However, the spread of rabies in developing regions remains a public health crisis that requires coordinated international efforts to control.

World Rabies Day (WRD), an initiative launched to raise awareness and educate communities about rabies prevention, has successfully reached over 55 million people worldwide. Participants from more than 85 countries, including governments, professionals, media, and the public, are taking steps toward rabies elimination. Educational materials translated into multiple languages have been disseminated, teaching communities the importance of proper medical care after a rabid bite, rather than relying on ineffective traditional treatments.

Recent scientific advancements are paving the way for improved vaccines and treatments. Researchers are working on innovative vaccines that could be more affordable and accessible to populations in developing countries, especially those most affected by rabies. These new-generation vaccines could provide immunity with fewer doses and at a lower cost than current options, making them more feasible for large-scale immunization programs.

For now, post-exposure prophylaxis (PEP) with vaccines and rabies immunoglobulin (RIG) remains critical for those bitten by rabid animals. However, the supply of these life-saving treatments is limited, particularly in developing countries, exacerbating the already high mortality rates. Alternatives, such as monoclonal antibodies, are being explored as cost-effective substitutes for RIG.

The challenges of rabies control also involve wildlife, especially in regions where wildlife species serve as reservoirs for the virus. Strategies like oral rabies vaccination (ORV) programs for wildlife have been successful in countries like the United States, Canada, and Mexico. These programs rely on sophisticated surveillance and interjurisdictional collaboration to detect and control rabies outbreaks.

As diagnostic techniques improve, molecular tools are becoming more accessible, allowing for faster and more accurate detection of rabies virus. These advancements are essential for tracking and controlling rabies, particularly in resource-poor settings. In the coming years, scientists aim to develop novel vaccines and diagnostic methods that will make rabies prevention more efficient and affordable.

Ultimately, eliminating human rabies deaths begins with controlling canine rabies through mass dog vaccination. While the challenges are significant, especially in Africa and Asia, the scientific and public health communities are optimistic that with the right strategies, rabies can be eliminated globally within the 21st century. The progress made in developed countries and the ongoing efforts in developing regions serve as hopeful indicators of what can be achieved with sustained commitment and collaboration.

Challenges and Future Directions:

One major problem is the limited availability of rabies immunoglobulin (RIG), which is crucial for post-exposure treatment after a rabid animal bite. Efforts are underway to find cheaper and more widely available alternatives, such as monoclonal antibodies.

Rabies is difficult to treat once it reaches the central nervous system (CNS). Scientists are studying how rabies evades the immune system and are exploring ways to enhance the body's immune response to the virus. New treatment strategies may emerge from this research.

Conclusion:

To eliminate dog-mediated rabies sustainably, key measures include building partnerships among stakeholders—governments, private sector, NGOs, and communities—and using integrated surveillance data to guide cost-effective strategies. A One Health approach, providing data on dog and human populations, rabies cases, and vaccination status, is crucial for effective control frameworks.

Improved coordination across animal, human, and environmental health sectors, along with expanding access to post-exposure prophylaxis (PEP) and animal vaccinations, are essential. Raising community awareness, enhancing diagnostic capacities, scaling up research, and securing government commitment with sustainable investments are vital to achieving rabies elimination.

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