ISSN: 2474-3658

Mehndiratta et al. J Infect Dis Epidemiol 2023, 9:308
DOI: 10.23937/2474-3658/1510308
Volume 9 | Issue 8
Open Access

Journal of
Infectious Diseases and Epidemiology

REVIEW ARTICLE

'Don't Let the Problem go Unheard. Let's Get Rid of Rabies' - A Review of the Past, Present and Future Perspective of Rabies

Man Mohan Mehndiratta[1], Renuka Upadhyaya[2*], Vasundhra Agarwal[3] and Monalisa Vegda[4]

[1]Senior Director, Department of Neurology, BLK-MAX Hospital, Centre for Neurosciences, Pusa Road, New Delhi, India

[2]Specialist Medical Microbiologist, Department of Clinical Microbiology, Ph Diagnostic Laboratory, Bur Dubai, Dubai, United Arab Emirates

[3]Associate Professor, Department of Neurology, Janakpuri Superspeciality Hospital Society, Janakpuri, New Delhi, India

[4]Associate Consultant, Department of Neurology, BLK-MAX Hospital, Centre for Neurosciences, Pusa Road, New Delhi, India

***Corresponding author:** *Renuka Upadhyaya, Specialist Medical Microbiologist, Department of Clinical Microbiology, Ph Diagnostic Laboratory, Bur Dubai, Dubai, United Arab Emirates*

Abstract

Background: Rabies, a negative strand RNA virus belonging to the genus Lyssavirus has existed since hundreds of years. Available historical texts called it 'an ancient curse'. From Aristotle in fourth century BC to present day, rabies virus has existed in various species of animals. Modern day molecular epidemiology has proven the evolving nature of the virus. The virus showcases considerable genetic plasticity and hence it still exists as a tangible threat in the 21st century.

Text: The 2019 Global Burden of Disease Study revealed a considerable number of Rabies related human deaths. The global strategic plan, proposed by World Health Organization (WHO) was to be canine- rabies free by 2030 (Zero by 30). Adopting this plan, affected countries would come closer to fulfilling Sustainable Development Goal (SDG) 3.3. This goal encompasses the WHO strategy to end epidemics of neglected tropical diseases like Rabies through education, awareness and specific medical treatment. Rabies is mainly concentrated in Asia and Africa but America, Canada and Europe are facing renewed threats via bat rabies. Disease among travelers to Rabies-endemic areas and risk of re-introduction of canine Rabies is a matter of concern. Renewed efforts to tackle Rabies include newer laboratory techniques, novel vaccines and immunoglobulin. Some diagnostic techniques have been standardized internationally. Mouse inoculation tests are being replaced by cell cultures. Specific nucleic acid probes and DNA sequencing techniques are being used for rapid confirmation of the clinical cases. Post-Pasteur vaccinologists have developed next-generation vaccines, overcoming the conventional drawbacks of the old ones. These efforts were gravely hampered by the COVID-19 pandemic in 2020. Unlike other infectious diseases, telemedicine cannot be a solution for animal-bite victims. Anti-rabies clinics were shut down and there were logistical issues where patients could not receive timely post-exposure prophylaxis. There were significant disruption of health care services and major Rabies control targets were wiped out especially in low and middle income countries. There are questions on the affordability, availability and accessibility of therapeutic options in the present day.

Conclusion: Existing in the past and in our present, numerous scientific articles have been written on Rabies. This comprehensive review is one step towards analyzing a unified global effort 'One Health Approach' for achieving zero human deaths by 2030. Elimination of this zoonotic disease in near future will be a test case for World Health Organization. In spite of a pandemic setback, it will help reduce global health inequality and strengthen our fight against neglected tropical infections. It will help in our preparedness for future infectious disease emergencies.

Citation: Mehndiratta MM, Upadhyaya R, Agarwal V, Vegda M (2023) 'Don't Let the Problem go Unheard. Let's Get Rid of Rabies' - A Review of the Past, Present and Future Perspective of Rabies. J Infect Dis Epidemiol 9:308. doi.org/10.23937/2474-3658/1510308

Accepted: August 29, 2023: **Published:** August 31, 2023

Copyright: © 2023 Mehndiratta MM, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Abbreviations

WHO: World Health Organization; PCR: Polymerase Chain Reaction; RIG: Rabies Immunoglobulin; DFAT: Direct Florescent Antibody Test; PrEP: Pre Exposure prophylaxis; PEP: Post Exposure prophylaxis; AIDP: Acute Inflammatory Demyelinating Polyneuropathy

Introduction

Rabies, a viral zoonotic disease forms part of the 'Neglected Tropical Diseases (NTD)' enlisted by World Health Organization (WHO) [1]. According to the study on Global burden of Rabies, it causes approximately 14000 human deaths annually, children below 14 years of age constitute 40% of the bite victims and Africa, Asia bear the burden of maximum cases of canine rabies [2].

Being largely ignored by global funding agencies, rabies prevention programs have hit many roadblocks. Limited resources have been made available to countries across the globe especially the developing ones. WHO, the World Organization for Animal Health (OIE), Global Alliance for Rabies Control (GARC) and their partners have formulated specific targets and a common goal of 'Zero Human Deaths by 2030' [3]. These targets have been aligned with the Sustainable Development Goals (SDG) Program, specifically SDG 3.3 [4]. The Covid-19 pandemic hit this renewed combat against Rabies mainly affecting communities with high burden. Hence, accurate scientific information and discussions regarding this largely preventable disease in post-Covid era becomes essential.

Rabies has been the subject of hypotheses and research since its discovery by Louis Pasteur in the 20th century. Studies on origins of Rabies disease associate human rabies with canine rabies. Since ancient times, dogs have been considered as the main vector of this disease. However with the advent of modern diagnostic and genetic tools, it has been established well without doubt that rabies virus exists in many animal species [5].

Historical Background of the Virus

The word rabies comes from the Latin word 'rabere' meaning 'to rage', also known as canine madness or hydrophobia [6]. Aristotle, the famous Greek polymath, in his book 'History of Animals' quoted 'if the rabid dog bites, all the animals bitten become rabid' [7]. Reference to Rabies occurs in texts from ancient Mesopotamia (circa 2200 BC). The disease was associated with the appearance of Dog Star Sirius in summers when the dogs were prone to spells of madness. In the 1st century AD, famous Indian text 'Susrutasamhita' mentioned this disease with its signs and symptoms [8]. Arab and Persian authors have mentioned rabies in their texts in the 11th and 15th centuries. In 1804, Georg Gottfiel Zinke performed an experiment transmitting rabies from rabid dog to normal dog and then to rabbit and hen [9].

Pasteur established the theory of rabies virus being present in the infected animals' brains. By serial inoculation of the rabies virus in rabbits, he was successful in obtaining a 'fixed' virus. He then demonstrated how multiple injections of this 'fixed' virus to dogs could render them immune. It was a scientific triumph when the same experiment could be replicated in humans. In July 1885, Joseph Meister, a nine-year-old boy was bitten by a rabid dog. He was inoculated with 13 injections of this crude vaccine by Pasteur. The boy survived and a breakthrough was obtained in the treatment of Rabies infection.

Epidemiology

Humans are a 'dead end' host in Rabies. Direct person to person transmission has not been documented in literature. However, unusual rare modes of transmission which has been recorded are through infected corneal grafts and solid organs [10]. The donors had died of unsuspecting Rabies and their tissues harbored the virus.

Current scientific knowledge confirms the prevalence of Rabies virus in terrestrial warm blooded mammals and bats. Ancient scriptures mention of a 'disease of madness' among wild carnivores but prevalence of Rabies in bats was a relatively recent discovery. Unfortunately, comprehensive data on global epidemiological trends, especially from endemic countries, remains scarce.

Two types of Rabies exist in nature-Urban Rabies, which is transmitted by domesticated animals like dogs (canine), cats and the other, Sylvatic type which involves foxes, raccoons, wolves, jackals and others. In developed nations like the United States, the canine rabies virus variant has been eliminated, but wildlife variants (such as bat, raccoon rabies virus variants) remain [11]. In Asia and Africa, 90 percent of human rabies is through exposure to rabid dogs. India leads the tally in human deaths due to rabies. Prevalence and the status of rabies control programs in the Indian sub-continent are mentioned in detail, later in the article. To give a better understanding, the world-wide prevalence of endemic human Rabies is illustrated in the given **World Map** (Figure 1). The data has been sourced from WHO Rabies prevalence fact sheet 2021.

Microbiological Perspective

Structure of the virus

The rabies virus is a rod or bullet shaped, unsegmented, enveloped RNA virus. Comparative genomic sequencing places it in the family Rhabdoviridae and genus Lyssaviruses. The virus is composed of an internal protein core or nucleocapsid containing the nucleic acid and an outer envelope, a lipid bilayer covered with glycoprotein spikes. The virus genome has 5 proteins. Few of these proteins aggregate in the cytoplasm of virus infected neurons and form Negri Bodies, the pathognomonic histopathological finding in Rabies infection [12].

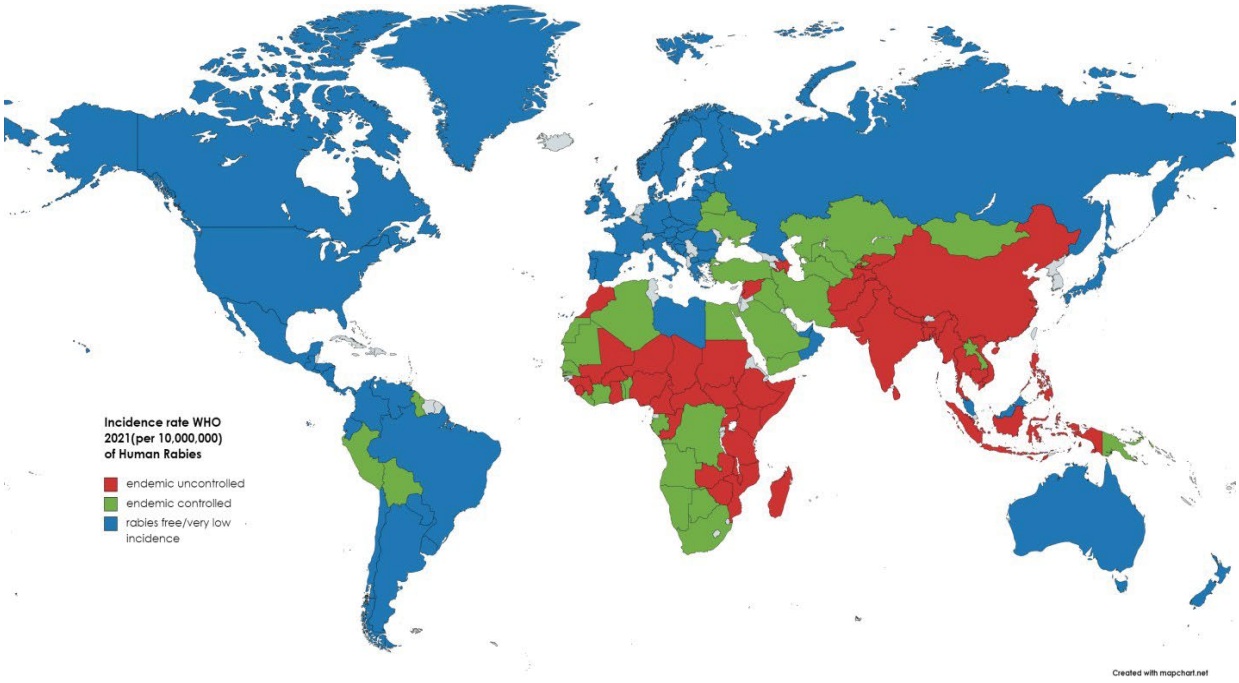

Figure 1: Incidence rate WHO 2021 (per 10,000,000) of Human Rabies.

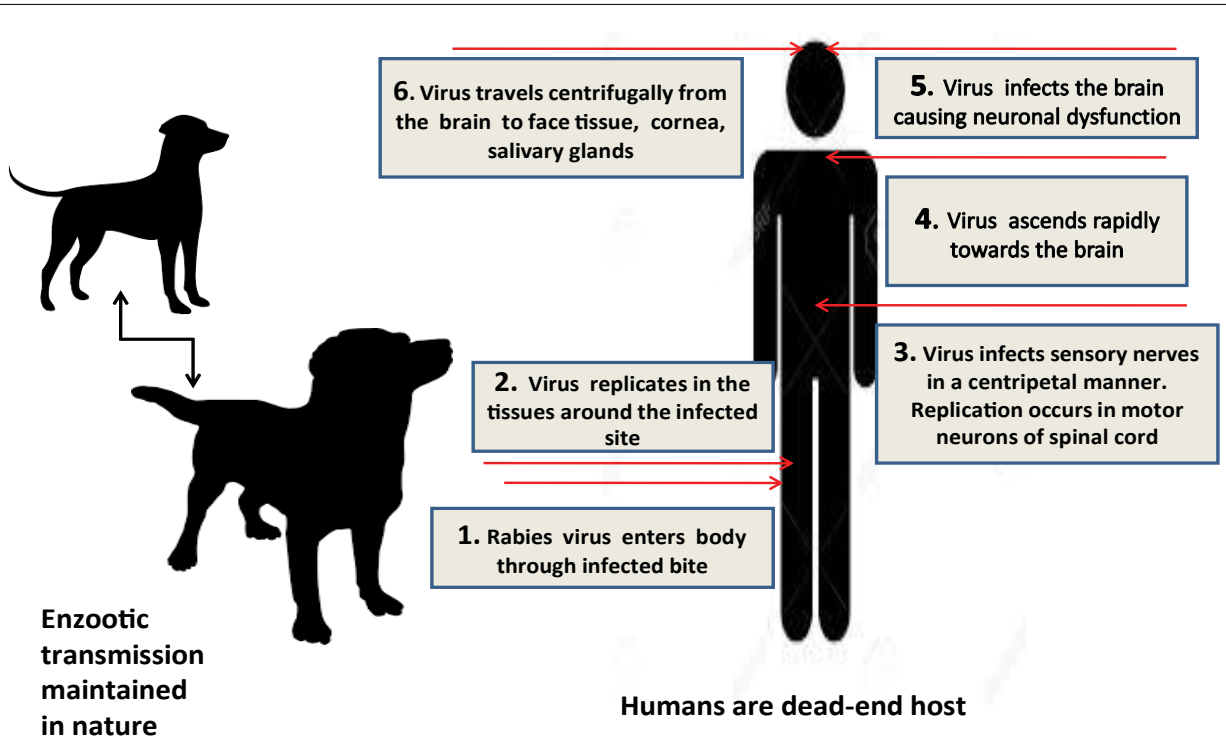

Figure 2: Pathogenesis in domestic rabies.

Pathophysiology

Human infection almost always occurs via the bite of an infected animal. Non bite infections like contamination of an open wound via scratches/licks and through aerosols have been documented rarely [13].

The virus exists in the saliva of the rabid animal. Initially, the virus may replicate in the skin and muscle tissue around the site of inoculation. This may last for 48-72 hours. The virus then enters the nervous system via transmission across neuromuscular junctions. It moves centripetally along the axons towards the spinal cord and brain. Rapid replication occurs in the brain after which the virus is disseminated centrifugally to many tissues and organs. It primarily resides in the salivary glands, cornea and facial tissue. Replication occurs in the salivary glands due to which constant virus shedding occurs in saliva. The virus may be shed in milk and urine also. The pathophysiology has been depicted in Figure 2.

Antigenicity

Glycoprotein G is the main component present in the spikes of the viral envelope. These are chiefly responsible for virulence and immunity. These spikes bind to the acetyl choline receptors of the neural tissue stimulating hemagglutination-inhibiting (HI) and neutralizing (protective) antibodies. Therefore, it provides an effective and safe vaccine model. The nucleocapsid protein or the internal viral core protein also induces antibodies. These are called complement fixing antibodies but these are not protective in nature [14].

Clinical Spectrum of the Disease

Eliciting a history of bite or lick/scratches from possible rabid animal is the key in early diagnosis of rabies [15]. The progression of the disease depends on the nature and extent of infection.

The incubation period is mainly 1-3 months though it may vary from few days to years. The incubation period was found to be shorter in those individuals bitten on the head or face. This is probably related to the distance the virus travels to reach the brain. Scientists have divided the course of disease into four categories: Prodrome, acute encephalitis stage, coma and death.

The prodrome is marked by non specific symptoms. In case, history of bite cannot be elicited, it may be extremely difficult to make accurate diagnosis during this stage. Anorexia, fever, headache, malaise and paresthesia/pain at the site of virus entry may be seen. It may last for 2-4 days. Encephalitis occurs when the virus reaches the brain and starts replicating. There may be bouts of extreme hyperactivity along with seemingly normal behavior. Delirium and hallucinations are common symptoms seen. One characteristic feature in patients is termed as hydrophobia or fear of water. In spite of intense thirst, patients dread the sight of water. This is because any attempts to drink result in painful spasms of the pharyngeal muscles. A majority of patients die due to respiratory arrest in the encephalitic stage. It may last for 2-10 days. Some patients progress to paralysis. Rarely, there may be no signs of hyperactivity and there is appearance of paralytic disease from the onset. This kind of clinical presentation can be a diagnostic dilemma for the clinicians. It can be confused with demyelination induced quadriparesis. Acute Inflammatory Demyelinating Polyneuropathy (AIDP) can also have a similar clinical picture. Thus, the clinical spectrum can prove to be one of the most difficult conundrums for the experts. Death is preceded by coma which may last for hours or few days. Unvaccinated individuals with history of rabid bites have 100% fatality.

Laboratory Diagnosis of Rabies

Until recently, there was minimal focus on laboratory confirmation of Rabies disease. Due to the fatality of the disease, no serious attempt was made on confirming Rabies or treatment except heavy sedation. If a person survived, it was considered a non-rabid infection. In the present day, when survival from established rabies has been documented in rare instances [16], there has been renewed emphasis on making laboratory distinction between Rabies and other encephalitis-causing diseases. Several diagnostic tests are being marketed commercially which prove to be key assets in the battle against Rabies.

The laboratory diagnosis of Rabies dates back to the year 1903-5 when the microscopic detection of Negri Bodies marked a milestone in the fight against Rabies [17]. Aldechi Negri demonstrated these intra-cytoplasmic inclusion bodies in the brains of rabid animals. Unfortunately, there is lack of absolute confirmation as Negri bodies may be absent in about 20% of suspected Rabies. In 1936, Webster and Claw successfully grew the Rabies virus in tissue culture [18]. We present an overview of the various methodologies used in the diagnosis:

1. Virus detection- Intracerebral inoculation of suspected rabid samples in mice is one of the conventional methods [19]. Samples can be saliva, cerebrospinal fluid or urine from patients which can be collected at multiple intervals. Chances of isolation are better early in the disease when neutralizing antibodies have not been produced. The inoculated mice are observed for signs of illness and their brains are examined postmortem for Negri bodies (28 days post-inoculation). This test is not in the list of World Health Organization's recommended tests for Rabies. There is delay in results due to the 28 day waiting period. Negri bodies might be absent in many cases. Additionally, animal testing facilities are required. There might be potential ethical conflicts.

   A more rapid and sensitive method is the isolation of virus in tissue culture cell lines [20]. Many commercially available cell lines arising from neural ectoderm are sensitive for the Rabies virus. One of the commonly used is the Neuroblastoma cell line. Samples are inoculated into these cell lines and repeatedly examined under immunofluorescence. Cytological changes patho gnomonic of Rabies start appearing as early as 3-4 days post-inoculation. Unfortunately, this test is confined to research laboratories as they are labour-intensive. Stringent bio-safety protocols have to be adhered along with the requirement for fluorescent microscopy and trained virologists.

2. Viral DNA detection- Molecular techniques like Polymerase Chain Reaction (PCR) and Real Time Reverse Transcriptase PCR have been

utilized as confirmatory tests for Rabies [21]. These are highly sensitive tests applicable to any available suspected rabid samples. Though many commercial versions are available, they are still limited to few laboratories. Primers have been designed for Reverse Transcriptase Loop Mediated Isothermal Amplification (RT-LAMP). This is an attempt to improve the molecular diagnosis. Another promising test is the Nucleic Acid Sequence Based Amplification (NASBA) which overcomes the disadvantages of traditional RT-PCR. Sometimes, there is destruction of cell morphology and diffusion of amplified products in the conventional methods. NASBA utilizes three enzymes- reverse transcriptase, T7 RNA Polymerase and RNaseH under isothermal conditions. All the PCR protocols have to be validated initially under stringent conditions. This is essential to prevent cross-contamination and false positive results. The diagnostic handbook by WHO details out explicitly this molecular methodology [22].

3. Viral Antigen detection- Recommended by WHO and the main diagnostic assay used worldwide, rabies viral antigen test is done using Direct Fluorescent Antibody Methodology (DFAT) [19,23]. The tested samples are corneal smears, skin tissue or saliva ante mortem and brain samples post mortem. The sensitivity and specificity of this test nears 99%. The main limitation is that the test is extremely observer-dependent. At least two observers should spend sufficient time examining the slides under fluorescent microscope.

There are three other tests which appear to be legal alternatives to DFAT [21]. Though they are less sensitive and specific, they can be used in diagnosis of Rabies. The results obtained have been variable hence a confirmation should always been done. These are

Rapid Rabies Enzyme Immunodiagnosis (RREID)

Rapid Immunodiagnostic Test (RIDT)

Direct Rapid Immuno-histochemical Test (dRIT)

Importance of Serology in Rabies

Serological tests are seldom useful due to late seroconversion in humans. Commercial kits are available for detection of rabies antibodies in animals post-vaccination. Serological evaluation is also mandated in cases where Pre-exposure Prophylaxis is given. Antibody levels should be checked at regular intervals for people at high risk. There are immense complexities surrounding the interpretation of rabies serology. Moore, et al. have highlighted this issue extensively in their recent article [24].

Therapeutic Approach for Control of Rabies

Critical step towards elimination of rabies would be to reduce the high proportion of cases in endemic countries. Owing to the fatality of the disease, preventive immunization or Pre-Exposure Prophylaxis (PrEP) is highly recommended by WHO. The cost-effectiveness of these PrEP programmes has been compiled extensively by various organizations. WHO has formulated models especially for endemic countries where PrEP has been considered part of childhood immunization programmes [25]. An article by Royal, et al. [26] elucidates timely intervention in school going children in India. Latest guidelines and recommended target groups for rabies PrEP can be accessed on the Centers for Disease Control and Prevention (CDC) website [27].

Consequences of rabid animal-human exposure yield results with varying severity. There is interplay of various factors like location of bite on body, severity of wound, quantity of virus inoculated and well-timed post wound management. The wound management includes post-bite wound care, Post Exposure Prophylaxis (PEP) and administration of rabies immunoglobulin (RIG). RIG have a unique way of providing passive protection. They neutralize the Rabies virus before vaccine induced antibodies appear. These are usually prepared from humans who have been immunized against Rabies and have very high titers of antibodies. Equine RIG is also available and equally effective. RIG should always be used alongside Rabies vaccine in previously unvaccinated individuals. There are no contra-indications. Unfortunately, there is a global shortage of RIG especially in developing countries.

The category of exposure (three categories) determines the PEP. This has been elaborated in Table 1.

With the contemporary understanding of rabies pathology, it is clear that rabies virus can expertly evade host immunity. Without vaccination, the chances of survival are slim. For elimination of deaths by 2030, vaccination becomes immensely important.

Table 2 gives a detailed description of the timeline of rabies vaccines [28-35].

Table 3 gives an overview of the promising future of rabies vaccines [36-40].

Rabies in Post-Covid Era: Major Impact of the Pandemic

Covid-19 pandemic has had huge ramifications on public health programs and vaccination campaigns. This is true for many diseases especially Rabies which is included in the 'Neglected Tropical Diseases (NTD)' category [1]. With the pandemic cloud hovering, there was a sudden global shift in priorities. Health gains achieved over past few years declined or were wiped out in the shortest period of time.

Table 1: Categories for post exposure prophylaxis.

	Category I	Category II	Category III
Immunologically naïve person	Thorough washing of exposed skin with soap. No PEP required	Thorough washing and immediate vaccination 2 sites ID on days 0, 3 and 7 OR 1 site IM on days 0, 3, 7 and between 14-28 OR 2 Site IM on day 0 and 1 site IM on days 7 and 21 RIG not indicated	Thorough washing and immediate vaccination 2 sites ID on days 0, 3, 7 OR 1 site IM on days 0, 3, 7 and between 14-28 OR 2 site IM on day 0 and 1 site IM on days 7 and 21 RIG indicated
Previously immunized	Thorough washing of exposed skin with soap. No PEP required	Thorough washing and immediate vaccination 1 site ID on days 0 and 3 OR 4 sites ID on day 0 OR 1 Site IM on days 0 and 3 RIG not indicated	Thorough washing and immediate vaccination 1 site ID on days 0 and 3 OR 4 sites ID on day 0 OR 1 site IM on days 0 and 3 RIG not indicated
Category I- Intact skin (no exposure) ID - Intradermal Ref :WHO Rabies fact sheet	Category II- Minor scratches (no bleeding) IM- intramuscular	Category III- Wounded skin/multiple bites RIG- Rabies immunoglobulins	

Table 2: Timeline of rabies vaccine.

VACCINE	CHARACTERISTICS	REFERENCE
'Fixed' Rabies Virus Pasteur vaccine	First generation vaccine. Developed from infected rabbit spinal cord. Major drawback was the increasing virulence of the rabies virus. However, it was in use for more than 50 years till modifications were made.	[28]
Fermi vaccine (1908) Semple vaccine(1911)	Vaccine developed from phenol treated inactivated sheep or goat brain. It was widely used all across the world until WHO discontinued it. There were serious side effects like Guilliain Barre Syndrome(GBS), fatal encephalitis.	[29,30]
Myelin free inactivated vaccine (1964)	Developed by Fuenzalida and his team , this vaccine was developed from Suckling mouse brain. It was a good alternative , less reactogenic vaccine. However, the claims of being myelin free was not found true. Remnants of myelin tissue in the vaccine caused adverse events in the vaccinated group. It was subsequently discontinued after being in use for a decade.	[31]
Embryo vaccines(1930-1980) Flury Low egg passage (LEP) vaccine Flury High egg passage (HEP) vaccine Duck embryo vaccine	Novel idea of propagation in embryonated eggs by Ernest W. Goodpasture provided a platform for new generation vaccines. These vaccines were considered primitive in terms of safety, efficacy and immunogenicity. They were discontinued in 1980's and research targeted towards new vaccine platforms.	[32,33]
Cell culture vaccines(1970-present) HDCV PCECV PVRV PVRV-Next Generation(PVRV-NG)	Second generation vaccines. In 1970's, the first Human Diploid Cell Vaccine(HDCV) was licensed . It was the first adjuvant -free purified vaccine. WHO has recommended it as reference vaccine. Further vaccine research resulted in vaccine with increased efficacy, safety and increased virus yield. Purified Chick Embryo Cell Vaccine(PCECV) was approved in Europe in 1984. The introduction of purified Vero Cell rabies vaccine(PVRV) enhanced commercial production. It became widely accepted across the globe. The launch of PVRV- next generation vaccine has provided an excellent alternative.	[34,35]

Table 3: Novel vaccine platforms.

Proposed Vaccine Platform	Characteristics	Reference
ADJUVANTED RABIES VACCINE	Adjuvants have been used as complement to boost immunogenicity and produce more potent vaccines. Many conventional adjuvants like alum, aluminum salts are being discarded because of their toxicity. Newer synthetic derivatives like beta-glucans, monophosphoryl-lipid A and bacillus Calmette-Guerin purified protein derivative(PPD) have been studied. They show promising results in terms of robust immune response and safety profile.	[36,37]
RECOMBINANT RABIES VACCINE	Extensive research has been done to design a recombinant vaccine which encodes two copies of Glycoprotein gene. This has enhanced expression of G gene leading to improved immunity and safety. These are promising vaccine candidates.	[38]
RABIES DNA VACCINE	Using recombinant DNA technology the Glycoprotein gene can be cloned into vector models leading to its increased expression. This has been the basis of DNA vaccine successfully. However, integration of plasmid DNA into host chromosome carries adverse effects. There may be auto-immunity flares. More studies are hence required before wider acceptance.	[39]
RABIES RNA VACCINE	These are the simplest nucleic acid vaccines and offer a promising alternative to already existing vaccines. m-RNA based rabies vaccine have been found to be immunogenic in experimental pigs. Key issue to be addressed is the instability of RNA vaccines.	[35,40]

Surveys, involving 47 countries, were carried out by World Health Organization (WHO) in early 2021 in order to assess current status of Rabies and damage done by the pandemic [41]. These surveys questioned government officials, animal ministry officials, non-governmental organizations, dog shelter officials, animal activists and academia. The major operations which were hit by the pandemic were tabulated. Some of the key ones were:

1. Delay in diagnosis, treatment and patient care.
2. Delay/cessation of surveillance services.
3. Delay in vaccine manufacture, dispatch and allocation especially to resource-poor countries.
4. Discontinuation of monitoring and evaluation services.
5. Re-allocation of human resources and budget towards pandemic control.
6. Absenteeism due to illness, mortality and care-giving responsibilities.
7. Lockdowns, curfews and public transport woes.

WHO has deployed damage control measures and set new target goals to tackle rabies. Various remedial strategies have been formulated which can be accessed in detail on its official website [42]. Robust infrastructure for human rabies prophylaxis has been recommended to prepare for any future pandemics. Gongal, et al. have highlighted many cost-effective measures in their study on Rabies post exposure prophylaxis impacted by Covid-19 [43].

Rabies-endemic countries need a proper road map and resources to tackle this preventable disease. It is definitely going to be a challenge for them to stretch their already-bulging health care facilities post 2020.

Rabies in Indian Context

As it is common knowledge, India is endemic for Rabies and accounts for about 35% of the total deaths due to canine rabies [44]. This zoonotic disease is widespread all across the sub-continent except in the islands of Andaman-Nicobar and Lakshadweep. India reported a total of 72, 77,523 cases of animal bites in 2019. Unfortunately, there has been an upsurge in the cases after a dip in the year 2021. A record 14.5 lakh animal bites were reported in just initial 7 months of 2022 [45]. According to a recent newspaper article, there has been an alarming increase in rabies case in the Indian state of Kerala [46]. Probably, increased dog aggression and vaccine shortage post Covid- 19 pandemic are some of the reasons. 75% of deaths in India occur in rural communities owing to lack of suitable emergency health care and vaccines [47].

Due to the debate on India's rabies control measures and the quality-efficacy of vaccines, the National Rabies Control Programme (NRCP) was launched as part of the 12th 5-year plan (2012-2017). The National Action Plan for Dog-Mediated Rabies Elimination (NAPRE), in accordance with WHO, has declared its target of zero deaths human deaths by year 2030 [48]. There is frugal data available regarding the success rate of this plan. Open data Government website also yields no results [49].

Various scientific articles elucidate fallibility of the rabies control program in India [50-52]. However as the adage goes, 'Every cloud has a silver lining'. Gibson, et al. has highlighted effective implementation of the rabies control program in the Indian state of Goa [53]. The authors highlight key issues to be addressed:

1. Curbing rapidly growing population of stray dogs.
2. Increasing surveillance, both active and passive.
3. Targeting poor vaccination rates in canines.
4. Maintaining consistency in policy formulation and implementation.

Rabies control is still not seen as a top public health investment project in India. There is an urgent need for a political, social and scientific road-map to conquer this vaccine-preventable disease.

Conclusion

Diagnosis of rabies is complicated and largely dependent on history of contact. Laboratory tests are not routinely available and only confirm clinical suspicion. Vaccines and immunoglobulin are expensive and scarce, especially in Asia and Africa. To re-iterate the idiom 'catching the bull by its horns'; approach to elimination of rabies requires drastic measures. 'One Health Approach for Zero human deaths' cannot be achieved without collaboration that cuts across boundaries of human research, animal behavior and administrative will. Only then, the future generations will read about Rabies as a disease of antiquity eradicated in the 21st century.

Authors Declaration

The authors declare no potential conflict of interests.

References

1. World Health Organization. Neglected tropical disease.
2. Bote K, Nadal D, Abela B (2023) WHO's latest rabies recommendations and guidance save lives and reduce the cost of treatment. One Health Implement Res 3: 11-4.
3. Food and Agriculture Organization, World Organization for Animal Health, World Health Organization, Global Alliance for Rabies Control. Zero by 30. The global strategic plan to end human deaths from dog-mediated rabies by 2030.
4. World Health Organization. Ending the neglect to attain the sustainable development goals: A road map for neglected tropical diseases 2021-2030.
5. Jean B. The evolution of rabies epidemiology in wildlife.
6. Pearce J (2002) Louis Pasteur and Rabies: A brief note. J Neurol Neurosurg Psychiatry 73: 82.
7. Theodorides J (1986) Histoire de la rage. Cave Canem. Masson. Paris 289.
8. Patel MK, Gramopadhye NG, Hingmire NS (2015) Ayurvedic Aspect of Alark (Rabies) - A Peer Review. IRJIMS 1: 80-86.
9. Blancou J. History of surveillance and control of transmissible animal diseases. Paris: Office International des epizootics 193-291.
10. Centers for Disease Control and Prevention (CDC) (2004) Investigation of rabies infections in organ donor and transplant recipients--Alabama, Arkansas, Oklahoma, and Texas, 2004. MMWR Morb Mortal Wkly Rep 53: 586-589.
11. Arai YT (2005) Epidemiology of rabies virus and other lyssaviruses. Nihon Rinsho 63: 2167-2172.
12. Rupprecht CE (1996) Rhabdoviruses: Rabies virus. In: Baron S Medical Microbiology. (4th edn), Galveston (TX): University of Texas Medical Branch at Galveston.
13. Zhu JY, Pan J, Lu YQ (2015) A case report on indirect transmission of human rabies. J Zhejiang Univ Sci B 16: 969-970.
14. Ananthanarayan R, Paniker CKJ Rhabdoviruses. Ananthanarayan and Paniker's Textbook of Microbiology. (11th edn).
15. Warrell MJ, Warrell DA (2015) Rabies: The clinical features, management and prevention of the classic zoonosis. Clin Med (Lond) 15: 78-81.
16. Subramaniam R (2016) Human rabies survivors in India: An emerging paradox? PLoS Negl Trop Dis 10: e0004774.
17. Lahaye X, Vidy A, Pomier C, Obiang L, Harper F, et al. (2009) Functional characterization of negri bodies (NBs) in rabies virus-infected cells: Evidence that NBs are sites of viral transcription and replication. J Virol 83: 7948-7958.
18. Webster LT, Clow AD (1937) Propagation of rabies virus in tissue culture. J Exp Med 66: 125-131.
19. Mani RS, Madhusudana SN (2013) Laboratory diagnosis of human rabies: Recent advances. ScientificWorldJournal 2013: 569712.
20. Barrat J, Barrat MJ, Picard M, Aubert MF (1988) Diagnosis of rabies by cell culture: Comparison of the results of inoculation of a murine neuroblastoma cell line and mouse inoculation. Comp Immunol Microbiol Infect Dis 11: 207-214.
21. Fooks AR, Johnson N, Freuling CM, Wakeley PR, Banyard AC, et al. (2009) Emerging technologies for the detection of rabies virus: Challenges and hopes in the 21st century. PLoS Negl Trop Dis 3: e530.
22. World Health Organization (2019) Laboratory techniques in Rabies.
23. Bourhy H, Rollin PE, Vincent J, Sureau P (1989) Comparative field evaluation of the fluorescent-antibody test, virus isolation from tissue culture, and enzyme immunodiagnosis for rapid laboratory diagnosis of rabies. J Clin Microbiol 27: 519-523.
24. Moore SM (2021) Challenges of rabies serology: Defining context of interpretation. Viruses 13: 1516.
25. WHO (2018) Rabies Vaccine: WHO position paper - April 2018.
26. Royal A, John D, Bharti O, Tanwar R, Bhagat DK, et al. (2022) A cost-effectiveness analysis of pre-exposure prophylaxis to avert rabies deaths in school-aged children in India. Vaccines (Basel) 11: 88.
27. Pre exposure Prophylaxis (PrEP) Rabies Centers of Disease Control (CDC).
28. Sureau P (2005) Rabies vaccine production in animal cell cultures. Vertrebrate Cell Culture I 111-128.
29. Fermi C (1908) Über die Immunisierung gegen Wutkrankheit (in German). Zeitschrift für Hygiene und Infektionskrankheiten 58: 233-276.
30. Semple D (1911) The preparation of a safe and efficient antirabic vaccine. Sci Mem Med Sanit Dept India 44: 1-31.
31. Svet-Moldavskij GJ, Andjaparidze OG, Unanov SS, Karakajumcan MK, Svet-Moldavskaja IA, et al. (1965) An allergen-free antirabies vaccine. Bull World Health Organ 32: 47-58.

32. Koprowski H, Cox HR (1948) Studies on chick embryo adapted rabies virus; Culture characteristics and pathogenicity. J Immunol 60: 533-554.

33. Koprowski HI, Black JA, Nelsen DJ (1954) Studies on chick-embryo-adapted rabies virus. J Immunol 72: 79-106.

34. Wu X, Smith TG, Rupprecht CE (2011) From brain passage to cell adaptation: The road of human rabies vaccine development. Expert Rev Vaccines 10: 1597-1608.

35. Natesan K, Isloor S, Vinayagamurthy B, Ramakrishnaiah S, Doddamane R, et al. (2023) Developments in rabies vaccines: The path traversed from Pasteur to the modern era of immunization. Vaccines (Basel) 11: 756.

36. Chen C, Zhang C, Li R, Wang Z, Yuan Y, et al. (2019) Monophosphoryl-Lipid A (MPLA) is an efficacious adjuvant for inactivated rabies vaccines. Viruses 11: 1118.

37. Paris S, Chapat L, Martin-Cagnon N, Durand PY, Piney L, et al. (2020) β-Glucan as trained immunity-based adjuvants for rabies vaccines in dogs. Front Immunol 11: 564497.

38. Wang J, Jiang H, Yang R, Zhang S, Zhao W, et al. (2020) Construction and evaluation of recombinant *Lactobacillus plantarum* NC8 delivering one single or two copies of G protein fused with a DC-targeting peptide (DCpep) as novel oral rabies vaccine. Vet Microbiol 251: 108906.

39. Kaur M, Rai A, Bhatnagar R (2009) Rabies DNA vaccine: No impact of MHC class I and class II targeting sequences on immune response and protection against lethal challenge. Vaccine 27: 2128-2137.

40. Deering RP, Kommareddy S, Ulmer JB, Brito LA, Geall AJ (2014) Nucleic acid vaccines: Prospects for non-viral delivery of mRNA vaccines. Expert Opin Drug Deliv 11: 885-899.

41. Nadal D, Beeching S, Cleaveland S, Cronin K, Hampson K, et al. (2022) Rabies and the pandemic: Lessons for One Health. Trans R Soc Trop Med Hyg 116: 197-200.

42. World Health Organization (2020) Pulse survey on continuity of essential health services during the COVID-19 pandemic: Interim report.

43. Gongal G, Sampath G, Kishore J, Bastola A, Punrin S, et al. (2022) The impact of COVID-19 pandemic on rabies post-exposure prophylaxis services in Asia. Hum Vaccin Immunother 18: 2064174.

44. Goel K, Sen A, Satapathy P, Kumar P, Aggarwal AK, et al. (2022) Emergence of rabies among vaccinated humans in India: A public health concern. Lancet Reg Health Southeast Asia 9: 100109.

45. Sudden spike in rabies cases in India: Economic times.

46. 21 rabies deaths, nearly 2 lakh dog bites this year in Kerala: Report Onmanorama Thiruvanathapuram.

47. Sudarshan MK, Madhusudana SN, Mahendra BJ, Rao NSN, Narayana DHA, et al. (2007) Assessing the burden of human rabies in India: Results of a national multi-center epidemiological survey. Int J Infect Dis 11: 29-35.

48. National Rabies Control Programme. Ministry of Health and Family Welfare. Government of India.

49. Search/Open Government Data (OGD) Platform India.

50. Radhakrishnan S, Vanak AT, Nouvellet P, Donnelly CA (2020) Rabies as a public health concern in India-A historical perspective. Trop Med Infect Dis 5: 162.

51. Kumar SK, Gupta P, Panda PK (2020) Death from rabies: The reason being poor compliance to vaccination or its failure. J Family Med Prim Care 9: 4437-4440.

52. India wants zero rabies cases by 2030 but there is no central data on dogs and dog-bites.

53. Gibson AD, Yale G, Corfmat J, Appupillai M, Gigante CM, et al. (2022) Elimination of human rabies in Goa, India through an integrated One Health approach. Nat Commun 13: 2788.

CLINMED INTERNATIONAL LIBRARY