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History, evolution and newer perspectives of rabies vaccines

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Abstract

Rabies continues to be one of the most deadly infectious diseases known to human race since antiquity, with a case fatality rate almost 100 per cent after the onset of clinical disease. The disease still has a significant impact on human and animal living all over the globe. It is found on all continents where terrestrial animals exist, with the bulk of animal and human cases documented in resource-constrained African and Asian countries, where thousands of human deaths are being recorded annually. The disease produces one of the most agonising deaths in humans and it is likely that the global statistic of roughly 59,000 human rabies fatalities per year is an underestimate. Scientific innovations that led to the successful development of several vaccines and immunisation policies in identified 'at risk'human and animal populationshave gained a great reputation in minimising the impact of disease across wide portions of the globe.Vaccines continue to be the most significant triumphs of the combined global efforts of the public and animal health communities and has achieved significant strides in the treatment, prevention, and control of disease. This paper describes the history, evolution, and accomplishments of human ingenuity, scientific endeavour, and the joint global efforts of the public and animal health communities that resulted in evolving an effective prevention and control strategies.

Keywords: *Evolution, history, rabies, vaccination*

Rabies, an ancient zoonotic viral disease associated with man's closest vertebrate companions, dogs, as animal vectors, was first identified and studied over 4000 years ago. It is a preventable yet devastating illness that kills around 60,000 people each year (Hampson *et al*., 2015). However, because of the rampant under reporting of cases, the true number of deaths is likely to be greater. In many countries of Asia and Africa, poor and rural people are disproportionately affected, who bears the burden and majority of deaths happening in children under 15 years. Dog bites cause 99 percent of human rabies infections and hence control of rabies in dogs still remains the key factor in control of the disease. Once symptoms appear, the disease is nearly always lethal with case fatality rate 100 per cent, being the hall mark of infection. According to WHO reports, the disease is extremely lethal, killing one person every nine minutes. The disease was often

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characterised as a neglected tropical zoonotic disease, which has inflated its potential to be a major worldwide public health issue. However, fortunately the disease is one of the few infectious diseases that could be prevented with vaccination even after exposure. Vaccination is critical in preventing fatalities and is the most effective method. Indeed, for more than a century, rabies vaccines have had a significant impact on health through averting deaths.

HISTORY OF RABIES TREATMENT

Man has been terrified by rabid dog bites for millennia.The disease is of great historical significance, having been described approximately four thousand years ago in the pre-Mosaic Eshnunna Code of ancient Mesopotamia as follows: "If a dog is vicious and the ward officials have made known to its owner, but he does not keep it in, and it attacks a man and kills him, the owner of the dog shall pay 2/3 of a mina of (Rosner, 1974)".

The disease has been chronicled perhaps more exhaustively than any otherviral disease. Since the time of Aristotle, a plethora of viewpoints and theories on its aetiology have been recorded. The disease has also been described by poets and thinkers from practically every civilization. Scholars from ancient Babylon, China, India, Persia, Greece, and Rome all wrote about a syndrome linked to disease and animal bites.One common misconception was that rabies was induced by a little "worm" near the base of the tongue. GrattiusFalistcus, an Ovid (1st century BC) contemporary poet, believed the mythological origin of the sublingual 'lyssa' of rabid dogs popularised by Pliny; they believed that extracting the worms totally cured the dog.This worm was also thought to possess magical curative powers in preventing the disease in the person bitten when it was injected, but only after having been carried around a fire (Baer, 2007).

By the Middle Ages, a more nuanced approach to the prescription of cures for the exposed person had evolved. It is unusual in that the time and location of the bite are nearly always known to the patient. However, until the nineteenth century, there was no reliable diagnosis of the disease in humans or animals. There was no isolation of the infectious agent, no animal control, and human treatment (Baer, 2007).

The incurability of the disease has spawned a myriad of superstitions and myths, some of which are still prevalent in specific areas today. Throughout history, the herbal cures for rabies have ranged from filbert nuts to hellebore and rose oil, to camomile tea. Eating a cock's brain, coxcomb, goose fat combined with honey, salted flesh of a rabid dog, and maggots from a dead dog's carcass were among the other treatments (Wilkinson, 1977).

Traditional procedures were used by non-medical personnel and the general people to halt the spread of the disease. Some physicians thought such techniques ought to be tried or advised them; one physician travelled to the seaside, apparently to bathe in the waves. Hot water or steam baths, cold affusions and Galvanism were frequently recommended for patients who receive dog bites (Carter, 1982).

St. Hubert was considered and worshipped as the patron of rabies and 'dullighedon,' or mental illnesses. People who had been bitten by dogs went to priests for the 'cutting' procedure, in which the priest made a tiny incision and inserted a small portion of the saint's tole.Animals attacked by rabid dogs were also 'treated' in the cult of St. Hubert: a key that St. Hubert got from the hands of the pope which was heated and applied red hot to the wound of the animal. This cauterization was accompanied by five to nine day period of penance placed on the owner, as well as a diet of 'holy' oat bread (Baer, 2007).

During the first century B. C., Cicero called attention to hydrophobia- thirst and fear of water and outlined the precautions to be followed, including quick cauterization of the wound or suction. In 1735, Shrewsbury cited two individuals who advertised their skills as successful 'Dippers of Man and Beast'demanding hefty fees for immersing unfortunate dog bite victims in the tidal waters of the River Severn.

Most nineteenth-century physicians who wrote about rabies therapy suggested that wounds be cauterised as soon as possible - an opinion that may be traced back to classical literature. Some people believed that any sort of cauterization was insufficient, and they advocated for excision or even amputation.

Nonetheless, rabies has intrigued the imaginations of poets and thinkers throughout antiquity. Despite the limited number of victims, the outbreaks have been extensively recorded due to the symptoms in both humans and dogs, the extended suffering of the victim and the unavoidable fatality of the established clinical condition. The alarming symptoms in both humans and dogs, the prolonged suffering of the victim and the unavoidable fatality of the established clinical disease: the distressing syndrome as a whole have meant that outbreaks of the disease have been meticulously out of proportion to the small number of victims claimed in comparison to the major scourges of mankind.

TOWARDS VACCINE DEVELOPMENT: THE WAY FORWARD…

Despite decades of superstitions and inaccurateappraisals, several pre-Pasteurian personalities gradually added more introspection (Table 1) as science finally held more influence than dogmatic repeats of "learned" expert opinion.

However, the first scientific attempt to prevent the development of rabies was made

Table 1. Pre- Pasteurian personalities related to rabies

Sl. No.	Individual	Period	Importance
1.	Aulus Cornelius Celsus	~ 25 AD	Roman author of De Medicina and an early proponent of wound treatment after bite
2.	Pliny the Elder	~ 70 AD	Roman naturalist with attribution in the influence of temperatures on disease and believed dogs were most susceptible to rabies during the hottest seasons of the year, as well as the alleged importance of "tongue worms
3.	Galen of Pergamon	~ 200 AD	Greek physician who advised prompt local treatment and that bite wounds be kept open to avoid viral absorption
4.	IbnSina (Avicenna)	~ 1000 AD	Persian physician who wrote a famous Canon of Medicine
5.	Moses Maimonides	~ 1198	Talmudic scholar and author of a treatise on Poisons and their Antidotes, who described long incubation periods in bitten persons
6.	Girolamo Fracastoro	~ 1546	Italian physician who recognized a clear material basis of contagion for rabies infections
7.	Giovanni Battista Morgani	~ 1769	Italian anatomist and author of On the Seats and Causes of disease, who established a fundamental pathological principle that diseases such as rabies are not dispersed vaguely throughout the body, but originate locally, in specific organs and tissues, such as the nerves
8.	Georg Gottfried Zinke	~ 1804	German investigator who demonstrated that virus could be transmitted by infectious saliva
9.	Apollinaire Bouchardat	~ 1852	French pharmacist who was one of the first to speculate on the potential utility of inoculations against rabies
10.	Pierre-Victor Galtier	~ 1881	French veterinarian who showed pathogen transmission via injection and bite, used rabbits as a research model, developed a concept for an early experimental intravenous vaccine producing immunity in sheep and who had a major influence upon Pasteur's later work

(Adapted from Nagarajan and Rupprecht, 2020)

by Louis Pasteur, one of the doyens in the field of vaccine development who was renowned as the 'Germ Hunter'. Vaccines have evolved from the first generation of crude nerve tissue based products to recombinant vaccines. Cell culture based inactivated vaccines for intramuscular (IM) and in tradermal (ID) use in humans continue to play a pivotal role when it comes to rabies prophylaxis. Parenteral and oral vaccinations have repeatedly proven to be effective strategies for rabies management in both domestic and wild animals.

THE FIRST GENERATION VACCINES

Nerve tissue vaccines

Louis Pasteur created history by developing the first rabies vaccine, which was based on rabbit CNS and physical inactivation of rabies virus by drying. However, due to the presence of nerve tissue and myelin basic protein, this method posed a risk of residual live virus and severe allergic reactions. As a result of this, Sir David Semple developed a newer nerve tissue vaccines (NTV) at Central Research Institute (CRI), Kasauli, India from adult sheep (Semple vaccine). It was made by propagating rabies virus(RABV) in adult sheep brain, followed by phenolic inactivation. It was widely used in numerous nations despite numerous drawbacks, including low efficacy, the necessity for multiple dosages, and severe side effects, including Guillain–Barre Syndrome (GBS) and the danger of transmitting Transmissible Spongiform Encephalopathies (TSE) owing to the presence of myelin, it was widely used by many nations.Because of these disadvantages, the WHO has consistently discouraged its use, leading to its eventual abolition in almost all countries.

The journey for a less reactogenic, better alternative resulted in the development of a newer vaccine derived from the brain of suckling mouse (SMB vaccine) by phenolic inactivation followed by its partial purification (Fuenzalida*et al*., 1964). Due to the lack of myelin in tissues derived from newborn animals, the SMB vaccine is not as reactogenic as the Semple vaccine but is similar to it in that it has a lesser potency and requires multiple doses to be administered. Its decades-long use in nearly all countries came to an end when most national regulatory authorities decided to stop using it in accordance with the WHO recommendation.

Duck embryo vaccines

The purifiedchick/ duck embryo technique was an inexpensive and convenient method for cultivating a wide variety of animal viruses and were being used for vaccine production (Peck *et al*., 1955) and are still used today for the production of vaccines against a variety of agents, including RABV. The ease of availability, handling, presence of naturally sterile environment within the limits of egg components, inability of the embryo to produce antibodies against the viruses used as inoculaand availability of eggs with a relatively uniform genetic constitution popularised its use. Since 1983, the World Health Organization has advocated for the use of embryonated eggs as a manufacturing platform. However, there are a number of drawbacks including the risk of limited supply, time-consuming processes with variable yields, high manufacturing costs and the possibility of allergic reactions to egg components (Montomoli*et al*., 2012).

The purified duck embryo vaccine (PDEV) production entails propagation of the Pitman-Moore (PM) strain of RABV in embryonated duck eggs and the extraction of RABV from the brains of infected embryos under mild conditions to avoid the release of soluble avian antigens that can cause purification issues and adverse reactions. Nonviral lipids are removed by continuous density-gradient centrifugation and the purified RABV is subsequently inactivated using beta-propiolactone (BPL). The improved extraction and purification method enabled the production of purified duck embryo vaccine that was almost completely free of egg proteins and other components such myelin basic protein. It is worth noting that the classic DEV contained myelin basic protein, which has been linked to the development of allergic encephalomyelitis. More than 25 nations have registered and marketed the contemporary DEV. Similar to previous tissue culture-derived human rabies vaccinations, it is immunogenic, safe and well-tolerated.

THE SECOND GENERATION VACCINES

Tissue culture vaccines

One of the first commercial applications of *in vitro* animal cell technology was the production of vaccines utilizing animal cell substrate.The ability to execute successive infectious cycles in cell culture was a critical step for research on viral diseases and vaccine development (Jordan and Sandig, 2014). The cultured cells could act as substrates for the production of vaccines. Currently,numerous cell types are being used by manufacturers for the production of human rabies vaccines. This includes the primary cells produced without passage in tissue culture, diploid cells with a finite life span and passaged in tissue culture and continuous cell lines with an infinite life span and apparently unlimited capacity to replicate.

Many viral vaccines are now being produced using cell culture, which has several benefits over nerve tissue vaccines and egg-based manufacture. It offers a proven safety and efficacy profile, as well as a shorter lead time and better process flexibility, regardless of the type of cell substrate, production method, or purification and formulation procedures used (Rupprecht*et al*., 2002). However, the challenge is to strike a balance between the desire for a very efficient production system and the goal of minimizing risks.

CELL SUBSTRATES FOR VIRUS PROPOGATION

Primary cells

Primary cells are directly obtained from an animal. They retain the characteristics of the tissue from which they originate and do not have tumorigenic properties. The most important source of primary cells intended for the production of human rabies vaccines is the cells from avian embryo like chicken embryo fibroblasts (CEFs) (Hernandez *et al*., 2010). Because CEFs have a limited lifespan, the embryonated eggs must be retrieved on a regular basis. Each new preparation carries a certain risk of variation in the permissivity of the target virus, inconsistent starting material and contamination with potential adventitious agents.

In accordance with current pharmacopoeia and WHO regulations, the purified chick embryo cell vaccine (PCECV) is made in CEFs utilising SPF fertilised eggs and the Flury low egg passage (LEP) RABV strain. The FluryLEP RABV is inactivated with Beta-propiolactone, purified via continuous density-gradient centrifugation and stabilised with polygeline (Barth and Franke, 1996).In both animal and human investigations, the PCECV shows comparable immunogenicity and tolerability to the human diploid cell vaccine (HDCV) (Barth *et al*., 1984; Briggs *et al*., 2000). It meets or exceeds the 2.5 IU per single IM dose minimum potency level. Human serum albumin (HSA), a stabiliser and a crucial component in most vaccinations, is known to be very low in it. Rabipur is the brand name for the PCECV, which is sold all over the world, manufactured by Chiron Behring.

Diploid cells

Diploid cells are defined as having a finite *in vitro* life span and contain the full complement of the genetic material. They undergo senescence and are non-tumorigenic (Barret*et al*., 2009).The human diploid cells have several advantages over primary cells because they allow multiple expansion passages of material obtained from well-characterized cryogenically preserved master and working cell banks in essentially a closed system; and screening for the absence of adventitious agents (Jordan and Sandig, 2014). However, they have a number of drawbacks, including cellular aging when serially passaged, difficulties scaling up in bioreactors, particularly when utilising microcarriers, and a requirement for a demanding growth media as well as trouble propagating under serum-free circumstances (Barret*et al*., 2009).Two well-known international human diploid cell reference strains are WI-38 and MRC-5 (Hayflick, 1989).

The original human diploid cell vaccine, which was created at the Wistar Institute in WI-38 human diploid cells approximately 3–4 decades ago, received the most attention,

around 3–4 decades ago. They were derived from a human embryonic lung and have been thoroughly tested and used (Wiktor*et al*., 1964).

PM 1503 3M strain of fixed RABV derived from a strain originally isolated byPasteur and maintained by the National Institutes of Health (NIH), USA was used as the vaccine virus strain.The virus was customised to grow in WI-38 cells in the early 1960s and was propagated for 52 passages. In the mid-1960s, a master seed pool was created, and the seed was transferred to l'InstitutMerieux, a vaccine production laboratory, in 1966. In 1969, the seed strain was supplied to Behringwerke. WI-38 cells were used to make the early batches of Merieux vaccine. However, later batches composedof whole virion preparations were grown in MRC-5 human diploid cells andinactivated with BPL. The Behringwerke vaccine was concentrated and purified.

Continuous cell lines

Increasing demands for vaccine production, yields and safety have prompted the development of safer, less expensive, and more efficient cell substrates. Continuous cell lines derived from animal tissues are critical cell substrates for the synthesis of numerous types of biological pharmaceuticals. They have the ability to cause tumours and have an unlimited lifespan.Despite this, a growing body of evidence suggests that cells below a certain passage number are not tumorogenic. They can also be cultivated in large-scale fermentors on microcarriers, which contributes to the standardization, safety, and upscaling of the production system resulting in consistent yields. The Vero cell line, which was developed from the kidney tissue of an African green monkey, is one of the most commonly used mammalian cell lines for vaccine manufacturing. It is a continuous cell line that has been approved by regulatory agencies for the production of viral vaccines. At low passage numbers, it displays pseudo-diploid karyotypes and is non-tumorigenic. It was chosen primarily because it produces high viral yields and batches that are free of adventitious agents. The Vero cell line as a cell substrate is distinguished in terms of cell culture technology by certain limitations. Because of its anchorage-dependent nature, it necessitates cell culture systems with large culture surfaces, such as roller bottles, microcarriers, Cell Factories, CellSTACK, CellCubes, and fixed bed bioreactors.

A significant advancement in rabies prevention was the introduction of purified vero cell-derived rabies vaccine (PVRV) which has a superior industrial scalability.Prior to PVRV, the world depended mainly on eitherofHDCV, PCECV, or NTV.

Over 40 million doses of PVRV (Verorab) have been provided in over 100 countries. The immunogenicity of Verorab has been evaluated in a variety of clinical scenarios and research using a 0.5 IU/mL antibody titer as the cutoff point. This level is highly correlated with clinical rabies protection. Verorab induces acceptable VNA titers when delivered by IM or ID for pre-exposure prophylaxis (PrEP), albeit levels tend to be lower following ID immunisation. Raksharab is an inactivated rabies virus vaccine manufactured by Indian Immunologicalswhichcontaintissue culture rabies virus, CVS strain, propogated on BHK21 cell line, and inactivated with aziridine compound. Aluminium hydroxide gel is used as adjuvant is an commonly used vaccine in veterinary practice

NEWER PARADIGM IN RABIES VACCINE DEVELOPMENT

The persistent high prevalence of rabies in developing countries, the economic burden of post exposure prophylaxis (PEP), and the global scarcity of RIG necessitate the development of innovative, cost-effective rabies vaccines for preventive vaccination or PEP. Virologic developments in the twentieth century resulted in better rabies vaccinations and treatments. Diagnostic, antigenic, and genetic breakthroughs along with a focus on isolation of infected animals, and adaptation from an etiological and pathogenic standpoint provided a solid foundation for better therapeutic and prophylactic strategies. In this section, we will go through some of the more interesting prototypes and their prospective applications in humans.Almost every vaccine prototype, from peptides to plant-derived vaccines, has

been tested in experimental animals and has shown efficacy in numerous circumstances. Monoclonal antibodies are being generated from either human B cells or mouse hybridomas, with the latter being genetically modified to humanise the antibodies constant region are being developed, which could eventually replace rabies immunoglobulin (Smith *et al*., 2011).

Inactivated 'enhanced' traditional rabies vaccines

Inactivated rabies vaccinations are less immunogenic, and repeated doses are required to produce protective VNA titers. In the United States, for example, rabies vaccines are devoid of adjuvants like alum. Unlike alum-fixed vaccines, rabies vaccine formulations incorporating CpG-oligodeoxynucleotides resulted in greater and faster VNA responses in mice (Wang *et al*., 2008).

Protein and peptide vaccines

The viral glycoprotein, a 65-k Da protein, is the basis for protein or peptide vaccinations. Following synthesis, the protein forms trimers and is mildly N-glycosylated at one of three possible locations. However, the proper folding into the natural trimeric structure of the rabies virus glycoprotein, which is required for the generation of neutralising antibodies, remains a challenge with protein vaccines. Although extremely safe, peptide vaccinations are mildly immunogenic and induce very limited B cell responses. Rabies virus glycoprotein have been produced in a variety of plant cells (maize, carrot, spinach or *Nicotianatobaccum* plant cells), insect cells (*Spodopterafrugiperda* (Sf-9) cells (Ramya*et al*., 2011,7) or in*Drosophila melanogaster* Schneider 2 cells (Astray *et al*., 2014)or yeast cells. A peptide expressing a linear epitope of the rabies virus glycoprotein only produced modest VNA titers that failed to neutralise an escape mutant in one research (Niederhauser*et al*., 2008). However, given that rabies vaccinations must elicit a wide antibody response against numerous isolates and genotypes, this method is unlikely to succeed in replacing present vaccines.

Virus particle vaccine

Some viruses can be altered to express the rabies virus glycoprotein on the virion's surface. Here, the protein is immediately available for inducing immunological responses, perhaps permitting its usage in PEPs.Pre-existing immunity to the parent virus or low amounts of the rabies virus glycoprotein, which could decrease immunological responses, are both potential drawbacks. The New Castle disease virus (Ge*et al*., 2011), baculovirus (Wu *et al*., 2014) and Parainfluenza 5 (Chen *et al*., 2013) viruses are the common pseudotyped viruses employed as vaccines to rabies virus.

Genetically altered vaccines

Reverse genetics can be used to alter the rabies virus. As a result, highly attenuated rabies virus and/or virus with increased immunogenicity have been developed, which could be used for animal or human vaccination. The rabies virus is weakened when the P gene, which encodes a component of the viral polymerase, is knocked out.Even when injected intracerebrally into adult or suckling immunocompetent mice or immunodeficient mice, the virus is apathogenic, though the P gene-deleted vaccine moved from the periphery into the central nervous system in the latter. A virus-neutralizing antibody response is induced by the P gene deleted rabies viruses(Morimoto *et al*., 2005). The response begins slowly but eventually outperforms that of an inactivated vaccine based on wild-type virus, indicating that such a design could be considered for PrEPbut not PEP. The P-gene deleted rabies vaccine was further modified to express two copies of the viral glycoprotein gene to improve immunogenicity. This vaccine produced rabies virus neutralising antibodies more quickly.

VACCINATION

Pre-exposure prophylaxis

Fortunately, the fatalities associated with rabies can be avoided with immunizations. The virus clearance prior to the onset of sickness,is crucial, which in turn, is dependent on the presence of VNAs. As a result,

rabies prevention relies mostly on rabies vaccines capable of rapidly producing VNA. A combination of local viral neutralisation by antibodies or antibody mediated clearance of virus infected cells provides protection. Pre exposure prophylaxis is commonly administered to high risk groups on days 0, 7, 21 or 28 by intramuscularly (IM) route. However, ID vaccination is considered by the WHO to be a cost-effective and acceptable alternative to IM immunisation, although it is technically more difficult, requiring sufficient staff training and skilled medical expertise.

Post exposure prophylaxis

Worldwide, millions of exposures to rabies are registered, resulting in tens of thousandsof human deaths, with most occurring in Asia and Africa. Based on the types ofinteraction with suspected rabid animals, exposure is broadly classified into threecategories I, II, and III. All exposures determined to represent a risk for rabies requirePEP, which includes immediate local treatment of all bite wounds and scratches withthorough washing and disinfection, local wound infiltration with RIG (for categoryIII alone) and vaccination. The main purpose of PEP is to prevent the developmentof clinical rabies after exposure has occurred. The combination of active and passiveimmunization is considered for PEP, except for those persons whohave been previously immunized with a rabies vaccine via the WHO approved vaccination regimen.

Intramuscular versus intradermal vaccination

A conservative cost estimate for human rabies prophylaxis of 4 million patients utilising IM versus ID regimens over a five-year period in Southeast Asia reveals that the cost of PEP can be considerably lowered if the (IM) regimen is gradually replaced with the ID regimen. The ID method of rabies vaccination was initially approved in the United States in 1986 for pre-exposure immunisation. As a result, in 1991, the WHO Expert Committee endorsed intradermal injection of current rabies vaccines (Gongal and Sampath, 2019).

Later on, throughout the previous three decades, intradermal multisite regimen for post-exposure prophylaxis(PEP) was developed.The eight site regimen, also known as the Oxford regimen (Warrell*et al*., 1984), was introduced in the 1980s, but due to the large number of inoculations required on days 0 and 7, it was difficult to persuade patients, particularly children, to complete the full vaccination course, and as a result, the regimen did not become popular. In 1986, the Queen Saobabha Memorial Institute of Thailand introduced another low-cost, multi-site ID immunisation approach called as the Thai Red Cross (TRC) regimen. It is a 2-site intradermal regimen which is administered as 2-2-2-0-1-1. However, the initial TRC regimen was intended to provide a full immunisation course over a three-month period.In the previous three decades, this has been improved in terms of dose, frequency of vaccination, and length of vaccination to increase acceptance by health professionals and patient compliance without jeopardising vaccine efficacy.

According to the ninth WHO expert consultation, the original Thai Red Cross Regimen has been changed with a one-month schedule, with two doses of vaccine given on days 0, 3, 7, and 28 (“2-2-2-0-2” regimen).The modified Thai Red Cross Regimen significantly improves compliance rates because patients receive the entire course of immunisation within one month. In 2017, the Strategic Advisory Group of Experts (SAGE) Working Group on Rabies Vaccine advocated a one-week ID immunisation schedule based on evidence gathered in Asian countries (WHO, 2018a).A one-week ID schedule was also proposed by the WHO Expert Consultation on Rabies, Third Report 2018 (WHO, 2018b).

There are several alternatives for PEP of already immunised patients. On days 0 and 3, one intradermal dose of 0.1 mL per location is suggested. If time is a constraint, the patient may be offered a single-visit 4-site intradermal regimen consisting of 4 injections of 0.1 mL evenly divided over the left and right deltoids as an alternative to this regimen (Gongal and Sampath, 2019).

Conclusion

Amidst the most agonising death posed by the rabies virus and the pioneering works that formed the cornerstone of successful vaccine development, rabies still remains a neglected tropical zoonosis that kills about 60,000 people annually.It is of no doubt that vaccination remains the holy grail for the therapeutic management and prophylaxis of rabies and is the most effective public health intervention strategy. Despite the fact that rabies is vaccine preventable, the high expense of cell culture vaccinations for intramuscular delivery prevents their widespread usage in many rabies-endemic areas. However, the development of a low-cost multi-site intradermal (ID) immunisation approach prompted high-burden countries to phase out the production and use of rabies vaccine derived from nerve tissue in the subsequent years.

FUTURE PROSPECTS

The concept of One Health remains relevant to vaccine development also where both the human and animal vaccine companies can collaborate to tackle the shared obstacles. The need for improved programmatic delivery, demonstrating non-inferiority of new rabies vaccine regimens, immunising people who have had multiple rabies virus exposures, efficacy and clinical outcomes of abbreviated PEP and PrEP schedules, novel vaccine delivery technologies, and the use of RIG are all new avenues for research that will aid in the formulation of strategic interventions to eradicate this disease.

Vaccines that are both feasible and cost-effective to administer for community programmes are still in high demand. Better dosage fractionation, vaccines labelled for ID use, and developments in ID vaccine delivery technology (e.g., microneedles) could make ID rabies PEP and PrEP easier to use and more widely adopted.

Rabies vaccines that can be stored and transported outside of the traditional 2–8 cold chain have the potential to revolutionise vaccine delivery by boosting the cost-effectiveness, efficiency, and reach of immunisation programmes. This is especially significant in underserved rural areas where access to vaccines may be prevented by the cold chain.

Clinicians may turn to the ID route of immunisation and customised equipment to administer vaccines in order to improve patient compliance. Traditional rabies vaccine production is likely to be dominated by bioreactor-based mass cell cultivation, which is essentially free of animal and human raw materials. These novel products would inturnbe subjected to new regulatory criteria in terms of advanced molecular techniques for vaccine strain authentication for licensure and ELISA-based potency testing for batch releases.

Changes in wildlife rabies management programmes may occur in terms of authentication of viral strains used for vaccination, designing novel baits that facilitate better absorption by target hosts, and improved monitoring of oral rabies vaccine by assessment of serological responses using approved procedures and enhanced sample collection. Direct rabies vaccine inoculation into rabid animal bite wounds could be utilised as part of a PEP.

Rabies vaccines using novel and adaptable adjuvants or without adjuvants may serve as a low-cost, safe, and effective method of prevention in endemic areas around the world.

In comparison to domestic animal vaccination, which will continue to range from modified-live to inactivated products and recombinant vaccines, human vaccination will remain conservative. Regardless of whether any of these predictions come true, all of the tools necessary to prevent human deaths, eliminate canine rabies, and control disease in mesocarnivore populations are now available.

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