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Challenges and advances in anti-rabies vaccine development in sub-saharan Africa

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Abstract

Zoonotic infection, such as rabies disease, causes devastating brain disorders. Rabies causes almost 100 % fatality rate in humans, and it is also 100 % preventable. Thousands of people die from rabies each year, with the majority occurring in Sub-Saharan Africa. The disease is one of the deadliest viral diseases known to humans, which claims about 60,500 human lives annually, mostly in countries with low income. Over 90 % of rabies infections are transmitted via dogs. Rabies vaccines are the major means to prevent and to control rabies. The vaccines can be administered both pre- and post-exposure prophylaxis. The rabies vaccine was first developed with a virus-infected nerve tissue. In its evolutional stages, different types of vaccines have evolved, such as toxoid vaccines, live attenuated vaccines, inactivated vaccines and subunit vaccines. Future trends of novel vaccines development are targeted towards nuclei-based vaccine and therapeutic vaccine for specific diseases. These advances in technology are limited in Sub-Saharan Africa, owing to lack of infrastructure, high cost, low power supply and economic constraint. The vaccine market size is small, and those with the greatest need for vaccine, cannot afford to purchase them at market price. The delivery systems remain another important area of focus, which when addressed will help in effective shipping and access of the product. This review examines the key challenges and recent advances in addressing vaccine development in Sub-Saharan Africa, with the aim of highlighting effective strategies to improve vaccine quality and acceptance coverage.

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1. Introduction

Rabies disease is one of the deadly zoonotic diseases. It causes progressive neurological infection by the rabies virus of the genus *Lyssavirus* in the *Rhabdoviridae* family of the *Mononegavirales* order [1, 2]. It is a neglected tropical disease as highlighted by the World Health Organization (WHO) [3]. Rabies is a neglected tropical disease that affects the less privileged in rural populations, with deaths due to the disease being always alarming and with inaccurate reported figures. It occurs mostly in developing countries, with more than 150 countries, where human vaccines and immunoglobulin are not affordable and readily accessible [4]. Numerous variants of lyssaviruses are found in a wide range of animal species throughout the world. Although dogs are the main reservoir in developing countries, the epidemiology of the disease differs from one region to another [5, 6], all of which may cause fatal human

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rabies [7], with children being more vulnerable victims [8]. Unfortunately, data on dog bite cases and related mortality are under estimated in most Sub-Saharan African countries [9]. Rabies is a viral disease that is transmitted to humans or other animals through contact with infected animal secretions and is therefore classified as a zoonotic disease. Vaccination is the major means of prevention and control of rabies disease, which is very low in Sub-Saharan Africa due to poor awareness and cost of the vaccine [10].

Rabies vaccines can be administered both pre-exposure prophylaxis (PREP) and post-exposure prophylaxis (PEP) [11]. When administered accurately, the vaccines are very effective even after exposure to rabies infection. Post-exposure prophylaxis exercise involves first aid treatment of a wound, administering rabies immunoglobulin and requires doses of the rabies vaccine [12]. The World Organization Animal Health, the Food and Agriculture Organization, the World Health Organization [9] and the Global Alliance for Rabies Control set a goal for action towards rabies prevention and control. The goal is to target zero human deaths from dog-mediated rabies by 2030 [13, 14].

Louis Pasteur formulated the first rabies vaccine administered as PREP and PEP vaccine [15]. Thereafter, many vaccines were made for the control and prevention of rabies in animals and humans. Several developing nations use inactivated rabies nerve tissue vaccines; however, these vaccines need several doses to achieve immunity. Even though inactivated nerve tissue vaccines (NTVs) are very cost effective, they have been phased out in some countries because of neuro-paralytic effects [16]. Live attenuated vaccines formulated using SAD-Bern strain can effectively provide immunity in the host even with less volume of the vaccine, though it has the problem of mutations chances during viral multiplication in the host [17]. The quest for more immunogenic, purified, and less reactogenic vaccine has led to the development of new vaccines, including next-generation vaccines [16]. Different strains of fixed rabies virus are used worldwide for the production of different forms of rabies vaccines, especially in cell line vaccine. The traditional strains of rabies virus developed and used by Pasteur were the predominantly used for the production of Semple vaccines and also modified further to Human Diploid and Purified Vero Cell vaccines [18].

Usually, vaccines are classified into inactivated, attenuated and component vaccines [19]. However, each of these vaccines has their own limitations such as insufficient immunological protective response. Several researches on moderate pathogenic viruses with carrier molecules for rabies virus globulin have been carried out, with a 'rebirth' of viral vector vaccines and have proven results for different vaccine methods [20]. The current development on the introduction of intradermal immunization of rabies vaccine has brought an innovation for PEP treatment [21].

Rabies disease is by far the deadliest *lyssavirus* infection of humans globally, which causes millions of potential human infections and thousands of deaths from rabies virus occurring annually [22, 23]. Estimated cost expenditure on rabies disease-related problems is placed at $ 583.5 million yearly, and dogs' cases represent about 94 % of human rabies infection globally. The National Veterinary Research Institute (NVRI), Vom, Plateau State, Nigeria is the only laboratory in West Africa that engages in the production of rabies vaccine. From 1928 to 2005, the institute diagnosed about 4810 cases of animal rabies in the country. The first general anti-rabies campaign was held in Nigeria in 1982. During the campaign period, only 44,627 of the dog population were vaccinated [24] leaving about 98.5 % percentage of dogs unvaccinated.

This study critically examines the key challenges and recent advances in addressing vaccine development and combating anti-rabies sentiments in Sub-Saharan Africa with the aim of identifying effective strategies to improve vaccine acceptance coverage and public trust in immunization. The gaps in the current vaccines development will guide the design of improved vaccines and control strategies, supporting the plan of action to achieve zero human deaths from rabies by 2030 [14].

2. Historical development of rabies vaccines

The control of rabies started in the first century, with many beliefs and different biological preparations in an attempt towards rabies prevention and cure [19]. There were no specific preventive measures to the disease until the Pasteur era. Different techniques were used for the treatment of rabies victims, and in some patients, health care providers amputated the area of infection, since about 98 % of bites on humans usually occur in the legs and hands. However, all of these beliefs were not solutions for treatment of rabies in humans and animals. In 25 AD, the treatment of rabies wounds was performed by Aulus Cornelius Celsus. Another attempt was made in 1881, when immunizations of animals were achieved by inoculating the rabies virus into the animal, which was carried out by Louis Pasteur, a French Veterinarian [19]. The vaccine concept started from the pre-Vaccinologists; however, Louis Pasteur [19] started the actual history of rabies vaccine development for the control of the disease, before the agent of the infection was known through several researches [15]. The invention of electron microscope in 1936 resolved the issue of virus size and the virion, which revealed the structure of the rabies causative agent (virus) in 1962. Other scientists were able to trace the presence of rabies virus in the central nervous systems of infected individuals [25].

Around 1930, the rabies virus adaptation was actualized through embryonated eggs with many passages that maintained the virus [19]. Further works were based on the cultivation of the virus in brain tissues of small animals [26]. Plotz and Reagan, were able to isolate and cultivate wild rabies virus from an infected animal to embryonated chicken eggs which led to the first concept of adapting virus in non-neuronal tissues [27]. From 1960 to 1963 different scientists also successfully adapted wild rabies virus from different strains to different cell lines such as primary hamster kidney cell line. They were able to maintain the virus to different passage levels [28]. Moreover, after several trials and improvement in rabies vaccine, the WHO proposed the change from tissue cell line to cell

culture vaccine which is effective, with many other advantages, over the former vaccines [29]. Now, purified Vero cell-derived rabies vaccine is available and commonly used worldwide.

3. Epidemiology

The rabies is a threat to public health and food security worldwide, especially in Sub-Saharan Africa. Among viral diseases, rabies virus is different, as it has the ability to infect and spread among a wide range of animals and humans [22, 30]. The disease usually claims several human lives yearly, with infection rate of 36 % and 59.6 % in Africa and Asia respectively [24], while South Asia alone records about 40 % fatality rate globally. If we consider the status of rabies in Asia and Africa, it is clear that majority of the developing nations of these continents are the fatal sufferers of rabies [24].

Rabies disease is endemic in many countries, except in Australia and Antarctica [9]. According to the World Health Organization [6], any country that has no record of indigenously acquired case of rabies within a two-year period due to surveillance and import regulations can claim a rabies-free status. But reintroduction from neighbouring countries exists, in spite of undertaking preventive measures on both human and animals [30–32].

In Sub-Saharan African countries, estimated report of human rabies cases do not match with actual incidence of rabies cases [33]. The major animal agent transmission of rabies is dog. However, many factors have been highlighted by some studies [34] to be responsible for the persistent increase in cases, both in animal and human populations. These factors include; dogs population, socio-economic disposition, lack of awareness and knowledge of the disease, vaccine and vaccine-related factors, weak surveillance system, game activities involving dogs, slaughtering dogs for meat consumption, lack of accurate data on true reported cases of the disease, lack of government commitment to certain control measures, amongst others.

Generally, in Africa, notification of rabies disease is not mandatory; however, vaccination of animals against rabies virus is compulsory, most especially in Western and Central African countries [35]. Report from global analysis of rabies-endemic countries stated that 49 African countries (90 %) were rated as moderate to high risk countries for human rabies. It was also observed that surveillance system was not adequate [1, 34, 36]. A review of 20 studies across Africa showed that bites from rabid dogs has 91.9 %, while the estimate of cats was 2.9 %. The review also showed 0.8 % for jackal bites and 4.40 % for other animals like goat, horse, rat, pig, monkey, hyena and cattle [37, 38].

4. Vaccine types and technological advances

Trial of rabies prevention began with herbal remedies toward the treatment of the disease by traditional healers. There was no specific diagnosis or treatment for rabies disease then [39].

4.1. First generation of anti-rabies vaccine

Louis Pasteur formulated nerves tissues infected with rabid virus to form the first vaccine. The era is called 'first-generation rabies vaccine'. He used the brain of an infected rabbit by inactivation and/or attenuation of the virus. He adapted and passaged the rabies virus (wild-type) to laboratory animals [40] which changed the infective properties in terms of genetic materials and virulence of the virus. After much experimentation on natural hosts, in 1885, Pasteur administered his trial rabies vaccine to a human being, who had multiple rabid bites and the person survived the condition. However, the major challenge of the first generation anti-rabies vaccine is that it had the chances of revert the virus back to infective status [25]. Still, the fear of inactivated vaccine was that cases of post-vaccination reaction were reported in some individuals, although NTV is comparably less expensive.

4.2. Fermi and Semple rabies vaccine

Fermi and Semple improved Pasteur's vaccine through chemical modification [15]. In the Central Research Institute, Kasauli, India, Sir David Semple pioneered the newer nerve tissue vaccines. They inactivated infected animal brain with phenol [41]. Though the phenol really inactivated Pasteur's traditional vaccine, the chemical distorted the structure of the protein there by disrupting the antigenicity of the vaccine. However, the fear was the transmission of Spongiform Encephalopathies and Guillain-Barre Syndrome, which were the side effects. The vaccine was used in many nations; however, the WHO later suspended its use in almost all the countries.

Although Fermi and Semple vaccine was used, it caused reactions and encephalitis in some immunized people as a result of the quantity of myelin, which brought about an alternative lower vaccine reactogenic. Also, a study was conducted in 1940s, on encephalomyelitis and demyelinating diseases due to vaccines side effects which attract attention and called for change to the embryonated eggs and neonatal rodent brains as the growth medium for the virus. Since myelin which is responsible for the side effect, is absent in the embryonated and neonatal growing medium [42]. Fuenzalida and team successfully produced free-myelin inactivated rabies vaccine from mouse brain and inactivated it with phenol [43]. The absence or insignificant amount of myelin in embryonated eggs and/or neonatal brains vaccine from such media made the vaccine less reactogenic and more acceptable.

4.3. Embryo vaccines

The adaptation of viruses in embryonated eggs provides an improvement in vaccine production. Although nerve tissue and embryonated eggs are used in the production of rabies vaccines, eggs- based attenuated vaccine usually undergoes several passages in flurry low egg [44] and then is fridge-dried (compound) from a 33 % whole-embryo suspension in peptone. The low egg passage vaccine was used in mass animal vaccination. It was later discovered that it contained virulence residue [45]. Long turn over-time in egg-based vaccine production unavailability of specific pathogenic free eggs are among the challenges encountered in egg-based vaccine production [46].

4.4. Second generation rabies vaccine

The development of cell line method in rabies vaccine production has resulted in the cell culture vaccines formulation [24, 47]. Nerve tissue vaccines and egg-based vaccines have some drawbacks of impurities compared to the cell culture vaccine which made cell line useful in adapting to the virus. The cell line vaccines have higher process flexibility with good profile, as well as a reduced lead time [45, 48]. Vero cell line was derived from kidney cells of African green monkey. The cells line is a good medium that supports the growth and replication of many viruses. In the production of rabies vaccine, Vero cell line is found to bring out quality virus with good titers. The long history of safe usage and the scaling up of cell culture system in vaccine production have made the Vero cell line useful for virus propagation. Vero cells line has considerably lowered the turn-over time of production and made rabies vaccine accessible to countries. Furthermore, the introduction of the cell line-derived rabies vaccine in clinical practice remains crucial for rabies vaccine safety [49].

Tissue culture techniques have long been used in studies related to rabies virus, and there are now a number of continuous cell line used in research on pathogenesis, vaccine production and diagnosis of rabies [49]. Cell culture rabies vaccines are cleaner, devoid of egg lipids and proteins. They are more potent with a large volume of vaccine produced at a time. Vero cell line is a continuous aneuploidy cell line extracted from vervet monkey kidney which is used as the medium for the cultivation of viruses. The cell culture vaccines are currently in use in different parts of the world.

4.5. Third generation vaccines

RNA and DNA vaccines are recombinant vector and nucleic acid vaccines [44]. In 2016, DNA vaccine for Zika virus was tested in Bethesda at the National Institute of Health Clinical Center, Maryland, United States of America [50]. Separately, Inovio Pharmaceuticals and Gene One Life Science began work on different DNA vaccines against Zika in Miami, Niger Republic. The large-scale manufacturing of nucleic acid vaccines remained unresolved in 2016 [51]. Clinical trials for DNA vaccines to prevent HIV are ongoing [52], while an mRNA vaccine (BNT162b2) was developed in 2020, with the help of Operation Warp Speed, and massively deployed to combat the CONVID-19 pandemic. In 2021, Katalin and Drew were given Columbia University Award Prize for their pioneering research in mRNA vaccines development [53].

4.6. Modern vaccines

Advancement in science has brought different phases of vaccine development like genetic engineering and tissue culture technologies [42, 54]. All these led to the design and production of large quantities of pure antigens. Modern rabies vaccine is aimed to produce potent, effective and inexpensive vaccines with longer shelf life and with immunization-ease approach [45]. Emerging trends in vaccine development are focused on modular approach, multi-product facilities, and high containment facilities, using genetic engineering application of technology for faster production. It is also based on the application of single-use technologies and reduction in logistics, with focus on the certifiable product and its ease of reach to the end user [49]. These are geared towards vaccines of lower risks, easily developed from indigenous isolates, stable, easy to handle and low storage costs.

Rabies vaccines have progressed through several generations with different production methods and distinct types. Table 1 depicts the various types and generation of the vaccines with their production methods [55, 56]. Louis Pasteur developed the first rabies vaccine, with an infected nerve tissue through physical inactivation. Fermi and Semple advance the rabies vaccine with chemical inactivation [57, 58]. The creation of cell culture system for the propagation of virus has provided a new novel for rabies vaccine production [59]. The advert of technologies, for example recombinant vaccine, has given a good understanding of the rabies viral genome manipulations [56].

The concise milestones in rabies vaccine development in Sub-Saharan Africa from the first generation to the current rabies vaccine are presented in Table 2. Louis Pasteur's lays the foundation for the modern rabies vaccines development, using an attenuated virus in tissue nerve, which was later adopted in Sub-Saharan Africa and other part of the world [15, 59].

5. Trends in rabies incidence across sub-saharan Africa

The current trends in rabies incidence in Sub-Saharan Africa are almost certainly under-represent the true fatality rate [22]. Sixteen studies showed rabies-related fatalities in Sub-Saharan Africa. Studies conducted in Ethiopia were 320 people were clinically diagnosed, died of rabies in a 5-year study conducted in the national level [60, 61], mortalities of 386 human rabies were reported in

Table 1: Rabies vaccines (types, generations and production methods).

Vaccine Types	Generation	Production methods
Nerve tissue vaccine (NTV)	First	Physical inactivation of the rabies virus through sun drying
Fermi and Semple	First	Inactivation of NTV with chemical such as phenol
Embryo vaccine	First	Live attenuated virus that undergone egg passages
Cell culture vaccine	Second	Cultivation of the rabies virus in primary explants cells
RNA and DNA vaccine	Third	Recombinant vector and nucleic acid
Genetically modified vaccine	Next	Modification of the virus genome through deletion, insertion, changes in nucleotide sequences or artificial synthesis through biological methods.

Table 2: Key milestones in rabies vaccine development.

Time	Vaccine Advancement	Reference
Pre-vaccine era Before the 19th century	Rabies was universally fatal once symptoms appeared, with no preventive measures.	[15]
Foundation of vaccination 1885	Pasteur and Emile Roux developed a vaccine through drying the nerve tissue cords	[41]
Improving safety 1908	Chemical-inactivated nerve tissue vaccine	[62]
Semple vaccine 1911-1920	Phenol-inactivated rabies virus from sheep brains Development of embryo vaccines, with reducing myelin-related challenges	[57] [63]
Modern cell culture vaccines 1960s	Change from nerves tissue to Cell-culture vaccines	[63]
1980	Human diploid cell vaccines. Highly purified and well tolerated vaccine	[64, 65]
Recent innovations vaccines 2000s	Advances in recombinant rabies vaccines for both humans and animals	[43, 66, 67]
Present	Research into nucleic acid vaccines ongoing (CureVac's and Moderna's mRNA-1440)	[56, 59, 68, 69]

an 8-year retrospective study with an annual range of 35–58 deaths in Addis Ababa and environs [61]. Also 32 cases of human rabies were recorded from which 3 mortality occur in North Gondar administrative zone. In another study conducted in Tanzania were Kilombero, Ulanga and Serengeti communities reported human rabies fatality rate of 0.8, 2.4 and 1.4/100,000 annually [70]. There 1291 bite human victims and sixteen deaths due to rabies were recorder in the Integrated Bite Management case Study in 20 districts across 4 regions in Southern, Central and Northern Tanzania [33]. Further studies in Serengeti and Ngorongoro with 1.5/100,000 and 2.3/100,000 respectively, were 28 deaths from suspected rabies cases during the 5-year period in the two districts [22]. In Nigeria, Osaghae reported the prevalence of dog bite was highest (50.6%), in the hot season and low (17.3%), during the wet season [71]. Another record in Nigeria shows the highest number of dog bites with two peaks in April and October 2008 [72]. In general, the numbers of dog bite cases recorded were lower at the beginning of the year and increased during the last few months of the year 2006. In Uganda, three studies records fatalities. Among them, there were 592 deaths, were one dose of PEP was sufficient for protection following a rabid animal bite [4]. Another research in Uganda, estimated a total of 371 deaths of rabies with a cumulative total of 117085 rabies cases in 9 years [61]. A research carried out in Madagascar recorded a yearly incidence of about 42-110 rabies bites and 1-3 deaths of 100,000 people [16]. An estimated seven rabies deaths per year was recorded in N'Djamena in Chad.

6. Rabies vaccination coverage across sub-saharan Africa

Dogs vaccination remains below the recommended 70 % threshold vaccination covered, with South Africa reporting ~ 60 % relatively outlier threshold in recent years [8]. A proactive strategy of mass dog vaccination enhanced expanded access to post-exposure prophylaxis (PEP) and reduces the annual incidence of rabies exposures and deaths annually in Madagascar [17]. Measures such as vaccination of dogs in communities where human rabies cases had occurred, vaccination campaign of dogs, collection of stray dogs in selected neighborhoods, participation of private veterinary clinics in animal vaccination, and community education regarding prevention and control measures had drastically reduced rabies cases in humans to 14 during the study period in Mozambique [34, 73]. Nigeria estimated national dog-vaccination coverage is 12.3 %, underscoring the gap to the 70 % target, with large urban-rural variation. Malawi and Tanzania has met or exceeded 70 % target [6].

7. Challenges in sub-saharan Africa

The challenges faced in the production of anti-rabies vaccines in Sub-Saharan African countries are funding for research and modern equipment such as bioreactors to change from analog to digital technology [42]. The myelin content is much in Semple vaccine which gives higher incidence of neuro-paralysis [41]. Other limitations of NTV are less immunogenic and more reactogenic. Also, many numbers of doses are required for the administration which involves many injections. Modern tissue culture vaccine (MTCV) is more antigenic and convenient for all ages [41], The MTCV lacks immunologic response in puppies below 11 weeks of age is the limitation of the modified live virus vaccines [68]. MLV withdrew from most developed countries due to virus reversion in vaccinated dogs and the short shelf life of the vaccine [74]. Another reason is the high cost of imported materials, biological and equipment, some of which are: biosafety cabinets, dispensing/capping machines, freeze-drying machines, incubators, labeling machines and freezers, which are all capital intensive [24, 41].

Nigeria uses embryonated chicken eggs in the production of rabies vaccine, even though the eggs are relatively expensive but affordable. The major challenge is availability of the specific pathogen-free (SPF) breeder stock birds for the production of SPF eggs [41].

Another challenge faced in the production of vaccine in the country is the issue of constant electricity supply, which is an important requirement in any facility where vaccines are produced, handled and stored; although alternative local electricity power supply could save the menace but with additional burden on the final product (vaccine) [41]. Generally, the vaccine market size is small and the demand of vaccine within the Sub-Saharan African countries is not encouraged. Poor countries, who have the greatest need for vaccines, cannot afford to purchase them at market prices. There is a growing demand for safe and potent rabies vaccines worldwide. One of the advantages of the newer molecular technology is improved safety, although zero risk is very rare. Dog vaccination coverage in African countries- South Africa, Tanzania, Algeria, Morocco, Egypt and Nigeria -had dog vaccination coverage of 63 %, 37.24 %, 23.7 %, 25 %, 23.7 %, 10.5 % respectively as against the 70 % recommended by the World Health Organization [60, 75, 76]. The studies also reveal that rabies vaccination coverage has reduced in the last two decades. This is an indication of low patronage and use of the few available anti-rabies vaccines in circulation. These can be attributed to lack of awareness, inaccessibility of the vaccine, poverty and government will [24, 76]. Other challenges to be considered are: absence of compulsory enforcement of registration and vaccination of dogs in some developing countries, lack of regular mass vaccination campaigns for dogs and lack of subsidy on vaccine cost [8, 77]. Rabies Immunoglobulin (RIG) is one of the first aids treatments given in post-exposure management, in addition to the prophylaxis rabies vaccine, which is commonly unavailable in some health facilities in Sub-Saharan African countries, which could lead to reactogenicity of the vaccine [41, 78, 79].

Rabies vaccine advancements from the nerve tissue vaccine to the modern tissue culture vaccine have led to the development and production of large volumes of pure antigens, a major component of the vaccines [80], with greater changes to manipulate the organism to the development of inactivated vaccines. However, most of these advancements in technology are not found in Sub-Saharan Africa due to paucity of infrastructure, production cost and low technical know-how. Generally, the present vaccines in circulation are quite appreciable, but the delivery (transportation) systems remain an important area of focus, which will help in effective shipping.

Bioreactors are used in cell culture-based vaccine production, especially during the Coronavirus disease 2019 (COVID-19) pandemic. In this context, the development and application of bioreactors provide a more efficient and cost-effective vaccine production to meet the global vaccine demand [81]. The production of anti-rabies vaccine is inseparable from other biological processes. Therefore, it is necessary to evaluate the existing biological processes, to enable the selection of a pilot-scale plan to maximize the yield and quality of vaccine development and production. On this basis, a comprehensive analysis and evaluation of the various process optimization methods for the production of various viruses (anti rabies virus, SARS-CoV-2, Influenza virus, Tropical virus, Enterovirus, Rabies virus) in bioreactors is presented [44, 81].

Rabies vaccine failure due to exposure to temperature above the cold chain ranges during storage and transportation brought about the development of thermostable vaccines that can be stored and shipped outside the required cold temperature. This has helped in vaccines availability to rural areas. Scientists have developed novel nucleic acid vaccines with high potency and safety for combating diseases, with fewer side effects. However, due to limitations in funding, it is still quite challenging to promote these projects in Sub-Saharan Africa which makes the vaccines very expensive [82].

Some Sub-Saharan African countries have progressed in the production of cell-cultured anti-rabies vaccines. These include Ethiopia and South Africa. The presence of steady power supply, trained manpower and political will has propelled their capacity to produce cell-culture anti-rabies vaccines. Other countries can emulate these approaches in order to achieve a wider coverage of anti-rabies vaccine production across Sub- Saharan Africa. Developments of newer vaccines are in different stages of completion. An example is 'ETHIORAB' cell-culture vaccine produced in Ethiopia at the Health and Nutrition Institute [77], with neutralizing antibody titer higher than value mandated standard. This shows that Sub-Saharan African countries lagging in novel vaccine production can adopt the Ethiopian approach to adapt modern technology for vaccine production.

8. Recommendations

Advancement in science has brought about improvement in technology in vaccine development aimed at eradicating rabies. This has led to the production of vaccines in a large scale which Sub-Saharan Africa must emulate. The cold chain system of vaccine storage and transportation needs to be overhauled to evade vaccine failure. Resources must be directed and focused to fund vaccine production in Sub-Saharan African countries. In addition, there is need for government, regulatory agencies, health systems and donors to commit to rabies control measures, such as educating patients, administering vaccines, ensuring timely delivery of vaccines and provision of financial support for research, development, and distribution of the vaccine. -

9. Conclusion

The trend in development and usage from traditional to modern rabies vaccine has passed through many challenges globally. The pioneer research of Pasteur on vaccine development is still the basis for the development of the present rabies disease vaccines in use. In Sub-Saharan Africa, rabies vaccines development has also faced challenges, such as lack of modern technology and research funding, and high cost of materials, such as reagents and equipment. In African countries also, infrastructure is one of the major problems in mass vaccination due to the topography of some areas. With the advance in science and man power, Sub-Saharan Africa has potentiates to develop her own vaccine production equipment in the near future. Some of the advances include: cells culture vaccine production, emergence of more scientists in vaccine production science, and improvement in cold chain system of the vaccine. To achieve all these, government should brace up in funding and place priority on rabies vaccine. Also, there is a need for the Government to adopt a one-health approach by fostering collaboration among human, animal, and environmental health sectors for effective rabies control.

Data availability

Data will be made available upon reasonable request from the corresponding author.

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References

[1] R. Singh, K. P. Singh, S. Cherian, M. Saminathan, S. Kapoor, S. Manjunatha & G. B. Reddy, “Rabies epidemiology, pathogenesis, public health concerns and advances in diagnosis and control: a comprehensive review”, Vet Q **37** (2017) 212. https://doi.org/10.1080/01652176.2017.1343516.
[2] P. J. Walker, J. Freitas-Astúa, N. Bejerman, K. R. Blasdell, R. Breyta, R. G. Dietzgen, A. R. Fooks, H. Kondo, G. Kurath, I. V. Kuzmin, “ICTV virus taxonomy profile: Rhabdoviridae”, J Gen Virol **103** (2022) 10. http://doi.org/10.1099/jgv.1001689.
[3] A. Bahiru, W. Molla, L. Yizengaw, S. A. Mekonnen, W. T. Jemberu & A. Bahiru, “Knowledge, attitude and practice related to rabies among residents of Amhara region, Ethiopia”, Heliyon **8** (2022) e11366. https://doi.org/10.1016/j.heliyon.2022.e11366.
[4] E. Kenu, V. Ganu, C. L. Noora, R. Adanu & M. Lartey, “Management of dog bites by frontline service providers in primary healthcare facilities in the Greater Accra Region of Ghana, 2014–2015”, Infect Dis Poverty **7** (2018) 18. https://link.springer.com/doi/10.1186/s40249-018-0398-3.
[5] World Health Organization, “Rabies”, (2020). https://www.who.int/news-room/fact-sheets/detail/rabies.
[6] World Health Organization, “Rabies, countries or areas at risk”, 2013. Available [Online]. https://www.woah.org/en/home/.
[7] A. C. Jackson, “Human rabies”, Curr Infect Dis Rep **18** (2016) 38. https://doi.org/10.1007/s11908-016-0540-y.
[8] Y. J. Atuman, A. B. Ogunkoya, D. A. Y. Adawa, A. J. Nok & M. B. Biallah, “Dog ecology, dog bites and rabies vaccination rates in Bauchi State, Nigeria”, Int J Vet Sci Med **2** (2014) 41. https://doi.org/10.1016/j.ijvsm.2014.04.001.
[9] M. Kaur, R. Garg, S. Singh & R. Bhatnagar, “Rabies vaccines: where do we stand, where are we heading?”, Expert Rev Vaccines **14** (2015) 369. https://doi.org/10.1586/14760584.2015.973403.
[10] D. K. Yang, H. H. Kim, S. S. Choi, J. T. Kim, W. H. Jeong & J. Y. Song, “Oral immunization of mice with recombinant rabies vaccine strain (ERAG3G) induces complete protection”, Clin Exp Vaccine Res **4** (2015) 107. https://doi.org/10.7774/cevr.2015.4.2.107.
[11] A. R. Fooks, F. Cliquet, S. Finke, C. Freuling, T. Hemachudha, R. S. Mani, T. Müller, S. Nadin-Davis, E. Picard-Meyer & H. Wilde, “Rabies”, Nat Rev Dis Primers **3** (2017) 17091. https://doi.org/10.1038/nrdp.2017.91.
[12] A. Tarantola, M. C. Tejiokem & D. J. Briggs, “Evaluating new rabies post-exposure prophylaxis (PEP) regimens or vaccines”, Vaccine **37** (2019) 88. https://doi.org/10.1016/j.vaccine.2018.10.103.
[13] Global Alliance for Rabies Control, “Working to eliminate human deaths from dog rabies by 2030”, 2017. Available [Online]. https://rabiesalliance.org/country/nigeria.
[14] World Organization for Animal Health, “Global strategic plan to end human deaths from dog-mediated rabies by 2030”, (2018). http://www.who.int/rabies/resources/9789241513838/en.
[15] N. Krithiga, I. Shrikrishna, V. Balamurugan, R. Sharada, D. Rathnamma & R. F. Anthony, “Developments in rabies vaccines: the path traversed from Pasteur to the modern era of immunization”, Vaccines **11** (2023) 756. https://doi.org/10.3390/vaccines11040756.
[16] A. El-Sayed, “Advances in rabies prophylaxis and treatment with emphasis on immunoresponse mechanisms”, Int J Vet Sci Med **6** (2018) 8. https://doi.org/10.1016/j.ijvsm.2018.05.001.
[17] S. Zhu & C. Guo, “Rabies control and treatment: from prophylaxis to strategies with curative potential”, Viruses **8** (2016) 279. https://doi.org/10.3390/v8110279.

[18] R. Cid & J. Bolivar, "Platforms for production of protein-based vaccines: from classical to next-generation strategies", Biomolecules **11** (2021) 1072. https://doi.org/10.3390/biom11081072.

[19] T. Tantawichien & C. E. Rupprecht, "Modern biologics for rabies prophylaxis and the elimination of human cases mediated by dogs", Expert Opin Biol Ther **20** (2020) 1347. https://doi.org/10.1080/14712598.2020.1766021.

[20] G. Yale, M. Lopes, S. Isloor, J. R. Head, S. Mazeri, L. Gamble, K. Dukpa, G. Gongal & D. Gibson, "Review of oral rabies vaccination of dogs and its application in India", Viruses **14** (2022) 155. https://doi.org/10.3390/v14010155.

[21] G. Gongal & G. Sampath, "Introduction of intradermal rabies vaccination—a paradigm shift in improving post-exposure prophylaxis in Asia", Vaccine **37** (2019) A94. https://doi.org/10.1016/j.vaccine.2018.08.034.

[22] K. Hampson, L. Coudeville, T. Lembo, M. Sambo, A. Kieffer, M. Attlan, J. Barrat, J. D. Blanton, D. J. Briggs & S. Cleaveland, "Estimating the global burden of endemic canine rabies", PLoS Negl Trop Dis **9** (2015) e0003709. https://doi.org/10.1371/journal.pntd.0003709.

[23] S. Rajendra, P. S. Karam, C. Susan, S. Mani, K. Sanjay, R. Manjunatha & P. Shibani, "Rabies - epidemiology, pathogenesis, public health concerns and advances in diagnosis and control: a comprehensive review", Vet Q **37** (2017) 212. https://doi.org/10.1080/01652176.2017.1343516.

[24] P. P. Mshelbwala, E. R. Charles, O. O. Modupe, O. N. Emmanuel, G. O. Terese, J. W. Scott & J. C. Nicholas, "Factors influencing canine rabies vaccination among dog-owning households in Nigeria", One Health **18** (2024) 100751. https://doi.org/10.1016/j.onehlt.2024.100751.

[25] X. Wu, T. G. Smith & C. E. Rupprecht, "From brain passage to cell adaptation: the road of human rabies vaccine development", Expert Rev Vaccines **10** (2011) 1597. https://doi.org/10.1586/erv.11.140.

[26] S. Rourou, Y. Ben Ayed, K. Trabelsi, S. Majoul & H. Kallel, "An animal component free medium that promotes the growth of various animal cell lines for the production of viral vaccines", Vaccine **32** (2014) 2767. https://doi.org/10.1016/j.vaccine.2014.02.040.

[27] K. Dhama, S. Chakraborty, M. Y. Mahima, A. K. Verma, R. Deb, R. Tiwari & S. Kapoor, "Novel and emerging therapies safeguarding health of humans and their companion animals: a review", Pak J Biol Sci **16** (2013) 101. https://doi.org/10.3923/pjbs.2013.101.111.

[28] Tenzin & M. P. Ward, "Review of rabies epidemiology and control in South, South East and East Asia: past, present and prospects for elimination", Zoonoses Public Health **59** (2012) 451. https://doi.org/10.1111/j.1863-2378.2012.01489.x.

[29] A. Velasco-Villa, L. E. Escobar, A. Sanchez, M. Shi, D. G. Streicker, N. F. Gallardo-Romero, F. Vargas-Pino, V. Gutierrez-Cedillo, I. Damon & G. Emerson, "Successful strategies implemented towards the elimination of canine rabies in the Western Hemisphere", Antiviral Res **143** (2017) 1. https://doi.org/10.1016/j.antiviral.2017.03.023.

[30] H. Wilde, T. Hemachudha, S. Wacharapluesadee & B. Lumlertdacha, "Rabies in Asia: the classical zoonosis", in *One health: the human-animal-environment interfaces in emerging infectious diseases*, Springer, Berlin, Germany, 2013, pp. 185. https://doi.org/10.1007/82_2012_228.

[31] D. K. Yang, I. S. Cho & H. H. Kim, "Strategies for controlling dog-mediated human rabies in Asia: using "One Health" principles to assess control programmes for rabies", Rev Sci Tech **37** (2018) 473. https://doi.org/10.20506/rst.37.2.2816.

[32] C. Mbilo, J. B. Kabongo, P. P. Pyana, L. Nlonda, R. W. Nzita & B. Luntadila, "Do ecology, bite incidence, and disease awareness: a cross-sectional survey among a rabies-affected community in the Democratic Republic of the Congo", Vaccines (Basel) **7** (2019) 98. https://doi.org/10.3390/vaccines7030098.

[33] L. Konzing, J. Kwaga, G. Kia & H. A. Kazeem, "A retrospective study of dog bite cases reported to some hospitals in Plateau State, Nigeria", Sokoto J Vet Sci **17** (2019) 56. https://doi.org/10.4314/sokjvs.v17i1.7.

[34] N. Caffrey, M. Rock, O. Schmidt, D. Anderson, M. Parkinson & S. L. Checkley, "Insights about the epidemiology of dog bites in a Canadian city using a dog aggression scale and administrative data", Animals (Basel) **9** (2019) 324. https://doi.org/10.3390/ani9060324.

[35] I. Tekki, C. Meseko, S. Omotainse, Y. Atuman, S. Olaleye & P. Okewole, "Incidences of rabies in domestic animals and consequent risk factors in humans", J Med Microbiol Diagn **3** (2014) 1. https://doi.org/10.4172/2161-0703.1000143.

[36] P. P. Mshelbwala, J. S. Weese, O. A. Sanni-Adeniyi, S. Chakma, S. S. Okeme, A. A. Mamun, C. E. Rupprecht & R. J. S. Magalhaes, "Rabies epidemiology, prevention and control in Nigeria: scoping progress towards elimination", PLoS Negl Trop Dis **15** (2021) e0009617. https://doi.org/10.1371/journal.pntd.0009617.

[37] M. Kaur, R. Garg, S. Singh & R. Bhatnagar, "Rabies vaccines: where do we stand, where are we heading?", Expert Rev Vaccines **14** (2015) 369. https://doi.org/10.1586/14760584.2015.973403.

[38] J. E. Norton, A. G. Lytle, S. Shen, E. P. Tzvetkov, C. L. Dorfmeier & J. P. McGettigan, "ICAM1-based rabies virus vaccine shows increased infection and activation of primary murine B cells in vitro and enhanced antibody titers in vivo", PLoS One **9** (2014) e87098. https://doi.org/10.1371/journal.pone.0087098.

[39] P. Vescovo, N. Rettby, N. Ramaniraka, J. Liberman, K. Hart, A. Cachemaille, L. D. Piveteau, R. Zanoni, P. A. Bart & G. Pantaleo, "Safety, tolerability and efficacy of intradermal rabies immunization with DebioJect™", Vaccine **35** (2017) 1782. https://doi.org/10.1016/j.vaccine.2016.09.069.

[40] F. Qin, F. Xia, H. Chen, B. Cui, Y. Feng, P. Zhang, J. Chen & M. A. Luo, "Guide to nucleic acid vaccines in the prevention and treatment of infectious diseases and cancers: from basic principles to current applications", Front Cell Dev Biol **9** (2021) 633776. https://doi.org/10.3389/fcell.2021.633776.

[41] N. Ito, T. Okamoto, M. Sasaki, S. Miyamoto, T. Takahashi, F. Izumi, M. Inukai, S. Jarusombuti, K. Okada & K. Nakagawa, "Safety enhancement of a genetically modified live rabies vaccine strain by introducing an attenuating Leu residue at position 333 in the glycoprotein", Vaccine **39** (2021) 3777. https://doi.org/10.1016/j.vaccine.2021.05.002.

[42] U. Molini, R. Hassel, S. Ortmann, A. Vos, M. Loschke, A. Shilongo & C. M. Freuling, T. Müller, "Immunogenicity of the oral rabies vaccine strain SPBN GASGAS in dogs under field settings in Namibia", Front. Veterinary Science **8** (2021) 1224. https://doi.org/10.3389/fvets.2021.737250.

[43] R. Li, L. Huang, J. Li, Z. Mo, B. He, Y. Wang, X. Wu, M. Minutello, F. Guinet-Morlot & S. Pichon, "A next-generation, serum-free, highly purified vero cell rabies vaccine is safe and as immunogenic as the reference vaccine verorab when administered according to a post-exposure regimen in healthy children and adults in China", Vaccine **31** (2013) 5940. https://doi.org/10.1016/j.vaccine.2013.10.043.

[44] D. K. Yang, H. H. Kim, K. W. Lee & J. Y. Song, "The present and future of rabies vaccine in animals", Clinical Exp. Vaccine Research **2** (2013) 19. https://doi.org/10.7774/cevr.2013.2.1.19.

[45] A. Regalado, "The U.S. government has begun testing its first zika vaccine in human", (2016). https://www.cphi-online.com/news/research-and-development.html.

[46] Y. Chen & S. Wang, S. Lu, "DNA immunization for HIV vaccine development", Vaccines **2** (2024) 138. https://doi.org/10.3390/vaccines2010138.

[47] K. Katalin & W. Drew, "Awarded horwitz prize for pioneering research on convid-19 vaccines", Columbia University Irving Medical Center (2021). https://www.cuimc.columbia.edu/news/horwitz-prize-2021.

[48] E. S. Starodubova, O. V. Preobrazhenskaia, Y. V. Kuzmenko, A. A. Latanova, E. I. Yarygina & V. L. Karpov, "Rabies vaccines: Current status and prospects for development", Molecular Biology **49** (2015) 577. https://doi.org/10.7868/S0026898415040175.

[49] C. E. Rupprecht, C. A. Hanlon & T. Hemachudha, "Rabies reexamined", Lancet Infectious Disease **2** (2002) 327. https://doi.org/10.1016/S1473-3099(02)00287-6.

[50] A. Giesen, D. Gniel & C. Malerczyk, "30 years of rabies vaccination with rabipur: A summary of clinical data and global experience", Expert Rev Vaccines **14** (2015) 351. https://doi.org/10.1586/14760584.2015.1011134.

[51] P. Admasu & Y. Mekonnen, "Rabies and its folk drugs remedies in Ethiopia: A review", International Journal of Basic and Applied Virology **3** (2014) 22. https://doi.org/10.5829/idosi.ijbav.2014.3.2.8332.

[52] A. Mesfin, T. Wogayehu, A. Amelework, A. Sintayehu, G. Garuma, H. Alemnesh, T. Yirgalem, K. Gutu, B. Endalkachew, F. Ibsa, G. Abebe & M. Yimer,

"Situation of rabies in Ethiopia: A five-year retrospective study of human rabies in addis ababa and the surrounding regions", Journal of Tropical Medicine **2021** (2021) 6662073. https://doi.org/10.1155/2021/6662073.
[53] K. L. O'Brien & T. Nolan, "WHO position on rabies immunization - 2018 updates", Vaccine **37** (2019) A85. https://doi.org/10.1016/j.vaccine.2018.10.014.
[54] L. Shuai, N. Feng, X. Wang, J. Ge, Z. Wen, W. Chen, L. Qin, X. Xia & Z. Bu, "Genetically modified rabies virus ERA strain is safe and induces long-lasting protective immune response in dogs after oral vaccination", Antiviral Res **121** (2015) 9. https://doi.org/10.1016/j.antiviral.2015.06.011.
[55] G. Galvez-Romero, M. Salas-Rojas, E. N. Pompa-Mera, K. Chávez-Rueda & A. Aguilar-Setién, "Addition of C3d-P28 adjuvant to a rabies DNA vaccine encoding the G5 linear epitope enhances the humoral immune response and confers protection", Vaccine **36** (2018) 292. https://doi.org/10.1016/j.vaccine.2017.11.047.
[56] D. K. Yang, H. H. Kim, K. W. Lee & J. P. Song, "The present and future of rabies vaccine in animals", Clinical and Experimental Vaccine Research **2** (2013) 19. https://doi.org/10.7774/cevr.2013.2.1.19.
[57] X. Wu, T. G. Smith & C. E. Rupprecht, "From brain passage to cell adaptation: The road of human rabies vaccine development", Expert Review of Vaccines **10** (2011) 1597. https://doi.org/10.1586/erv.11.140.
[58] A. Saleh, S. Qamar, A. Tekin, R. Singh & R. Kashyap, "Vaccine development throughout history", Cureus **13** (2021) e16635. https://doi.org/10.7759/cureus.16635.
[59] S. Rourou, Y. Ben Ayed, K. Trabelsi, S. Majoul & H. Kallel, "An animal component free medium that promotes the growth of various animal cell lines for the production of viral vaccines", Vaccine **32** (2014) 2767. https://doi.org/10.1016/j.vaccine.2014.02.040.
[60] H. Birhanu, T. Belete, N. Dagmar, M. Abebe & K. Gezahegn, "Safety and immunogenicity of ethiorab rabies vaccine", Journal of Vaccines & Vaccination **4** (2013) e117. https://doi.org/10.4172/2157-7560.1000e117.
[61] G. Tefera, E. Yimer & A. Geyid, "Endemic existence of rabies in Ethiopia", Ethiopian Medical Journal **40** (2002) 163. https://eurekamag.com/research/003/750/003750147.php.
[62] E. Olayan, M. El-Khadragy, A. F. Mohamed, A. K. Mohamed, R. I. Shebl & H. M. Yehia, "Evaluation of different stabilizers and inactivating compounds for the enhancement of vero cell rabies vaccine stability and immunogenicity: In vitro study", BioMed Research International **2019** (2019) 4518163. https://doi.org/10.1155/2019/4518163.
[63] G. Gongal & G. Sampath, "Introduction of intradermal rabies vaccination - A paradigm shift in improving post-exposure prophylaxis in Asia", Vaccine **37** (2019) A94. https://doi.org/10.1016/j.vaccine.2018.08.034.
[64] R. E. Kissling & D. R. Reese, "Anti-rabies vaccine of tissue culture origin", Journal of Immunology **91** (1963) 362. https://doi.org/10.4049/jimmunol.91.3.362.
[65] R. Shipley, E. Wright, F. Z. X. Lean, D. Selden, D. L. Horton, A. R. Fooks & A. C. Banyard, "Assessing rabies vaccine protection against a novel lyssavirus, kotalahti bat lyssavirus", Viruses **13** (2021) 947. https://doi.org/10.3390/v13050947.
[66] J. Maki, A. L. Guiot, M. Aubert, B. Brochier, F. Cliquet, C. A. Hanlon, R. King, E. H. Oertli, C. E. Rupprecht & C. Schumacher, "Oral vaccination of wildlife using a vaccinia-rabies-glycoprotein recombinant virus vaccine (Raboral V-RG): A global review", Veterinary Research **48** (2017) 57. https://doi.org/10.1186/s13567-017-0459-9.
[67] J. Guo, M. Mondal & D. Zhou, "Development of novel vaccine vectors: Chimpanzee adenoviral vectors", Human Vaccines & Immunotherapeutics **14** (2018) 1679. https://doi.org/10.1080/21645515.2017.1419108.
[68] F. Napolitano, R. Merone, A. Abbate, V. Ammendola, E. Horncastle, F. Lanzaro, A. Esposito, E. I. Latanova, V. L. Yarygina, M. Karpov, A. M. Contino, R. Sbrocchi & A. Sommella, "Correction: A next generation vaccine against human rabies based on a single dose of a chimpanzee adenovirus vector serotype C", PLoS Neglected Tropical Disease **15** (2021) e0009348. https://doi.org/10.1371/journal.pntd.0009348.
[69] C. Li, Y. Wang, H. Liu, X. Zhang, D. Baolige, S. Zhao, W. Hu & Y. Yang, "Change in the single amino acid site 83 in rabies virus glycoprotein enhances the BBB permeability and reduces viral pathogenicity", Frontiers in Cell and Developmental Biology **8** (2021) 632957. https://doi.org/10.3389/fcell.2020.632957.
[70] M. Sambo, S. Cleaveland & H. Ferguson, "The burden of rabies in Tanzania and its impact on local communities", PLoS Neglected Tropical Diseases **7** (2013) e2510. https://doi.org/10.1371/journal.pntd.0002510.
[71] D. O. Osaghae, "Animal and human bites in children", West African Journal of Medicine **30** (2011) 421. https://www.ajol.info/index.php/wajm/issue/view/10724.
[72] T. I. Isek, J. Umoh & A. A. Dzikwi, "A retrospective study of dog bite occurrence and anti-rabies vaccination of dogs in a state veterinary hospital in Ogoja, Cross River State, Nigeria", Veterinaria Italiana **55** (2019) 163. https://doi.org/10.12834/VetIt.150.431.5.
[73] A. Stokes, J. Pion, O. Binazon, B. Laffont, M. Bigras, G. Dubois, K. Blouin, J. K. Young, M. A. Ringenberg & N. Ben Abdeljelil, "Nonclinical safety assessment of repeated administration and biodistribution of a novel rabies self-amplifying mRNA vaccine in rats", Regulatory Toxicology and Pharmacology **113** (2020) 104648. https://doi.org/10.1016/j.yrtph.2020.104648.
[74] W. Zhang, N. Cheng, Y. Wang, X. Zheng, Y. Zhao, H. Wang, C. Wang, Q. Han, Y. Gao & J. Shan, "Adjuvant activity of PCP-II, a polysaccharide from poria cocos, on a whole killed rabies vaccine", Virus Research **270** (2019) 197638. https://doi.org/10.1016/j.virusres.2019.06.001.
[75] T. Jibat, H. Hogeveen & M. C. Mourits, "Review on dog rabies vaccination coverage in Africa: A question of dog accessibility or cost recovery?", PLoS Negl Trop Dis **9** (2015) e0003447. https://doi.org/10.1371/journal.pntd.0003447.
[76] S. S. Elizaveta, O. V. Preobrazhenskaia & Y. V. Kuzmeko, "Rabies vaccines: Current status and prospects for development", Molecular Biology **49** (2015) 577. https://doi.org/10.7868/S0026898415040175.
[77] H. I. Koprowski, J. A. Black & D. J. Nelsen, "Studies on chick-embryo-adapted rabies virus", Journal of Immunology **72** (1954) 79. https://doi.org/10.4049/jimmunol.72.1.79.
[78] H. C. J. Ertl, "New rabies vaccines for use in humans", Vaccines **7** (2019) 54. https://doi.org/10.3390/vaccines7020054.
[79] T. P. Scott & L. H. Nel, "Rabies prophylactic and treatment options: An in vitro study of siRNA- and aptamer-based therapeutics", Antiviral Research **123** (2015) 881. https://doi.org/10.1016/j.antiviral.2015.10.002.
[80] S. Prakash, "Development of covid 19 vaccine: A summarized review on global trials, efficacy, and effectiveness on variants", Diabetes & Metabolic Syndrome: Clinical Research & Reviews **16** (2022) 102482. https://doi.org/10.1016/j.dsx.2022.102482.
[81] Z. Fang, J. Lyu, J. Li, C. Li, Y. Zhang, Y. Guo, Y. Wang, Y. Zhang & K. Chen, "Application of bioreactor technology for cell culture-based viral vaccine production: Present status and future prospects", Frontiers in Bioengineering and Biotechnology **10** (2022) 921755. https://doi.org/10.3389/fbioe.2022.921755.
[82] Global Alliance for Rabies Control, "Recent research", 2017. Available [Online]. https://rabiesalliance.org/resource/recent-research-november-2017.