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Updates on the development of vaccines and therapeutic options against rabies

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Abstract: Even though rabies has been claiming more than 50,000 deaths annually worldwide, it is considered as a vaccine-preventable viral disease. More than 95 % of the total human rabies cases are caused by dogs. During the initial stage of infection, affected individuals usually show weakess at the bitten extremities and the virus can ultimately travel to the brain causing neurological signs. In attenuated (inactivated) form, the currently in use vaccines have been recommended by WHO for the prevention (i.e. pre-exposure prophylaxis, PrEP) and treatment (i.e. post exposure prophylaxis, PEP) regime against the rabies virus (RABV). However, given that they normally require refrigeration and are costly, there have been discussions revolving around potential development of newer, safer and cheaper alternative that can perform better and more convenient than the ones that are currently in use. The current review aims to explore general characteristics of RABV before looking into potential candidates of vaccines that have been studied. Further studies on the pathogenic mechanism of RABV and therapeutic approaches are still required to prevent the deathly infection following clinical manifestation. In sum, integrated interventional strategy emphasizing human health and animal health is essential and requires collaboration between health authorities and the public.

Keywords: rabies; vaccines; treatment; development; therapeutic

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Introduction

Rabies is one of the dangerous zoonotic diseases, claiming more than 50,000 deaths per year worldwide[1]. The "culprit" behind rabies is known as rabies virus (RABV) which can be transmitted by animals including bats, raccoons and foxes[1–3]. Still, dog-mediated rabies infection accounts for more than 95% of the total human rabies cases as the virus can replicate in salivary glands of infected dogs. As a results, RABV can be easily transmitted from affected dogs through bite wounds, licking of damaged skin, or direct mucosal contact[1,4]. The virus attaches itself to its cellular targets by its surface protein (i.e. RABV-G), rapidly gaining access to peripheral nerves. Via retrograde axonal transport and trans-synaptic spread, RABV ultimately enters the brain[5]. If the disease is not treated in a prompt manner, death can occur within 5–7 days upon onset of symptoms[6]. The incubation time before clinical manifestation is influenced by several variables including distance of injection site from the central nervous system (CNS) and virus load at the wound site[7]. Shorter incubation period was observed in victims with a wound on the head/neck or category III exposure[8].Commonly, initial presentation of rabies-infected victims is the weakness at the bitten extremities, which subsequently progresses into acute neurological signs[6,9]. However, there are circumstances in which the victims presented unusual symptoms including severe abdominal pain and abnormal sexual behaviours[10,11]. Rabies infection can manifest as furious or paralytic form. Limbic signs are predominant in furious rabies while paralysis of lower motor neuron is hallmark for paralytic rabies[10,12]. Even after recovery, most rabies survivors suffer from neurological impairment[6,13]. As a consequence, an "ideal" effective immunological defense against rabies would be the interception of virus before productive neuronal infection, considering

there is still established, effective therapy for those who developed rabies encephalomyelitis[14].

Canine rabies remains endemic in most developing countries, it is a huge global burden with estimated 3.7 million disability-adjusted life years and 8.6 billion USD economic losses every year[15]. The World Health Organization (WHO) has issued a notice in the past to discontinue the usage of nerve tissue vaccine and replace the vaccination program with newer vaccine produced from cell-culture or embryonated eggs[1,16]. These newer vaccines typically consist of purified inactivated virus that can be used as prevention (i.e. pre-exposure prophylaxis, PrEP) and treatment (i.e. post exposure prophylaxis, PEP). Thus, the current review aims to provide an overview on the characteristics of RABV before exploring available vaccines and those which are in development. Indeed, rabies may not seem like a disease that can be eradicated completely worldwide, thus it is imperative to continuously seek for safer vaccines or drugs with higher efficacy to curb the spread of such harmful pathogens.

Discovery and characteristics of RABV

As one of the oldest communicable disease known to man, rabies was documented several times in historical records, as early as 4,000 years ago in the pre-Mosaic Eshnunna Code[17–19]. In the code, it was stated that the owner of a rabid dog that bit a person who later died due to rabies must pay a fine. Rabies is an acute, lethal disease marked by encephalomyelitis in which the causative agents are identified to be viruses belong to the genus *Lyssavirus*. RABV or taxonomically known as *Rabies Lyssavirus* (under family: Rhabdoviridae, genus: *Lyssavirus*) is a negative-strand RNA virus. In general, those within the genus *Lyssavirus* are enveloped RNA virus that are viewed as bullet-shaped when cut tangentially or "bulls-eye" in cross sectional view under transmission electron microscope[20,21].

The genome of Lyssaviruses is approximately 11–12kb in size, encoding five proteins including glycoprotein (G), phosphoprotein (P), nucleoprotein (N), matrix protein (M), RNA-dependent RNA polymerase (L) (Figure 1)[22,23]. Belonging to phylogroup I, RABV seems to be far more "adaptable" compared to other strain in the same phylogroup — circulates in both *Chiroptera* (i.e. bats) and *Carnivora* (i.e carnivores) including wolves, foxes, shunks and dogs[24]. Several strains of RABV have been previously described and it has been discussed that certain polymorphisms within the genome can alter virulence and transmission[25]. For RABV, its genome encodes viral proteins in the sequence of 3'-N-P-M-G-L-5'[26,27]. The viral structure consists of M protein encoded by gene M and transmembrane G protein encoded by gene G. G protein plays critical roles in the pathogenesis of rabies by binding to neural receptors and cellular entry via fusion with the cellular membrane[28–30]. As the only surface proteins, G protein is the only protein that is capable of inducing production of virus neutralizing antibodies (VNAs) by the host, therefore essential in determining the evasiveness of RABV against the host immune system[30,31]. A study in 2019 compared laboratory-adapted RABV strain (B2c) and a wild type (wt) RABV isolated from rabid dog in Mexico in 1990s (DRV); the team discovered that lesser G molecules were incorporated into mature virions by wt RABVs when compared to laboratory-adapted RABVs[30]. While recombinant virus with additional G protein (i.e. triple G expression) showed higher expression and incorporation of G protein, the virus activated more dendritic cells (DC) compared to its corresponding wild type form. Conversely, wild type RABVs that were treated with subtilisin or Dithiothreitol (DTT)/Nonidet P-40 (NP40) to remove G protein failed to activate any DC and/or VNAs expression. Without G protein, these G protein-depleted virus evaded the host immune response and caused lethal infection in mice. Furthermore, another study showed that single amino acid change(s) at position of 255 or 349 in G protein decreased the viral pathogenicity of RABV[31,32]. For instance, after introducing the amino acid change at position 349 nucleotide substituting glycine with glutamine ($Gly_{349} \rightarrow Glu_{349}$), the mutant strain (known as rGDSH-G349) exhibited decreased RABV pathogenicity without affecting its propagation rate[32]. On top of that, the same strain was able to induce higher immunogenicity in mice with higher level of VNA observed compared to its parent strain. Altogether, these important findings greatly benefited the scientific community by providing crucial insights into "behaviour changes" of the virus while at the same time enabling researchers to exploit these mutation points for development of therapeutic drugs and vaccines against rabies.

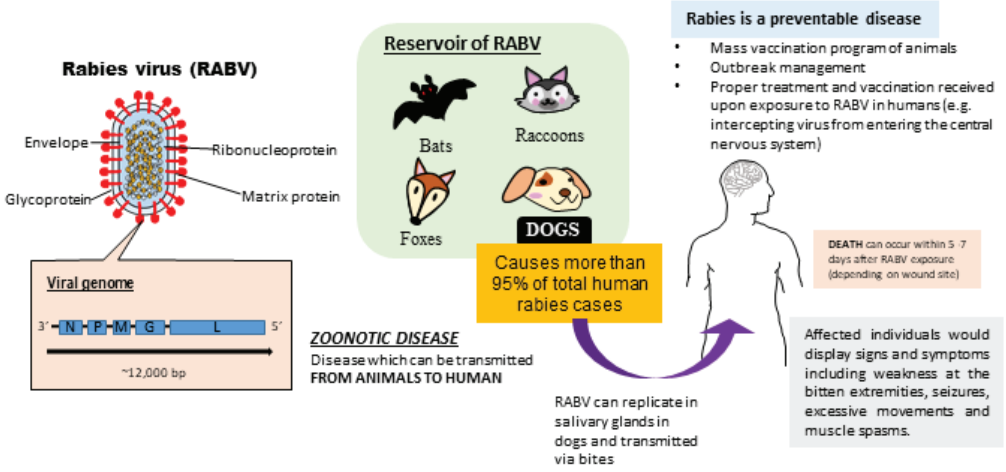

Figure 1. Illustration of rabies virus genome and its common animal reservoir.

On the other hand, the N protein is thought to be a preferred target for phylogenetic studies given that it's highly conserved and expressed while accountable for activating immunogenic response from the host[33–35]. As a matter of fact, N protein which forms the major component of helicoidal nucleocapsid that encapsidates the genomic RNA plays a determining role in viral replication; it facilitates the temporal transition between transcription and replication of the viral genome during the replicative cycle[35]. In contrast, the phosphoprotein encoded by gene P serves as a cofactor for L protein, connecting it to N protein and finally leading to the formation of ribonucleoprotein complex in viral RNA synthesis[36,37]. Besides polymorphism, the rearrangement of viral genes such as P and N has been shown to affect its pathogenicity and immunogenicity. A team led by Mei *et al.* in 2019 found that the rearrangement of gene P in RABV led to its low gene expression which then suppressed N gene and attenuated the pathogenicity of the virus [32,33]. Similar results were reported by Morimoto and team whereby the P-gene deficient (def-P) virus was apathogenic in adult and suckling mice. It was also described that even though the def-P virus can perform the primary RNA transcription, no further progeny virus was produced by the infected host (with def-P virus)[37].

Located on the third position in RABV genome, the M protein encoded by gene M is an important component during viral assembly and budding, covering the RNP coil and maintaining the viral bullet-shaped form [38,39]. On top of that, some studies have highlighted the role of M protein in viral transcription, whereby genetic manipulation on gene M via codon deoptimization led to inhibition of RABV replication at the initial stage of infection but increased viral titre at later stages[40,41]. Likewise, the codon deoptimization strain caused higher level of apoptosis in neuronal cell compared to its parental strain[42]. Besides shedding light on the transmission and replication mechanisms of RABV, the understanding on its genomic content allows researchers to identify and exploit these "weak points" in designing treatments or vaccines against this deadly virus, while monitoring RABV outbreaks and evolution.

Treatment and vaccines development against *Rabies lyssavirus* for human use

In order to fend off infections, the infected host needs to have sufficient and/or adequate immune response to first recognize the infectious agent(s) before eliminating it from the body. Before discussing in-depth about each vaccines that are in-use or in development (i.e. novel), it is important to note that currently in-use vaccines for rabies can be used as prevention (i.e. pre-exposure prophylaxis, PrEP) and treatment (i.e. post exposure prophylaxis, PEP); however, the only difference between these two lies in immunization schedule[43,44]. Moreover, there are two forms of immunizations: (a) passive immunization — by administration of monoclonal antibodies (e.g. human rabies immunoglobulins (HRIG), equine rabies immunoglobulin (ERIG)) and (b) active immunization which involves the use of cell culture- or embryonated egg-based inactivated virus[44,45]. In 1888, crude nerve tissue-based vaccines were developed and used as rabies vaccine but they are being phased out in most countries in the 21st century since the introduction of non-neural tissue-based vaccines. In addition, the crude neural vaccines made from sheep or mouse brains caused severe adverse effects and neurological sequalae including acute demyelinating encephalitis[46,47]. Even so, a few countries including Ethiopia are still using neural vaccines due to their affordability and high cost of newer vaccine[46,48]. As for preventive measures, WHO recommends rabies PrEP for individuals who are at high risk of exposure to rabies including veterinarians, laboratory workers, travellers or residents of rabies-endemic nations[1,49]. PrEP obviates rabies immunoglobulins administration and reduces the number of vaccine doses required when an individual is exposed to rabies[1,49-51]. According to WHO guidelines, a complete PrEP consists of single-dose intramuscular (IM) or two-site intradermal (ID) vaccination on both day 0 and day 7.

At the same time, WHO has also published a detailed guidelines and recommendation on PEP to assist physicians in making decision on treatment: (i) Category I involves touching of animals or licks on intact skin; (ii) Category II involves nibbling of uncovered skin or non-bleeding minor abrasions; and (iii) Category III involves transdermal bites, direct contact with bats, licks on broken skins or mucous membranes[1,51]. No PEP is indicated for category I exposure, but only active immunization (i.e. vaccine) will be given for those with category II exposure. For category III exposed individuals, they will be given both active and passive immunization (i.e. vaccine and monoclonal antibodies administration). The recommended dose of passive immunization is given at 20 IU/kg body weight for HRIG and 40 IU/kg body weight for ERIG and F(ab')2 products. Full dose of rabies immunoglobulins (RIG) can be given into or around wound site, but it can be diluted with physiological buffered saline to ensure better wound coverage in severe cases. Instead, purified cell-culture- or embryonated-egg-based rabies vaccines can be administered intramuscularly or intradermally[1,36]. PEP regimens recommended by WHO include two-sites ID rabies immunization (2-2-2-0-0) on day 0, 3 and 7; two-weeks IM rabies immunization (1-1-1-1-0) on day 0, 3, 7 and 14; three-weeks IM rabies immunization (2-0-1-0-1) on day 0, 7 and 21–28[1,50,51]. IM and ID immunization were commonly recommended because subcutaneous injections of rabies vaccines failed to induce sufficient antibody response after 1 month completing immunization protocol[52]. Receiving rabies vaccination and RIG within first 7 days and 48 hours respectively is considered as timely PEP response[53]. Though, people who received at least two doses of rabies pre-exposure vaccines do not require RIG infusion [1,51]. In events of re-exposure to animal bites, a previously immunised patient only require booster injections on day 0 and 3[49-51].

So the next important question would be — What are these vaccines make of? As discussed earlier, the host immune system must first recognize the pathogens before initiating "attacks" on the intruders. Having that said, it may seem to be unwise to inject someone with live virus to activate someone's immune system; nevertheless, looking at the history, one of the earlier version of "vaccination program" was done in small pox known as variolation, whereby they

inoculate a boy with materials from cowpox pustule and observed protective effect against matter from smallpox lesion[54]. For RABV, there have been many studies looking into potentially more effective vaccines over the years, apart from the attenuated RABV vaccines that are currently in use.

Nucleic acid-based vaccines are getting more popular these days, as researchers are working around the clock to develop them given that this approach combines the positive attributes of both live-attenuated and subunit vaccines[55]. A research team in Germany successfully developed a synthetic messenger RNA (mRNA) based vaccine which consists of an optimized non-replicating rabies virus glycoprotein (RABV-G) mRNA sequence in 2016. When compared with licensed rabies vaccines, this mRNA vaccine managed to induce comparable $CD4^+$ T cells and $CD8^+$ T cells responses upon two injections[56]. Subsequently in 2017, Stitz and team described another attractive feature for their mRNA vaccine — thermostability; they showed that the mRNA vaccine that retained its immunogenicity and protective effects against RABV even after exposure to temperatures as high as 70°C[57]. The development of thermostable vaccines provides extended shelf life in challenging conditions especially in tropical countries and economical vaccine stockpiling in preparation for epidemic threats. In fact, a Phase I clinical trial carried out in 2016 using the same mRNA vaccine technology (RNActive®), studying the safety of and immunogenicity of this vaccine in healthy volunteers (NCT02241135)[58]. A total of 101 participants were enrolled and vaccinated with 306 doses of mRNA (80–640 μg) by needle-syringe or needle-free devices (via intradermal or intramuscular route). As the first drug substance of mRNA vaccine against RABV, CV7201 or nadorameran (as named by WHO) was described as generally safe with a reasonable tolerability profile. The same study reported the observation on VNA titres of 0·5 IU/mL or more across dose levels and schedules in 71% of participants given 80 μg or 160 μg CV7201 doses intradermally and 46% of participants given 200 μg or 400 μg CV7201 doses intramuscularly. Nonetheless, 57% of them (i.e. 8 out of 14 participants) achieved titres of 0·5 IU/mL or more after receiving needle-free booster shot of CV7201 at 80 μg intradermally, while those underwent intradermal or intramuscular needle-syringe injection failed to respond (i.e. no immune response) except one participant who received 320 μg of CV7201 intradermally. Additionally, another recent study highlighted that the co-administration of RNA-based adjuvant CV8102 with licensed vaccine for rabies, Rabipur® in Phase I clinical trial (EudraCT No. 2013-004514-18, NCT02238756) indicated that CV8102 was safe up to 50 μg and enhanced immunogenicity of the licensed rabies vaccine significantly[59]. Even so, there is still much to do to determine the appropriate vaccination dose and schedule of mRNA vaccine alone or as adjuvant for PrEP and/or PEP regime.

Besides that, there are several groups discussing the use of viral vector-based vaccines against RABV, such as via the incorporation of RABV glycoprotein genes into West Nile virus backbone to induce protective effect [7,60–62]. In the study by Giel-Moloney and team, the RABV G protein expression remained stable after multiple *in vitro* passages and the vaccine exhibited durable protective immunity with high titres of complementing T helper cells[60]. The vaccine which uses RepliVax® technology is a highly promising vector delivery system, given that immunized dogs displayed durable protective immunity when tested at one- and two-year post immunization. In addition to that, there are other recombinant rabies vaccines generated using different viral vector systems, such as poxvirus[7,63,64], Newcastle disease virus[65], parainfluenza virus[66], adenovirus[67,68], or baculovirus[69,70]. Despite of that, these vaccines may not be available for clinical use at the moment, particularly regarding efficacy restricted to certain species but not human, safety considerations, and similar to the concern with mRNA vaccines—usage as PEP and/or PrEP vaccination. Looking on the bright side, there are two ongoing Phase I clinical trial studying the safety and immunogenicity of novel recombinant rabies vaccines, ChAd155-RG (NCT04019444) and ChAdOx2 RabG (NCT04162600)[71,72].

In reality, another critical point to consider in designing recombinant vaccine is that the viral vector used must not be pathogenic while being able to trigger protection against certain pathogens (including RABV)[73,74]. Decades have passed since the first vaccine for smallpox and an increasing number of researchers are considering the possibility of immunization against multiple pathogens with the use of single viral vector carrying fragments of another virus (e.g. multivalent vaccine)[74,75]. For instance, a novel vaccine consisting of inactivated RABV that expressed protein fragments of Middle East respiratory syndrome coronavirus (MERS-CoV) was proven to be effective in producing antibodies against rabies and MERS-CoV infection[74]. Developed by Wirblich and team, BNSP333-S1 is an inactivated RABV-MERS S-based vaccine and the team observed increased antigen-specific IgG responses over time after each immunization. Besides that, there is another genetically modified RABV vector-based Rift Valley fever virus (RVFV) vaccine which induced significant rabies VNA level but it is still unsure whether it can protect against RVFV as it failed to induce RVFV VNA (despite high titres of anti-RVFV IgG antibodies)[75]. Therefore, multivalent vaccines against rabies and other infectious diseases can be developed, but further validation tests should be conducted thoroughly in clinical studies to confirm its efficacy and safety.

Current measures in place to control the spread of RABV from animals to humans

Animal mass vaccination

While the development of RABV vaccine for human use is essential to combat against RABV, the preventive measures and management of wild life including carrier of RABV are equally important. WHO recommended that mass vaccination of at least 70% rabies-susceptible dog population is essential to achieve herd immunity and contain the virus as 95% of human rabies cases were caused by dog bites[1]. Although mass vaccination of dogs is the most cost-effective method for significant decrease

in human rabies cases and mortality, local government particularly in endemic countries often neglect these preventive efforts [76,77]. According to World Organization for Animal Health (OIE), animals are considered to have protective immunity against rabies infection if they have minimum post-vaccination rabies VNA of 0.5 IU/mL[78]. Several canine rabies control strategies including immunization, movement restriction and culling of stray dogs were carried out in several Asian and African countries over many decades but were not effective in eliminating rabies from the population[79,80]. Introduction of a simple centralised canine rabies vaccination campaign to a rural area in Africa increased vaccination coverage from initial estimated 9.5% to between 60 and 70%[79]. There was a significant decline in incidence of dog rabies by 97% after the second vaccination programme with more than 60% coverage of the dog population. However, in Korea, canine rabies was successfully controlled with low vaccination coverage, which ranged between 30% and 50%[81]. Genetic, temporal and spatial heterogeneities that influence contact and transmission rate can have significant impact on the design of immunization program[82]. Besides vaccination coverage, relative success of large-scale vaccination program is also determined by frequency of vaccination campaign and dog density in the area[83]. Satisfactory rabies knowledge and awareness in the population will increase rabies immunization coverage[84]. In countries with high birth and death rate of dogs, there is substantial risk of outbreaks occurrence between vaccination campaigns due to rapid decline in overall population coverage following a campaign[79].

Oral rabies vaccination (ORV) is a cost-effective and socially acceptable technique that can be incorporated into large scale rabies control programmes for canine or wildlife reservoirs[85]. International researchers have generated several effective vaccines over the years. In the late 20th century, a mass vaccination programme using live attenuated RABV vaccine (ERA-BHK21) successfully eliminated Arctic rabies virus variant from red fox population in eastern Ontario[86]. Similar result was observed in Europe where the spread of rabies infection was prevented by vaccinating approximately 60% of fox population with a different live vaccine (SAD)[2]. Despite the successful results and cost-effectiveness, the use of live-attenuated vaccines in ORV programmes remains controversial due to residual pathogenicity, vaccine-induced rabies infection, thermal instability and ineffectiveness of oral immunization in rabies reservoirs including skunks and raccoons[2,85–91]. Alternatively, recombinant vaccines were constructed from heterologous virus vectors expressing RABV glycoprotein and were proven to have improved safety profile and thermal stability[92,93]. ONRAB® is a recombinant oral RABV vaccine generated using human adenovirus vector that expresses RABV glycoprotein and often distributed as bait to animals[92]. ONRAB® induced sufficient immune response in wildlife reservoirs including red foxes, raccoons and skunks with high survival rate after rabies challenge test 1 year post-vaccination[92,94,95]. During oral vaccination campaign, muscle extracts and thoracic liquid are considered potential samples for virus neutralization tests when other samples collected are of low quality[96]. Therefore, bi-annual and annual bait distribution schedules are sufficient for rabies control in wildlife reservoirs[92].

Outbreak prevention

Appropriate health promotion measures, coordinated rabies surveillance and mass vaccination program can prevent rabies outbreaks[97]. Introduction of rabies-infected subject to a community could be an imminent threat and trigger an outbreak, especially for a previously rabies-free region[98]. In developing countries, significant stray dog population and inevitable dog movement are recognized as public health risk and could result in rabies outbreak with subsequent bites to other animals by an infected animal[99,100]. While stray dog population in rural regions is correlated with carcass availability, economic implications of dog bites and rabies infections are significant following decline in vultures population. Local government should implement strategies for carcass disposal including incinerations. As significant stray dog population and rabies infection are major concerns, Bhutan had implemented catch-neuter-vaccinate-release (CNVR) program[99]. Moreover, rabies outbreak in wildlife is of huge concern as animals like fox and wild dogs are highly mobile and travel over a long distance between habitats in different countries, further enhancing the spread of rabies infection[101]. Health promotion measures including domestic dog control regulation and mass vaccination program had been implemented in the early 19th century during the Japanese colonial period[102]. However, the Japanese colonial government was widely criticized in Korea for brutality and poor understanding of traditional dog-human relationship. In the 21st century, cultural obligations to dog population remains significant in the rural communities, especially Indigenous community, as harming dogs will result in sickness[98]. During an outbreak in India, most people only received rabies preventive measures from friends and consumed traditional herbal medicines[100]. Poor knowledge and practices of preventive measures reflected on the health-seeking behaviour of rural communities following an outbreak. As a previously rabies-free region, rabies remains endemic in Bali since the introduction of the virus by a sub-clinically infected dog in 2008[103,104]. Poor surveillances, diagnostic facilities and treatment policy in 2008 had resulted in circulation of rabies virus across the island following the outbreak[104]. However, local authority in Bali has implemented Program Dharma to improve dog care practices and facilitate mass vaccination program, in addition to reducing roaming dog density. Hence, public health officials should organise education awareness campaign to emphasize the significance of dog ownerships and public cooperation as preventive strategies of outbreak[103]. Poor handling of outbreak in wildlife or local community could facilitate transmission of zoonotic diseases to human. Despite its rabies-free status, Australia has identified potential areas of rabies incursion and implemented community-based health promotion approach to increase preparedness of the local community[98]. Rabies surveillance including strict monitoring programs is important for prompt control measures as potential cases are identified to halt spreading[97].

Conclusion and future recommendation

Since the description of rabies by the historical records, humans have made a long way in the discovery and development of vaccines for RABV. In actual, thorough research into molecular virology, immunology and epidemiology have provided remarkable understanding of the circulation of rabies virus. Even though the current inactivated vaccine may seem to be working well, it is still far from "perfect" with some studies found inadequate antibodies titre among veterinary students at 2 years after pre-exposure rabies vaccination; the levels of antibodies was independently influenced by several variables including gender, vaccine type or manufacturer, BMI and interval between first and third vaccine doses[105,106]. Furthermore, the currently approved vaccine for rabies needs to be refrigerated, complicating the logistics problem which can lead to delay in treatment time[107].

Global burden of rabies infection is notable, but the zoonotic diseases as such is preventable. Collaborative efforts from several countries have played an important role in improving public health and relieving the economic burden. As part of the drug discovery process, researchers have been studying the potential of small molecules or even peptides expressed by microorganisms and plants to be used to prevent and/or treat infectious diseases including RABV[108–117]. Among these studies, tobacco mosaic virus (TMV) isolated from chimeric plants expressed spherical particles (i.e. coat protein of alfalfa mosaic virus fused with antigenic peptides of RABV) that can improve rabies vaccine protective properties due to the presence of RABV antigenic peptides[108,109]. Yusibov and team showed that using plants as tool to produce antigens to be used in vaccines provide several advantages including lack of contamination of other human pathogens, reasonable ease of genetic manipulation and economical production[108]. After purification steps, spherical particles formed from the recombinant AIMV CP was used to immunize mice and subsequently resulted in an antigen-specific humoral immune response, accompanied with VNA. Apart from that, nucleoside analogs are potential antiviral compounds because they can act as competitive inhibitors to interfere nucleic acid biosynthesis during replication of viral genome. For example, small molecule drugs such as ribavirin (which is an antiviral drug against respiratory syncytial virus) and favipiravir (i.e. antiviral drug against influenza) have been shown to be effective against RABV as well by acting as competitive inhibitors that interfere with nucleic acid biosynthesis during replication of viral genome[110–113]. Along with these, there is also potential use of these molecules in combination and/or as adjuvant (booster) to increase the efficacy or performance of the vaccine. However, further studies on the pathogenic mechanism of rabies virus and therapeutic approaches are still required to prevent the deathly infection following clinical manifestation. Having that said, integrated interventional strategy emphasizing human health and animal health is essential and via the collaboration between health authorities and the public, it is highly possible to control and prevent further spread of zoonotic disease like rabies.

Author Contribution

The literature review and manuscript writing were performed by R-AA and H-LS. H-LS and VL provided vital guidance and support as content expert and proofread of the writing.

Conflict of Interest

All the authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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