Chapter

Vaccines Targeted to Zoonotic Viral Infections in the Wildlife: Potentials, Limitations, and Future Directions

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Abstract

Currently, emerging viruses such as arboviruses, flaviviruses, filovirus, and *orthohepeviruses* are important agents of emerging zoonoses in public health, because their cycles are maintained in the nature or wildlife, involving hematophagous arthropod vectors and a wide range of vertebrate hosts as the bats. Development of blocking-transmission vaccines against these emerging viruses in wildlife will allow disease control at the veterinary field, preventing emerging human viral infections.

Keywords: vaccines, HEV, hantavirus, RABV, wildlife

1. Introduction

Emerging and/or re-emerging zoonotic viral infections affect significantly the human health in many geographic areas of the world, highlighting their potential to spread from animal reservoirs and their ability to evolve their virulence properties. While the transmission of viruses from wild animal species to human is intermittent or rare, vaccines against zoonotic viral infections should be focused in wildlife reservoirs in order to prevent human disease.

In this chapter, we will focus on the vaccination in wildlife reservoirs, such as bats, rodents, boars, and carnivores, which play an important role in transmission of three emerging zoonotic viruses, rabies virus (RABV), hantavirus, and hepatitis E virus (HEV), to domestic species and humans.

We discuss the main challenges for efficacy improvement of vaccines, considering the diversity of viral *quasispecies* and antigenic and immunogenicity variations, as well as the biosafety and logistic problems associated to the delivery systems in the wildlife scenery. Finally, other emerging lethal viruses and the current approach to the development of vaccines will be discussed.

2. Hantavirus

Hantaviruses belong to family *Bunyaviridae*; they are enveloped viruses and have a negative-sense RNA organized in three segments denoted as small (S), medium (M),

and large (L) [1, 2]. Unlike the other genera in the family, the hantaviruses are not transmitted by arthropods; their hosts are rodents and insectivores, and there is often an association of a type of virus with a host species [2]. In addition, new hantaviruses have been described in moles and shrews, as well as in bats, which increases the host range [3, 4]. Hantaviruses are maintained in rodent populations asymptomatic. Human infections are accidental (spillover), since for epidemiology and/or virus transmission cycle, the latter are a dead end (except for the case of Andes virus, where human-human transmission has been reported) [1, 5]. Transmissions among organisms occur by aerosol exposure, either by urine, feces, or saliva of infected animals, mainly [1].

In rodents, hantavirus infection has an acute phase (peak viremia) during first 2–3 weeks, with virus replication in target tissues and finally a persistent infection [1]. In humans, hantavirus infection can produce two presentations of the disease, depending on the type of virus with which it is infected: hemorrhagic fever with renal syndrome (HFRS) that occurs in Europe and Asia (Old World) mainly and the syndrome cardiopulmonary by hantavirus (HCPS) reported in the Americas (New World) [6]. It is important to note that HFRS can be caused by different viruses, the most common being Puumala and Dobrava in Europe and Hantaan and Seoul in Asia, while for the HCPS, the most common and lethal are *Sin Nombre* in North America and Andes in South America [7].

3. Vaccines against hantavirus

Currently, vaccine for humans approved by the FDA or any other institution for use in the USA or Europe is not available. An inactivated virus vaccine produced in mouse brain or in cell culture infected with Hantaan virus (HFRS vaccine) is applied in China and Korea. However, this vaccine may not be as effective against the other viruses that produce HFRS in Europe (Puumala and Dobrava) and not for those who produce HCPS (Sin Nombre and Andes) [7].

Considering the variety of hantaviruses and hosts, as well as the fact that there is no authorized or commercialized vaccine for human use that protects against all types of hantavirus, the development of a vaccine that can be applied to the natural reservoir (in this case rodents) is an option that should be considered.

When talking about vaccinating wildlife, the best option is the use of baits, which contain antigenic vaccine material, with stability under different environmental conditions. Since the capture and direct application of a vaccine would be unfeasible and the dispersion by a liquid or air (aerosol) constitutes a not selective administration, which might reach undesirable species and risk the risk of adverse effect, dispersion of the vaccine in species that had not been in contact naturally (in the case of attenuated vaccines) may not reach the desired species.

The viral target to which the vaccines are directed could be the Gn and Gc glycoproteins, which interact with the cellular receptor (integrins) for the entry of the virus into the cell [8]. We must consider the variability among the hantaviruses that can infect humans, since, as mentioned above, the vaccine applied in China and Korea runs the risk that, if it is not well designed, different vaccines against the hantavirus should be applied according to the region. Another point to consider in the design of this vaccine is the host variability that hantaviruses have as a group [6].

Mendoza et al. [9] described several characteristics desirable in the vaccine baits, such as having palatable baits for different species and stability of the vaccine in different environmental conditions among others. Development vaccine for animal use is faster in the process approval for commercial use. In this regard, the cost-benefit ratio is better, since the cost of production and distribution of a vaccine for veterinary use is lower, among other things [9].

The idea of One Health program, recently developed and adopted (due to the concern for all environmental changes that generate various human activities) [10], is the hypothesis that vaccination of natural reservoirs of host animals could stop the transmission of diseases to humans. Thus, vaccines targeted to wildlife reservoirs would affect the environment less and improve the health of the wild species in order to improve our health.

4. Rabies

Rabies is a zoonotic disease characterized by acute and lethal encephalitis, and it is caused by rabies virus (RABV), a *Lyssavirus* from *Rhabdoviridae* family. Rabies occurs after bites or scratches from rabid animal [11]. As a result of the increase in the human population (together with their companion animals) and the invasion of natural habitats and other anthropogenic activities, such as the traffic of wild species, there is also a high risk in the exposure to infectious pathogens coming from the wildlife. In the last decades, the knowledge of the diseases produced in wild animals that could produce spillover phenomena in the human population and zoonoses has been of special interest [12].

The majority of cases of rabies in humans are transmitted by dogs. It has been estimated that infection causes 60,000 cases per year, mainly in Asian, African, and American countries, [13].

There have been considerable efforts in vaccination campaigns in domestic fauna in the Americas, in order to control rabies virus transmission [13, 14]. However, wild mammals such as bats and carnivores play an important role in transmission to humans, particularly bats constitute the principal rabies reservoir in the Americas [15–17].

In Europe, during the 1960s, the only method used to contain wild rabies transmitted by red foxes was capturing and poisoning. However, it was an expensive and inefficient method in the long term [18]. One of the most cost-effective mechanisms to prevent the transmission of infection diseases is immunization. Since then, several approaches had been made for vaccination in the field with low effectiveness [18].

Nevertheless, the oral infection of mice coupled with the development of attenuated rabies strains gave the guideline for oral rabies vaccination (ORV) in wildlife [18–20].

Since the end of the 1970s, the ORV by means of baits was implemented in Europe using live attenuated rabies virus from 11 different strains, of which SAD Bern and SAD B19 were the most used [21]. This vaccination strategy resulted in the reduction of rabies by 80% and the eradication of the rabies disease in foxes in Western and Central Europe. In this regard, calendar of vaccination campaigns, the adequate distribution and density of baits, as well as the duration and follow-up of the ORV campaigns, were considered [21–23].

In the United States of America and Canada, the success story with ORV was replicated with the use of recombinant vaccines, employing the vaccinia virus (VRG) and a human adenovirus (ONRAB) that expresses the RABV glycoprotein [24]. In this case, the ORV programs were targeted at raccoons, gray foxes, and coyotes [25]. However, chiropters and carnivores are the main host of Lyssaviruses, and major spillover events have been detected from bats to carnivores [25].

As the European case, in Latin-American countries, the rabies control has been based in reservoir population reduction which means bat population reduction using anticoagulants [26]. Some approximations have been made for the development of ORV for bats taking advantage of the habit of constant grooming and close contact with other members of the population [27]; the recombinant vaccine is

mixed with petrolatum paste or glycerin jelly and applied topically on the back of a bat vector [28–30]. These works are carried out in controlled environments with promising results, obtaining survival rates between 80 to 70% in *Eptesicus fuscus* bats and 70 to 100% in *Desmodus rotundus* [28–30].

5. Hepatitis E

Hepatitis E is a liver disease caused by infection with a virus known as hepatitis E virus (HEV), globally considered as an emerging public health problem [31]. While hepatitis E is considered as self-limited liver disease in humans, it can evolve as a chronic liver disease, whose complications are responsible for 44,000 deaths in 2015 [31, 32]. HEV infection can be acquired by fecal-oral route or contaminated water and other routes less frequent, such as zoonotic via ingestion of undercooked meat or meat products derived from infected animals, transfusion of infected blood products, and vertical transmission to fetus during pregnancy or occupational exposition [33, 34].

Since the first identification of HEV in 1983 [35], it was thought that the virus was only limited to animal species. However, in the recent years, an increasing number of HEV infections in humans have been reported [36–39]. Thus, and based on several anti-HEV antibody serosurveillance studies [37–46], it is important to highlight that the worldwide HEV prevalence seems to be higher than reported, as outbreaks or sporadic in pregnant women and immunocompromised patients [46–49].

This virus has a single, positive-stranded RNA genome of 7.2 kb in length. The genome contains three open reading frames (ORF1, ORF2, and ORF3). ORF2 encodes for viral capsid, which have immunogenic properties [50]. Hepatitis E virus is an RNA virus classified within the *Hepeviridae* family, belonging to the genus *Orthohepevirus* [51]. Four species are recognized. *Orthohepevirus A* viruses has been identified in several mammals, such as swine, wild boars, mongoose, camels, rabbits, and humans. In this regard, swine is considered the main reservoir, and the consumption of uncooked pork products has been associated with the disease [52]. *Orthohepevirus* A is divided into eight genotypes of HEV (HEV-1 to HEV-8). HEV-1 and HEV-2 genotypes can infect humans, while HEV-3 and HEV-4 have been isolated from humans, swine, and wild boars, being HEV-3 the genotype with the highest worldwide distribution [53].

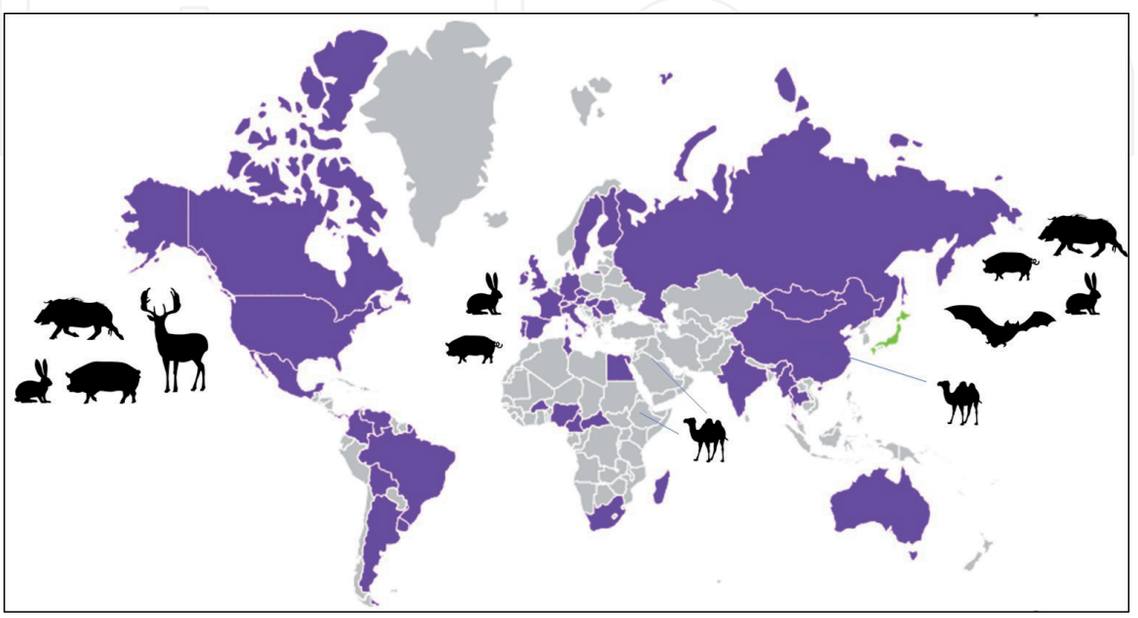

Figure 1.
Worldwide distribution of HEV and their reservoirs in the wildlife.

Genotypes HEV-5 and HEV-6 have been identified in wild boars, while HEV-7 and HEV-8 genotypes are isolated from camelids (**Figure 1**) [54]. *Orthohepevirus B* viruses infect mainly birds, *Orthohepevirus* C viruses infect rodents, and *Orthohepevirus* D virus has been restricted to bats [55]. Although a majority of species mentioned above are not in close contact with humans, some of them participate as intermediate hosts, thus causing infection in humans [56].

6. Vaccines anti-HEV

Vaccines represent the most effective prophylactic approach against several viral infections. Current WHO position considers vaccination against HEV [13], in order to prevent disease in high-risk groups such as pregnant women and immunocompromised individual. In this regard, anti-HEV recombinant vaccine, based on the capsid protein, was developed, showing efficacy of 88.5% [57]. In addition, a vaccine, anti-HEV 239 Hecolin (Xiamen Innovax Biotech), based in two epitopes from capsid (368–606 aa of ORF2), of genotype HEV-1, was only approved in China, with an efficacy of 86.8% [58, 59]. DNA anti-HEV vaccines have been developed (**Table 1**). In this regard, DNA vaccines have some advantages over use of attenuated viruses, besides to their stability at room temperature, making more affordable at veterinary field and the wildlife [60]. Thus, the delivery system for vaccination and genetic diversity of HEV must be considered in order to develop effective vaccines, especially in intermediate hosts such swine or wildlife reservoirs.

Finally, like the control strategies of wildlife rabies [65], the use of vaccine-laden bait delivery to intermediate hosts represents attractive alternatives useful to reduce the spread of HEV RABV circulation. While this approach is promising, it remains to be investigated.

Example	Immune response	Host	Reference
DNA vaccine ORF2 gene (1–660 amino acids, aa)	Anti-HEV IgG	Mouse	[61]
DNA vaccine based on HEV genes ORF2 (112–660) and ORF2(112–608), using papillomavirus pseudoviruses	IgG antibodies	Mouse	[62]
DNA vaccine based on complete ORF2 gene (1983 bp) in pVax plasmid	IgG-neutralizing antibodies	Rhesus monkey	[63]
Capsid protein/ORF2 HEV genotype 4	Anti-HEV IgG	Rhesus monkey	[64]

Table 1.
Experimental anti-HEV vaccines.

7. Zika vaccines

Zika virus (ZIKV) is an arthropod-borne virus (arbovirus), belonging to the family *Flaviviridae*, which was first isolated from a rhesus monkey in the Zika forest of Uganda in 1952 [66]. Since Brazil reported in 2015, the association ZIKV infection and microcephaly [67]; outbreaks and evidence of their transmission in many areas of Americas Africa and other regions have been reported [68]. Although ZIKV infection is considered as self-limited illness and minimally symptomatic for most individuals, it can be threatening for human health worldwide, in particular to unborn fetus [69].

Because arboviruses are often maintained in complex cycles involving vertebrates and blood-feeding vectors, not only humans are at high risk of ZIKV infection but also another species such as monkeys, domestic sheep, goats, horses, cows, ducks, rodents, bats, orangutans, and carabaos [69]. ZIKV infection has likely been present in bats since time. In this regard, anti-ZIKV antibodies with cross-reactivity to flaviviruses (yellow fever virus, West Nile virus, among others) were detected in bats from Uganda and Angola [70, 71]. Although it is unclear how ZIKV could circulate in bat populations, it is noteworthy that bats represent a competent reservoirs in wildlife, with potential for amplifying flaviviruses and, contributing thus in the sylvatic transmission of ZIKV [72]. In contrast, Bittar et al. [73] did not find serological and molecular evidence of past or latent arbovirus infections in captured bats from many areas of Brazil. Nevertheless, future studies are required to evaluate the role of bats as arbovirus reservoirs and to determine if these animal species are an important part of enzootic cycle of arboviruses [72].

Currently, there are no approved vaccines available to protect against infection. Unlikely to other antiviral vaccines, Zika vaccination must be approached mainly for the prevention of vertical transmission of the virus to the unborn fetus [74].

Finally, as long as a prophylactic vaccine is developed, it is important to consider that ZIKV is spreading rapidly into regions around the world where other flaviviruses, such as dengue virus (DENV) and West Nile virus (WNV), are endemic. In this regard, Zika virus is closely related to other flaviviruses, and cross-reactive antibody has the potential to exacerbate secondary flavivirus infections through antibody-dependent enhancement (ADE), leading to more severe forms of flavivirus disease [75].

8. Ebola and SARS-CoV vaccines

Ebola is a viral illness caused by *Ebola virus*. Five species of the genus *Ebolavirus* from Africa have been recognized, *Zaire ebolavirus* (ZEBOV), *Sudan ebolavirus* (SEBOV), *Cote d'Ivoire ebolavirus* (CEBOV), *Bundibugyo ebolavirus* (BEBOV), and *Reston ebolavirus* (REBOV), all belonging to *Filoviridae* family. Viral replication have a lethal nature, which involve necrosis of several lymph organs, kidneys, liver, testes, and ovaries; changes in vascular permeability; activation of the clotting cascade; and damage in platelets, among others [76]. Although the natural reservoir of the virus is unknown, it is assumed that bats represent a natural reservoir in the wildlife species, without causing disease [77], highlighting extensive coevolution of Ebola virus and bats, over time [76]. Therefore, feasibility of Ebola vaccine must focus on the prevention of Ebola in endemic areas as well as usage during sporadic outbreaks in humans [78]. Ideally, candidate vaccine must be able to confer interspecies cross-protection against SEBOV, BEBOV, and ZEBOV [76].

With respect to SARS-CoV, the development of a vaccine that is applied to wild vectors is a little more complex. Bats have been proposed as potential reservoirs, and there may be an intermediate host, such as civets [79]. However, there are still epidemiological studies that help us understand the dynamics of animals, *coronavirus*, and humans, in order to establish the best vaccination strategy, since not all zoonotic disease vector vaccination can be the solution.

9. Conclusions

Hantavirus, RABV, HEV, ZIKV, Ebola virus, and SARS-CoV are currently considered as emerging infectious pathogens to humans, whose reservoirs are in wildlife animals. While the transmission of these viruses from wildlife reservoirs to human

is rare, it is important to develop control strategies in order to reduce the substantial impacts on human health and agricultural production. In several cases, such as rabies disease the vaccines targeted to wildlife reservoirs, represent a control measure friendly with the environment, in virtue of they help to the conservation of healthy habitats with available niches and wild prey for bats, avoiding the migration of these species to another areas.

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