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Ebolavirus Vaccines for Humans and Apes

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Abstract

Due to high case fatality proportions, person-to-person transmission, and potential use in bioterrorism, the development of a vaccine against ebolavirus remains a top priority. Although no licensed vaccine or treatment against ebolavirus is currently available, progress in preclinical testing of countermeasures has been made. Here, we will review ebolavirus vaccine candidates and considerations for their use in humans and wild apes.

I-Introduction

Ebolavirus infects both human and non-human primates (NHP). To date five different ebolaviruses species have been isolated; Zaire (ZEBOV), Sudan (SEBOV), Cote d'Ivoire (CIEBOV), Bundibugyo (BEBOV) and Reston (REBOV). While REBOV does not cause disease in humans and CIEBOV has caused only one documented non-lethal infection, the other three species have been associated with large human outbreaks of Ebola hemorrhagic fever (EHF) disease with a case fatality proportion ranging from 25 to 90%. All five ebolavirus species are lethal in the NHP model of ebolavirus infection ^{1,2}.

In order to better understand EHF pathogenesis and to design treatments against this lethal disease, mouse ³ and guinea pig ⁴ animal models of infection has been developed, but the NHP model most closely mimics the clinical symptoms of human disease ^{5–7}. Therefore, this is the preferred model for identifying vaccine or therapeutic regimens for licensure.

This review will focus on the current status of vaccine development, strategies for targeting at-risk populations, and identification of gaps that need to be filled in order to advance vaccine candidates for human use. In addition, the considerations for immunization of wild great apes will be discussed.

II-Ebolavirus Vaccine for Human

Existing vaccine candidates

The first indications that protective immunity could be mounted against the highly pathogenic ebolavirus arose from protection against ebolavirus challenge in rodents with inactivated viruses ⁸ and later with DNA vaccination ^{9,10}. Support for higher species immunity was provided by studies showing both humoral and cell mediated immune responses against ebolavirus in human survivors after natural infection ^{11,12}. The final proof that a vaccine could protect primates against ebolavirus infection was obtained using a DNA

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vector prime, replication-defective recombinant adenovirus type 5 (rAd5) vector boost regimen, or rAd5 alone, each expressing ebolavirus glycoprotein (GP) and nucleocapsid protein (NP) in macaques^{13,14}. Of note, it was later demonstrated that rAd5 encoding GP alone is sufficient to induce protection against ebolavirus challenge^{15,16}. Currently, several successful vaccine regimens demonstrate protection of NHP. A single immunization with a replication competent vesicular stomatitis virus vector (VSVΔG) encoding GP from ZEBOV (GP[Z])^{17,18} and a bivalent rAd vector (CAVax) encoding GP from both SEBOV and ZEBOV protect against ZEBOV challenge; the bivalent vaccine given in two shots also protected against SEBOV challenge¹⁹. Uniform protection against ZEBOV challenge was also achieved after three immunizations with RIBI-adjuvanted virus like particles (VLP) comprising ebolavirus GP, VP40 and NP²⁰ or after two injections of a human parainfluenza virus type 3 (HPIV) vector encoding GP[Z]²¹.

Vaccination of at risk populations

The ideal characteristics of an ebolavirus vaccine will be influenced by the nature of the population targeted for protection (Table 1). At-risk populations such as medical personal or lab scientists will require long-term immunity against ebolavirus infection given that the potential for virus exposure occurs over an undefined time interval. Prime-boost regimens might be required to achieve this goal since this method elicits both humoral and cellular response of higher magnitude and quality than single-shot vaccination^{22,23}. Generation and maintenance of a sufficient pool of functional ebolavirus-specific T cells is important since CD8 T cells are required for efficient ebolavirus clearance, as demonstrated by CD8 T-cell depletion studies¹⁶ and by cross protection in the absence of antigen-specific antibodies²⁴. Although humoral responses are not sufficient for complete protection against Ebola virus infection^{16,25,26}, antibody titer against Ebola GP correlates with protection after rAd immunization²⁷. As such, antibodies may be a surrogate measure for cell-mediated immunity, and may also contribute to limiting virus spread as indicated by a recent study illustrating a protective effect of antibodies in the context of a host immune response to virus challenge²⁸.

The link between prime-boost vaccination and durability of immunological memory for ebolavirus was illustrated by the finding that the immune response against ebolavirus GP generated by DNA immunization in macaques was boosted with rAd5 a full year after the last DNA injection²⁴. In addition, protective immunity was generated for at least 3 months after the last inoculation in macaques immunized with a DNA/Ad5 prime/boost regimen encoding ebolavirus GP¹³ while uniform protection after a single-shot immunization has only been reported 4 weeks after vaccination.^{14–21}

In addition to the need for long-term immunity, an ebolavirus vaccine that can also protect against sudden outbreaks would be useful for at-risk populations in ebolavirus endemic areas of sub-Saharan Africa. The identification in 2007 of a new species of ebolavirus, Bundibugyo, emphasizes the need for an ebolavirus vaccine to protect not only against current species but also against emerging ones²⁹. It is encouraging that some cross protection has been demonstrated. Macaques immunized with a DNA prime, rAd5 boost regimen encoding GP[Z] all survived BEBOV challenge²⁴. In another study, partial protection against BEBOV disease was achieved by a rVSV-GP[Z] vaccine, but little or no protection following vaccination with rVSV-GP[CI]³⁰. Although ebolavirus IgG antibody cross reactivity in humans is wider than initially thought³¹, cross-reactive neutralizing antibodies have not been demonstrated as yet. Therefore it will be important to identify and optimize cellular immune responses needed for cross-protection.

The success of multiple vaccine candidates in macaques is a promising start for the development of a human vaccine. Since ebolavirus vaccine candidates will undergo FDA

approval using the “Animal Rule” (discussed in this issue), vaccine efficacy performed in NHP will be linked to immune correlates of protection that should be achieved in humans²⁷. Gene-based ebolavirus vaccines have been tested in Phase I human clinical trials with encouraging results. The immunogenicity of ebolavirus vaccine candidates has been demonstrated in two separate Phase I trials. During the first clinical trial, a DNA vaccine encoding GP and NP from ZEBOV and GP from SEBOV was shown to be safe and immunogenic³². Similar results were obtained in a second clinical trial testing the safety and immunogenicity of a single injection with rAd5-GP[Z] and rAd5-GP[S]³³. Both vaccines were demonstrated to be safe and immunogenic in humans. Although the CD8 T-cell response was modest for both vaccines, reaching a maximum rate of about 30%, DNA immunization induced humoral and CD4 T-cell responses against at least one of the three antigens (NP[Z], GP[Z], GP[S]) in all vaccinees. Similar to DNA immunization, rAd5 at the highest dose tested induced antibodies against either GP(Z) or GP(S) in all vaccinees, and CD4 T cells were generated in most subjects (82% against GP(S) and 64% against GP(Z)). Since the immune correlate of protection in NHP for these vaccines was found to be antibody-based²⁷, the induction of antibody responses by both vaccines in humans is an important first step toward review using the Animal Rule. However, this regulatory pathway is as yet untested for vaccines so licensure of an ebolavirus vaccine for humans is likely several years away.

Ebolavirus vaccination during outbreaks

Most natural ebolavirus outbreaks occur in remote areas of Africa. In addition, due to the unpredictability of outbreak timing and location, it is difficult to anticipate the population at risk for ebolavirus infection¹. As a result, it is probable that an ebolavirus vaccine will be used after the start of an outbreak, when the at-risk population can be more accurately defined. In the macaque model of ebolavirus infection, partial protection has been reported with vaccine administration up to 30 min post challenge³⁴ or full protection when given 4 weeks prior to challenge^{14–21}. Whether prophylactic vaccination can elicit protective immunity against ebolavirus earlier than 4 weeks needs to be tested. Similarly, the window of treatment for protection by a therapeutic vaccine is unclear. Although prophylactic vaccines rely on induction of adaptive immunity for ebolavirus clearance, protection by viral-vector vaccines administered minutes after exposure more likely results from a strong vaccine-induced innate immune response since the time needed to develop adaptive immunity is on the order of many days³⁴. As a result, administration of therapeutic vaccines after the onset of symptoms should be considered carefully, as fatal cases of ebolavirus infection are associated with higher levels of circulating pro-inflammatory cytokines and chemokines prior to death, and vaccine stimulation of inflammation could contribute to immune dysregulation that is associated with EHF fatalities³⁵. Since prophylactic NHP vaccines show uniform protection within weeks, the vaccine strategy most likely to provide human benefit in an outbreak setting would be based on rapid vaccination of healthy subjects at risk of exposure during an outbreak. For subjects already infected but prior to the onset of symptoms, an ebolavirus post exposure prophylaxis strategy that includes both passive and active immunization similar to human rabies treatment could be considered³⁶, especially if the treatment is started early after exposure.

III-Vaccination of wild primates

Considerations for potential ape vaccines

Although habitat loss and poaching are critical contributors to great ape population decline, infectious diseases including viral respiratory infections and EHF are also proposed to be risk factors for wild apes³⁷. Ebolavirus outbreaks in humans have been associated with handling NHP carcasses in Gabon and Republic of Congo, some of which have tested

positive for ebolavirus antigens or gene fragments³⁸. While some population-based studies aimed to estimate the impact of ebolavirus in great apes have been carried out in central Africa^{39,40}, to date there are no comprehensive studies demonstrating the contribution of EHF compared to other pathogens in great ape mortality. However, anticipating the potential threat of ebolavirus in ape survival, vaccination of wild apes is under consideration. Since there are very few reports of attempts to immunize wild apes⁴¹, vaccination against ebolavirus for gorillas and chimpanzees requires a careful assessment to insure that such intervention would be beneficial, given that vaccine-induced immunity in laboratory macaques does not necessarily predict the response in wild apes. As with vaccines considered for human use, it will be necessary to generate safety and immunogenicity data for ebolavirus vaccine candidates in chimpanzees, gorillas or bonobos before considering widespread wild ape immunization. The ability to deliver a controlled dose, the number of doses required for protection, the length of protection after immunization and a means for follow up to demonstrate benefit and absence of risk is needed. Considering current bans on invasive biomedical research experiments with these endangered animals in several countries, there may be challenges to conducting such studies.

Vaccine administration routes

An ebolavirus vaccine for wild apes could be delivered by darting or oral baiting. Darting is preferable if the aim is to protect a selected population, for instance a known habituated population with economic or scientific interest, or an isolated population in danger of disappearance. Darting has been used to anesthetize⁴² wild gorillas in the past without detrimental side effects, demonstrating the feasibility of the procedure⁴³. In addition, more recent delivery systems show delivery at a greater distance from the target animals⁴⁴. If such systems can be adapted to ape immunization, they would greatly decrease the risk for the darter as well as potentially reduce exposure of wild apes to human diseases.

Vaccination of large populations of animals would require the use of an oral vaccine. Oral baiting has been successfully used for eradication of rabies from foxes in Europe⁴⁵, but this approach has never been tested for gorilla immunization. Furthermore, since the vaccine will be exposed to a tropical environment, the stability of the formulation will need to be assessed. For live vector vaccines, viral shedding could pose a safety issue. The impact of the vaccine on non-target wildlife, which also consumes the bait, needs to be considered.

An alternative approach to human and ape vaccination would be to directly immunize species of fruit bats which are thought to be the reservoir for ebolavirus^{46,47}. Due to the large size of the bat population, unconventional vaccine strategies such as the application of vaccine in a vaseline formulation on the back of carrier bats (Figure 1), as previously described for rabies immunization^{48,49} could be implemented.

Ethical questions

Great apes are in danger of extermination mainly because of habitat loss, hunting and infectious disease. An ape vaccination program should be focused on pathogens with demonstrated impacts on the target population. Endeavors for wild great ape immunization against any infectious disease should be driven by a proven benefit of intervention that surpasses the risk of the vaccination. Current estimates of the impact of EHF as a cause of ape decline are based on ecological survey or mathematical modeling, with some limitations in precision since population density estimates are based on nest counts that do not always reflect changes in a population^{50,51}. Despite an apparent loss of a significant number of great apes in Gabon and the Republic of Congo and more than 5 years of continuous and active surveillance in these countries, only 37 ape remains have ever been recovered, with evidence of prior ebolavirus infection in less than half of them^{39,52–54}. In the meantime, an

unexpected discovery of 125,000 gorillas, a far larger population than previously estimated, have been reported in the northern of Republic of Congo⁵⁵. Therefore, there is a great need for prospective epidemiological and ecological studies with improved laboratory screening for all potential lethal pathogens in great apes to establish a baseline estimate of ape populations and to determine the relative contribution of major threats.

IV-Discussion

Due to their ease of large-scale production, several gene-based vaccine platforms including rAd, CAdVax, VSV and HPIV 3 have been developed. However, pre-existing virus vector immunity as well as safety of replication competent vectors remain a concern for their use in humans. Although VLPs are not affected by pre-existing immunity, they require a longer vaccination regimen, and large-scale production and purity may be more difficult to achieve than with gene-based vaccines^{1,2}. The use of low seroprevalence viral vectors will help to circumvent issues of pre-existing vaccine vector immunity^{56–58}. Similarly, the development of robust, cost effective large scale manufacturing technology for VLPs will be needed⁵⁹.

The choice of vaccine candidates may differ depending on the target population and setting (Table 1). During ebolavirus outbreaks, vaccines able to generate rapid protective immunity with a single dose would be preferred. Vaccination of populations with a potential risk of infection in the future will require vaccines that generate broad (multiple ebolavirus species) and long term protection. Although great strides have been made in the success of cross-protective vaccines, durability of protection has not received as much attention and requires additional research. Finally, identification of immune correlates of protection in NHP and humans is needed for any candidates considered for licensure using the Animal Rule. An ebolavirus vaccine strategy intended for great apes requires similar testing and ethical review, with the same stringency afforded to protection of humans.

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Highlights

Successful EBOV vaccine candidates have been identified in preclinical studies

Gene-based EBOV vaccines are immunogenic in human clinical trials

An ideal EBOV vaccine will give rapid and durable immunity against multiple EBOV species

The role of EHF relative to other pathogens in great ape mortality should be assessed

A vaccine strategy for great apes requires strong scientific justification and ethical review

Figure 1. Impact of vaccination of bats or apes on human Ebola outbreaks

A-Vaccination of apes could prevent human outbreaks caused by NHPs to human transmission but is associated with logistical and ethical challenges. An alternative approach would be to vaccinate bats to protect both humans and wild apes from ebolavirus outbreaks. B-Unlike strategies for apes that would need to be vaccinated individually, broad-based bat immunization could be achieved through the use of carrier bats whereby (1) bats are captured and a vaseline formulation containing the Ebola vaccine is applied prior to release. (2) Close contact between carrier bats and other bats in the targeted colony results in (3) spreading of the vaccine which is then ingested when bats clean themselves.

Table 1
Requirement and restriction for an Ebola vaccine for human or apes
Desirable vaccine properties may differ between primates species and exposure conditions.

	Number of doses	Cross-protection against new species	Duration of protection	Interval for protection	Vectors replicative properties	Route of immunization
Epidemic settings	1	Desirable but not necessary	severals weeks [duration of outbreak]	As soon as possible (within days)	Desirable but not necessary (Human) Replication deficient (NHPs)	No restriction (Human) Oral or IM (NHPs)
Endemic setting	1 for humans 1 for NHPs	Yes [desirable]	long term [several years]	No time restriction	No restriction (Human) Replication deficient (NHPs)	No restriction (Human) Oral or IM (NHPs)