A respiratory vaccine for Ebola: close to a reality?

“The Ebola virus ... held the world’s attention for most of 2014 as it caused one of the most widespread outbreaks of Ebola virus disease ever recorded.”

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The Ebola virus, a single-stranded RNA virus encoding seven structural proteins and two nonstructural proteins, held the world’s attention for most of 2014 as it caused one of the most widespread outbreaks of Ebola virus disease (EVD) ever recorded. EVD generally occurs through compromised mucous membranes and breaks in the skin after contact with bodily fluids of infected humans, handling and consumption of infected animals and needle-stick injuries. The virus immediately wears down the body’s first line of defense by infecting mucosal monocytes, dendritic cells and macrophages and using them for transit to secondary lymphoid organs, lungs, liver and other ancillary sites of virus replication [1]. The length of the incubation period (2–21 days), nonspecific symptoms (fever, headache, nausea, diarrhea), poor sanitation, insufficient medical facilities and lack of approved vaccines and therapeutics all contribute to misdiagnosis and ultimately spread of the disease [2].

Vaccination, second only to purified water, is the most effective global public health intervention for saving lives and promoting good health [3]. Since the first

vaccine was discovered over two centuries ago, several major diseases including smallpox, diphtheria, tetanus and poliomyelitis have been controlled and in some cases eradicated. Breakthroughs in immunology, molecular biology and biochemistry in the last 25 years produced more than half of the vaccines used during the last century as vaccine development is often the first strategy for combating new, previously undescribed infectious diseases. This is reflected in recent efforts to combat EVD as vaccines are currently the only countermeasures with sufficient data to support clinical testing [4].

Initial evaluation of the immunogenicity of a vaccine candidate is often performed by direct injection into the muscle since it is very straightforward, ensures that the entire dose is given and induces strong systemic immune responses that are easy to assess *in vivo*. Candidates that fail to induce strong systemic immune responses by this route of administration are often re-evaluated with prime-boost strategies, reformulated with adjuvant or not pursued further. Immunization through alternative routes such as the respiratory tract induces

KEYWORDS

• adenovirus • Ebola • formulation
• mucosal • nasal • vaccine • VSV

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protective immune responses at the mucosa in addition to systemic immune responses that are sometimes lower than that achieved by injection. It is for this reason that the injectable form a vaccine is used as the ‘gold standard’ against which to compare the potency of mucosal vaccine platforms during early development.

In late September 2014, three vaccine candidates identified by the WHO and other regulatory agencies entered clinical testing. Each candidate was developed for Ebola Zaire, the most lethal strain of the virus responsible for the current outbreak. They were all developed in an injectable format. While this, as suggested above, is appropriate for the initial evaluation of the immunogenicity of a vaccine, the injectable platform poses several significant issues that complicate implementation in regions where Ebola vaccines are needed the most. Administration of these vaccines in large clinical trials requires the presence of trained medical personnel and infrastructure capable of handling volumes of biomedical waste safely. In regions such as those where the current outbreak continues, the WHO has found that training programs and precautions to prevent infection from accidental needlesticks increase the cost of vaccination campaigns by more than 25% and, despite having these programs in place, they report that 50% of the injections given in these regions are unsafe with 1.3 million early deaths resulting from hepatitis and HIV acquired by needle and syringe accidents [5]. In addition, results from some fast track clinical trials suggest that multiple injections in a prime-boost strategy may be necessary for protection from Ebola [6–8]. This coupled with generalized fear of injection, mistrust of Western medicine, stigma associated with EVD and long distances that exist between treatment centers and residential communities make large-scale vaccination campaigns for Ebola implausible [9,10].

Intranasal administration is an attractive option for each of the Ebola vaccine candidates. The respiratory tract is easily accessible and facilitates direct entry of intact antigen in the circulation and the draining lymph nodes, which would prime a line of defense against this deadly pathogen on a systemic level and at localized sites of entry [11]. Recent progress in respiratory delivery technology has led to the development of compact, single use, disposable devices that can easily be used for self-administration [12]. This alone will improve compliance rates in

immunization campaigns and significantly reduce expenditures associated with disposal and handling of waste. The Ebola vaccines entering the clinic have all been formulated to remain stable at ultralow temperatures (-80°C), requiring maintenance of a cold chain that cannot be supported by standard refrigeration/freezer systems. Formulations of currently marketed biologics for nasal administration support stability at refrigerated and ambient temperatures [13,14]. Several formulations that support stability of recombinant adenoviruses (the platform of two of the vaccine candidates) for nasal administration have been described [15,16]. Information about the stability of attenuated vesicular stomatitis V viruses (VSV), the third vaccine platform is limited and should be evaluated further since storing this vaccine at ultralow temperatures currently poses a significant administrative challenge and additional expense and delay in setting up clinical trials in Africa [17].

One of the most common limitations to developing a product for nasal administration is that the dose administered often must be adjusted for loss due to clearance mechanisms and the small volume that the nasal cavity can accommodate ($\sim 150\ \mu\text{l}$ in adults). Natural infections with adenoviruses and VSV occur in the respiratory tract [18,19], suggesting that clearance can be overcome by natural tropisms of each virus. Each of these vectors has been shown to have inherent adjuvant properties that boost unique facets of the immune response. This is important in the context of developing vaccines for nasal administration since many of the standard adjuvants have not been found to be efficacious when administered nasally while others have been associated with serious adverse effects such as a Bell’s palsy-like syndrome [13].

So is a nasal vaccine for Ebola a pipedream or can it be a reality? The 2014 outbreak in west Africa has heightened global awareness of the palpable lack of effective vaccines and therapeutics for Ebola virus disease. Vaccine candidates selected for fast track clinical trials, initially developed as injectable products that require storage and shipment at ultralow temperatures, will present significant challenges as testing begins in west Africa. Recent work showing that a single dose of a formulated respiratory vaccine fully protected nonhuman primates from a lethal dose of Ebola illustrates that the vaccines currently in the clinic could be retooled in a platform that would improve compliance, lower the

cost of mass immunization considerably and effectively eliminate infection and spread of Ebola in developing and industrialized nations.

Among the mucosal immunization routes, the nasal route has historically been deemed most acceptable for all ages, both genders and in all geographic regions and cultures [20]. This is reflected in the fact that within the last decade, 40 products marketed for nasal administration entered the global market, of which five are for vaccination [21]. Each of the vaccine vectors currently in clinical testing have been previously evaluated for intranasal delivery of recombinant antigens. Recombinant adenoviruses have been evaluated as a respiratory vaccine for Ebola [22,23]. VSV vectors have been evaluated for nasal immunization against HIV [24,25]. Formulations that stabilize recombinant adenovirus at ambient temperatures and improve the immune response have been developed for intranasal administration and could be implemented in products currently in the clinic [15–16,26].

However, these features should be considered before current Ebola vaccines enter the final stages of testing, making this a perfect example of how drug formulation technology can offer a tangible solution to a very serious global public health issue.

Disclaimer

The content and the views expressed in this manuscript are those of the authors and do not necessarily represent the official views of the National Institute of Allergy and Infectious Diseases of the National Institutes of Health.

Financial & competing interests disclosure

This work was funded by the National Institutes of Health NIAID Grant U01AI078045 (MA Croyle). The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

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