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A Long-Lasting, Single Dose Nasal Vaccine for Ebola: A Practical Armament for an Outbreak with Significant Global Impact

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Abstract

In response to the severity and scale of the 2014 Ebola outbreak, several experimental vaccines were granted fast-track status for clinical testing. While they may provide long-lasting protection from Ebola, they are, in their current states, far from optimal for populations that need them the most. In this context, nasal immunization addresses the a) immune response required at the mucosa where Ebola initiates infection, b) needs of a population in terms of cost and compliance and c) potency of each platform as they contain viruses that naturally infect the respiratory tract. Understanding the attributes of nasal immunization and its application will lead to potent vaccines that can effectively end Ebola and other emerging infectious diseases in developing and industrialized countries.

Keywords

Ebola; nasal vaccine; clinical trial; developing country; adenovirus; VSV; formulation

March 23, 2014 marked the start of the largest and most aggressive outbreak of Ebola virus disease (EVD) since its discovery nearly 40 years ago. A two-year old child in Guinea, contracting the disease after exposure to an infected fruit bat, was the source for person-to-person spread of EVD into West Africa, a region never before experiencing Ebola [1]. While the exact number of infected individuals remains unclear with many cases left unreported due to unvalidated surveillance systems, fear of authorities and stigma associated with EVD, this outbreak assumed global significance during the summer months when cases increased exponentially as the disease entered major metropolitan centers and confirmed cases appeared in the U.S., Europe and Australia. At this time, the World Health Organization (WHO) declared the situation “an international public health emergency”, making the need for effective therapeutics and preventative vaccines high priority. In

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September, officials met to discuss the most advanced vaccine candidates with respect to current supply, large-scale production, regulatory issues and resources to support clinical testing. Soon after, several candidates entered Phase I trials [2].

One candidate is a recombinant chimpanzee adenovirus serotype 3 (cAd3) expressing sequences for the glycoprotein (GP) coating the surface of two the most lethal strains of Ebola: Zaire, the virus involved in the current outbreak [3], and Sudan. In a Phase I trial, each of the 20 participants developed antibodies against Ebola GP four weeks after receiving an injection of the vaccine but the T cell response was variable [4]. In a separate Phase I trial with a cAd3 virus expressing only Ebola Zaire GP, antibody and T cell responses of 60 subjects fell below those of macaques protected from Ebola by the same vaccine [5]. No safety concerns were identified in either trial. The third candidate, a genetically engineered version of vesicular stomatitis virus (VSV) in which the gene for the outer G protein is replaced with the gene for the Ebola Zaire GP, has been studied as a therapeutic vaccine. When given 20-30 minutes after exposure to Ebola, it protected 50% of a primate population [6]. It has been given to a laboratory technician after a needle-stick injury with a syringe containing concentrated Ebola. Although she survived with no detectable symptoms of EVD, it remains unclear if she was actually infected with Ebola or protected by the vaccine [7]. The Phase I trial with this candidate was put on temporary hold when volunteers reported joint pain after injection [8]. Although each of these vaccines have demonstrated the potential for protection from Ebola and entered Phase 2 testing in West Africa [9], it is clear that they had been developed for use in industrialized countries and, in their current states, are far from optimal for populations that need them the most [10]. Thus, future efforts to refine these vaccine candidates and identify others should concentrate on the nature of the pathogen, target population and the vaccine platform.

Pathogen

Prior to 2013, 23 outbreaks of EVD were recorded. The Zaire strain has been responsible for 85% of the deaths from EVD [11], making it a logical target for vaccine development. Early studies identified the glycoprotein as the antigenic target as vaccines containing other virus components were not protective [12]. Pre-clinical evaluation of Ebola vaccine candidates has identified immunological requirements for protection against Ebola [13-15], which are vital for the design of clinical trials given that conventional evaluation of vaccine efficacy is not feasible.

EVD is contracted 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 [6]. Upon entering the mucosa, Ebola infects resident monocytes, macrophages and dendritic cells, re-directing this first-line defense from fighting infection and using them to travel to and infect lymph nodes, spleen, vasculature, liver, lungs, adrenal glands and other organs [6]. The optimal vaccine candidate must prime these cells to quickly recognize Ebola and prevent its entry in the circulation. Administration of an Ebola vaccine to the respiratory tract induces a systemic immune response comparable to the same vaccine given by injection on a somewhat shorter timescale [16]. Intranasal administration also

primes cells at mucosal sites while injection, the method of administration of all candidates in clinical testing, does not.

Population

The ideal characteristics for an effective Ebola vaccine should be greatly influenced by the population where infections are endemic. Injections are the most common reasons for iatrogenic pain and deter many from immunization. This, coupled with the fact that Ebola outbreaks occur in regions wrought with distrust of Western medicine, political unrest and the poorest physician-to-patient ratios in the world pose a significant barrier to implementation of an injectable vaccine. A nasal immunization platform would bolster compliance since it is needle-free and can be administered by a familiar caregiver or the patient.

A single respiratory dose of an adenovirus-based Ebola vaccine offered long lasting protection from lethal infection to primates [17]. To date, the longevity of a single dose of the injectable VSV platform has been established with moderate success in rodent models of EVD [18]. Recently it was shown that the cAd3 vaccine affords modest protection several months after injection and that prime-boost schedules may be necessary [3]. In a country where residents travel long distances for basic healthcare needs and where fear and stigma of disease force individuals to retreat from communities, a single dose, long lasting vaccine is necessary since repeated trips to vaccine clinics for prime-boost immunizations are inordinate. Injectable vaccine campaigns also create significant waste. For example, 19.5 million syringes (130,000 kg sharps waste and 72,000 kg non-hazardous waste) were generated in one month during the Philippine Measles Elimination Campaign [19]. Waste at this scale poses a significant threat for transmission of HIV and hepatitis to healthcare workers, medical waste handlers and communities where Ebola is endemic [20]. Recent advances in respiratory delivery devices have resulted in compact, single-use disposable systems that present minimal threat for disease transmission [21].

Platform

Vaccines entering clinical testing are recombinant viruses with inherent and unique abilities to prime an immune response against Ebola. Natural infection by the viruses used in these vaccines occur by the nasopharyngeal route, giving them enhanced affinity for the respiratory tract and making the need for adjuvants to boost immune responses unnecessary [22,23]. This is extremely important since known adjuvants have not been useful in priming immune responses in the respiratory tract and have been associated with serious side effects, some requiring market withdrawal [24].

One limitation of intranasal immunization is the potential for antigen delivery to the central nervous system through the olfactory region and subsequent development of neurological disorders [25]. While this could be significant if the current vaccine candidates were retooled for intranasal administration, the VSV vaccine has been shown to lack neurovirulence and associated symptoms in non-human primates after direct intrathalamic injection [26]. Moderate gene expression in the olfactory bulb without further dissemination to other regions of the brain after intranasal administration of adenovirus has only been

observed in rodents [27,28]. It is currently not clear if these effects could be seen in humans and are currently under evaluation.

Most vaccines are unstable at ambient temperatures and require refrigeration, contributing to 40% of the cost of a vaccine campaign [29]. Despite the efforts of the WHO to provide proper storage equipment, temperatures vary dramatically from site to site in undeveloped cultures [30]. As a result, UNICEF experienced an increase in expenditures (\$139 million U.S.) from loss of vaccines during transport and storage in 2005 alone [31]. In their current format, vaccines headed to West Africa for clinical testing are stable when stored at ultra low temperatures (-80°C), much colder than standard issue freezers. Establishing this sort of cold chain infrastructure in Africa will be expensive and cumbersome and may delay the start of clinical testing [32]. This is somewhat surprising since there is a significant body of literature describing methods for stabilizing adenoviruses for significant periods of time in both injectable and intranasal platforms[33,34]. In contrast, the physical stability of attenuated VSV is understudied, making this a significant area of study as this candidate progresses in the clinic [35].

Currently, 23,729 cases of EVD have been reported in the outbreak that started in 2014. EVD has claimed 9,604 lives [36]. Five percent of this total (495 cases) involved medical staff at Ebola treatment centers. These numbers have heightened global awareness of the desperate need for an Ebola vaccine. Moving the current vaccine candidates in the clinic required pharmaceutical companies, regulators, international aid organizations and governments to work together at an unprecedented speed and in an equitable manner that minimizes harm from unforeseen side effects. It is likely that all of the candidates will benefit people in regions where EVD is endemic, however, the current platforms should be refined as nasal vaccines to improve potency and address the needs of specific patient populations. The recent report demonstrating durable protection from a lethal dose of Ebola after a single dose of a recombinant adenovirus vaccine in primates clearly demonstrates that a long-lasting nasal Ebola vaccine is conceivable [17]. 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 [37]. Aside from the fact that it would improve compliance and greatly minimize cost of vaccination campaigns, there is evidence that respiratory/nasal immunization can provide rapid, long-lasting protection at mucosal sites, where Ebola exposure occurs. Changes in the delivery route and formulations to enhance long-term stability of medicinal products can be done throughout early and moderate stages of clinical testing, making an intranasal form of an Ebola vaccine highly possible [38]. The most direct approach to this would be inclusion of formulation scientists with extensive experience in the stabilization and delivery of recombinant vaccines to the respiratory tract in discussions with clinicians and regulatory agencies as the current trials progress. What will result is something capable of ending the turmoil caused by Ebola with a single, deep breath.

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Biography

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References

Papers of special note have been highlighted as:

* of interest

** of considerable interest

1. Marí Saéz A, Weiss S, Nowak K, Lapeyre V, Zimmermann F, Düx A, Kühl HS, et al. Investigating the Zoonotic Origin of the West African Ebola Epidemic. *EMBO Mol. Med.* 2014; 7(1):17–23. [PubMed: 25550396]
2. Maurice J. WHO Meeting Chooses Untried Interventions to Defeat Ebola. *Lancet.* 2014; 384(9948):e45–e46. [PubMed: 25247221]
- 3*. Stanley DA, Honko AN, Asiedu C, Trefry JC, Lau-Kilby AW, Johnson JC, Hensley L, et al. Chimpanzee Adenovirus Vaccine Generates Acute and Durable Protective Immunity Against Ebolavirus Challenge. *Nat. Med.* 2014; 20(10):1126–1129. [PubMed: 25194571] [One of the first studies to demonstrate long lasting protection from lethal Ebola infection with a cAd3 vector based vaccine in primates.]
- 4**. Ledgerwood JE, DeZure AD, Stanley DA, Novik L, Enama ME, Berkowitz NM, Hu Z, et al. Chimpanzee Adenovirus Vector Ebola Vaccine - Preliminary Report. *N. Engl. J. Med.* [ePub ahead of print (Nov. 26, 2014). The first report of results from a Phase I human clinical trial on a fast track Ebola vaccine during the 2014 outbreak.]
- 5**. Rampling T, Ewer K, Bowyer G, Wright D, Imoukhuede EB, Payne R, Hartnell F, et al. A Monovalent Chimpanzee Adenovirus Ebola Vaccine - Preliminary Report. *N. Engl. J. Med.* [ePub ahead of print (Jan 28, 2015). The second report of results the largest to date Phase I human clinical trial on a fast track Ebola vaccine during the 2014 outbreak.]

- 6*. Choi JH, Croyle MA. Emerging targets and novel approaches to Ebola virus prophylaxis and treatment. *BioDrugs*. 2013; 27(6):565–583. [PubMed: 23813435] [Comprehensive review of Ebola vaccines and therapeutics and their progression toward clinical testing.]
- 7*. Gunther S, Feldmann H, Geisbert TW, Hensley LE, Rollin PE, Nichol ST, Stroher U, Artsob H, Peters CJ, Ksiazek TG, Becker S, Ter Meulen J, Olschlager S, Schmidt-Chanasit J, Sudeck H, Burchard GD, Schmiedel S. Management of accidental exposure to Ebola virus in the biosafety level 4 laboratory, Hamburg, Germany. *J Infect Dis*. 2011; 204(Suppl 3):S785–90. [PubMed: 21987751] [First report of the use of an Ebola vaccine candidate in humans.]
8. Lyford, J. Ebola clinical trial suspended after volunteers complain of joint pains.. *The Pharmaceutical Journal*. (Online, 12 December 2014) <http://www.pharmaceutical-journal.com/news-and-analysis/news/ebola-clinical-trial-suspended-after-volunteers-complain-of-joint-pains/20067418.article>
9. National Institute of Allergy and Infectious Diseases (NIAID); National Institutes of Health Clinical Center (CC). Partnership for Research on Ebola Vaccines in Liberia (PREVAIL). *ClinicalTrials.gov* [Internet]. National Library of Medicine (US); Bethesda (MD): 2000. Available from: <http://clinicaltrials.gov/show/study/NCT02344407> NLM Identifier: NCT02344407 [2015 Feb 25]
10. Kochhar S, Rath B, Seeber LD, Rundblad G, Khamesipour A, Ali M. Vienna Vaccine Safety Initiative. Introducing New Vaccines in Developing Countries. *Expert Rev. Vaccines*. 2013; 12(12):1465–1478. [PubMed: 24195483]
11. Del Rio C, Mehta AK, Lyon GM, Guarner J. Ebola Hemorrhagic Fever In 2014: The Tale Of An Evolving Epidemic. *Ann. Intern. Med*. 2014; 161(10):746–748. [PubMed: 25133433]
- 12*. Marzi A, Feldmann H. Ebola Virus Vaccines: An Overview of Current Approaches. *Expert. Rev. Vaccines*. 2014; 13(4):521–531. [PubMed: 24575870] [Comprehensive review of Ebola vaccines and their progression toward clinical testing.]
- 13*. Choi JH, Schafer SC, Zhang L, Juelich T, Freiberg AN, Croyle MA. Modeling Pre-Existing Immunity to Adenovirus in Rodents: Immunological Requirements for Successful Development of a Recombinant Adenovirus Serotype 5-Based Ebola Vaccine. *Mol. Pharm*. 2013; 3(10):3342–3355. [PubMed: 23915419] [Study where models of pre-existing immunity to adenovirus identified antibody isotypes and polyfunctional CD8+ T cell responses that were necessary for protection from lethal Ebola infection in rodents.]
- 14**. Wong G, Richardson JS, Pillet S, Patel A, Qiu X, Alimonti J, Hogan J, Zhang Y, Takada A, Feldmann H, Kobinger GP. Immune Parameters Correlate with Protection Against Ebola Virus Infection in Rodents and Nonhuman Primates. *Sci. Transl. Med*. 2012; 4(158):158ra146. [Study where total anti-Ebola GP IgG and to a lesser extent polyfunctional CD4+ T cell responses were found to be necessary for protection from lethal Ebola infection in primates.]
- 15**. Sullivan NJ, Hensley L, Asiedu C, Geisbert TW, Stanley D, Johnson J, Honko A, Olinger G, Bailey M, Geisbert JB, Reimann KA, Bao S, Rao S, Roederer M, Jahrling PB, Koup RA, Nabel GJ. CD8+ Cellular Immunity Mediates rAd5 Vaccine Protection against Ebola Virus Infection of Nonhuman Primates. *Nat. Med*. 2011; 17(9):1128–1131. [PubMed: 21857654] [Study where CD8+ T cell responses were found to be a correlate of protection from Ebola infection in primates.]
16. Richardson JS, Pillet S, Bello AJ, Kobinger GP. Airway Delivery of an Adenovirus-Based Ebola Virus Vaccine Bypasses Existing Immunity to Homologous Adenovirus in Nonhuman Primates. *J. Virol*. 2013; 87(7):3668–3677. [PubMed: 23302894]
- 17*. Choi JH, Jonsson-Schmunk K, Qiu X, Shedlock DJ, Strong J, Xu JX, Michie KL, et al. A Single Dose Respiratory Recombinant Adenovirus-Based Vaccine Provides Long-Term Protection for Non-Human Primates from Lethal Ebola Infection. *Mol. Pharm*. Nov 1.2014 ePub ahead of print. [The first report demonstrating long-term protection from an adenovirus-based Ebola vaccine given by the nasal route.]
- 18**. Wong G, Audet J, Fernando L, Fausther-Bovendo H, Alimonti JB, Kobinger GP, Qiu X. Immunization with vesicular stomatitis virus vaccine expressing the Ebola glycoprotein provides sustained long-term protection in rodents. *Vaccine*. 2014; 32(43):5722–5729. [PubMed: 25173474] [The first report demonstrating the durability of a VSV vectored Ebola vaccine in primates.]

19. Ducusin, J.; Narvaez, D.; Wilburn, S.; Mahmoudi, F.; Orris, P.; Sobel, H.; Bersola, E.; Ricardo, M. Waste Management and Disposal During the Philippine Follow-Up Measles Campaign. Health Care without Harm and the Philippine Department of Health; Washington, D.C., U.S.A.: Manila, Philippines: 2004. p. 1-112.
20. Rothe C, Schlaich C, Thompson S. Healthcare-Associated Infections in Sub-Saharan Africa. *J. Hosp. Infect.* 2013; 85(4):257–267. [PubMed: 24209885]
- 21**. Djupesland PG. Nasal Drug Delivery Devices: Characteristics and Performance in a Clinical Perspective-A Review. *Drug Deliv. Transl. Res.* 2013; 3(1):42–62. [Comprehensive review of intranasal delivery devices.]
22. Fields BN, Hawkins K. Human Infection with the Virus of Vesicular Stomatitis During an Epizootic. *N. Engl. J. Med.* 1967; 277(19):989–994. [PubMed: 4293856]
23. Lion T. Adenovirus Infections in Immunocompetent and Immunocompromised Patients. *Clin. Microbiol. Rev.* 2014; 27(3):441–462. [PubMed: 24982316]
- 24**. Riese P, Sakthivel P, Trittel S, Guzmán CA. Intranasal Formulations: Promising Strategy to Deliver Vaccines. *Expert Opin. Drug Deliv.* 2014; 11(10):1619–1634. [PubMed: 24962722] [Comprehensive review of the current strategies for formulation of intranasal therapeutics and vaccines.]
- 25**. Djupesland PG, Messina JC, Mahmoud RA. The Nasal Approach to Delivering Treatment for Brain Diseases: An Anatomic, Physiologic, and Delivery Technology Overview. *Ther. Deliv.* 2014; 5(6):709–733. [PubMed: 25090283] [Comprehensive review of explaining physiological relationship between nasal cavities and the brain.]
26. Mire CE, Miller AD, Carville A, Westmoreland SV, Geisbert JB, Mansfield KG, Feldmann H, Hensley LE, Geisbert TW. Recombinant Vesicular Stomatitis Virus Vaccine Vectors Expressing Filovirus Glycoproteins Lack Neurovirulence in Nonhuman Primates. *PLoS Negl. Trop. Dis.* 2012; 6(3):e1567. [PubMed: 22448291]
27. Damjanovic D, Zhang X, Mu J, Medina MF, Xing Z. Organ Distribution of Transgene Expression Following Intranasal Mucosal Delivery of Recombinant Replication-Defective Adenovirus Gene Transfer Vector. *Genet. Vaccines Ther.* 2008; 6:5. [PubMed: 18261231]
28. Gau P, Rodriguez S, De Leonardis C, Chen P, Lin DM. Air-assisted intranasal instillation enhances adenoviral delivery to the olfactory epithelium and respiratory tract. *Gene Ther.* 2011; 18(5):432–436. [PubMed: 21085195]
29. Levine MM, Robins-Browne R. Vaccines, Global Health and Social Equity. *Immunol. Cell Biol.* 2009; 87(4):274–278. [PubMed: 19308074]
30. Matthias DM, Robertson J, Garrison MM, Newland S, Nelson C. Freezing Temperatures in the Vaccine Cold Chain: A Systematic Literature Review. *Vaccine.* 2007; 25(20):3980–3986. [PubMed: 17382434]
31. Chen D, Kristensen D. Opportunities and Challenges of Developing Thermostable Vaccines. *Expert Rev. Vaccines.* 2009; 8(5):547–557. [PubMed: 19397412]
32. WHO Virtual Press Conference Following the Second High-Level Meeting on Ebola Vaccines Access and Financing. World Health Organization; Geneva, Switzerland: 2015.
- 33**. Renteria SS, Clemens CC, Croyle MA. Development of a Nasal Adenovirus-Based Vaccine: Effect of Concentration and Formulation on Adenovirus Stability and Infectious Titer During Actuation From Two Delivery Devices. *Vaccine.* 2010; 28(9):2137–2148. [PubMed: 20044048] [First evaluation of compatibility of formulation and intranasal delivery device for adenovirus-based vaccines.]
- 34**. Croyle MA, Cheng X, Wilson JM. Development of Formulations That Enhance Physical Stability of Viral Vectors for Gene Therapy. *Gene Ther.* 2001; 8(17):1281–1290. [PubMed: 11571564] [First manuscript describing strategies for developing pharmaceutically acceptable formulations for long-term storage of recombinant adenoviruses at ambient temperatures.]
- 35**. Zimmer B, Summermatter K, Zimmer G. Stability and Inactivation of Vesicular Stomatitis Virus, a Prototype Rhabdovirus. *Vet. Microbiol.* 2013; 162(1):78–84. [PubMed: 22995872] [First manuscript to evaluate the physical stability of vesicular stomatitis virus.]
36. 2014 Ebola Outbreak in West Africa. Centers for Disease Control and Prevention; Atlanta, GA: 2014. <http://www.cdc.gov/vhf/ebola/outbreaks/guinea/index.html> [2015 February 25]

37. Levine MM. "IDEAL" Vaccines for Resource Poor Settings. *Vaccine*. 2011; 29(Suppl 4):D116–D125. [PubMed: 22486974]
38. Milligan, GN.; Barrett, AD. *Vaccinology: An Essential Guide*. Wiley Blackwell; Hoboken, NJ: 2015. The Regulatory Path to Vaccine Licensure..

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