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Clinical development of a recombinant Ebola vaccine in the midst of an unprecedented epidemic ☆

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ABSTRACT

The 2014–2016 Ebola outbreak caused over 28,000 cases and 11,000 deaths. Merck & Co. Inc., Kenilworth, NJ USA and NewLink Genetics are working with private and public partners to develop and license an Ebola vaccine that was evaluated extensively during the outbreak. The vaccine referred to as V920 is a recombinant vesicular stomatitis virus (rVSV) in which the VSV-G envelope glycoprotein (GP) is completely replaced by the Zaire ebolavirus GP (rVSVΔG-ZEBOV-GP). Eight Phase I and four Phase II/III clinical trials enrolling approximately 17,000 subjects were conducted in parallel to the outbreak to assess the safety, immunogenicity, and/or efficacy of V920. Immunogenicity data demonstrate that anti-GP antibodies are generally detectable by ELISA by 14 days postvaccination with up to 100% seroconversion observed by 28 days post dose. In addition, the results of a ring vaccination trial conducted by the WHO and their partners in Guinea suggest robust vaccine efficacy within 10 days of receipt of a single dose of vaccine. The vaccine is generally well-tolerated when administered to healthy, non-pregnant adults. The development of this vaccine candidate in the context of this unprecedented epidemic has involved the close cooperation of large number of international partners and highlights what we as a public health community can accomplish when working together towards a common goal.

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1. Introduction

The 2014–2016 Ebola epidemic resulted in more than 28,000 cases and more than 11,000 deaths and presented a critical public health emergency which mobilized public and private organizations around the world in response [1]. The outbreak was caused by the Zaire ebolavirus species and primarily affected Guinea, Liberia, and Sierra Leone in West Africa, although cases were also identified and treated in Italy, Mali, Nigeria, Senegal, Spain, the United Kingdom and the United States. The scale of the outbreak was unprecedented with more than 11 times the number of cases from all previous filovirus outbreaks combined. A Public Health Emergency of International Concern (PHEIC) was declared by the World Health Organization (WHO) on August 8, 2014 which triggered a broad international response. While the PHEIC was declared over in March 2016, maintaining vigilance and the ability to react quickly to newly emergent cases remains a high public health priority [1].

Accelerated vaccine development was one aspect of the response and a number of vaccine candidates were advanced into clinical trials in an effort to identify a prophylactic vaccine that might be helpful in containing the 2014–2016 or future outbreaks. Merck & Co., Inc., Kenilworth, NJ, USA (known as MSD outside of the US and Canada) became involved in Ebola vaccine development in the autumn of 2014 when the recombinant vesicular stomatitis virus based vaccine (rVSVΔG-ZEBOV-GP; V920) that had been ini-

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tially developed by the Public Health Agency of Canada [2–5] and licensed to NewLink Genetics was exclusively sublicensed to MSD. Since that time MSD and NewLink have collaborated with a global network of partners in unprecedented ways to speed the research, development, and implementation of the vaccine candidate to protect people at risk of Ebola virus disease (EVD). The efforts of all the partners in this development highlight what the public health community can accomplish with strong coordinated collaboration.

The extensive partnerships that have been pivotal for the rapid progression of the development of the V920 vaccine include global public health organizations (e.g. WHO, Médecins sans Frontières [MSF]), governmental agencies (e.g. Public Health Agency of Canada [PHAC], US National Institutes of Health [NIH], US Centers for Disease Control and Prevention [CDC], Norwegian Institute of Public Health [NIPH]), clinical researchers (e.g. WHO-led VSV Ebola Consortium [VEBCON], Canadian Center for Vaccinology, Walter Reed Army Institute of Research [WRAIR], Sierra Leone Medical School, Liberia-US clinical research partnership), funding organizations (The Wellcome Trust, the Biomedical Advanced Research and Development Agency [BARDA], the Defense Threat Reduction Agency [DTRA], Joint Vaccine Acquisition Program [JVAP]), vaccine developers (NewLink Genetics and MSD), and regulatory agencies/Ministries of Health (e.g. US Food and Drug Administration, European Medicines Agency, Health Canada, Ministry of Health and Social Welfare of Liberia, Ministry of Health and Public Hygiene of Guinea, Ministry of Health and Sanitation of Sierra Leone). Through these partnerships eight Phase I, one Phase II, and three Phase III studies were conducted during the outbreak across North America, Europe, and Africa as highlighted in Fig. 1.

2. V920 vaccine development

The V920 vaccine candidate is a live-attenuated, chimeric virus which is based on a recombinant vesicular stomatitis virus (rVSV) backbone. In V920 the G glycoprotein of the rVSV is deleted and completely replaced by the glycoprotein (GP) of Zaire ebolavirus (rVSVΔG-ZEBOV-GP) attenuating the virus [6]. This substitution eliminates the neurovirulence associated with wild type VSV and is believed to impact the host range and cellular tropisms [6,7]. rVSVΔG-ZEBOV-GP is replication competent and displays the Zaire ebolavirus GP on the surface of the virion in its native conformation while maintaining the bullet-like shape of the native VSV (Fig. 2).

Investigators at PHAC conducted a number of preclinical studies that showed that V920 could protect non-human primates (NHPs) from challenge with wild type Zaire ebolavirus following a single intramuscular (IM) dose of vaccine administered at potencies of $1–2 \times 10^7$ plaque forming units (pfu) [3–6,8]. These promising data served as an important part of the decision to advance the vaccine candidate into Phase I clinical trials in the autumn of 2014. A NHP study conducted at the US Army Medical Research Institute for Infectious Diseases (USAMRIID) in parallel to the start of the Phase I trials demonstrated that a single immunization at dose levels of 2×10^7 and 1×10^8 pfu resulted in 100% protection against mortality upon IM challenge with approximately 1000 pfu of wild type Zaire ebolavirus. Administration of 3×10^6 pfu resulted in protection of 7 out of 8 animals. Immunogenicity assessments showed that all vaccinated animals developed Ebola GP-binding antibodies (Filovirus Animal Non-Clinical Group GP-ELISA assay: FANG GP-ELISA) (Trefry et al., unpublished data). In addition, the vaccine was shown to be well tolerated in repeat dose toxicity studies in mice and cynomolgus macaques.

The goal of any clinical development program is to evaluate vaccine safety, immunogenicity, and efficacy to support product licensure. The requirements for licensure typically include an adequate safety database, demonstration of manufacturing consistency, and demonstration of clinical benefit. Demonstration of clinical benefit is the challenging component for diseases such as Ebola where outbreaks are sporadic and difficult if not impossible to predict, and often in settings where there is not sufficient infrastructure to conduct a trial to regulatory standards. Under US FDA regulations, the pathways to licensure for an Ebola vaccine include: (1) the "traditional" approval pathway by directly demonstrating efficacy/effectiveness; (2) the Accelerated Approval pathway which bridges human immune responses to immune responses

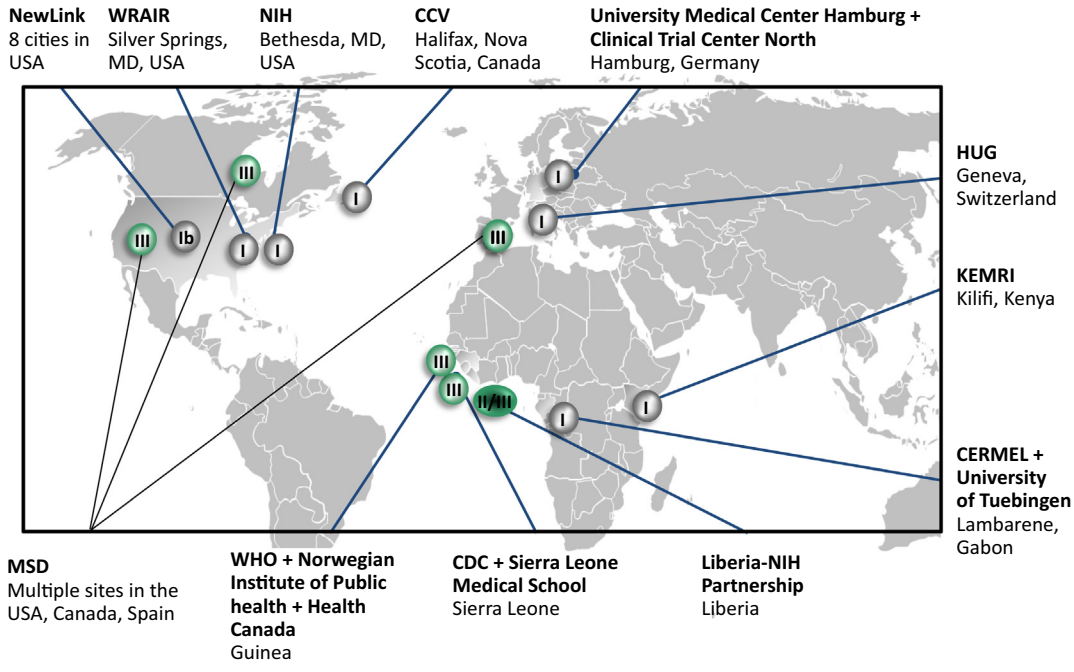

Fig. 1. Phase I, II, and III clinical trials sites spanning North America, Europe, and Africa. Twelve Phase I, II, and III clinical trials were conducted at sites spanning North America, at several sites in Europe, and in regions of Africa outside of the epidemic as well as the in countries involved in the Ebola epidemic.

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