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Closer than ever to an Ebola virus vaccine

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Forty years ago, in 1976, hemorrhagic fever outbreaks in former Zaire (now the Democratic Republic of the Congo) and Sudan devastated the local communities [1]. In Zaire, an international response team consisting of scientists and medical doctors from the USA, Europe, and Africa identified a filamentous virus similar to Marburg virus (MARV) as the causative agent. The pathogen, which infected 318 people and took the lives of 280 around a Belgian Catholic Mission Hospital in Yambuku, was named Ebola virus (EBOV) after the nearby Ebola river [1]. Since then, EBOV outbreaks have occurred sporadically in Central Africa but have never affected more than a few hundred people, due in large part to geographical isolation and rapid quarantines. The situation changed in December 2013, when the largest documented EBOV epidemic began in the small village of Meliandou, Guinea [2]. A 2-year-old boy developed a hemorrhagic fever, and the disease spread quickly to other people in nearby villages. It took 3 months until the infectious agent of the disease was identified – EBOV. For the first time, EBOV was found outside of Central Africa, and it spread quickly from Guinea to the neighboring countries Sierra Leone and Liberia, reaching rural communities as well as the heavily populated capital cities. On 8 August 2014, the World Health Organization (WHO) declared the West African EBOV epidemic a global health emergency [3], and the status was not lifted until 29 March 2016, almost 2 years later. The epidemic had devastated Guinea, Liberia, and Sierra Leone, causing almost 30,000 human infections with over 11,000 fatalities [4]. After 40 years of research, were there still no countermeasures?

We do have candidates for vaccines and therapeutics, but their development and licensure has been rather complicated. Unlike Malaria or HIV, EBOV does not have a reputation for causing millions of cases every year, and the interest from pharmaceutical companies, as well as research funding agencies, in developing and licensing a vaccine or treatment was therefore minimal. Moreover, the virus circulates in Africa where the majority of people

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Declaration of interest

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have no means to afford medication and vaccines. After the terrorist attacks on 11 September 2001, as well as the subsequent anthrax attacks that began shortly after, the threat that EBOV and other pathogens posed as agents of bioterrorism spurred government agencies to dramatically increase research funding. Research into countermeasure development was expanded, and within several years the first successful vaccine and treatment studies against EBOV infection in animal models were published [5]. Before the West African EBOV epidemic, only two vaccines were tested in human phase I clinical trials with limited success [5]. However, after the global health emergency was declared by the WHO in summer 2014, several experimental vaccine approaches and treatment options, which had previously been successfully tested in nonhuman primates (NHPs), were accelerated into human clinical trials [6]. Among these were the vesicular stomatitis virus (VSV)-based vaccine, VSV-EBOV (also known as rVSV-ZEBOV), and a chimpanzee adenovirus type 3 (cAd3)-based vaccine, cAd3-EBO. The cAd3-EBO vaccine was developed in the last 5 years at the Vaccine Research Center at the National Institutes of Health (NIH) in the USA, building off of several advances made with the human adenovirus 5 platform [7]. The VSVEBOV was developed in the early 2000s at the Public Health Agency of Canada (PHAC) and tested in collaborative projects in Canada and the USA [8]. In 2010, NewLink Genetics acquired the license to produce and market the VSV-EBOV vaccine, and in early 2014, PHAC had about one thousand doses available for phase I clinical trials. Merck acquired the license to produce and market the VSV-EBOV vaccine in late 2014, and with this support, phase I human clinical trials were started in October 2014. At the same time, GlaxoSmithKline and the NIH launched the first phase I clinical trials for the cAd3-EBO vaccine. In the following year, both vaccines were shown to be immunogenic with limited adverse effects [9–11], prompting phase II and III clinical trials in West Africa. While no phase III vaccine efficacy data are currently available for the cAd3-EBO vaccine, the VSV-EBOV vaccine showed promising efficacy in Guinea using a ring-vaccination approach [12]. Just this past December, the second report of the study was published demonstrating that the VSV-EBOV vaccine is indeed highly efficacious and may have contributed to controlling the later stage of the outbreak in Guinea [13]. Remarkably, after the minimum time to immunity (10 days) had been reached, the study documented no new EBOV cases among those who received the vaccine immediately, compared to 16 new infections in the delayed vaccination (control) group. Nevertheless, important questions about the durability of this vaccine remain unanswered and require further investigation.

Earlier in 2016, the VSV-EBOV vaccine produced by Merck was given the ‘Breakthrough Therapy Designation’ by the US FDA as well as PRIME status from the European Medicines Agencies, which will enable faster regulatory review once the licensure package is submitted. Furthermore, Merck signed an agreement worth over $5 million with the public-private organization Gavi (Global Alliance for Vaccine and Immunization) to submit the VSV-EBOV package for regulatory approval by late 2017 [14]. At this point, we are closer than ever to having a licensed EBOV vaccine that can be used in emergency situations to help control outbreaks and to vaccinate at-risk populations, like healthcare workers in EBOV-endemic areas. Taking this a step further, one could now argue that additional vaccines based on the VSV or adenovirus platform against other hemorrhagic fever viruses, like MARV or Lassa virus, should be accelerated into clinical testing.

The increasing emergence and re-emergence of infectious diseases over the last several decades has highlighted the need for countermeasures with established preclinical safety and efficacy profiles for emergency use in outbreak situations. The acceleration of the clinical testing of EBOV countermeasures in light of the West African epidemic contributed to ending the human transmission chain and stopping the outbreak. In order to be better prepared to intervene earlier in outbreak situations, we should not wait for another global health emergency before moving forward other vaccine and therapeutic candidates against highly pathogenic viruses.

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