The case of the rVSV-ZEBOV vaccine: tragic lessons from a delayed solution to the 2014 Ebola Outbreak

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Introduction

The Ebola virus disease (EVD) is a zoonotic infection that was discovered in 1976 when two of its strains, the Sudan strain and the Zaire strain, broke out in sub-Saharan Africa (1). Fruit bats are the suspected animal reservoir, and the disease can be transmitted to humans through exposure to bodily fluids or through the consumption of infected animals (2, 3). Individuals infected with EVD initially develop flu-like symptoms, vomiting, diarrhea, and, with the progression of the disease, internal and external bleeding, leading to a high possibility of mortality (1, 3). Moreover, EVD is a 'disease of poverty'—it disproportionately affects vulnerable populations in countries with weak healthcare infrastructure, insufficient health sector workforce, and general underdevelopment.

As with most neglected tropical diseases (NTDs), EVD usually does not threaten developed countries, making research funding for vaccine development and therapies a low priority. The 2014 Zaire ebolavirus outbreak revealed the consequences of neglecting these so-called rare diseases: by its conclusion in 2016, the outbreak had killed 11,310 people in Guinea, Sierra Leone, and Liberia (4). The delayed international response was an important contributor to the epidemic's deadliness: the World Health Organization (WHO) declared EVD a Public Health Emergency of International Concern (PHEIC) eight months after its initial outbreak in December 2013, convening again in September 2014 to evaluate the state of available treatments (5). Due to the escalating crisis, the WHO approved experimental vaccine clinical trials as potential prevention measures in West Africa. One of these vaccines was the joint Merck-Canadian vaccine, known as rVSV-ZEBOV.

Canada's contribution

The rVSV-ZEBOV vaccine was originally created in 2005 at National Microbiology Laboratory (NML), located in Winnipeg, Manitoba (6). While researching the role of glycoproteins at the surface of the virus, NML scientists discovered that mice exposed to an inactivated virus were subsequently immune to active Ebola. Though researchers at the U.S. National Institutes of Health (NIH) were developing their own vaccine, the Canadian vaccine required only one dose versus the NIH's two-dose regimen, and, unlike the U.S. vaccine, had been shown to be capable of reducing disease severity for those infected after immunization (7).

Though Canada's funding was focused on local public health issues, Dr. Heinz Feldmann, the NML's special pathogen chief, and Dr. Gary Kobinger, his successor, pushed hard and successfully convinced policymakers that their findings were relevant to the NML's mandate (8). The Public Health Agency of Canada (PHAC) funded the initial development of rVSV-ZEBOV. Though funding for EVD and other NTD treatments were limited until early 2000s, there emerged a surge in funding in relation to defence against bioterrorism—the use of biological weapons, such as viruses, to incite terror by causing disease and death—following 9/11 and the 2001 Anthrax attacks. This 2001 momentum propelled the Canadian Department of National Defence to, from 2002 to 2014, allocate $7 million towards biodefence research, and $4 million towards experimental therapies and vaccine development for Ebola (9, 10).

Still, Canada's options for commercializing the vaccine were limited due to the low risk of Ebola to Canadians and considerable costs associated with vaccine

development and licensing. Hence, following the creation of the vaccine, licensing rights were sold to U.S.-based pharmaceutical company NewLink Genetics in 2010 for a meager $205,000 (11). As part of this sale agreement, NewLink was expected to start clinical testing and mass produce the vaccine (12). In hindsight, the sale to NewLink was problematic: they did not have the manufacturing capacity nor resources to properly test the vaccine and prepare it for regulatory approval (13). In fact, PHAC had to allocate nearly a million dollars for a German company, IDT Biologika, to manufacture 1500 vials of the vaccine for human trials in 2013 (14). Seeing an opportunity with the 2014 Ebola outbreak, the pharmaceutical company Merck licensed the worldwide commercial rights for the vaccine from NewLink for $50 million to accelerate vaccine trials and expand the vaccine program (15).

Implementing rVSV-ZEBOV

Clinical trials

By the Ebola outbreak in late 2013, clinical trials had not yet begun. In 2015, phase 1 and phase 2 of the trials showed that the experimental rVSV-ZEBOV vaccine was effective in inducing a protective immune response with only minor adverse events after a single intramuscular injection (1, 16, 17).

After approval from the WHO, phase 3 trials began in Guinea in March 2015 (18). The trial employed a cluster-ring design in which direct and secondary contacts of EVD patients were randomized to receive the rVSV-ZEBOV vaccine either immediately or 21 days after a new case was reported (19). The trial excluded pregnant or breastfeeding women, those with a severe illness, and individuals under 18 years of age. In total, there were roughly 50 clusters with 2,000 people in each cluster. Individuals in the trial who were diagnosed with Ebola 10 days after randomization were considered confirmed Ebola cases. Among the immediate-vaccination group, no cases of Ebola were recorded, and interim trial results reported 100% efficacy (19). With the positive interim results, the delayed vaccination arm was discontinued and children over six years of age were included in the trial in order to maintain clinical equipoise. Compared to conventional clinical trials, the trial ended exceptionally fast by January 2016, and the final results were published a few months later, just over a year after the start of the trial (20).

The Guinea ring trial, having confirmed the vaccine's effectiveness in protecting against Ebola, can generally be considered as an overall success. The rVSV-ZEBOV vaccine was also the first proven single dose Ebola vaccine whereas none previously existed, making it a scientific breakthrough. Furthermore, the vaccine was shown to

provide an overall trial population effectiveness of 70.1% with only 52.1% of the trial population vaccinated, and the clinical trial itself helped stop the transmission of Ebola in Guinea near the end of the epidemic. In total, just under 6,000 people benefited from the vaccine. (19).

While overall the data suggests the vaccine to be highly effective and safe, there are still some shortcomings in regards to the trial results and methodology. The results of the Guinea Ring Trial, especially the report of 100% efficacy (95% CI 68.9-100.0 p=0.0045), should be examined beyond face value (19). First, the sample size entails some limitation. There were only 16 cases of EVD in the delayed vaccination group; while a statistically significant result was found, not enough cases existed to reliably estimate the vaccine's effectiveness. Secondly, the trial was conducted as the Ebola epidemic was waning, which may have inflated the efficacy results. Finally, it is important to consider the ways in which the initial exclusion of pregnant women, children under six years of age, and the severely ill affected the trial results. Although the trial population suited WHO requirements, ideally an EVD vaccine should protect anyone susceptible to acquiring the disease in the midst of an outbreak; thus, trial results lack a certain level of generalizability (20).

An Uncertain Future

In 2016, after the success of the Guinea trial, pharmaceuticals GAVI and Merck signed a purchase agreement worth $5 million to push rVSV-ZEBOV through initial licensing and to stockpile doses for clinical trials and emergency use. As of May 2016, 300,000 doses were to be available for emergency use in case of an outbreak (21). A small number of doses—800 to 1,000—are also currently stockpiled in Geneva for deployment in case of future outbreaks (27). Moreover, Merck is working to register the vaccine with the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA). However, as of the time of writing, the vaccine is not yet commercially available, and the FDA approval process has been pushed back to 2018 (28). Furthermore, an important hurdle in ensuring the availability of the vaccine is in acquiring approval for its usage in African countries with high risk for Ebola. Each country has its own National Regulatory Authorities (NRA) and Merck would need to apply to each individually. Nonetheless, since Merck submitted the vaccine to WHO's Emergency Use and Assessment Listing (EUAL), the vaccine can still be used in an emergency setting during declared PHEICs (29).

Even when rVSV-ZEBOV is commercially licensed for use by the FDA and EMA, financial limitations are unlikely to justify the use of a manufacturing plant, and

the uncertainty about the amount of vaccine required in the future may cause challenges for manufacturing and storage once an outbreak does occur (30). Moreover, as the vaccine is not yet commercially available, the current cost of each dose is unknown. A WHO draft of an outbreak scenario has detailed a single dose to cost USD 20$, but this price increases to USD $135 when including all associated storage and deployment costs (31).

Discussion

The Need for Continued Research and Development

The development of rVSV-ZEBOV changes how future Ebola outbreaks will be fought. The vaccine, while currently used only in emergency responses, may pave the way for future prophylactic Ebola vaccines and vaccines for other strains of Ebola. Prophylactic Ebola vaccines will protect crucial front-line healthcare workers in future outbreaks. This is especially important given the fact that healthcare workers, who were in contact with Ebola patients throughout the crisis, were amongst the first fatalities. The loss of primary healthcare workers left the already weak West African healthcare system in shambles, allowing the virus to decimate local populations. The Center for Disease Control (CDC) reported that, from the outset of the outbreak to November 2015, a total of 881 healthcare workers were infected in Guinea, Liberia and Sierra Leone (32). Of those infected, 513 died, leading to Liberia, Sierra Leone, and Guinea losing 8%, 7%, and 1% of their healthcare workers, respectively (32). The loss of healthcare workers and deterioration of healthcare services also had an indirect impact on the treatment of HIV, tuberculosis, and malaria. It was estimated that an additional 10,600 lives were lost due to the inability to access healthcare services as the epidemic and loss of healthcare workers had caused a 50% reduction in healthcare services in the three countries (32). Even after the outbreak, the World Bank estimated the economic loss to these three countries to be around USD $2.2 billion (32). To put this into perspective, the combined GDP of Guinea, Sierra Leone and Liberia was a total of USD $14 billion in 2016 (33-35). It may take decades before these three countries fully recover and stabilize their healthcare system.

Additionally, an effective vaccine that minimizes the risks to healthcare workers would encourage more foreign aid workers from NGOs such as Médecins Sans Frontières (MSF) as well as government agencies to assist affected countries during future outbreaks. Stockpiling the EVD vaccine in Geneva may quicken and consolidate the global response in future epidemics, and help train foreign aid workers in its deployment. At the same time, not stockpiling the vaccine in high-risk

countries may slow down the deployment of the vaccine in response to isolated cases of Ebola. This can be detrimental to containing the spread of the virus and protecting frontline healthcare workers; hence, an emergency supply of the vaccine should exist in high risk countries for safekeeping.

Lastly, one of the major challenges in global health is the last mile problem: financially and logistically, the last 'mile' of supply chain distribution is the most difficult to traverse. Solving this hurdle requires a broad reinforcement of infrastructure such as healthcare and transportation to reduce the difficulty of healthcare access. Moreover, since many affected countries lack the necessary cold storage for vaccine distribution, heat stability of treatments should be of paramount concern. The University of Hawaii is currently developing an EVD vaccine that is both heat-stable and orally available, making its foreseeable distribution to patients easier and more cost-effective (36). There is also a need for innovative solutions that address a weak or non-existent supply chain in reaching difficult-to-access and remote areas.

Ethical Considerations for Future Research and Development

The implementation of the Guinea ring trial was considered an overall success by both the public and academic communities, and the WHO considered the intervention of unregistered vaccines for clinical trials to be ethical. Still, certain questions about ethics merit discussion. In particular, the trial's participants were incentivized by access to quality healthcare, which was unlikely to be available to them if they declined to enroll in the study. Hence, participants may have felt pressured to participate due to their vulnerable circumstances (37).

In addition, the MSF requires investigators to indicate if blood samples will be destroyed after use and to inform patients about the storage and potential use of their data in other studies; however, given the lack of safe, cold storage, third-party laboratories that collected the trial samples exported them to other countries, and did not request explicit consent for the use of collected specimens. There is now a biobank of 80,000 specimens in an unreported location where the nature of the use of and access to these samples is still unclear (36). Informed consent and understanding of the possible risks may also be broken by a lack of communication due to language barriers (35). Furthermore, pregnant women were excluded from the trial despite their elevated risk of infection and health complications and a reported 100% fatality rate for their fetus. Given the need to prioritize pregnant populations in EVD vaccine development, wholesale exclusion denies access to the benefits of participation in research, leaving them more vulnerable to off-label or unguided use of medication.

In fact, the MSF ethics review board saw "no strong justification" for their exclusion from the trials (36).

The Broken Paradigm in NTD Drug Development

While Canadian scientists successfully developed an effective Ebola vaccine, the question remains as to why it took 10 years to begin clinical trials (38). One hurdle was in a lack of participants for phase 3 trials prior to the large-scale outbreak (4). Moreover, pharmaceutical companies had little financial incentive to put a risky EVD vaccine through years of clinical trials. Even now, four years after it has passed phase 3 clinical trials, rVSV-ZEBOV remains unregulated and unavailable for commercial use. Since the virus only primarily affects African countries, the general attitude of pharmaceutical companies towards NTDs is that there are no profits to be made, hence no need for vaccine development.

Moreover, the lack of concern about NTDs has implications for international security. Media hysteria revealed the cycle of panic and neglect in the crisis as the U.S. response to the outbreak was to enact travel bans from the three African countries—yet only one EVD case ever crossed onto American soil during the outbreak (39). This is an example of an overreaction by the West to health threats domestically while displaying general neglect for severe outbreaks internationally. However, in this era of porous borders, Ebola and other NTDs are a matter of national security as air travel makes fast cross-continental transmission very easy, and the only option to contain this risk is tackling the problem at the source.

Implications for Canada

Lastly, it is important to bring the attention back home: as mentioned earlier, Canada sold the licensing rights for rVSV-ZEBOV to NewLink Genetics for a meagre sum, and is only receiving "single-digit" royalties for the vaccine (7). Though the Ebola vaccine was funded primarily by public agencies, its commercialization and profits continue to fill private coffers. The reliance of pharmaceutical companies on publicly-funded research before commercializing the products derived from this research is not unprecedented. Still, in light of NewLink's technical failures and tremendous profit from the subsequent sale of the vaccine rights, Canadian taxpayers should be informed of this arrangement and its underlying reasons. Ideally, taxpayers ought not to bear the costs of research and development while multinational pharmaceutical companies reap all the benefits of commercialization.

Conclusion

The 2014 Ebola outbreak in Guinea, Sierra Leone and Liberia should be viewed as a major wakeup call for the world. As was the case at the time, complacency towards NTDs and development of NTD therapies by pharmaceutical companies has resulted in the loss of thousands of lives and massive economic damage. Moreover, the outbreak demonstrated a cycle of panic and neglect: though characterized by mass media hysteria and billions of funding at the time, interest and scientific development around EVD has waned after the crisis. To truly eradicate NTDs, Western governments must react swiftly and preventatively to outbreaks, continually provide resources for developing and strengthening healthcare systems, and supply an equitable access to life-saving drugs and therapies. With the rise of air travel, this approach is especially important as diseases are no longer constrained by borders, making disease transmission a global security risk. The slow global response present in the 2014 Ebola outbreak and dismissal of outbreaks needs serious reconsideration. The WHO has now set forth a blueprint to streamline further development of vaccines, diagnostics, and therapies during emergencies (40). The effect of this policy remains to be seen.

Acknowledgements

We would like to thank Dr. Harvey Artsob and Dr. Madhu Pai for answering our questions on the 2014 Ebola crisis and providing valuable feedback.

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