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Progress towards a vaccine against Ebola to meet emergency medical countermeasure needs

Daniel N. Wolfe *, Amanda G. Zarrabian, Gary L. Disbrow, Eric M. Espeland

Health and Human Services (HHS)/Assistant Secretary for Preparedness and Response (ASPR)/Biomedical Advanced Research and Development Authority (BARDA), Thomas P. O'Neill Federal Building (FOB8), 200 C Street, SW, Washington, DC 20024, United States

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ABSTRACT

The Ebola virus epidemic in West Africa proved to be the largest in the history of filovirus outbreaks, causing the World Health Organization to declare a public health emergency of international concern in August of 2014. In collaboration with domestic and international partners, the Biomedical Advanced Research and Development Authority (BARDA) initiated several vaccine development projects in support of the overall response efforts. The urgency associated with the epidemic triggered the clinical evaluation of lead vaccine candidates starting in late 2014. Here we will discuss development of the lead vaccine candidates for Ebola virus, specifically *Zaire ebolavirus*.

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1. Introduction

The mission of the Biomedical Advanced Research and Development Authority (BARDA) is to support the development and procurement of medical countermeasures (MCM) to be made available for chemical, biological, radiological, and nuclear (CBRN) threats, pandemic influenza, and emerging infectious diseases. The Division of CBRN Countermeasures within BARDA supports advanced research and development of vaccines, therapeutics, and diagnostics against viral hemorrhagic fever (VHF) caused by viruses of the family *Filoviridae*. This overview will focus only on the development of vaccines for *Zaire ebolavirus* (EBOV).

Prior to 2014, filovirus outbreaks were limited to tens to hundreds of confirmed cases. The potential impact of these viruses on public health systems was not fully realized until the EBOV epidemic in West Africa, which resulted in more than 28,000 cases and 11,000 deaths across Liberia, Sierra Leone, and Guinea [1]. In this case, the spread of EBOV may have been accelerated in part due to population density. The basic reproduction number (R_0), or the average number of secondary cases that may be expected from a given primary case, was higher in more densely populated districts [2]. The epidemic escalated throughout 2014, resulting in an urgent need of MCMs against EBOV to support the overall international response effort.

The epidemic has since waned, with no confirmed cases of EBOV in Liberia, Sierra Leone, or Guinea since April 2016. However, the potential re-introduction of cases from animal reservoirs or convalescent patients highlights the importance of MCM availability as a component of an overall preparedness posture. There have been multiple instances in which new EBOV cases emerged after documented human-to-human transmission had ended [3,4]. Effective vaccines may be an important piece of the overall response to future outbreaks.

2. Vaccines

In the fall of 2014, modeling efforts suggested that as many as 1.4 million cases of EBOV could occur by January 2015 [5]. Despite tremendous progress on early-stage vaccine candidates by the National Institute for Allergy and Infectious Diseases (NIAID) and Department of Defense (DoD), there were no vaccines against EBOV licensed by the Food and Drug Administration (FDA). As part of the 2014 response, a coordinated government approach enabled rapid progress into clinical development. BARDA supported the continued development of several EBOV vaccine candidates, with an emphasis on accelerating manufacturing activities, to ensure vaccine would be available to support additional clinical trials. Multiple vaccine candidates are now in clinical development and continue to progress towards FDA licensure.

3. Early vaccine landscape

By late 2013, a number of vaccine candidates had been evaluated in non-clinical efficacy studies; the most promising included viral glycoprotein (GP) in the vaccine formulation. Vesicular

* Corresponding author.
E-mail address: daniel.wolfe2@hhs.gov (D.N. Wolfe).

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Stomatitis Virus (VSV) was being pursued as a live virus-vector to express the GP of various filoviruses. A single-dose VSV vaccine expressing EBOV GP protected against a homologous challenge in a nonhuman primate model [6]. Adenovirus-vectored constructs were being evaluated as non-replicating platforms to deliver filovirus GP and also protected against EBOV [7,8]. Efficacy in nonhuman primate studies had also been achieved with a replicon vaccine using a Venezuelan equine encephalitis virus backbone [9] and virus-like particles consisting of viral protein 40 kDa (VP40), nucleoprotein (NP), and GP [10].

Clinical experience with Ebola vaccines was limited prior to the 2014 outbreak. A DNA-based vaccine using plasmids encoding EBOV NP and GP, as well as *Sudan ebolavirus* (SUDV) GP, was evaluated in a phase 1 clinical study [11]. The safety profile was promising, and antibody responses were detectable against at least one of the proteins in 19 out of 20 subjects. However, this study used a 3-dose, 12-week treatment regimen and antibody responses against EBOV GP peaked after the third dose and waned rapidly [11]. An Adenovirus serotype 5 (Ad5)-vectored candidate had also been evaluated in a phase 1 clinical study, using a 1:1 mix of Ad5-SUDV and Ad5-EBOV. The highest dose elicited a seroconversion rate of 55% for EBOV when measured by ELISA and neutralizing antibody titers were undetectable for most patients [12].

Although promising non-clinical efficacy data had been generated for multiple EBOV vaccines, there was a limited supply of vaccine that had been produced under cGMP guidelines. Thus, manufacturing was a bottleneck for clinical development and the international response as the outbreak escalated in 2014.

4. Progress of lead vaccine candidates

BARDA initiated support of several vaccine candidates and approaches that included rVSVΔG-EBOV (V920), rVSVN4CT1-EBOV, Chimpanzee Adenovirus serotype 3 vectored GP (ChAd3-EBOV), and an Adenovirus serotype 26 vectored GP (Ad26-EBOV) prime with a boost using Modified Vaccinia Ankara expressing the GPs of EBOV, SUDV, and Marburg virus (MARV) along with the NP of *Tai Forest ebolavirus* (MVA-FILO). The pace of clinical development was rapid during late 2014 and 2015, and a summary from http://clinicaltrials.gov/ as of May 2017 is provided in Table 1.

4.1. Vesicular Stomatitis Virus vectors

Two vaccine candidates utilize VSV as a vector to deliver EBOV GP. The gene for GP is inserted into a live, replicating VSV vector, and that virus is administered as an intramuscular injection. The virus elicits robust immune responses to EBOV GP. The two vaccines differ in the genomic construct of the vector. The wild type VSV genome encodes five proteins in the following order; Nucleoprotein (N), Phosphoprotein (P), Matrix (M), Glycoprotein, and Large protein (L) [13]. V920 contains a deletion of the wild type GP of VSV, with EBOV GP inserted in its place [14]. rVSVN4CT1-EBOV uses the VesiculoVax™ platform containing changes that further attenuate the vaccine strain, moving the N gene to the fourth position in the genome and truncating the cytoplasmic tail of the VSV GP [15]. The EBOV GP is then inserted in the first position in the genome.

Clinical development of V920 was initiated in the Fall of 2014 with both NIAID and DoD starting phase 1 clinical trials. Additional phase 1 clinical studies were initiated by the Canadian government, World Health Organization, and BARDA. V920 was utilized in phase 2–3 clinical studies in Liberia, Guinea, and Sierra Leone starting in February, March, and April of 2015, respectively. Phase 1 safety data showed that injection site pain was observed in 70–90% of patients. Headache, fever, and general malaise was noted in 25–50%, most of which were categorized as grade 1 or 2 adverse events [16–17]. A study conducted in Geneva, Switzerland showed arthritis was observed in 13 of 51 subjects. Arthritis events typically developed around day 10 post-vaccination and most resolved within 1–2 weeks with the exception of one event that persisted for 82 days [18].

Clinical efficacy of V920 was potentially demonstrated using a ring vaccination trial in Guinea. Interim analyses estimated efficacy with a confidence interval of 74.7–100% by evaluating the incidence of EBOV disease starting at day 10 post-vaccination [19]. The final analyses have since confirmed that no cases of EBOV were observed in vaccinated subjects after day 10 post-vaccination [20]. Immunogenicity data from phase 1 clinical studies looks promising to date as well. Using ELISA to quantify antibody titers against EBOV GP, titers at day 28 post-vaccination have typically been around 1000 or greater. PRNT titers, using pseudovirion-based neutralization assays, have usually been between 100 and 400 [16,17,21]. The limited amount of data published from phase 1 trials thus far suggests 95% seroconversion by day 14 and 100% by day 28 [21].

The development of rVSVN4CT1-EBOV is also continuing, having entered its first phase 1 trial in January 2016. Recent non-clinical toxicology has shown that this virus-vectored candidate is attenuated, showing no signs of toxicity in Swiss Webster mice upon intracranial inoculation [22]. Proof-of-concept efficacy against an EBOV challenge has also been demonstrated in cynomolgus macaques [23]. The initial clinical study will help to assess if viremia, arthralgia, and arthritis are observed.

4.2. Adenovirus vectors

Adenovirus serotype 5 (Ad5)-vectored constructs were among the first viral vectors used to express EBOV GP. Early non-clinical results were promising and Ad5-EBOV was advanced into a phase 1 clinical trial. Monitoring for effects of pre-existing immunity to the Ad5 vector was warranted, with Ad5-specific antibodies having a negative impact on Ad5-EBOV efficacy in a mouse model [24] and immunogenicity in humans [12]. Concerns about the use of the Ad5 vector were heightened following clinical data from an Ad5-vectored HIV vaccine which indicated a vaccine-associated risk of HIV infection in vaccinated individuals [25], prompting research in vaccines vectored by alternative Adenovirus serotypes.

NIAID supported non-clinical efficacy studies and early-stage manufacturing of ChAd3-EBOV, and multiple phase 1 Clinical Trials were initiated in the late 2014 and early 2015. Many of these trials evaluated ChAd3-EBOV in the context of a prime-boost regimen, usually with an MVA-vectored construct as a boost (Table 1). The safety profile of ChAd3-EBOV has been acceptable, with the most common side effects being mild to moderate injection site pain (55–75%), headache (35–50%), and fever (20–38%) [26–27]. The combined safety and immunogenicity profiles prompted the use of ChAd3-EBOV without a boost in the Phase 2–3 study in Liberia. However, the trial was halted after the phase 2 due to the lack of new EBOV cases. Without a boost, antibody titers peaked around day 28 post-vaccination typically ranging in titers from the high hundreds to low thousands [26,28].

Nonhuman primate studies have shown that ChAd3-EBOV is able to elicit protective immunity against EBOV challenge. One potential area to monitor was the duration of immunity elicited by the vaccine. Only partial protection was observed when animals were challenged at 10 months post-vaccination, but boosting with an MVA construct provided durable protection against a challenge at 10 months post vaccination [29].

Adenovirus serotypes 26 (Ad26) and 35 (Ad35) have also been investigated as potential alternatives to Ad5 due to their relatively low seroprevalence in humans. These vectors have been assessed

Table 1
List of clinical trials evaluating vaccines against EBOV.

ClinicalTrials.gov identifier	Phase	Prime vaccination		Boost vaccination (if applicable)	
		Vaccine	Doses	Vaccine	Dose
NCT02280408	1	rVSVΔG-EBOV	3×10^6, 2×10^7, 1×10^8 pfu	V920	3×10^6, 2×10^7, 1×10^8 pfu at day 28
NCT02374385	1	rVSVΔG-EBOV	1×10^5, 5×10^5, 3×10^6 pfu	None	N/A
NCT02296983	1	rVSVΔG-EBOV	3×10^6, 1×10^7 pfu	None	N/A
NCT02283099	1	rVSVΔG-EBOV	3×10^5, 3×10^6, 2×10^7 pfu	None	N/A
NCT02269423	1	rVSVΔG-EBOV	3×10^6, 2×10^7, 1×10^8 pfu	None	N/A
NCT02287480	1	rVSVΔG-EBOV	1×10^7, 5×10^7 pfu	None	N/A
NCT02314923	1	rVSVΔG-EBOV	3×10^3, 3×10^4, 3×10^5, 3×10^6, 9×10^6, 2×10^7, 1×10^8 pfu	None	N/A
NCT03031912	2	rVSVΔG-EBOV	2×10^7 pfu	None	N/A
NCT02788227	2	rVSVΔG-EBOV	2×10^7 pfu	±V920	2×10^7 pfu at 18 months
NCT02344407	2	rVSVΔG-EBOV	2×10^7 pfu	None	N/A
		ChAd3-EBOV	1×10^{11} PU		
NCT02876328	2	rVSVΔG-EBOV	2×10^7 pfu	rVSVΔG-EBOV	2×10^7 pfu at day 56
		rVSVΔG-EBOV	2×10^7 pfu	None	N/A
		Ad26-EBOV	5×10^{10} VP	MVA-FILO	1×10^8 IU at day 56
NCT02378753	2/3	rVSVΔG-EBOV	2×10^7 pfu	None	N/A
	3	rVSVΔG-EBOV	2×10^7 pfu	None	N/A
NCT02503202	3	rVSVΔG-EBOV	2×10^7, 1×10^8 pfu	None	N/A
NCT02718469	1	rVSVN4CT1-EBOV	2.5×10^4, 2.5×10^5, 2×10^6 pfu	rVSVN4CT1-EBOV	2.5×10^4, 2.5×10^5, 2×10^6 pfu
NCT02354404	1	ChAd3-EBOV	1×10^{10}, 1×10^{11} PU 2×10^{10}, 2×10^{11} PU	±MVA-EBOV	1×10^8 pfu at 36 weeks
NCT02231866	1	ChAd3-EBOV	1×10^{10}, 1×10^{11} PU	±MVA-EBOV	3.2×10^8 pfu
		ChAd3-EBOV/SUD	2×10^{10}, 2×10^{11} PU		
NCT02368119	1	ChAd3-EBOV/SUD	2×10^{10}, 2×10^{11} VP	MVA-EBOV	1×10^8 pfu at 4 or 16 weeks
NCT02408913	1	ChAd3-EBOV	2×10^{11} PU	MVA-EBOV	1×10^8 pfu
		MVA-EBOV	1×10^7, 1×10^8 pfu	None	N/A
NCT02240875	1	ChAd3-EBOV	1×10^{10}, 2.5×10^{10}, 5×10^{10} PU	±MVA-FILO	4.4×10^7, 2.2×10^8 $TCID_{50}$ at day 7 or 14
NCT02485912	1	ChAd3-EBOV	$2.5–3.7 \times 10^{10}$ PU	MVA-EBOV	1×10^8 pfu at day 7
NCT02451891	1	ChAd3-EBOV	2.5×10^{10} VP	MVA-EBOV	1×10^8, 1.5×10^8 pfu
		MVA-EBOV	1×10^8, 1.5×10^8 pfu	None	N/A
NCT02267109	1	ChAd3-EBOV	1×10^{10}, 2.5×10^{10}, 5×10^{10}, 1×10^{11} PU	MVA-FILO	1×10^8 pfu
NCT02289027	1	ChAd3-EBOV	2.5×10^{10}, 5×10^{10} PU	None	N/A
NCT02548078	2	ChAd3-EBOV	1×10^{11} PU	None	N/A
NCT02485301	2	ChAd3-EBOV	1×10^{11} PU	None	N/A
NCT02495246	1	ChAd3-EBOV	1×10^{11} VP	Ad26-EBOV	5×10^{10} VP at day 28 or 56
		Ad26-EBOV	5×10^{10} VP	ChAd3-EBOV	1×10^{11} VP at day 28 or 56
NCT02325050	1	Ad26-EBOV	5×10^{10} VP	MVA-FILO	1×10^8 pfu at day 15 or 29
		Ad26-EBOV	5×10^{10} VP	Ad26-EBOV	5×10^{10} VP at day 15
		MVA-FILO	1×10^8 pfu	MVA-FILO	1×10^8 pfu at day 15
		MVA-FILO	1×10^8 pfu	Ad26-EBOV	5×10^{10} VP at day 8, 15, 29, or 57
NCT02313077	1	Ad26-EBOV	5×10^{10} VP	MVA-FILO	1×10^8 pfu at day 15, 29, or 57
		MVA-FILO	1×10^8 pfu	Ad26-EBOV	5×10^{10} VP at day 29 or 57
NCT02376400	1	Ad26-EBOV	5×10^{10} VP	MVA-FILO	1×10^8 $TCID_{50}$ at day 29 or 57
		MVA-FILO	1×10^8 $TCID_{50}$	Ad26-EBOV	5×10^{10} VP at day 29 or 57
NCT02376426	1	Ad26-EBOV	5×10^{10} VP	MVA-FILO	1×10^8 pfu at day 29 or 57
		MVA-FILO	1×10^8 pfu	Ad26-EBOV	5×10^{10} VP at day 29 or 57
NCT02860650	1	Ad26-EBOV	5×10^{10}, 9×10^{10} VP	MVA-FILO	1×10^8 pfu
		MVA-FILO	1×10^8 pfu	Ad26-EBOV	5×10^{10}, 9×10^{10} VP
NCT02891980	1	Ad26-EBOV	5×10^{10} VP	Ad26-EBOV	5×10^{10} VP at day 29
		Ad26-EBOV	5×10^{10} VP	MVA-FILO	1×10^8 IU at day 29
		MVA-FILO	1×10^8 IU	Ad26-EBOV	5×10^{10} VP at day 29
		MVA-FILO	1×10^8 IU	MVA-FILO	1×10^8 IU at day 29
NCT02564523	2	Ad26-EBOV	5×10^{10} VP	MVA-FILO	1×10^8 pfu at day 29, 57, or 85
NCT02598388	2	Ad26-EBOV	5×10^{10} VP	MVA-FILO	1×10^8 IU at day 29
		MVA-FILO	1×10^8 IU	Ad26-EBOV	5×10^{10} VP at day 15, 29
NCT02416453	2	Ad26-EBOV	5×10^{10} VP	MVA-FILO	1×10^8 pfu at day 29, 57, or 85
NCT02543567	3	Ad26-EBOV	0.8×10^{10}, 2×10^{10}, 5×10^{10} VP	MVA-FILO	5×10^7, 1×10^8 pfu at day 57
NCT02509494	3	Ad26-EBOV	5×10^{10} VP	MVA-FILO	1×10^8 pfu at day 57
NCT02543268	3	Ad26-EBOV	5×10^{10} VP	MVA-FILO	1×10^8 pfu at day 57
NCT00072605	1	DNA-EBOV	2, 4, 8 mg	DNA-EBOV	2, 4, 8 mg at day 28 and 56
NCT00997607	1	DNA-EBOV	4 mg	DNA-EBOV	4 mg at weeks 4 and 8
		DNA-MARV	4 mg	DNA-MARV	4 mg at weeks 4 and 8
		DNA-EBOV + DNA-MARV	4 mg each	DNA-EBOV + DNA-MARV	4 mg each at weeks 4 and 8
NCT00605514	1	DNA-EBOV	4 mg	DNA-EBOV	4 mg at weeks 4 and 8
		DNA-MARV	4 mg	DNA-MARV	4 mg at weeks 4 and 8
NCT02464670	1	DNA-MAK	1, 2, 4 mg ±DNA-IL12	DNA-MAK	1, 2, 4 mg ±IL12, 2–3 doses
		DNA-EBOV	2 mg	DNA-EBOV	2 mg, 3 doses
		DNA-MAK/EBOV	1, 2, 4 mg ±DNA-IL12	DNA-MAK/EBOV	1, 2, 4 mg ±IL12, 2–3 doses

Table 1 (*continued*)

ClinicalTrials.gov identifier	Phase	Prime vaccination		Boost vaccination (if applicable)	
		Vaccine	Doses	Vaccine	Dose
NCT00374309	1	Ad5-EBOV/SUDV	2×10^9, 2×10^{10}, 2×10^{11} VP	None	N/A
NCT02401373	1	Ad5-EBOV	Low dose, high dose[&]	None	N/A
NCT02533791	1	None	N/A	Ad5-EBOV	4×10^{10}, 1.6×10^{11} VP[&]
NCT02326194	1	Ad5-EBOV	Low dose, high dose	None	N/A
NCT02575456	2	Ad5-EBOV	8×10^{10}, 1.6×10^{11} VP	None	N/A
NCT02564575	1	HPIV3-EBOV	1×10^6, 1×10^7 pfu	HPIV3-EBOV	1×10^6, 1×10^7 pfu at 4–8 week
NCT02370589	1	EBOV GP	Low, 2×, 4×, 8× ±Matrix-M	EBOV GP	Low, 2×, 4×, 8× ±Matrix-M at day 21
NCT03072030	4	GamEvac-Combi	No information	GamEvac-Combi	Boost at day 21

It provides a summary of completed, ongoing, and planned clinical trials for vaccines against Ebola and/or Marburg virus. The summary contains information gathered from https://clinicaltrials.gov/ as of May 2017. The table notes the phase of the trial, the vaccine construct, the dose of the vaccine, and any relevant information if a boost was included. Trials that were provided new identifier numbers but were only monitoring long-term duration of immunity from previous trials are not included here.

as prime-boost regimens with MVA expressing EBOV GP, or the MVA-FILO construct. Phase 1 clinical studies assessed a range of prime-boost regimens (Table 1), but the lead vaccine candidate moving forward into phase 2–3 clinical studies is an Ad26-EBOV prime with an MVA-FILO boost at day 15, 29, or 57. Multiple phase 3 clinical studies were initiated in 2016 (Table 1).

Similar to other candidates that have been evaluated in clinical studies, Ad26-EBOV and MVA-FILO have acceptable safety profiles with mild to moderate injection site pain (86.7%), headache (56.7%), and malaise (60%) being the most common side effects [30]. Titers of GP-specific antibodies ranged from the mid- to high-hundreds at day 28 post-vaccination in a phase 1 study. However, the boost offers a potential advantage increasing peak antibody titers to around 10,000 measured at day 78 [30]. Promising data has also been shown in terms of the duration of antibody response, with titers still in the low- to mid-thousands 240 days post-vaccination [30].

5. Conclusion

Since 2006, BARDA has supported the development of over 160 vaccine, drugs, diagnostics or other countermeasures and 34 of these MCMs have achieved FDA approval, clearance, or license to be used to respond to public health emergencies. In response to the 2014 ebola virus outbreak, BARDA received a budget supplement and was able to accelerate the development of vaccines, therapeutics and diagnostics for EBOV. Significant progress was made as several promising vaccine candidates moved from early development into late stage clinical development. The near-term goal is to complete development efforts to ensure that at least one FDA-licensed product is available to provide a response capability for future EBOV outbreaks. The long-term goal includes the expansion of the VHF vaccine program to protect against a broader range of filoviruses such as SUDV and MARV.

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