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COMMENTARY

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A two-dose heterologous prime-boost vaccine regimen eliciting sustained immune responses to Ebola Zaire could support a preventive strategy for future outbreaks

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ABSTRACT

The consequences of the 2013–16 Ebola Zaire virus disease epidemic in West Africa were grave. The economies, healthcare systems and communities of Guinea, Sierra Leone and Liberia were devastated by over 18 months of active Ebola virus transmission, followed by sporadic resurgences potentially related to sexual transmission by survivors with viral persistence in body fluids following recovery. The need to develop and implement strategies to prevent and mitigate future outbreaks is now beyond dispute. The potential for unpredictable outbreaks of indeterminate duration, and control challenges posed by the possibility of sporadic re-emergence, mean that implementation of an effective vaccination program for outbreak containment necessitates a vaccine providing durable immunity. Heterologous prime-boost vaccine regimens deliver the same or similar antigens through different vaccine types, the first to prime and the second to boost the immune system. Ad26.ZEBOV/MVA-BN-Filo is an investigational Ebola Zaire vaccine regimen that uses this heterologous prime-boost approach. Preliminary Phase 1 data suggest that Ad26.ZEBOV/MVA-BN-Filo confers durable immunity for at least 240 d and is well-tolerated with a good safety profile. This regimen may therefore be suitable for prophylactic use in a regional or targeted population vaccination strategy, and could potentially aid prevention and control of future Ebola outbreaks.

KEYWORDS

Ebola virus; heterologous prime-boost; Ad26.ZEBOV/MVA-BN-Filo; viral persistence; sustained immunity; population vaccination strategy

Introduction

The 2013–16 outbreak in West Africa was caused by the Ebola Zaire species, one of 5 species of Ebolavirus. This particular species has been responsible for 4 of the 5 most serious Ebola outbreaks,[1] however this was the first emergence of the Zaire species recorded in a high-density urban population,[2] resulting in its rapid and widespread transmission. The resulting epidemic was of unprecedented scale, causing over 28,000 total cases (suspected, probable and confirmed), and more than 11,000 deaths.[3]

Ebolavirus is a member of the *Filoviridae* family of viruses and causes Ebola virus disease (EVD), also known as Ebola hemorrhagic fever (EHF), in both human and non-human primates. Human-to-human transmission of the virus results from contact with infected body fluids and secretions.[4] The virus can persist in some body fluids for months or years following clearance of viraemia.[5] In particular, viral persistence in the semen has been recorded up to 488 d.[6]

The Ebola virus epidemic of 2013 is thought to have begun in an 18-month-old boy in Guinea, having been transmitted to him from an infected wild animal, probably a bat.[7,8] The virus then spread to the neighboring countries of Liberia and Sierra Leone, where weak health systems and poor surveillance hindered risk assessment and potentially contributed to its accelerated transmission.[9,10] Sporadic flare-ups occurred in Sierra Leone, Guinea and Liberia in early 2016, in all cases following declaration of the end of the epidemic in each country.[11-13] At least some of these flare-ups have been proven to have arisen as a consequence of re-emergence of previously active transmission chains, perhaps resulting from transmission by a persistently infected survivor.[14,15]

Although the West African epidemic has now been declared over, a new outbreak could arise at any time. It is now clear that Ebola spread resulting from human-to-human transmission, including infection by survivors and mother-to-child transmission, can give rise to an epidemic of much greater scale and impact than previously anticipated. Trends suggest that future outbreaks could be even more serious than the West African epidemic if effective control measures are not put in place.[16] Adequate preparation, encompassing early detection, management and prevention, is vital to control any future outbreaks and prevent a repetition of the human and economic impact of the West African epidemic.

Role of vaccination in managing potential future outbreaks

The prevention of Ebola virus transmission must form a key element of any control plan. The availability of a vaccine conferring durable immunity would undoubtedly aid the implementation of such a plan. Several vaccine candidates are

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currently in development. These include ChAd3-EBO, a chimpanzee Adenovirus vector vaccine,[17] and rVSV-ZEBOV, which utilizes a Recombinant Vesicular Stomatitis Virus (rVSV). Interim results from studies of rVSV-vectored vaccines expressing Ebola virus glycoprotein have demonstrated a rapid immune response. The preliminary data suggest that the vaccine is efficacious in the context of a reactive ring vaccination strategy and could aid containment of an active outbreak when used in such a setting;[18] furthermore, Agnandji et al (2016) have indicated that further evaluation is needed to assess safety and efficacy.[19] Additionally, Ad26.ZEBOV/MVA-BN-Filo is an investigational heterologous prime-boost regimen that has demonstrated strong immunogenicity together with a good safety profile in preliminary Phase 1 data.[20]

Different vaccination strategies may be used to prevent and mitigate the spread of Ebola, depending on the circumstances. The three strategies that have been modeled for the Ebola epidemic are ring vaccination, targeted vaccination of high-risk individuals (such as front-line workers and healthcare workers) and population vaccination (Table 1). During an outbreak where ring vaccination is the strategy used to disrupt chains of transmission and prevent the outbreak spreading, rapid onset of protection is important and duration of immunity is a lower priority. In at-risk populations in which the virus is not actively circulating, a prophylactic population vaccination strategy using a vaccine regimen that confers sustained immunity may be more appropriate.[21]

Ebola transmission modeling data suggest that ring vaccination at the start of an outbreak would probably not be sufficient to contain the spread, particularly where individual cases and contacts are difficult to identify.[22] This was the case in West Africa early in the course of the epidemic, and is likely to be in the future, particularly in densely populated areas and those with mobile populations. Therefore, regional population vaccination is likely to be necessary to bring sustained transmission under control. In addition, targeted vaccination of at-risk groups such as front-line workers is a vital adjunct to such a strategy in order to protect the members of the community at highest risk of exposure. Because the timing of front-line workers' exposure to the virus is difficult to predict, durability of protection is an important consideration in implementing such a program. To implement an effective regional population vaccination strategy and provide suitable protection for front-line workers, a vaccine conferring sustained immunity and with a good safety and tolerability profile will be needed.[23] The utilization of a heterologous prime-boost strategy, such as in the Ad26.ZEBOV/MVA-BN-Filo vaccine regimen, represents an innovative approach to fulfilling this need.

Table 1. Overview of potential Ebola vaccination strategies.

Ring vaccination	Targeted vaccination of at-risk groups	Population vaccination
• Focuses on contacts of cases • Prevent an ongoing outbreak from spreading	• Priority vaccination of front-line workers, e.g. ○ Healthcare / funeral workers ○ Community response teams ○ Critical infrastructure personnel	• Mass vaccination in targeted areas • Establish herd immunity to protect larger groups/ regions

Heterologous prime-boost approach to enhancing durability of immune response

Multiple-dose prime-boost vaccination regimens are well established. Several homologous prime-boost regimens, whereby the same vaccine is used for the prime and boost doses, are routinely recommended. Examples include the tetanus, hepatitis B, measles and injectable polio vaccines.[24] More recently, heterologous prime-boost regimens have been developed with the goal of producing stronger and longer-lasting immunity to a disease. Heterologous prime-boost delivers the same or similar antigens for the disease through different vaccine types, the first to prime the immune system and the second to boost the immune system. Evidence has emerged that such a heterologous prime-boost approach may in some cases be even more effective in producing durable immunity than homologous boosting (Fig. 1).[25,26] Although single-dose vaccinations are preferred due to ease of deployment, the heterologous prime-boost approach can potentially offer significant durability benefits compared with single-dose alternatives, justifying its more complex administration. In the case of the Ad26.ZEBOV/MVA-BN-Filo regimen, the priming vaccine component is Ad26.ZEBOV, and the boosting vaccine component is MVA-BN-Filo.

Ad26.ZEBOV/MVA-BN-Filo clinical development

Several Phase 1–3 clinical studies are currently being conducted in support of potential eventual registration for the Ad26.ZEBOV/MVA-BN-Filo Ebola vaccine regimen. Since 2008, Janssen have pursued the development of an adenovirus-based Filovirus vaccine. The Ad26.ZEBOV/MVA-BN-Filo study program was accelerated in 2014 as part of the public health response to the West African epidemic. To this end, 4 Phase 1 and 3 Phase 2 studies are assessing safety, tolerability and immunogenicity of the regimen in healthy adults and populations including subjects with HIV, elderly people, adolescents and young children. An expanded safety and immunogenicity trial in Sierra Leone, the EBOVAC-Salone study, is

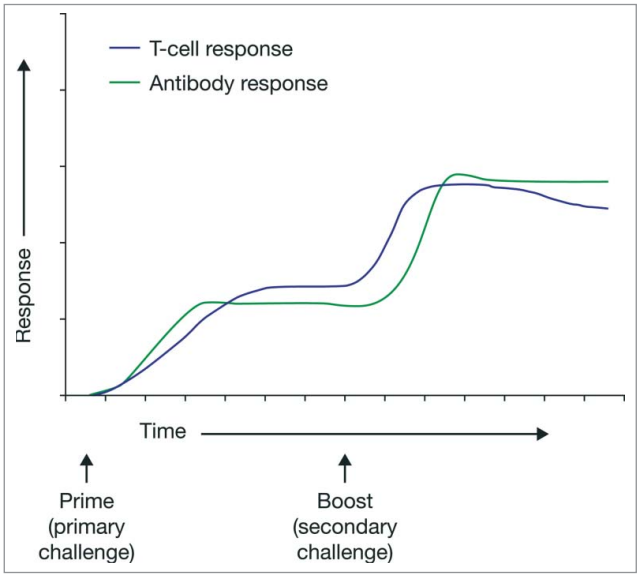

Figure 1. Schematic illustrating the prime-boost concept. *Note*: High levels of antibodies and memory T-cells both contribute to rapid, effective immune response to infection.

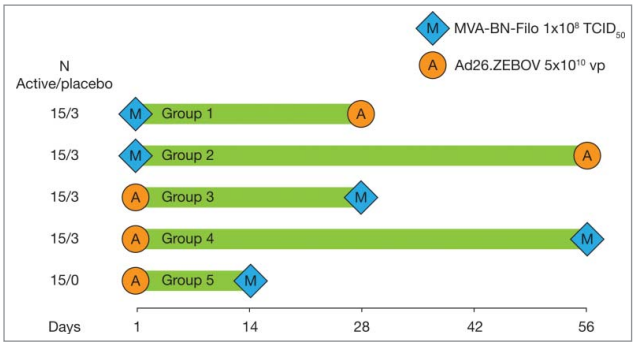

Figure 2. Dosing schedule for groups receiving heterologous prime-boost MVA-BN-Filo and Ad26.ZEBOV in EBL1001 study (Clinicaltrials.gov: NCT02313077). *Note*: Groups 1–4 were randomized and blinded to active vaccine/placebo; group 5 was open-label.

underway,[27] and 2 supporting Phase 3 studies are currently ongoing with different vaccine lots of Ad26.ZEBOV and MVA-BN-Filo for quality assessment of the vaccines. Finally, a prospective registry has been established to follow subjects who received Ad26.ZEBOV and/or MVA-BN-Filo in clinical studies, to document their long-term safety profile.

Preliminary safety and immunogenicity data

The Phase 1 clinical studies being conducted in the US, Europe and Africa all share the overall aim of establishing sufficient safety and immunogenicity data to rapidly progress the selected prime-boost sequence and schedule(s) toward licensure. Studies in the UK (EBL1001) and US (EBL1002) are intended to establish preliminary safety and immunogenicity, identify optimal short schedules and investigate durability of immune responses, while the studies in Africa (EBL1003 and EBL1004) aim to replicate data of first in human (FIH) study in countries unaffected by the West African epidemic and confirm preliminary safety and immunogenicity.

The EBL1001 trial is a single-center, randomized, placebo-controlled, observer blind trial held in the UK. MVA-BN-Filo and Ad26.ZEBOV were administered in different sequences and schedules in healthy 18–50 y olds (n = 87) (Fig. 2). EBL1001 data have been reported in a preliminary communication by Iain Milligan and colleagues.[20] Preliminary safety data in healthy volunteers are indicative of a well-tolerated vaccine regimen with a good safety profile. No safety concerns with either vaccine were identified, and no vaccine-related serious adverse events occurred. The most frequent adverse events were mild in intensity and short in duration.

In terms of immunogenicity, Ad26.ZEBOV priming has been observed to induce antibody and T cell responses to Ebola virus glycoprotein, detectable as early as Day 14 post-prime in 80% of participants. Post-prime immune responses were stronger and more rapid following Ad26.ZEBOV priming versus MVA.BN-Filo priming (Fig. 3; Fig. S1). Substantial post-boost strengthening of antibody and T cell responses was observed in participants receiving all tested heterologous prime-boost regimens. Responses were sustained for at least 240 d post-prime, with no apparent effect of varying the prime-boost interval (56 vs. 28 days) on the durability of immune responses (Fig. 4). Follow-up is ongoing. Notably, 8 months following prime vaccination, 100% of individuals in the study maintained Ebola-specific antibodies, and furthermore T cell

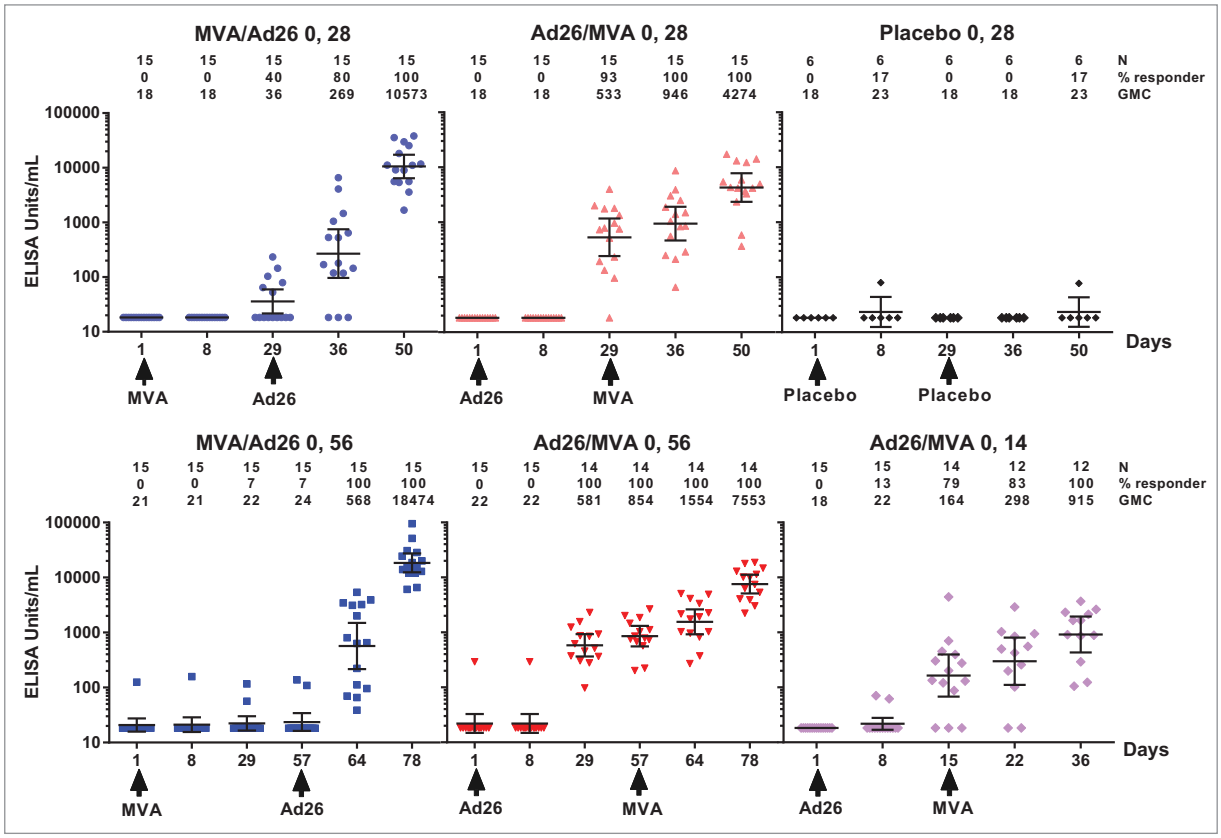

Figure 3. EBOV GP-specific antibody responses to different orders of prime and boost administration, with 14-, 28- and 56-day prime- boost interval (EBL1001 study data, shown up to 21 d post-boost), assessed by ELISA (enzyme-linked immunosorbent assay). GMC, geometric mean concentration; GP: glycoprotein.

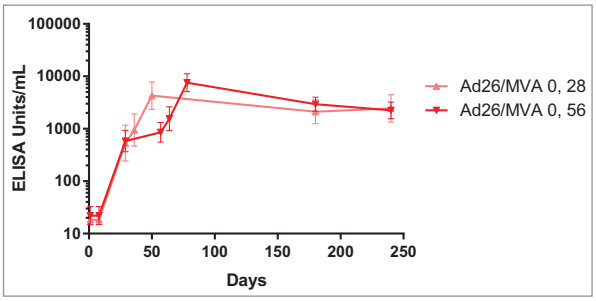

Figure 4. EBL1001 duration of anti-Ebola GP antibody response (assessed by ELISA) up to 240 d post-prime ELISA: Enzyme-linked immunosorbent assay; GP: glycoprotein.

responses persisted in 77–80% of individuals receiving the Ad26.ZEBOV/MVA-BN-Filo regimen (Fig. 4).

In summary, Phase 1 findings so far reported indicate that Ad26.ZEBOV prime immunization readily induces an immune response which is enhanced further by MVA-BN-Filo boosting, that the Ad26.ZEBOV/MVA-BN-Filo heterologous prime-boost regimen induces durable immunity to Ebola Zaire, and that both the prime and boost are well tolerated with a good safety profile.

Concluding remarks

The West African epidemic of Ebola Zaire was unprecedented in scale. It is not enough to wait for another runaway epidemic to emerge, at the immense cost of thousands of lives and millions of dollars, to invest in preparation for the prevention and mitigation of future outbreaks. Lessons from the epidemic include the importance of co-ordinating and adequately resourcing control measures, the crucial importance of robust and resilient health systems, and key role of community engagement in enabling contact tracing and early reporting.[28] It is now apparent that spread of Ebola through human-to-human transmission can greatly worsen the scale of outbreaks, and that viral persistence and sexual transmission from survivors can perpetuate an epidemic and result in flare-ups long after the outbreak is thought to have ended.[29]

Data from preliminary studies suggest that the heterologous prime-boost Ad26.ZEBOV/MVA-BN-Filo vaccine regimen confers durable immunity with a good safety and tolerability profile. This regimen may therefore be well-suited to prophylactic use, potentially underpinning preventive vaccination strategies in the event of a new outbreak. The protection of frontline workers such as healthcare providers, as recommended in the WHO target product profile for Ebola vaccines,[30] is key to mitigating the impact of a developing outbreak. Because the timescale during which frontline workers may be at risk of exposure to the virus cannot easily be determined in advance, durability of protection is a key consideration for such a strategy. Furthermore, the lessons of the West African outbreak, including the newfound understanding of the risks associated with prolonged viral persistence, highlight potential risks to frontline workers even after active transmission is thought to have ended.[31] Protection of frontline workers is necessary, but may not be sufficient to achieve control and prevent a future outbreak from becoming another widespread epidemic.[21] An effective targeted population vaccination program may be required, and once again sustained, robust immunity will be necessary for success.[32]

Janssen have dramatically scaled up manufacturing capabilities for both components of the regimen in preparation for the next outbreak, leveraging existing platforms to facilitate rapid production in response to an emergency. The vaccine has demonstrated standard cold-chain (2–8°C) compatibility and suitability for long-term refrigerated storage in field conditions. Efforts to determine how best to deploy the heterologous prime-boost regimen are ongoing; the stability findings suggest that the vaccine components are appropriate for field deployment as part of such a regimen and for the potential implementation of a large-scale prophylactic population vaccination strategy. In addition, taking consideration of the possibility that the next major filovirus outbreak may involve a species other than Ebola Zaire, a multivalent Ad26/MVA-BN-Filo vaccine regimen is in ongoing development; first-in-human trials are scheduled to begin in the fourth quarter of 2016.

An effective vaccine with an acceptable safety profile could, with suitably reliable distribution arrangements, form an integral part of control measures in the case of a future outbreak.[23] Based on the preliminary safety and immunogenicity data presented here, Ad26.ZEBOV/MVA-BN-Filo has demonstrated considerable promise as a regimen well-suited to such a strategy.

Abbreviations

EBOV GP	Ebola Virus Glycoprotein
EVD	Ebola Virus Disease
EHF	Ebola Hemorrhagic Fever
FIH	First In Human
rVSV	Recombinant Vesicular Stomatitis Virus

Disclosure of potential conflicts of interest

All authors are employees of Janssen Pharmaceuticals.

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