Expedited delivery of Ebola vaccine trials: Recruiting to a phase I vaccine trial in response to an epidemic

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Background: During the 2013-2015 Ebola epidemic in West Africa, the WHO published an Ebola Response Roadmap, pledging to accelerate the development of vaccines against Ebola virus disease (EVD)[1]. The UK has been at the forefront of international efforts to expedite testing of candidate vaccines. The delivery of phase 1 vaccine trials in the context on an infectious diseases emergency could offer lessons for future epidemic preparedness.

Methods: We setup the first phase I, randomised, observer-blinded clinical trials designed to assess the safety and immunogenicity of a prime-boost vaccine combination of two viral-vectored vaccines expressing Ebola glycoproteins (Ad26.ZEBOV [Crucell, Netherlands] and MVA-BN-Filo® [Bavarian Nordic, Denmark]). Using an independent, multidisciplinary team of doctors, nurses, laboratory technicians and trial administrators we were able to expedite delivery of this 'first-in-human' study. Recruitment methods included poster advertisement, direct mail out, media engagement and web-based self-screening.

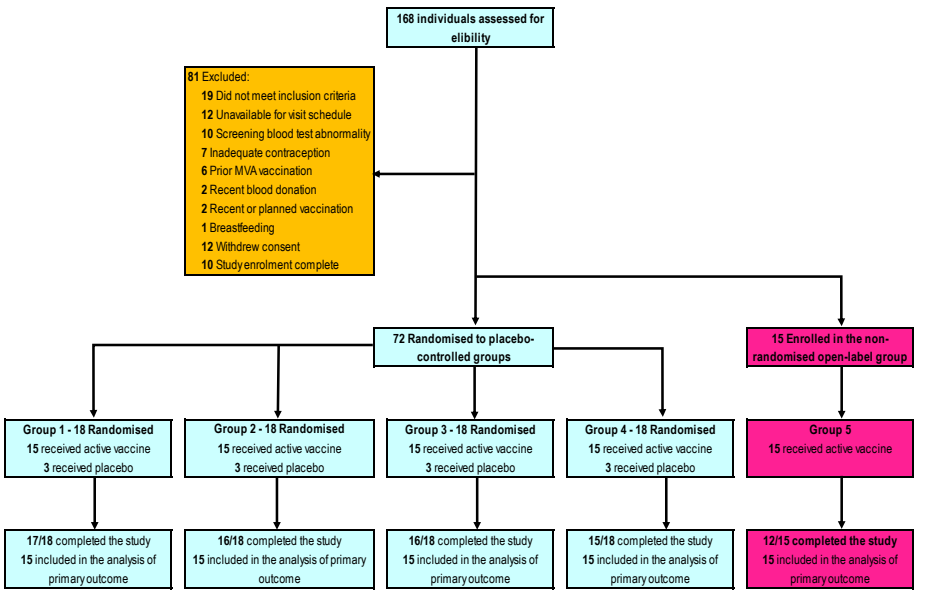

Figure 1. *Consort Diagram.* 72 participants were initially enrolled in the randomised, observer-blinded trial to either receive active vaccination (Ad26.ZEBOV prime with MVA-BN-Filo® boost or vice versa) or placebo. A further 15 participants were enrolled following an amendment to the protocol assessing whether a 14 day prime-boost regime was safe and efficacious. **All vaccinated participants were included in the analysis of the primary outcome (safety and tolerability of both vaccines).** Based on Milligan et al. (2016) [3].

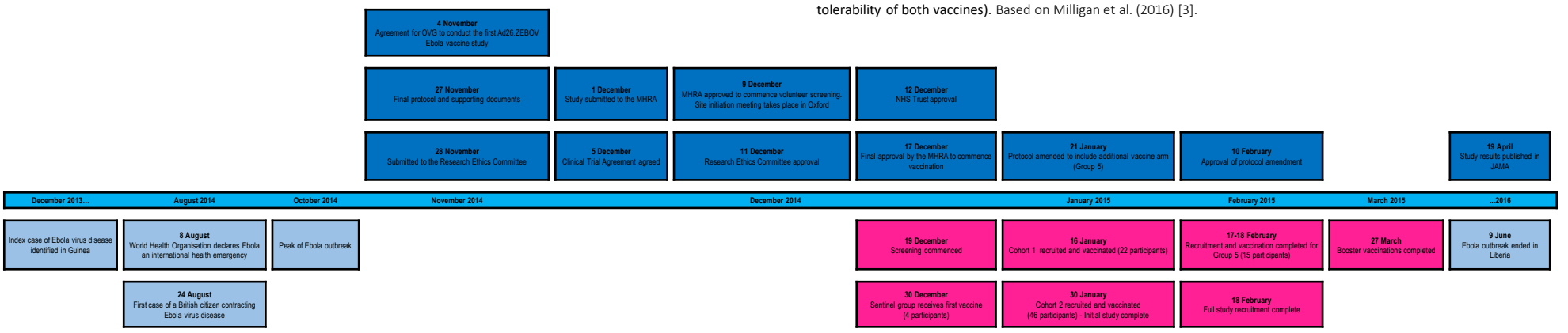

Figure 2. *'EVE' Study Setup Timeline.* Light blue indicates the timeline of the EVD outbreak. Dark blue indicates key dates in the setup of the trial including regulatory approvals. Pink indicates key recruitment, screening and vaccination targets.

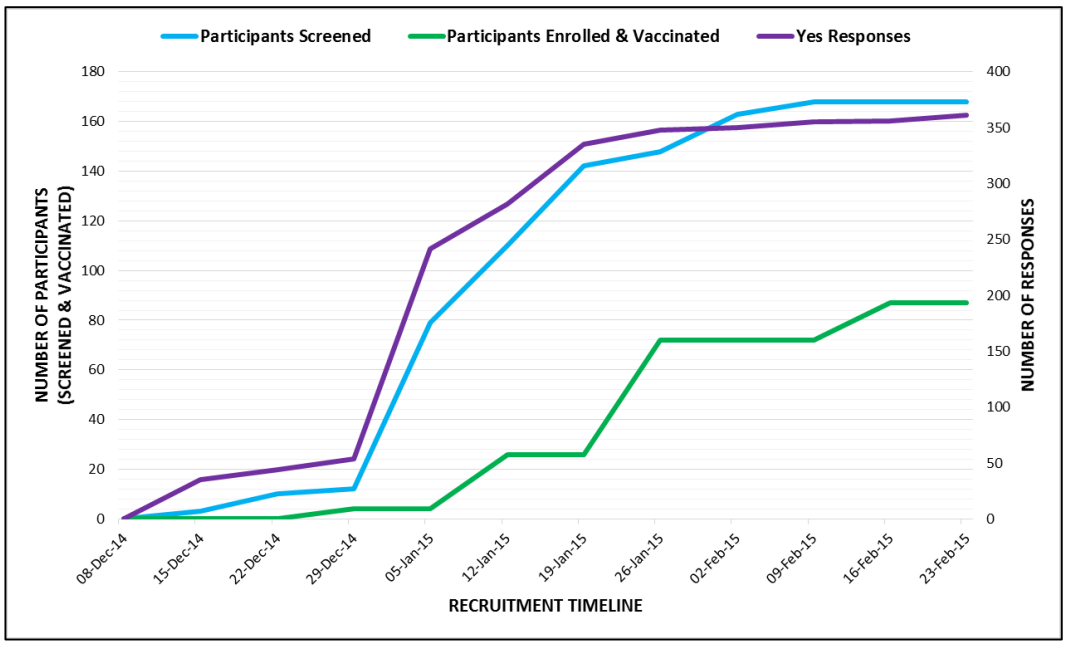

Figure 3. *Recruitment to the 'EVE' Study.* A total of 361 'yes' responses were received from members of the public interested in volunteering for this first-in-human study, of which 168 participants had attended a screening appointment and 87 participants were enrolled and vaccinated within 50 days.

Results: Setup of trial, including protocol development, document preparation and staff training was completed within 3 weeks. Following expedited submission and review, regulatory approval was granted within eight working days by the Medicines and Healthcare products Regulatory Agency (MHRA) and within ten days by the Research Ethics Committee (NRES Committee South Central - Oxford A). Within 7 weeks we screened 168 volunteers and vaccinated 87 participants. Concurrently, daily safety reviews of clinical and laboratory participant data, continued eligibility assessment and immunological testing of samples occurred. The vaccines were well tolerated and demonstrated persistent antibody responses up to 1 year post-vaccination[3,4].

Discussion & Conclusions: Our response to the Ebola outbreak is our second test of expedited vaccine evaluation in the last decade[2] and demonstrates the capacity to respond quickly in an epidemic. Researchers in the UK have arguably benefitted from a robust and flexible research environment, with critical support across the relevant government departments, and dependent on an experienced multidisciplinary team. Remarkably, 4 out of the 5 Ebola vaccines that entered clinical trials in West Africa had their first-in-human dose given in Oxford. Together with the publics willingness to participate in such studies, the expedited delivery of this trial and the responsive UK research infrastructure and approvals processes, we have demonstrated a successful model for the conduct of rapidly responsive clinical trials. Preparedness for future epidemics could be aided by lessons learned from the EVD outbreak and the pre-emptive development of vaccine protocols for potential outbreak pathogens.

References:

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