



Real-time dynamic modelling for the design of a cluster-randomized phase 3 Ebola vaccine trial in Sierra Leone



A. Camacho^{a,1}, R.M. Eggo^{a,*,1}, N. Goeyvaerts^b, A. Vandebosch^b, R. Mogg^c, S. Funk^a, A.J. Kucharski^a, C.H. Watson^a, T. Vangeneugden^b, W.J. Edmunds^a

^a Department of Infectious Disease Epidemiology, London School of Hygiene & Tropical Medicine, Keppel Street, London WC1E 7HT, UK

^b Janssen Research & Development, Beerse, Belgium

^c Janssen Research & Development, LLC, Spring House, PA, USA

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ABSTRACT

Background: Declining incidence and spatial heterogeneity complicated the design of phase 3 Ebola vaccine trials during the tail of the 2013–16 Ebola virus disease (EVD) epidemic in West Africa. Mathematical models can provide forecasts of expected incidence through time and can account for both vaccine efficacy in participants and effectiveness in populations. Determining expected disease incidence was critical to calculating power and determining trial sample size.

Methods: In real-time, we fitted, forecasted, and simulated a proposed phase 3 cluster-randomized vaccine trial for a prime–boost EVD vaccine in three candidate regions in Sierra Leone. The aim was to forecast trial feasibility in these areas through time and guide study design planning.

Results: EVD incidence was highly variable during the epidemic, especially in the declining phase. Delays in trial start date were expected to greatly reduce the ability to discern an effect, particularly as a trial with an effective vaccine would cause the epidemic to go extinct more quickly in the vaccine arm. Real-time updates of the model allowed decision-makers to determine how trial feasibility changed with time.

Conclusions: This analysis was useful for vaccine trial planning because we simulated effectiveness as well as efficacy, which is possible with a dynamic transmission model. It contributed to decisions on choice of trial location and feasibility of the trial. Transmission models should be utilised as early as possible in the design process to provide mechanistic estimates of expected incidence, with which decisions about sample size, location, timing, and feasibility can be determined.

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1. Introduction

West Africa experienced the largest outbreak of Ebola virus disease (EVD) to date during 2013–16. This epidemic resulted in more than 25,000 cases and 10,000 deaths. As the epidemic unfolded in 2014, development of candidate vaccines was accelerated, including evaluation in phase 1–2 studies and phase 3 planning. However, the rapidly changing incidence both geographically and in time posed major challenges to the design and planning of phase 3 trials. Typical study design calculations do not allow for varying infection rates within and between communities over time, which is especially problematic during the tail of an epidemic, when few cases occur. Computer simulations employing empirical statistical models can mitigate some of these

concerns however they require accurate assumptions on incidence, heterogeneity and, in addition, do not capture the mechanism of an outbreak. Moreover, an effective vaccine used widely in a given area (as would be the case in large-scale, population-based vaccine trials) could in itself further reduce the incidence.

Dynamic models of EVD transmission were developed during the epidemic to understand the patterns of spread of the virus and predict the course of the outbreak [1–4]. If these models are appropriately parameterised and updated, then they can be used to predict incidence and how it may change in space and time [5]. In addition, dynamic models can account for both the direct and indirect effect of vaccine-induced immunity and its impact on the transmission dynamics. That is, they can be used to assess the extent that the trial itself may affect the transmission dynamics.

Collaboration between the Centre for Mathematical Modelling of Infectious Disease (CMMID) at the London School of Hygiene & Tropical Medicine and Janssen Research & Development (Janssen R&D) was established to rapidly extend a mathematical model of

* Corresponding author.

E-mail address: r.eggo@lshtm.ac.uk (R.M. Eggo).

¹ These authors contributed equally.

EVD [3] to simulate a cluster-randomized phase 3 vaccine trial in Sierra Leone. The dynamic model and trial simulations were updated in real-time to match the latest incidence data available. This collaboration thus enabled a real-time, dynamic assessment of the feasibility of a potential phase 3 trial, which ultimately was implemented as a safety and immunogenicity study: EBOVAC-Salome (NCT02509494). This paper describes how the model was used to inform the planning of the trial as well as the decision-making to abandon the effectiveness part of the protocol.

2. Methods

2.1. Collaboration

Collaboration was initiated between CMMID and Janssen R&D in February 2015. Janssen R&D was seeking a partner to guide study design and feasibility planning of a phase 3 effectiveness trial for their heterologous prime-boost vaccine regimen (Ad26.ZEBOV as prime and MVA-BN[®]-Filo 28 days later as boost), for which phase 1 trials were on-going.

CMMID had previously developed mathematical models of EVD transmission to assess the potential for large outbreaks [6], impact of community care centres on the evolving epidemic [7], and bed capacity in Sierra Leone [3]. In addition, CMMID members liaised with WHO on the design and analysis of the WHO EVD vaccine trial [8].

Collaboration offered a unique opportunity to explore the use of a dynamic transmission model to evaluate study feasibility. In this paper, we present the model-based incidence projections and trial simulations from 15th February 2015, similar to those sent from LSHTM to the team at Janssen on a weekly basis from February 2015 to May 2015. These were in turn employed by the clinical study team to evaluate and guide power calculations, study design as well as trial feasibility. To illustrate the impact of the evolving epidemic, an update of the projections and simulations at the end of April is provided as [supplementary materials](#).

2.2. Vaccine trial design

A large-scale cluster-randomized phase 3 trial was designed to evaluate the effectiveness of prime-boost vaccine regimen against laboratory-confirmed EVD in an outbreak setting in Sierra Leone [9]. Sierra Leone is administratively divided into districts, districts into chiefdoms, and chiefdoms into sections. A trial cluster would be a section. With vaccine availability at time of study design of up to four hundred thousand doses of both prime and boost vaccine, approximately 160 clusters of 5000 participants (800,000 in total) were to be assigned in a 1:1 ratio to immediate vaccination versus no vaccination (control), whereby vaccination would be offered to the control group after effectiveness was established.

Initially, feasibility, statistical power, and type I error of the trial were evaluated using simulations which assumed constant incidence through time [9]. Control incidence assumptions of 3, 5, 10, 20 and 40 EVD cases per arm per month (400,000 person-months) were evaluated, with allowance for heterogeneity between clusters based on CMMID projections and simulations. However, the rapidly changing epidemic dynamics in early 2015 meant that these static predictions were unlikely to capture the epidemiological picture.

2.3. Transmission model for trial

The transmission model extended a previously published model for transmission of EVD [3]. It was a stochastic compartmental model, where the population was divided into classes (Fig. 1): Sus-

ceptible (*S*), Exposed (*E*), Infectious not yet notified (*I*), Infectious and notified (*J*) and Removed (*R*, for recovered and immune, or dead). The infectious compartment was split in two sub-compartments *I* and *J* in order to account for a delay of (on average) 4.8 days to notification of new cases [4]. The model was extended to mimic the trial design closely, but modelling cluster-level randomization was not possible because there was insufficient data available at this spatial scale for fitting. It is often difficult to predict the tails of epidemics, which are characterized by small, local outbreaks, and stochastic variation. Instead, we assumed a 1:1 randomization at the district level and treated the clusters as independent units.

Susceptible people were assumed to be recruited to the trial for the length of the accrual time, T_p , by entering either the vaccine (V_S) or control (C_1) arms. An average of 2 weeks after receiving the prime, vaccinated participants entered the compartment, V_p , where they were assumed to have a reduced risk of infection, σ_p . On receipt of the boost vaccine, they were assumed to enter V_B , and immediately gain the target vaccine efficacy, σ_b (Fig. 1). Control participants were assumed to proceed from C_1 to C_2 at the same rate as V_S to V_p to maintain comparability. Parameters that govern rates of transition are given in Table 1. To account for external influences on transmission – such as variation in human behavior and introduction of control measures – we assumed that the transmission rate could change over time; the extent and direction of change was estimated during the model fitting process [3]. Hypothetical vaccine efficacy values were defined in February 2015 for the power calculation of the effectiveness trial. These values were conservative estimates, chosen to ensure that the planned trial would have sufficient power in the event of unpredicted changes in incidence, and to decrease the risk of the study. These hypothetical assumptions are only working hypotheses and do not necessarily reflect the potential effect of this candidate vaccine, and these hypothetical values need to be assessed in the future.

2.4. Incidence data

The model was fitted to weekly confirmed and probable EVD incidence data from three districts in Sierra Leone (Kambia, Port Loko, and Western Area) that had on-going epidemics in February 2015 and were therefore candidate areas for a potential vaccine trial. Data were drawn from the WHO and Sierra Leone situation reports and ran from 25th May 2014 until the date of fitting and forecast [10,11]. We used Bayesian methods to fit the model to the data, namely particle Markov Chain Monte Carlo, which allows parameter estimation in a stochastic framework.

2.5. Forecasting

We sampled the reproduction number (R_t) 5000 times at the last fitted data point, and forecasted the epidemic until extinction under the assumption that the reproduction number did not change from that time. We retained only forecasts that went extinct by 1st January 2016 because all regions showed waning epidemics, and although persistence for a further year was possible, it was deemed unlikely (Fig. S2). Sampled reproduction numbers therefore usually lie below 1 (Fig. S1). Updated estimates of the reproduction number distribution made in April 2015 have very little density above 1, which suggests this was a reasonable assumption.

The forecasted persistence probability at each point of time t was defined as the probability that at least one infectious individual remains in the arm at that time, and was computed empirically by summing over the N forecast trajectories that went extinct by 1st January 2016:

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