Supplementary Information

for

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

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1. Effect of extinction by end of year

1.1. Reproduction number, R_t

We condition our epidemic projections on extinction by 31^{st} December 2015. This means that only simulations that are extinct by that date are retained and included in trial simulations. This decision was made because the epidemic was already in decline by February 2015 (Figure 2 in the main text) and it was deemed very unlikely that transmission would be ongoing due to community transmission in 2016. The simulations that were retained have a lower R_t than all fitted simulations (Figure S1). The coloured bars show the distribution of the fitted final R_t values at the two forecast dates, and the grey are the values used creating the forecast trajectories. By 26th April 2015 (blue) the distribution of final R_t values is shifted to lower values compared with February (red), which lends support to the choice to assume the end of the community epidemic by 31^{st} Dec 2015.



Figure S1. Comparison of the posterior fitted final R_t values at two forecast dates, and the distribution of R_t values used for projections.

1.2. Epidemic trajectories

In this section we examine the effect of the constraint on epidemic persistence assumed in the main text. Epidemic trajectories forecast on 15th February 2015 that are not constrained to be extinct on or before 31st December 2015 frequently show a second expanding phase (Figure S2, upper panels). This was deemed unlikely at the time of these forecasts, and indeed, the observed weekly incidence that occurred after these forecasts were made, bears this out, shown as the red points on the graphs. The constrained epidemics, where extinction must occur on or before 31st December 2015, show excellent agreement with the observed incidence. For Kambia, Port Loko, and Western Area respectively, 65, 59, and 65% of later data points lie within the 50% credible interval (CI) of forecasted incidence, and 92, 92 and 94% of points lie within the 95% CI of the forecasted incidence.



Figure S2. Epidemic trajectories for forecasts made on 15th February 2015. Upper panel shows epidemics that are not constrained to extinction on or before 31st December 2015, and lower panel the constrained epidemics. Red points mark observations that occurred after the forecasts were made.

Epidemic forecasts made on 26th April 2015 that are not constrained to go extinct on or before 31st December 2015 frequently show an expanding phase, shown by the increase in forecasted incidence (Figure S3). In late April 2015, this was deemed an extremely unlikely scenario, and the constrained epidemics show much closer agreement with incidence that was observed after these forecasts were made. For Kambia, Port Loko, and Western Area respectively, 54, 50, and 67% of later data points lie within the 50% CI of forecasted incidence, and 88, 67, and 92% of points lie within the 95% CI of the forecasted incidence.



Figure S3. Epidemic trajectories for forecasts made on 26th April 2015. Upper panel shows epidemics that are not constrained to extinction on or before 31st December 2015, and lower panel the constrained epidemics. Red points mark observations that occurred after the forecasts were made.

2. Trial simulations: number of cases

Complete results of the number of simulations giving a negative effect, positive effect or equal number of cases are given here (Table S1). The vaccine efficacy is assumed to have a hypothetical value of 80% after prime-boost vaccination. Forecasts were made using data up to 15 February 2015. A negative effect occurs when there are more cases in the vaccine arm by chance, a positive effect when there are more cases in the control arm, and no effect can be detected when there are equal cases in each arm, or zero cases in either arm.

Area	Trial Start Date	Negative effect	Positive effect	Equal cases (>0)	0 cases in both arms
Kambia	1 May	18.1	55.2	3.0	23.8
	1 June	16.0	31.2	0.4	52.4
	1 July	12.1	15.0	0.5	72.4
Port Loko	1 May	11.8	32.4	1.8	54.1
	1 June	6.0	12.7	0.6	80.7
	1 July	3.8	5.2	0.1	90.9
Western Area	1 May	11.3	37.7	2.4	48.6
	1 June	5.3	12.8	0.6	81.3
	1 July	2.7	4.0	0.1	93.2

Table S1. Percent of 5,000 simulations in each category.

3. Real-time update April 2015

In this section we update the three key results from the main paper with simulations using observed data up to 26th April 2015. During the epidemic, CMMID supplied these updates to Janssen R&D every two weeks.

1.3. Effect of start date on number of cases in each arm

Figure S2 is homologous with Figure 3 in the main text, and shows the effect of the start date of the trial on the number of cases in each arm. In this case, the vaccine is assumed to have a hypothetical value of 80% after prime-boost vaccination. The values shown in the main paper are very similar to the values in figure S4, except in Port Loko, where there was a steep decline in incidence. This decline then shapes the updated projections.



Figure S4. Effect of start date on number of cases in vaccine and control arms, and persistence probability in each region, stratified by start date of the trial. Cumulative cases are only shown for trajectories that persist until that month. When no boxplot is shown, this indicates that all trajectories were extinct by that month.

1.4. Distribution of cases in each arm

Figure S5 is homologous with Figure 4 in the main text, and shows the distribution of cases in the vaccine and control arms using data up to 26th April 2015. In this case, the

vaccine is assumed to have a hypothetical value of 80% after prime-boost vaccination. A value above the diagonal represents a negative effect, where there are more cases in the vaccine arm than the control arm, even when the vaccine is efficacious.

The percentage negative (simulations above the diagonal) vs positive (simulations below the diagonal) for a trial starting in May is 20% vs 56% in Kambia, 5% vs 6% in Port Loko and 14% vs 43% in Western Area. For a trial starting in July, the difference shrunk to 8% vs 10%, 0.5% vs 0.5% and 2% vs 3% in those three districts respectively.



Figure S5. Distribution of total cases observed in each arm of the trial, stratified by start date. Note that the colour scale is logarithmic. The p-value shown is the result of a one-sided Wilcoxon signed rank test for difference between vaccine and control arms.

1.5. Effect of vaccine efficacy

Figure S6 is homologous to Figure 5 in the main text. Using data up to April 26th 2015 the general pattern is similar, but the epidemic has changed in Port Loko, and is now forecast to have a lower persistence probability. Therefore in model simulations, the number of cases predicted in either arm is lower in Port Loko than shown in Figure 6.



Figure S6. Effect of hypothetical vaccine efficacy on number of cases in vaccine and control arms and persistence probability, for a trial starting on May 1st 2015. Forecasts start on 26th April 2015. Cumulative cases are only shown for trajectories that persist until that month. When no boxplot is shown, this indicates that all trajectories were extinct by that month.