PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Estimating the probability of demonstrating vaccine efficacy in the declining Ebola epidemic: a Bayesian modelling approach
AUTHORS	Camacho, Anton; Eggo, Rosalind M; Funk, Sebastian; Watson, Conall; Kucharski, Adam; Edmunds, John

VERSION 1 - REVIEW

REVIEWER	Gerardo Chowell Georgia State University
REVIEW RETURNED	06-Aug-2015

GENERAL COMMENTS	Authors have used a sensible approach to evaluate the feasibility of showing vaccine efficacy in the context of the waning Ebola epidemic in West Africa. The paper is well-written, results are sound and derived conclusions appropriate. I have a couple of comments: 1. The infectious period has certainly declines over the course of the epidemic. How have you taken this into account? Table 1 shows a fixed value. It is possible that your time-dependent Bt has absorbed some of these effective changes reflected in the reproduction number. This deserves some discussion. 2. The time from vaccination to protection is modeled with an average of 14 days. How are results sensitive to a shorter delay, e.g., 7 days instead? 3. Figure 1 could benefit from a vertical line to separate the forecasting period and a horizontal line to show R=1 for reference.

REVIEWER	Hiroshi Nishiura The University of Tokyo, Japan
REVIEW RETURNED	13-Aug-2015

GENERAL COMMENTS	Comments on: Estimating the probability of demonstrating vaccine efficacy… Submitted to: BMJ Open Overall comments: The submitted study investigated the power of implementing simple randomization of vaccination against Ebola in low incidence setting. The intent is very clear: since the vaccination involves herd immunity, the authors would like to explicitly assess the chance of detecting significant reduction in the risk of infection due to vaccination in Guinea. I have only minor comments.

	Specific comments: 1. Page 2, Line 51: increase the epidemic=> increase in the number of cases 2. Page 2, Line 55: change of success => chance of success 3. Page 3, Line 62: largest outbreak Ebola => largest epidemic of Ebola 4. Page 3, Line 70: The authors may emphasize that the ring vaccination design does not allow simply estimating the vaccine efficacy based on aggregated population data. Only effectiveness can be seen without very good design with conditional assessment. 5. Page 3, Line 91: Please explain inference framework of [8] even briefly in this section. 6. Page 3, Line 97: incubation => latent 7. Page 4, Table 1: How did the authors incorporate parameter uncertainty of latent and infectious periods? (in light of [8] and earlier studies). 8. Page 5, Line 164: and immune response => an immune response 9. Page 6, Line 175: persistence probability is low => (very difficult to follow the persistence probability among the general readers. I understand that this is one minus the probability of extinction, but the method section never touched the definition of persistence, and moreover, the persistence is always used for some other purposes. Please consider rewording and explaining it in advance) 10. Page 7: The authors should have explicitly acknowledged that their model is not capable of detecting clusters at small scales as is usually achieved by network model. For that reason, the authors could have overestimated vaccine efficacy, given that the majority of transmission event may be seen in clusters formed at confined space (e.g. hospital or household) and also in a small spatial scale. That must be acknowledged in this context if you stick to SEIR model.

VERSION 1 – AUTHOR RESPONSE

Referee 1:

1. The infectious period has certainly declines over the course of the epidemic. How have you taken this into account? Table 1 shows a fixed value. It is possible that your time-dependent Bt has absorbed some of these effective changes reflected in the reproduction number. This deserves some discussion.

As suggested by the referee, any change in the effective infectious period or intensity of transmissible contacts that would be reflected in the time-varying reproduction number (Rt), is absorbed in the time-varying effective contact rate, βt. This assumption is necessary since it is not possible to estimate both a change in the infectious period and the transmission rate for structural identifiability issues. We prefer to avoid discussing this assumption in the discussion section because
1. This assumption is unlikely to have any effect on our results in comparison to the other assumptions we are testing, i.e. protection delay, start date of vaccination, etc

2. Structural identifiability issues are quite technical and beyond the message of the paper.
That said, we agree that clarification would improve the manuscript, and therefore we have added the following text to the methods section:

We have added the following description on line 97:
To account for external influences on the reproduction number (Rt), for example, variation in population behaviour, or epidemic control measures, we assumed that the transmission rate could change over time. Therefore the change in βt would also absorb any effective change in the infectious period during the epidemic.

2. The time from vaccination to protection is modeled with an average of 14 days. How are results sensitive to a shorter delay, e.g., 7 days instead?

We thank the referee for this suggestion. Recently published intermediate results from the Ebola vaccine trial in Guinea suggest that the rVSV vaccine is efficacious after 7 days, although this short delay probably depends on the type of vaccine used and may not be correct for all vaccine candidates. We conducted a sensitivity analysis on this parameter and updated Figure 4 to show that reducing the protection delay from 2 weeks to 1 week, leads to a slightly earlier and higher peak in power after adjusting for extinction probability: from 8 to 10% in the best case scenario. This is due to a greater sample size and number of events being included in the analysis. On the other hand, because shorter delay in protection increases the herd immunity effect, it leads to faster extinction of the epidemic, and thus reduces the adjusted power at later time points. We have added the following description on line 261:

Reducing both the protection delay and exclusion period from 2 to 1 week leads only to a slightly earlier and higher power peak due to greater sample sizes and number of cases included in the analysis. In addition, shorter delay increases herd immunity effect, leads to faster extinction of the epidemic, and thus reduces the adjusted power at later time (Figure 4).

3. Figure 1 could benefit from a vertical line to separate the forecasting period and a horizontal line to show R=1 for reference.

We thank the referee for this suggestion and we have updated Figure 1 accordingly.

Referee 2:

1. Page 2, Line 51: increase the epidemic=> increase in the number of cases
This has been corrected.

2. Page 2, Line 55: change of success => chance of success
This has been corrected.

3. Page 3, Line 62: largest outbreak Ebola => largest epidemic of Ebola
This has been corrected.

4. Page 3, Line 70: The authors may emphasize that the ring vaccination design does not allow simply estimating the vaccine efficacy based on aggregated population data. Only effectiveness can be seen without very good design with conditional assessment.

Although we agree with the referee that different vaccine trial designs may lead to different definitions and measures of vaccine efficacy/effectiveness, we feel that this technical comments goes beyond

the aim of this introductory paragraph, which only briefly states the different types of vaccine trials that have been proposed for the current outbreak.

5. Page 3, Line 91: Please explain inference framework of [8] even briefly in this section.

We have added a section to the methods section entitled: “Model fitting and forecast”, with additional details on the inference framework (line 103):

We used the same Bayesian inference framework as in [9]. Briefly, we defined the likelihood of the data through a negative binomial observation process accounting for over-dispersion in the reporting of cases (the mean reporting rate was fixed at 60% and the dispersion parameter was inferred). Then, we used a particle Monte-Carlo Markov Chain [11] algorithm implemented in the SSM library [12] to sample from the marginal posterior distribution of the parameters and the states of the model.

6. Page 3, Line 97: incubation => latent
This has been corrected.

7. Page 4, Table 1: How did the authors incorporate parameter uncertainty of latent and infectious periods? (in light of [8] and earlier studies).

We used the mean and standard deviation reported in the patient database (ref [1]) in order to estimate the rate (=1/9.4) and shape (=2) of the gamma distribution for the latent period. For the infectious period, this was not possible as we used a weighted average between the time from onset to death and the time from onset to discharge. However, as detailed in the answer to the first referee, any variation of the infectious period would be absorbed in the time-varying estimate of the transmission rate, βt. This assumption is necessary in order to avoid identifiability issues.

8. Page 5, Line 164: and immune response => an immune response
This has been corrected.

9. Page 6, Line 175: persistence probability is low => (very difficult to follow the persistence probability among the general readers. I understand that this is one minus the probability of extinction, but the method section never touched the definition of persistence, and moreover, the persistence is always used for some other purposes. Please consider rewording and explaining it in advance)

We thank the referee for this suggestion. In the revised manuscript we have reworded the corresponding sentences. For instance:

In all cases, the probability that the epidemic persists long enough to accurately measure vaccine efficacy is low.

Becomes:

In all cases, there is high probability that the epidemic goes extinct before vaccine efficacy can be accurately measured.

10. Page 7: The authors should have explicitly acknowledged that their model is not capable of detecting clusters at small scales as is usually achieved by network model. For that reason, the authors could have overestimated vaccine efficacy, given that the majority of transmission event may be seen in clusters formed at confined space (e.g. hospital or household) and also in a small spatial scale. That must be acknowledged in this context if you stick to SEIR model.

We agree with the referee and acknowledge the potential for overestimation of power. We have therefore added the following text to line 282:

We note that this adjusted power is probably an overestimate since our model operates at the population level and does not account for clustering effect at small scales.

We also conclude with (line 297):

More realistic models accounting for network structure could be even more precise given that the majority of transmission events may be seen in clusters formed at confined space (e.g. hospital or household) and also at a small spatial scale.

VERSION 2 – REVIEW

REVIEWER	Gerardo Chowell Georgia State University, Atlanta, GA, USA
REVIEW RETURNED	11-Sep-2015

GENERAL COMMENTS	The reviewer completed the checklist but made no further comments.

REVIEWER	Hiroshi Nishiura The University of Tokyo, Japan
REVIEW RETURNED	04-Sep-2015

GENERAL COMMENTS	The reviewer completed the checklist but made no further comments.