USING SENSITIVITY ANALYSIS TO EXAMINE THE EFFECTS OF AN EBOLA VACCINE

Stephanie Wiafe

Department of Interdisciplinary Health Sciences
The University of Ottawa
585 King Edward Ave
Ottawa, ON, Canada
swiaf079@uottawa.ca

Emma Veilleux-Gravel

Department of Mathematics
The University of Ottawa
585 King Edward Ave
Ottawa, ON, Canada
eveil039@uottawa.ca

Robert Smith?

Department of Mathematics and Faculty of Medicine
The University of Ottawa
585 King Edward Ave
Ottawa, ON, Canada
rsmith43@uottawa.ca

ABSTRACT

Several Ebola vaccines currently under development have demonstrated promising results in clinical trials. We propose a compartmental model representing the various stages in the development of the Ebola virus disease based on vaccination status. Investigation of the model's basic reproduction number allows us to determine the perversity threshold, which describes the conditions in which the number of secondary infections could increase due to the vaccine. We analyze the influence of each parameter in the model through the use of Partial Rank Correlation Coefficients and Latin Hypercube Sampling. We show that the reproduction number could be significantly reduced if the vaccine is widely administered to individuals who are incubating the disease or if the contact rates with unvaccinated individuals are kept to less than one per week. It follows that the prophylactic properties of the candidate Ebola vaccines can decrease the severity of future outbreaks if applied carefully.

Keywords: Ebola, vaccination, differential equations, Latin hypercube sampling, partial rank correlation coefficients

1 INTRODUCTION

In March 2014, West Africa experienced the largest Ebola virus epidemic in history, largely affecting Liberia, Sierra Leone and Guinea (CDC 2016b). With a case-fatality rate raging from 25% to 90%, averaging 50%, the Ebola Virus Disease has caused 11,325 deaths as of April 13th, 2016. Ebola's high fatality rates and its ability to spread easily within and between populations pose a significant threat to public health worldwide.

The transmission of the Ebola virus to humans is known to occur through direct contact in three ways: from a reservoir, between humans, and from the infected deceased. Fruit bats, which experience asymptomatic infections of the virus, serve as a reservoir of the Ebola virus and contribute to its transmission to other wild animals and humans (Leroy et al. 2005). In West Africa, wild animals such as fruit bats are hunted, sold and consumed, creating the opportunity for the exchange of bodily fluids resulting in zoonotic transmission of the virus (Williamson and Bakker 2005). The virus is spread from human to human through direct contact of bodily fluids such as blood, saliva, vomit, feces, urine, sweat, nasal secretions, semen and genital secretions (Funk and Kumar 2014). Once infected, individuals start developing symptoms within an average span of 11 days. Individuals begin to experience an onset of symptoms including: headaches, vomiting, loss of appetite, diarrhea, stomach pains, lethargy, aching muscles or joints and difficulties swallowing and breathing, in addition to unexplained bleeding (Alyward et al. 2014). Following this, symptoms further progress to weakened liver and kidney functions in addition to more serious hemorrhagic symptoms such as internal and external bleeding (WHO 2016). Upon developing these symptoms, infected individuals are able to spread the virus to others, making them infectious. Individuals who develop Ebola virus disease die within a mean of 10 days from the onset of the illness (Chowell and Nishiura 2014).

Although the Ebola virus is spread through direct contact, making it relatively difficult to proliferate, with the world being deeply interconnected through travel and migration, it is possible for Ebola to be transferred from one continent to the next within a matter of hours. As seen with the epidemic in West Africa, existing preventative measures have not been effective safeguards in controlling an outbreak, partially due to cultural and societal influences such as burial and funeral practices that influence the rapid spread of the virus to a large extent (WHO 2014). Given the insights gained from the outbreak, in West Africa, various public-health stakeholders, including governments and researchers, recognized the substantial threat that the Ebola virus poses to public health. As a result, governments and industries saw the potential benefit that an Ebola virus vaccine could bring to outbreak occurrences. Currently, several vaccines are being developed by countries including Sierra Leone, Russia, China, the United States and Canada. These are at varying stages of clinical trials. One of the most promising vaccines is the VSV- EBOV vaccine developed by NewLink Genetics and Merck Vaccines USA, in collaboration with the Public Health Agency of Canada. It is currently in Phase III clinical trials and is being tested in humans in Guinea and Sierra Leone (WHO 2015).

Immunization has proven to be an effective measure in reducing the mortality and morbidity rates of diseases. Moreover, a herd-immunity approach to immunization has historically proven to be an efficient approach to vaccination programs (Fox et al. 1971). Employing herd immunity entails immunizing a significant proportion of the population who, as a result of being immunized, protect those who have not been vaccinated, such as newborns and the elderly, from contracting the infectious agent. The VSV-EBOV vaccine, combined with a herd immunity approach, is therefore a promising potential intervention for containing and reducing the impact of a potential Ebola virus outbreak. Vaccines have also been shown to benefit countries and individuals financially and economically, since vaccination programs often cost less than treating the illness that would occur without immunization (Bloom et al. 2005). Consequently, by immunizing a significant proportion of the population against the Ebola virus, countries that would have otherwise been unprepared economically for an epidemic may see less dramatic costs if an outbreak were to occur.

Here we model the Ebola virus in a population in West Africa with the presence of the VSV-EBOV vaccine. The vaccine possesses a high efficacy in individuals and therefore proves to be a favorable candidate for a herd-immunity approach in protecting communities from outbreaks of the Ebola virus. By utilizing this vaccine, we believe that the Ebola virus should not be able to spread as widely, since a smaller proportion of the population will be susceptible to contracting the disease.

A compartmental model is used to describe the dynamics of an outbreak with a base population of around 1000 individuals, representing a community in West Africa. A proportion of the population will receive an imperfect vaccine. Vaccinated individuals can still be infected, but at a lower rate. Vaccine-induced

immunity may wane over time, while vaccinated deceased individuals may still transmit the virus. In order to consider the context and particularities of the Ebola virus outbreak in West Africa from 2013–2014, an SEIRD (susceptible, exposed, infected, recovered and deceased) model is used. Through the use of a compartmental model, it is possible to analyze the behavior of the Ebola virus in a population with both vaccinated and unvaccinated individuals.

Previous models of Ebola have focused on interventions such as quarantine, distribution of household kits, Emergency Treatment Care (ETC) expansion and accelerating case tracking. For instance, Lewnard et al. suggested that the existing ETC capacity necessary to decrease the severity of the current outbreak was impractical (Lewnard et al. 2014). Legrand et al., provided a stochastic compartmental model incorporating transmission in the community, in the hospital and during burial ceremonies in order to suggest where interventions are best suited (Legrand et al. 2007). Rivers *et al.* (Rivers, Lofgren, Marathe, Eubank, and Lewis 2014) investigated the efficiency of increased contact tracing, improved infection-control practices and a hypothetical pharmaceutical intervention to improve survival of hospitalised patients aimed at reducing the reproduction number of the Ebola virus. Chowell *et al.* (Chowell, Hengartner, Castillo-Chavez, Fenimore, and Hyman 2004) used an SEIR model to determine R_0, the final size of the epidemic and performed a sensitivity analysis, showing that education and contact tracing with quarantine would reduce the epidemic by a factor of 2. Fisman *et al.* (Fisman, Khoo, and Tuite 2014) used a two-parameter model to determine the degree to which the epidemic was being controlled, finding only weak control in West Africa as of the end of August 2014 and essentially no control in Liberia. Webb and Browne (Webb and Browne 2016) developed an age-structured model, tracking disease age through initial incubation, followed by an infectious phase with variable transmission infectiousness. Browne *et al.* (Browne, Gulbudak, and Webb 2015) showed that, if contact tracing was perfect, then the critical proportion of contacts that need to be traced could be derived. Do and Lee (Do and Lee 2016) developed an SLIRD model to show stability of a disease-free equilibrium if safe burial practices without traditional rituals were followed and $R_0 < 1$. Bartlett et al. (Bartlett et al. 2016) utilized a discrete-time model to represent the clinical progression of the Ebola virus and estimate the number of infections and deaths in Sierra Leone.

Our model builds upon these and other previous mathematical models of the Ebola virus by demonstrating the interaction between vaccinated and unvaccinated individuals in a given outbreak. Our conceptualization of vaccination is based on the VSV-EBOV vaccine, a promising future intervention method with high immunogenicity. Our model contributes to the growing knowledge surrounding interventions for Ebola virus outbreaks through the use of a vaccine as primary prevention.

2 METHODS

2.1 The Model

The mathematical model is is illustrated in Figure 1 and is represented via the following set of differential equations:

$$
\begin{aligned}
X' &= \Lambda(1-\varepsilon\rho) - \beta c_u X I_u - \beta c_v X I_v - \beta c_d X (D_u + D_v) + \varphi V - \mu X \\
E_u' &= \beta c_u X I_u + \beta c_v X I_v + \beta c_d X (D_u + D_v) - (\omega + \eta + \mu) E_u + \varphi E_v \\
I_u' &= \omega E_u - (\alpha + \gamma) I_u \\
R_u' &= \gamma I_u - \mu R_u \\
D_u' &= \alpha I_u - \theta D_u \\
V' &= \Lambda\varepsilon\rho - (1-\psi)\beta c_u V I_u - (1-\psi)\beta c_v V I_v - (1-\psi)\beta c_d V (D_u + D_v) - (\varphi + \mu) V \\
E_v' &= (1-\psi)\beta c_v V I_v + (1-\psi)\beta c_u V I_u + (1-\psi)\beta c_d V (D_u + D_v) + \eta E_u - (\omega_v + \mu + \varphi) E_v \\
I_v' &= \omega_v E_v - (\alpha_v + \gamma_v) I_v \\
R_v' &= \gamma_v I_v - \mu R_v \\
D_v' &= \alpha_v I_v - \theta D_v.
\end{aligned}
$$

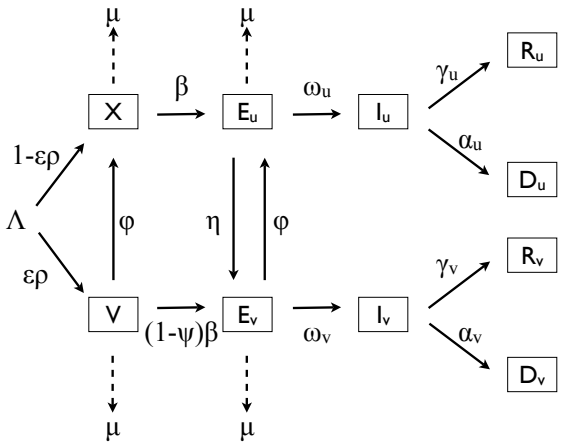

Figure 1: Model Flowchart. The movement of individuals through the compartments via infection, vaccination, recovery and death. Individuals are initially susceptible (X) or vaccinated (V). They may die from unrelated causes and exit the system or they may be infected either by an infectious individual or corpse and become non-symptomatic infected (E_u, E_v). Non-symptomatic infected individuals become infectious (I_u, I_v) or they can die from an unrelated cause and exit the system. Individuals can be vaccinated after exposure to the virus, although the vaccine may also wear off. Infectious individuals can recover (R_u, R_v) from the disease or they may die from the disease and become an infectious dead body (D_u, D_v). Recovered individuals can no longer be infected; they die at the background death rate. Infectious dead bodies stop being infectious after safe burial or after the live virus is no longer in the corpse. Note that both infectious and dead individuals of either type can infect susceptibles, whether vaccinated or not. These mechanisms are not drawn in, to avoid overcluttering the figure.

Each equation listed above represents the rate of change over time of a compartment that individuals move through during an Ebola virus epidemic. Individuals enter the cohort at rate Λ either through birth or immigration. The vaccine immunogenicity is represented by multiplying the take of the vaccine, ε, by the proportion of the population that receives an immunization, ρ. Vaccinated and unvaccinated individuals then move to their corresponding susceptible compartments. The susceptible compartment (X) represents individuals who are unvaccinated and susceptible to contracting the Ebola virus, and the vaccinated suscep-

tible compartment (V) represents those who are have been vaccinated but are still susceptible to becoming infected (whether due to waning of the vaccine or failure of the vaccine to "take"). Those who are susceptible may die from causes other than an Ebola virus infection and exit the model at a background death rate of μ. Individuals who have been infected with the Ebola virus but have not yet shown symptoms move from the susceptible compartment (X) to the exposed unvaccinated compartment (E_u). Similarly, those who have been infected with the Ebola virus who have not yet developed symptoms and have also received a vaccine progress to the exposed vaccinated compartment (E_v). The rate of movement from compartment X to E_u is given by the sum of the forces of infection based on transmission rates from the three sources of transmission: the infected deceased (βc_d), infected unvaccinated individuals (βc_u) and infected vaccinated individuals (βc_v). These exposed (incubating) classes for both unvaccinated and vaccinated individuals have the effect of introducing a delay before an individual is infectious.

Since the VSV-EBOV vaccine can be used as a prophylaxis measure for those who are infected but not yet infectious, individuals can move from E_u to E_v if immunized at a rate η. At the same time, vaccines tend to wane and lose their immunizing effect over time. As a result, individuals who have been vaccinated move from compartment V to X at rate φ. Individuals subjected to vaccine waning move from E_v to E_u at the same rate φ. In order to be protected from developing Ebola virus disease, the vaccine has to efficiently trigger an immune response, denoted by vaccine immunogenicity ψ. Vaccinated individuals who do not develop an immune response move to the infected vaccinated I_v compartment at rate ω_v. Likewise, unvaccinated exposed individuals who develop symptoms of the Ebola virus disease advance to the unvaccinated infected I_u compartment at rate ω. As shown in a compartmental model of the Ebola virus by Salem and Smith? (Salem and Smith? 2016), those who are deceased and infected with the Ebola virus serve as a significant route of transmission. Hence, it is important to adjust the SEIR model accordingly by adding in a deceased (D) compartment representing the infectious deceased. Individuals either recover or die while infected with the Ebola virus. Those who die become part of the unvaccinated or vaccinated infectious deceased compartments D_u and D_v, at rates α_u and α_v, respectively. Other infectious individuals recover at rates r by γ_u and γ_v, representing unvaccinated and vaccinated individuals, and transfer to the recovered unvaccinated compartment R_u and recovered vaccinated compartment R_v, respectively.

The parameters are listed in Table 1. Note that parameters that are coefficients of linear terms have the property that their inverse represents the average time spent in the compartment in question. Thus, for example, the recovery rate for vaccinated individuals γ_v with range 0.75–1 per week means that vaccinated individuals are infectious for 1–1.333 weeks, whereas the vaccine waning effect of 0–1 per week means that immunity due to the vaccine will last between one week and infinite time. The vaccine-specific parameters α_v and ω_v were given the same ranges as their unvaccinated counterparts, whereas the recovery rate γ_v was assumed to be slightly faster. The vaccine waning effect was limited to 0–1 weeks^{-1} on the assumption that the vaccine would last at least one week, but could theoretically last forever. The rate of post-exposure vaccination η was limited to 0–7 weeks^{-1} on the assumption that the vaccine would be not be given less than one day after infection. The transmissibility was assumed to be in the upper half of the proportion range, reflecting Ebola's severity. The contact rates with infectious individuals (whether unvaccinated, vaccinated or dead) were built off our previous numerical exploration of parameter ranges (Salem and Smith? 2016). Although preliminary reports of vaccine efficacy have been stated to be 100% (Global Biodefence 2015), we nevertheless allowed the efficacy to range between 0 and 100%. All other parameter ranges were taken from primary sources.

A number of assumptions were made in creating of this model. First, we are assuming that countries affected by an Ebola virus epidemic have adequate access to, and availability of, vaccines and sufficient amount of human and non-human resources to implement a vaccination program. A base population of 1000 is used in the model, and the corresponding birth and background death rates were retrieved from the Centers for Disease Control and Prevention (CDC 2016c) as well as the Central Intelligence Agency (CIA 2017).

Table 1: List of parameters.

Parameter	Description	Range	Units	Reference
α	Disease death rate for unvaccinated individuals	0.5–1	weeks^{-1}	(CDC 2016a)
α_v	Disease death rate for vaccinated individuals	0.5–1	weeks^{-1}	assumed
γ	Recovery rate for unvaccinated individuals	0.5–1	weeks^{-1}	(Hunter and Strickland 2000)
γ_v	Recovery rate for vaccinated individuals	0.75–1	weeks^{-1}	assumed
μ	Background death rate	0.014–0.02	years^{-1}	(WHO 2017)
Λ	Birth/immigration rate	0.035–0.037	people/week	(CIA 2017)
θ	Safe burial rate	0.33–10	weeks^{-1}	(Prescott et al. 2015)
c_u	Contact rate with infectious unvaccinated individuals	0–10	people/week	(Salem and Smith? 2016)
c_v	Contact rate with infectious vaccinated individuals	0–10	people/week	(Salem and Smith? 2016)
c_d	Contact rate with infectious dead individuals	0–10	people/week	(Salem and Smith? 2016)
β	Transmissibility	0.5–1	$\text{people}^{-2}\text{weeks}^{-1}$	assumed
ω	Incubation rate for unvaccinated individuals	0.33–3	weeks^{-1}	(WHO 2016)
ω_v	Incubation rate for vaccinated individuals	0.33–3	weeks^{-1}	assumed
$\varepsilon\rho$	Proportion vaccinated who mounted an immune response	0.5–1	(proportion)	(Henao-Restrepo et al. 2015)
φ	Vaccine waning effect	0–1	weeks^{-1}	assumed
ψ	Vaccine efficacy	0–1	(proportion)	(Global Biodefence 2015)
η	Rate of post-exposure vaccination	0–7	weeks^{-1}	assumed

We model a disease-modifying Ebola vaccine that is given to a fraction of the population, that will "take" in proportion of these individuals and where immunity to the vaccine will wane over time. Since the VSV-EBOV vaccine has a high immunogenicity (Henao-Restrepo et al. 2015), those who are vaccinated and have developed the Ebola virus disease may recover at faster rates because of the presence of some residual immunity as a result of vaccination. Those who are naturally immune to the Ebola virus are not considered in this model. Once individuals recover, we assume that they are immune to a subsequent infection of the virus. Lastly, susceptible and exposed individuals who die at the background death rate are not assumed to be infectious deceased; conversely, those who are infectious and die at the background death rate are assumed to be the infected deceased.

2.2 Analysis

The disease-free equilibrium (DFE) represents the absence of an epidemic, where there are no exposed, recovered or infected deceased individuals. The stability of the DFE allows for further investigation into characteristics of the model. The DFE is:

$$(X^0, E_u^0, I_u^0, D_u^0, R_u^0, V^0, E_v^0, I_V^0, D_V^0, R_v^0) = \left(\frac{\Lambda(1-\varepsilon\rho)}{\mu} + \frac{\varphi\Lambda\varepsilon\rho}{\mu(\varphi+\mu)}, 0, 0, 0, 0, \frac{\Lambda\varepsilon\rho}{\varphi+\mu}, 0, 0, 0, 0 \right).$$

The basic reproductive number of the unvaccinated population (R_0) represents the number of secondary infections of the Ebola virus caused by a single unvaccinated infected individual in a wholly susceptible population. Similarly, the basic reproductive number of the vaccinated population (R_v) represents the number of subsequent individuals infected caused by a vaccinated infected individual in a wholly vaccinated population. We used the next-generation method (van den Driessche and Watmough 2002) to calculate

$$R_0 = \frac{\beta\omega X^0}{(\alpha+\gamma)(\omega+\eta+\mu)}\left[c_u + \frac{c_d\alpha}{\theta}\right] \qquad \text{and} \qquad R_v = \frac{\beta\omega_v V^0}{(\alpha_v+\gamma_v)(\omega_v+\varphi+\mu)}\left[c_v + \frac{c_d\alpha_v}{\theta}\right].$$

Susceptible individuals for whom the vaccine generates an authentic immune response (vaccine immunogenicity) to the Ebola virus are considered to be initially vaccinated and enter the model at rate $\varepsilon\rho$. Vaccinated individuals either exit the model through the background death rate (μ) or are subjected to vaccine waning (φ) in which the immunological effects of the vaccine wear off over time. The probability that the vaccine will protect these individuals from becoming infected is given by the vaccine efficiency (ψ).

The proportion of "successfully" vaccinated individuals is given by $S = \frac{V^0}{X^0+V^0} = \frac{\varepsilon\rho\mu}{\mu+\varphi}$. With the proportion of "successfully" vaccinated individuals (S), the population reproductive number (R_p) can be calculated. R_p represents the total number of secondary Ebola virus infections caused by a single infectious individual in the entire population of both vaccinated and unvaccinated individuals. It provides insight into the degree of proliferation of the virus within the population. Along with the proportion of "successfully" vaccinated individuals, other factors influence the number of secondary infections, such as the vaccine efficiency (ψ) and the basic reproductive numbers of both the vaccinated and unvaccinated populations (R_v, R_0). R_p can be expressed as $R_p = S(1-\psi)R_V + (1-S)R_0$.

A perverse outcome will occur if the introduction of vaccination makes the epidemic more severe (Smith and Blower 2004). We define the fitness ratio to be the relationship between the vaccinated basic reproductive number (R_v) and the unvaccinated basic reproductive number (R_0): $f = R_v/R_0$.

Perversity will occur if the reproduction number with vaccination exceeds the current reproduction number; i.e., $R_p > R_0$. In the absence of behavior changes, this will occur if $f > \frac{1}{1-\psi}$. See Figure 2. For low-efficacy vaccines, this corresponds to an f close to one. That is, if the vaccine does not protect vaccinated individuals very much, then very little increase in the reproduction number due to vaccinated individuals could be tolerated. Such an outcome may occur if vaccinated individuals increase their contact with either the living or the dead, whether due to a perceived sense of security or simply by living longer.

3 NUMERICAL SIMULATIONS

We conducted a sensitivity analysis on all of the parameters' influences on the basic reproductive number R_p determined by Latin Hypercube Sampling (LHS) and partial rank correlation coefficients (PRCCs). LHS is a statistical sampling method that evaluates sensitivity of an outcome variable to all input variables. PRCCs evaluated the relative effect of each parameter on the outcome, while all other parameters are held at their median values (Blower and Dowlatabadi 1994). Each parameter was sampled 1000 times for 1000 total runs and is ranked based on its influence on the model's R_p. Parameters with coefficients of lower absolute values have less of an influence on the value of R_p, whereas coefficient with a higher absolute value have more of an influence on the value of R_p. Parameters used for LHS outputs are summarized in Table 1. We used a uniform distribution for all parameters.

The influence of seventeen individual parameters on R_p are shown in Figure 3A. The three most influential parameters are the contact rate with unvaccinated individuals, the post-exposure vaccination rate and the incubaton rate for unvaccinated individuals. A positive PRCC value indicates an increase in R_p as the parameter increases, while a negative PRCC value indicates a decrease in R_p as the parameter increases.

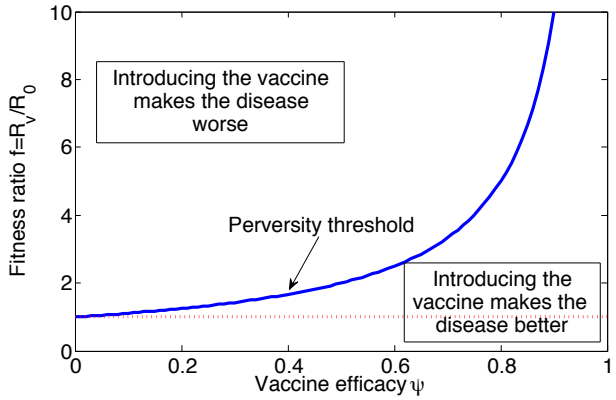

Figure 2: The dependence of the fitness ratio on the vaccine efficacy. For low-efficacy vaccines, only fitness ratios close to 1 can be tolerated, meaning that the reproduction number due to vaccination cannot be increased beyond that of the current reproduction number. For high-efficacy vaccines, larger fitness ratios can be tolerated.

For example, an increase in the number of contacts with infectious unvaccinated individuals will increase R_p and significantly more than contact with vaccinated individuals, even for an imperfect vaccine.

Two interventions are examined in Figure 3B: increasing the post-exposure vaccination rate η to 6–7 per week and reducing the number of contacts with unvaccinated individuals c_u to a maximum of one per week. The full range of simulation outputs for these scenarios is shown in the boxplots. The latter intervention has a greater effect on reducing the mean value of R_p than rapid post-exposure vaccination, although it has a longer tail. Reducing contacts keeps the interquartile range below the threshold $R_p = 1$.

Figure 4 shows the change in R_p values as the three most influential parameters are individually varied while all other parameters are kept at their median values. Each dot represents a simulation. There is a distinct trend in two of these figures, showing that altering the parameter in question have have an effect on the reproduction number, even if all other parameters remain in flux. Specifically, if the contact with infectious unvaccinated individuals can be kept below 1 per week, then the majority of simulations predict $R_p < 1$, regardless of the variations in any other parameters. Increasing the post-exposure vaccination rate to about 6–7 (corresponding to vaccinating within about one day) may also achieve disease control, although this may be difficult to achieve in practice. We expect to have no control over the unvaccinated incubation rate, and there is no region where this parameter strongly predicts disease control.

The effect of these reductions is shown in Figure 5. The simulations were re-run twice, once with the post-exposure vaccination being limited to 6–7 weeks^{-1}, the other with the contact rate with unvaccinated individuals limited to 0–1 per week. In these figures, the majority of simulations are below the threshold; this is especially apparent when the contact rate is reduced.

4 DISCUSSION

After the 2014 Ebola virus epidemic in West Africa, public- and global-health stakeholders saw the need for an Ebola virus vaccine. Since many are now in the final stages of trials, it is important to consider how a vaccine would influence a potential epidemic and what approach to subscribe to when planning immunization programs. We have demonstrated how the VSV- EBOV vaccine using a herd-immunity approach would potentially affect an Ebola virus epidemic in West Africa. We have also shown that an Ebola vaccine is a multifaceted intervention involving multiple interacting parameters.

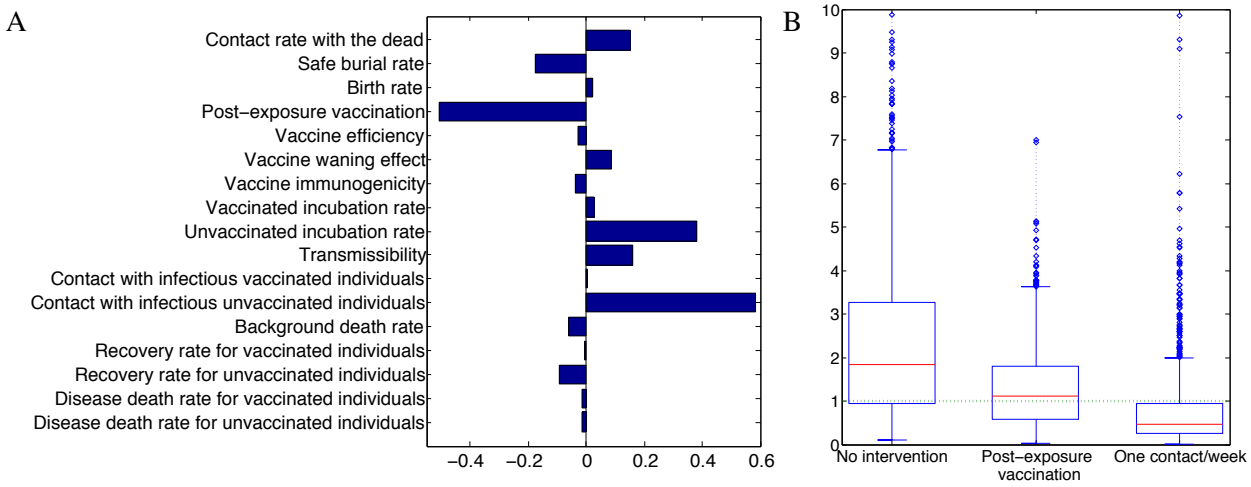

Figure 3: A. Partial Rank Correlation Coefficient sensitivity analysis of parameters. Sensitivity analysis of R_p with respect to all the parameters. B. Box plot of all 1000 R_p values with no intervention, vaccinating exposed individuals within 1–1.167 days after infection and reducing contact with unvaccinated individuals to one per week. Latin Hypercube Sampling (LHS) was used to sample parameters. The LHS ranges are given in Table 1. The horizontal red line indicates the median of all 1000 of the R_0 values.

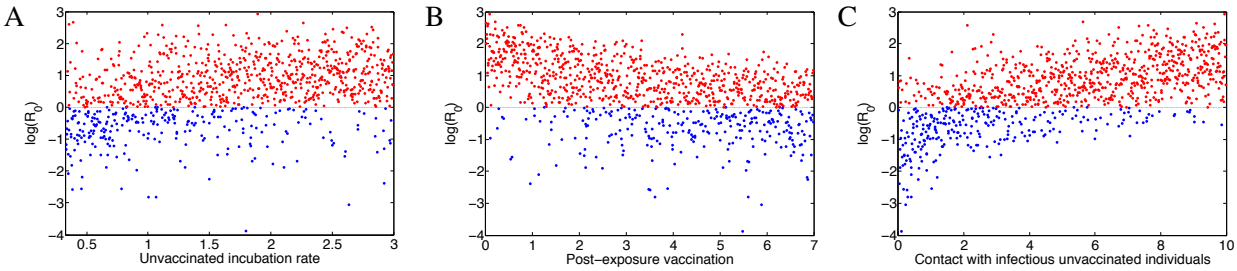

Figure 4: LHS output for R_p as a factor of the three most influential parameters: (A) the incubation rate for unvaccinated individuals ω, (B) the post-exposure vaccination rate, η and (C) the contact rate with unvaccinated individuals c_u. Values for all 17 parameters were sampled 1000 times. The horizontal line indicates the threshold $R_p = 1$.

Evaluation of the sensitivity analysis results allows us to clearly see each parameter's effect on the epidemic and draw conclusions accordingly. The sensitivity analyses yield the conclusion that the post-exposure vaccination rate, the contact rate with infectious individuals and the incubation rate for unvaccinated individuals have the most influence on the epidemic.

Reducing the incubation rate is highly unlikely to be possible; conversely, reducing the contact rate below one per week is theoretically possible, but in practice presents many challenges. These include identifying infected individuals early on, instigating effective quarantine practices, etc. In remote areas, this may be all but impossible. Post-exposure vaccination presents different challenges, such as identifying whether exposure has occurred. One possibility would be to vaccinate as widely as possible or in high-risk groups, with the aim of vaccinating any exposed individuals in this catchment process.

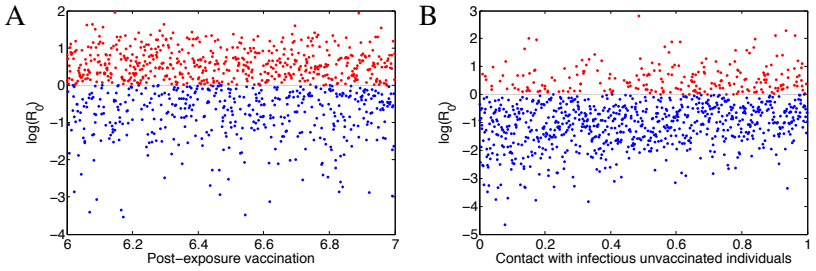

Figure 5: LHS output for R_p with (A) reduced contact and (B) rapid post-exposure vaccination, showing a greater proportion of simulations predicting disease control. Note the change of scales on the horizontal axes.

Other factors of importance include the safe burial rate, the transmissibility of the virus and contact with the dead. We have also shown that if low-efficacy vaccines are introduced, then it is critical that the fitness ratio be kept close to one in order that the vaccine not make the disease worse; this can be accomplished through stringent public health awareness campaigns that raise awareness that a vaccine is not a cure and may only work a fraction of the time. A danger with new and imperfect vaccines is that some vaccinated individuals may incorrectly assume total immunity to the virus as a result of immunization. As a result, we allowed the contact rate for vaccinated individuals to have a larger range than the contact rate with unvaccinated individuals; there was no noticeable effect from this (results not shown).

Future work will investigate strategies for implementation of and program development for various Ebola virus vaccines. Key health indicators, such as the three rates of transmission from our model, can be used to assess a community's risk of a potential Ebola outbreak.

Identifying communities that are at a particularly high risk or that are vulnerable to an Ebola outbreak will aid in immunization-program planning and allocation of resources. Furthermore, surveys and interviews can be conducted in areas affected by the Ebola virus epidemic in 2014 in order to collect data on attitudes towards an Ebola virus vaccine as an intervention in the prevention of the Ebola virus. This would also be an opportunity to harmonize both quantitative and qualitative methods for program implementation.

ACKNOWLEDGEMENTS

The authors are grateful to Raywat Deonandan for technical discussions and to reviewers Mike Famulare, Zvi Roth and Jacob Barhak for comments that greatly improved the manuscript. RS? is supported by an NSERC Discovery Grant. For citation purposes, note that the question mark is part of the author's name.

REFERENCES

Alyward, B., P. Barboza, L. Bawo, and et al. 2014. "Ebola Virus Disease in West Africa—The First 9 Months of the Epidemic and Forward Projections". *New England Journal of Medicine* vol. 371, pp. 1481–1495.

Bartlett, J., J. Devinney, and E. Pudlowski. 2016. "Mathematical modeling of the 2014/2015 Ebola epidemic in West Africa". *SIAM Undergraduate Research Online* vol. 9, pp. 87–102.

Global Biodefence 2015. "100 Percent Efficacy Shown for VSV-EBOV Ebola Vaccine". https://globalbiodefense.com/2015/07/31/100-percent-efficacy-shown-for-vsv-ebov-ebola-vaccine/.

Bloom, D. E., D. Canning, and M. Weston. 2005. "The Value of Vaccination". *World Economics* vol. 6, pp. 15–39.

Blower, S., and H. Dowlatabadi. 1994. "Sensitivity and Uncertainty Analysis of Complex Models of Disease Transmission: an HIV Model, as an example". *International Statistics Review* vol. 62, pp. 229–243.

Browne, C., H. Gulbudak, and G. Webb. 2015. "Modeling Contact Tracing in Outbreaks with Application to Ebola". *Journal of Theoretical Biology* vol. 384, pp. 33–49.

CDC 2016a. "2014 Ebola Outbreak in West Africa – Case Counts".

CDC 2016b. "2014 Ebola Outbreak in West Africa – Outbreak Distribution Map". https://www.cdc.gov/vhf/ebola/outbreaks/2014-west-africa/distribution-map.html.

CDC 2016c. "Global Health – Liberia". https://www.cdc.gov/globalhealth/countries/liberia/.

Chowell, G., N. W. Hengartner, C. Castillo-Chavez, P. W. Fenimore, and J. M. Hyman. 2004. "The basic reproductive number of Ebola and the effects of public health measures: the cases of Congo and Uganda". *Journal of Theoretical Biology* vol. 229, pp. 119–126.

Chowell, G., and H. Nishiura. 2014. "Transmission dynamics and control of Ebola virus disease (EVD): a review". *BMC Medicine* vol. 12, pp. 196.

CIA 2017. "CIA World Factbook: Liberia". http://teacherlink.ed.usu.edu/tlresources/reference/factbook/geos/LI.html.

Do, T. S., and Y. S. Lee. 2016. "Modeling the Spread of Ebola". *Osong Public Health and Research Perspectives* vol. 7, pp. 43–48.

Fisman, D., E. Khoo, and A. Tuite. 2014. "Early Epidemic Dynamics of the West African 2014 Ebola Outbreak: Estimates Derived with a Simple Two-Parameter Model". *PLoS Currents* vol. 6.

Fox, J., L. Elveback, W. Scott, L. Gatewood, and E. Ackerman. 1971. "Herd Immunity: Basic concept and relevance to public health immunization practices". *American Journal of Epidemiology* vol. 94, pp. 180–189.

Funk, D. J., and A. Kumar. 2014. "Ebola virus disease: an update for anesthesiologists and intensivists". *Canadian Journal of Anaesthesia* vol. 62, pp. 80–91.

Henao-Restrepo, A. M., I. M. Longini, M. Egger, N. E. Dean, W. J. Edmunds, A. Camacho, M. W. Carroll, and et al.. 2015. "Efficacy and effectiveness of an rVSV-vectored vaccine expressing Ebola surface glycoprotein: interim results from the Guinea ring vaccination cluster-randomised trial". *The Lancet* vol. 386, pp. 857–866.

Hunter, G. W., and G. T. Strickland. 2000. *Hunter's tropical medicine and emerging infectious diseases*, Volume 857. WB Saunders company.

Legrand, J., R. F. Grais, P.-Y. Boelle, A.-J. Valleron, and A. Flahault. 2007. "Understanding the dynamics of Ebola epidemics". *Epidemiology and infection* vol. 135, pp. 610–621.

Leroy, E. M., B. Kumulungui, X. Pourrut, P. Rouquet, A. Hassanin, P. Yaba, A. Delicat, J. Paweska, J. Gonzalez, and R. Swanepoel. 2005. "Fruit bats as reservoirs of Ebola virus". *Nature* vol. 438.

Lewnard, J. A., M. L. N. Mbah, J. A. Alfaro-Murillo, F. L. Altice, L. Bawo, T. G. Nyenswah, and A. P. Galvani. 2014. "Dynamics and control of Ebola virus transmission in Montserrado, Liberia: a mathematical modelling analysis". *The Lancet infectious Diseases* vol. 12, pp. 1189–1195.

Prescott, J. B., T. Bushmaker, R. J. Fischer, K. Miazgowicz, S. D. Judson, and V. J. Munster. 2015. "Postmortem Stability of Ebola Virus". *Emerging Infectious Diseases* vol. 21, pp. 856–859.

Rivers, C. M., E. T. Lofgren, M. Marathe, S. Eubank, and B. L. Lewis. 2014. "Modeling the impact of interventions on an epidemic of Ebola in Sierra Leone and Liberia". *PLOS Currents Outbreaks*.

Salem, D., and R. Smith?. 2016. "A Mathematical model of Ebola Virus Disease: Using Sensitivity Analysis to Determine Effective Intervention Targets". *Proceedings of the SummerSim-SCSC 2016 conference*, pp. 16–23.

Smith, R. J., and S. Blower. 2004. "Could disease-modifying HIV vaccines cause population-level perversity?". *The Lancet infectious Diseases* vol. 4, pp. 636–639.

van den Driessche, P., and J. Watmough. 2002. "Reproduction numbers and sub-threshold endemic equilibria for compartmental models of disease transmission". *Mathematical Biosciences* vol. 180, pp. 29–48.

Webb, G., and C. Browne. 2016. "A Model of the Ebola Epidemics in West Africa Incorporating Age of Infection". *Journal of Biological Dynamics* vol. 10, pp. 18–30.

WHO 2014. "Sierra Leone: a traditional healer and a funeral". http://www.who.int/csr/disease/ebola/ebola-6-months/sierra-leone/en/.

WHO 2015. "Ebola vaccines, therapies, and diagnostics". http://www.who.int/medicines/emp_ebola_q_as/en/.

WHO 2016. "Ebola virus disease fact sheet". http://www.who.int/mediacentre/factsheets/fs103/en/.

WHO 2017. "Liberia". http://www.who.int/countries/lbr/en/.

Williamson, D., and L. Bakker. 2005. "The Bushmeat Crisis in West Africa: An indicative overview of the situation and perception". *Foor and Agriculture Organization of the United States*.

AUTHOR BIOGRAPHIES

Stephanie Wiafe is an Honour's Bachelor of Interdisciplinary Health Sciences candidate at the University of Ottawa where she is a Dean's List and Merit Award Recipient. She is an executive member of the University of Ottawa Canadian Society for Epidemiology and Biostatistics. She works as a Science Student for the Canadian federal government and has participated in medical mobile clinic programs in Costa Rica and Nicaragua as a volunteer. Her email address is swiaf079@uottawa.ca

Emma Veilleux-Gravel graduated in 2016 from the University of Ottawa with a Joint Honours B.Sc. in Mathematics and Economics. During her studies, as a research assistant she conducted a literature review focusing on the impact of the Canadian 2012 Federal Deficit Reduction Action Plan on governmental programs and services. She has also completed for Health Canada a review of key measures and indicators used to monitor and report on Aboriginal People's health determinants and correlates. She has also provided research assistance for projects targeting infectious disease modeling, government debt modeling and program evaluation for both government agencies and third party review. Her email address is eveil039@uottawa.ca

Robert Smith? is a professor of disease modeling at the University of Ottawa. Using mathematics, he studies infectious diseases such as HIV, malaria, human papillomavirus, neglected tropical diseases and zombies. He has published 12 books on academic and pop culture, is the author of almost 100 academic publications, is a winner of a Guinness World Record for his work on modeling a zombie invasion and was the winner of the 2015 Mathematics Ambassador award, given by Canada's Partners in Research association. His email address is rsmith43@uottawa.ca

Detailed records of the review process can be found here:
https://groups.google.com/forum/#!topic/public-scientific-reviews/KHREQiTyErc