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Modelling the daily risk of Ebola in the presence and absence of a potential vaccine

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ABSTRACT

Ebola virus — one of the deadliest viral diseases, with a mortality rate around 90% — damages the immune system and organs, with symptoms including episodic fever, chills, malaise and myalgia. The Recombinant Vesicular Stomatitis Virus-based candidate vaccine (rVSV-ZEBOV) has demonstrated clinical efficacy against Ebola in ring-vaccination clinical trials. In order to evaluate the potential effect of this candidate vaccine, we developed risk equations for the daily risk of Ebola infection both currently and after vaccination. The risk equations account for the basic transmission probability of Ebola and the lowered risk due to various protection protocols: vaccination, hazmat suits, reduced contact with the infected living and dead bodies. Parameter space was sampled using Latin Hypercube Sampling, a statistical method for generating a near-random sample of parameter values. We found that at a high transmission rate of Ebola (i.e., if the transmission rate is greater than 90%), a large fraction of the population must be vaccinated (>80%) to achieve a 50% decrease in the daily risk of infection. If a vaccine is introduced, it must have at least 50% efficacy, and almost everyone in the affected areas must receive it to effectively control outbreaks of Ebola. These results indicate that a low-efficacy Ebola vaccine runs the risk of having vaccinated people be overconfident in a weak vaccine and hence the possibility that the vaccine could make the situation worse, unless the population can be sufficiently educated about the necessity for high vaccine uptake.

1. Introduction

Ebola is one of the deadliest viral diseases. The virus damages the immune system and organs, with symptoms including episodic fever, chills, malaise and myalgia (Leroy et al., 2011). The disease was originally known as Ebola hemorrhagic fever, due to bleeding inside and outside the body, but it is now referred to as Ebola virus (Feldmann & Geisbert, 2011). Ebola is a member of the Filoviridae family, which comprises three genera: Cuevavirus, Ebolavirus and Marburgvirus (Wong & Wong, 2015). The genus Ebolavirus (EBOV) includes five species: Zaire, Sudan, Bundibugyo, Taï Forest and Reston. The first three

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strains cause the majority of diseases in humans (World Health Organization and Report of an International Commission, 1978). Both Taï Forest and Reston Ebola virus cause diseases in non-human primates, but infections in humans from these strains are limited to one case of Taï Forest Ebola virus and largely asymptomatic infections with Reston Ebola virus (Coltart et al., 2017).

Ebola virus is highly transmissible among humans by close and direct contact with infected blood, secretions, tissues, organs and other bodily fluids from dead or living infected individuals (Bausch et al., 2007). The virus can survive in liquid or dried material for many days (Piercy et al., 2010). The mortality rate is around 90 percent, and case-fatality rates have varied from 25% to 90% in past outbreaks (Kadanali & Karagoz, 2015). Primates are also infected with Ebola viruses, although they are likely to be infected by natural reservoir hosts (e.g., pigs, bats) (Wong & Wong, 2015). Primates represent important vectors for the introduction of the disease into humans in rural Africa, and mortality in wild animals sometimes precedes human outbreaks of the virus (Rouquet et al., 2005).

Two promising candidate vaccines from a pool of seven potential vaccines have been developed and evaluated through clinical trials (Sameem & Dias, 2017). The most promising Ebola vaccine candidates are cAd3-ZEBOV, which successfully passed through clinical trials and entered into Phase III trials, and the live-replicating rVSV-ZEBOV that has been validated to be effective in Phase III clinical studies (Chowell & Nishiura, 2014). Recombinant Vesicular Stomatitis Virus (rVSV-ZEBOV) is currently the only Ebola vaccine with demonstrated clinical efficacy in a ring-vaccination clinical trial (Levy et al., 2017). This vaccine contains rVSV, a virus that causes disease in cattle, deer, horses and pigs but causes few problems in humans (Carney & Weber, 2015). rVSV-ZEBOV is a recombinant, replication-competent vesicular stomatitis virus-based candidate vaccine in which the VSV envelope glycoprotein was replaced with the Zaire strain ebolavirus (ZEBOV) glycoprotein (Carney & Weber, 2015). The genetically engineered VSV envelope expresses the homologous EBOV glycoprotein from the Zaire ebolavirus as the immunogen in response to the Ebola virus (Sameem & Dias, 2017).

The second candidate vaccine is the Replication-defective recombinant chimpanzee adenovirus type 3 (cAd3-ZEBOV). CAds are non-enveloped viruses, contrary to VSV-based vaccine vectors, meaning that the antigen is not present on the surface of the vector but is expressed at high levels once the vector enters the target cells of the vaccinated individual (Medaglini & Siegrist, 2017). The candidate cAd3-ZEBOV is a non-replicative vector-based Ebola vaccine (i.e., genes essential for the life cycle of the vector virus are deleted to restrict the transcription and replication) that encodes the glycoprotein from the Zaire ebolavirus (Burghardt et al., 2016). The chimpanzee adenovirus type 3 (ChAd3) is used as a carrier to deliver benign genetic material of the Zaire strain (Henao-Restrepo et al., 2017).

Among the many studies on Ebola virus, we note two recurring goals of most computational models: quantifying the effects of possible interventions on the incidence rate (Takaidza et al., 2017) and developing predictive models to estimate the total number of infected cases, the reproduction number, the number of deaths and the duration of outbreaks (Althaus, 2014; Do & Lee, 2016). Some other studies focus on examining assumptions about how the disease spreads, such as uniform transmissibility vs. homogeneous mixing within a population (Burghardt et al., 2016). There are also several studies with the common goal of understanding the impact of public-health initiatives on the dynamics of an outbreak and control of the virus (Chowell & Nishiura, 2014; Levy et al., 2017). Those studies often analyze the role of behavior change induced by health education or use consumer-centric models of public-health intelligence (Carney & Weber, 2015; Levy et al., 2017).

Other models of Ebola have focused on interventions such as quarantine, distribution of household kits, Emergency Treatment Care (ETC) expansion and accelerating case tracking. 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 et al., 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 et al., 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 et al., 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 & 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 et al., 2015) showed that, if contact tracing was perfect, then the critical proportion of contacts that need to be traced could be derived. 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. Waife et al. (Waife et al., 2017) used sensitivity analysis to show that an Ebola vaccine could be effective if contact rates with unvaccinated individuals could be sufficiently lowered.

Risk equations have been used to determine contributing morbidity and mortality factors for a variety of infections, such as heart disease (Muntner et al., 2014), kidney failure (Tangri et al., 2016), diabetes (Simmons et al., 2009) and HIV (Petoumenos et al., 2014). Per-day risk equations to assess the potential effect of treatment have been used for vaginal microbicides as a potential HIV prophylaxis (Smith et al., 2005). Although the use of such equations in infectious disease modelling is relatively

new, this kind of risk assessment has become an accepted component of clinical guidelines and recommendations in cardiovascular medicine, for example (Knobel et al., 2007).

Our aim in this paper is to determine the daily risk of Ebola infection during an epidemic, both before and after a potential vaccination using daily risk equations. We address the following research questions: 1. Could vaccination result in a net increase in risk? 2. Can we determine conditions that optimize vaccine efficacy? 3. Which is more important to maximise, vaccination efficacy or use?

2. The model

In order to evaluate the potential effect of vaccination, we develop risk equations for the daily risk of Ebola infection both currently and after vaccination. When hazmat suits, reduced contact with the living or dead or vaccination is employed, the probability that Ebola is transmitted is reduced from the probability β to β' (where $\beta' < \beta$). We have modelled single exposure events, and thus the transmission probability of each event is significantly less than the transmission probability over the duration of the outbreak. If β' is the probability of transmission during a single exposure event with a given protection type (hazmat suit, reduced contact, vaccination, any combination thereof, or no protection), then the probability of remaining uninfected during a single exposure event is $(1-\beta')$. The probability of remaining uninfected after N exposure events is thus $(1-\beta')^N$. Thus the probability of Ebola infection for an individual is

$$\text{Risk} = 1 - \prod_{i}^{\substack{\text{all protection}\\ \text{options}}} [1-\beta']^{p_i},$$

where p_i is the proportion of times a given protection protocol is employed (including no protection).

The risk equations account for the basic transmission probability of Ebola (β), the lowered risk due to various protection protocols: hazmat suits (e_h), reduced contact with the infected living (e_{c_I}), vaccination (e_v) and reduced contact with dead bodies (e_{c_D}). We denote the use of no protection by $1-\beta$. Our risk equations also include the proportions of use (individually or in combination) of these protection protocols. We denote these proportions by p_i if applied before vaccination and q_i if applied after. The proportion of use of all protection types sums to 1 in each case.

Since Ebola is a pervasive disease with extreme transmission rates, we focus our analysis on the higher range of transmissibility; i.e., when the basic risk of transmission (β) is between 0.5 and 1. As the exact transmission rate of the virus is still unknown, we have modelled low (50–55%), moderate (70–75%) and high (90–95%) levels of transmissibility to analyze how the performance of different protection protocols can change across these levels of transmission.

Currently (when the only protection protocols are to reduce contact with the infected living and dead (e_{c_I}, e_{c_D}), hazmat suits (e_h) and no protection ($1-\beta$)), the daily risk of contamination for a susceptible individual is

$$\begin{aligned} r_1 = 1 - &[1-(1-e_{cD})\beta]^{p_0}[1-(1-e_{cI})\beta]^{p_1}[1-(1-e_h)\beta]^{p_2} \\ &[1-(1-e_{cD})(1-e_{cI})\beta]^{p_3}[1-(1-e_{cD})(1-e_h)\beta]^{p_4}[1-(1-e_{cI})(1-e_h)\beta]^{p_5} \\ &[1-(1-e_{cI})(1-e_{cD})(1-e_h)\beta]^{p_6} \\ &[1-\beta]^{1-p_0-p_1-p_2-p_3-p_4-p_5-p_6}, \end{aligned}$$

where p_0, p_1, p_2, p_3, p_4, p_5 and p_6 are the proportions of use of protection protocols outlined in Table 1.

Post-vaccine (when the available protection protocols are vaccination (e_v), reduced contact with the infected living and dead (e_{c_I}, e_{c_D}), hazmat suits (e_h) and no protection ($1-\beta$)), the daily risk of contamination is

$$\begin{aligned} r_2 = 1 - &[1-(1-e_{cD})\beta]^{q_0}[1-(1-e_{cI})\beta]^{q_1}[1-(1-e_h)\beta]^{q_2} \\ &[1-(1-e_{cD})(1-e_{cI})\beta]^{q_3}[1-(1-e_{cD})(1-e_h)\beta]^{q_4}[1-(1-e_{cI})(1-e_h)\beta]^{q_5} \\ &[1-(1-e_{cI})(1-e_{cD})(1-e_h)\beta]^{q_6} \\ &[1-(1-e_v)\beta]^{q_7}[1-(1-e_v)(1-e_{cI})\beta]^{q_8}[1-(1-e_v)(1-e_h\beta]^{q_9}[1-(1-e_v)(1-e_{cD})\beta]^{q_{10}} \\ &[1-(1-e_v)(1-e_{cD})(1-e_h)\beta]^{q_{11}}[1-(1-e_v)(1-e_{cI})(1-e_h)\beta]^{q_{12}} \\ &[1-(1-e_v)(1-e_{cD})(1-e_{cI})\beta]^{q_{13}} \\ &[1-\beta]^{1-\sum_{i=0}^{13} q_i}, \end{aligned}$$

where q_0, q_1, …, q_{13} are the proportions of use of protection protocols available after the vaccine is introduced. Parameter values are given in Table 1.

Initially, we assumed a uniform use of all protection protocols available (including using no protection). There are eight possible combinations of protection protocols: p_0 through p_6 and the fraction of people using no protection

Table 1
Parameter values before and after vaccine introduction. We assumed a uniform use of all available protection protocols (including no protection) before the vaccine. Thus, there are eight possible combinations of protection protocols: p_0 through p_6 and no protection ($1 - p_0 - p_1 - p_2 - p_3 - p_4 - p_5 - p_6$). The upper bound of the range of values for each proportion is equal to 0.125. After the introduction of a vaccine, we considered the extreme case where vaccination was the only available protection protocol ($0 < q_7 < 1$) and that the vaccine was at least 35% effective.

Parameter	Definition	Range
β	Transmissibility	0.5–1
e_{c_l}	Reduced contact with the infected living	0–1
e_{c_D}	Reduced contact with the dead	0–1
e_h	Hazmat suit	0–1
e_v	Vaccine efficacy	0.35–1
p_0	Fraction of people reducing contact with dead bodies	0–0.125
p_1	Fraction of people reducing contact with the infected living	0–0.125
p_2	Fraction of people using hazmat suits	0–0.125
p_3	Fraction of people reducing contact with the infected living and dead bodies	0–0.125
p_4	Fraction of people using hazmat suits and reducing contact with dead bodies	0–0.125
p_5	Fraction of people using hazmat suits and reducing contact with the infected living	0–0.125
p_6	Fraction of people using hazmat suits and reducing contact with the infected living and dead bodies	0–0.125
q_0	Fraction of people reducing contact with dead bodies	0
q_1	Fraction of people reducing contact with the infected living	0
q_2	Fraction of people using hazmat suits	0
q_3	Fraction of people reducing contact with the infected living and dead bodies	0
q_4	Fraction of people using hazmat suits and reducing contact with dead bodies	0
q_5	Fraction of people using hazmat suits and reducing contact with the infected living	0
q_6	Fraction of people using hazmat suits and reducing contact with the infected living and dead bodies	0
q_7	Fraction of people using the vaccine	0–1
q_8	Fraction of people using the vaccine and reducing contact with the infected living	0
q_9	Fraction of people using the vaccine and wearing hazmat suits	
q_{10}	Fraction of people using the vaccine and reducing contact with dead bodies	0
q_{11}	Fraction of people using the vaccine, wearing hazmat suits and reducing contact with dead bodies	0
q_{12}	Fraction of people using the vaccine, wearing hazmat suits and reducing contact with the infected living	0
q_{13}	Fraction of people using the vaccine and reducing contact with dead bodies and the infected living	0

$(1 - p_0 - p_1 - p_2 - p_3 - p_4 - p_5 - p_6)$. As such, the upper bound of the range of values for each proportion is set to 0.125 (see Table 1).

By equating the current daily risk of contracting the disease, r_1, and the daily risk after the introduction of the vaccine, r_2, we obtain an analytical expression for the threshold level of vaccine efficacy and use that would be necessary to induce a net decrease in the daily risk of infection:

$$
\begin{aligned}
r^* = \; & [1-(1-e_{cd})\beta]^{q_0-p_0}[1-(1-e_{cI})\beta]^{q_1-p_1}[1-(1-e_h)\beta]^{q_2-p_2} \\
& [1-(1-e_{cd})(1-e_{cI})\beta]^{q_3-p_3}[1-(1-e_{cd})(1-e_h)\beta]^{q_4-p_4}[1-(1-e_{cI})(1-e_h)\beta]^{q_5-p_5} \\
& [1-(1-e_{cI})(1-e_{cd})(1-e_h)\beta]^{q_6-p_6} \\
& [1-(1-e_v)\beta]^{q_7}[1-(1-e_v)(1-e_{cI})\beta]^{q_8}[1-(1-e_v)(1-e_h)\beta]^{q_9}[1-(1-e_v)(1-e_{cd})\beta]^{q_{10}} \\
& [1-(1-e_v)(1-e_{cd})(1-e_h)\beta]^{q_{11}}[1-(1-e_v)(1-e_{cI})(1-e_h)\beta]^{q_{12}} \\
& [1-(1-e_v)(1-e_{cd})(1-e_{cI})\beta]^{q_{13}} \\
& [1-\beta]^{\sum_{i=0}^{6} p_i - \sum_{i=0}^{13} q_i}
\end{aligned}
$$

Note that $q_i - p_i$ ($i = 0, 1, \ldots, 6$) and the exponent $\sum_{i=0}^{6} p_i - \sum_{i=0}^{13} q_i$ may be negative.

The risk ratio r^* serves as a threshold indicating when the introduction of a vaccine can improve the situation. In particular, r^* provides information on the levels of vaccine efficacy and use needed to reduce the daily risk of contamination. The benchmark value for r^* is 1. At this value, the risk before the vaccine is identical to the risk after vaccination of catching Ebola, which means that the introduction of a vaccine has no effect on the daily risk of infection. The vaccine will be favorable if $r^* > 1$ and detrimental (i.e., increase the daily risk) if $r^* < 1$.

We evaluated the impact of potential vaccination using Latin Hypercube Sampling (LHS) and partial rank correlation coefficients (PRCCs) to explore the sensitivity of the daily risk of infection to parameter variations. LHS is a statistical sampling method that generates a quasi-random sampling distribution. It allows for an efficient analysis of parameter variations across simultaneous uncertainty ranges in each parameter (Blower & Dowlatabadi, 1994; Blower et al., 2001). PRCCs rank each parameter by the amount of effect on the outcome, regardless of whether that effect is positive or negative (Blower & Dowlatabadi, 1994). We performed an uncertainty analysis using Monte Carlo simulations and multivariate sensitivity analysis to analyze our risk equations. We computed the risk over a wide parameter space to assess the variability of our dependent variable (risk per day of catching Ebola r_1 or r_2), using LHS to sample parameter space. Finally, we evaluated the potential risk-reduction effect of vaccination depending on the fraction of vaccinated people.

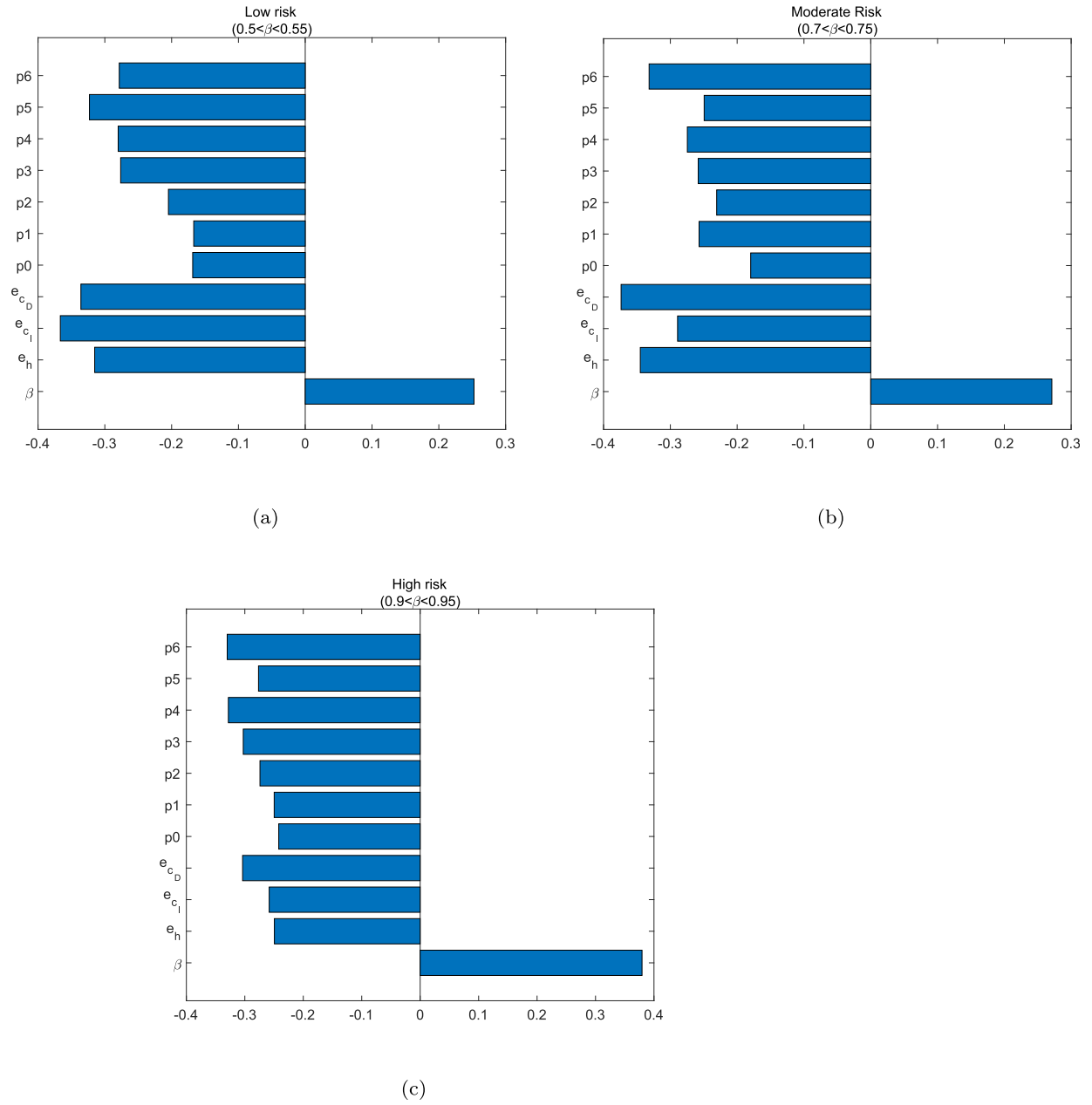


Fig. 1. PRCCs before vaccine introduction for low (50–55%), moderate (70–75%) and high (90–95%) levels of transmissibility. The outcome variable is the daily risk of infection before vaccination, r_1.

3. Results

A candidate vaccine will be beneficial (i.e., decrease the daily risk of infection) if the risk of transmission after the introduction of the vaccine is lower than the current risk. To show which parameters the daily risk is most sensitive to, we used plots of PRCCs for each of the independent parameters. Parameters with PRCC >0 increase a susceptible's daily risk as the parameter value increases, whereas parameters with PRCC <0 decrease a susceptible's daily risk as the parameter value increases.

Fig. 1 illustrates the degree of sensitivity of the daily risk of infection before the vaccine is introduced. At relatively low transmissibility levels, reducing contact with infected individuals (e_{c_I}) is the most effective alternative to decrease the daily risk of infection. When the rate of transmission is moderate and there is no vaccine, wearing hazmat suits and reducing contact with the dead has a better protective impact. As the transmission rate rises, a higher proportion of use of those

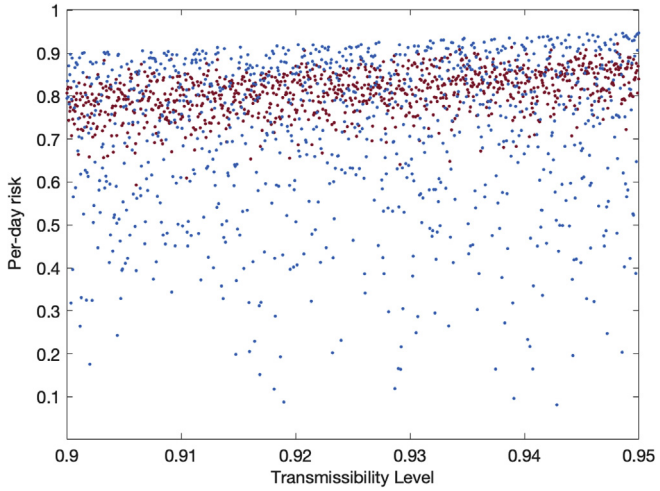


Fig. 2. Sensitivity of the daily risk of Ebola to transmission rates when the only protection protocol available is the vaccine. The red dots represent the current daily risk of infection while the blue dots represent the post-vaccine daily risk of contamination. The proportional vaccine uptake q_7 ranges from 0 to 1 and the transmission rate β is between 0.9 and 0.95.

protection protocols becomes necessary. When the transmission probability is high and there is no vaccine available, all protection protocols are similar in terms of their efficacy, but none has a substantial effect on protecting against the virus. It is here that the introduction of a vaccine will benefit populations at risk the most.

The remainder of our focus is on the case of high transmissibility when β ranges from 90% to 95%. We analysed the impact of a potential vaccine with efficacy that ranged from moderate to high (e_v ranges from 0.35 to 1). Fig. 2 illustrates the effect of the transmission rate (β) on the post-vaccination daily risk of infection (r_2) when susceptibles use the vaccine as their sole protection protocol. The proportion of vaccine use q_7 ranges from 0 to 1 (see Table 1). The red dots represent the current risk of infection, and the blue dots represent the risk after vaccination. As shown in Fig. 2, introducing the vaccine could result in one of two outcomes: in some cases, the vaccine may reduce the risk of contamination, but in others, we run the risk of having more cases following the introduction of an Ebola vaccine. As the outcome is uncertain, it is important to understand which variables play a role in effectively decreasing the risk of infection and what levels are needed for these parameters. Fig. 3 shows that a large fraction of the population must be vaccinated (>80%) to achieve a 50% decrease in the daily risk of infection.

Fig. 4 illustrates the ideal situation where everyone in an area at risk gets vaccinated. In this case, $q_7 = 1$. At any level of transmissibility, the daily risk of catching Ebola is significantly less than without the vaccine. A strong vaccine (>50% efficacy) leads to a 50% decrease in the daily risk of Ebola if everyone receives it. We can reasonably infer that, with an effective vaccination campaign and more awareness about how Ebola is transmitted, we can reach a stage of disease control if the vaccine is not too weak.

Fig. 5 illustrates three scenarios: currently (no vaccine), the vaccine being the sole protection protocol available (no protection is also an option) and with the vaccine being the only protection protocol used by everyone. Without a vaccine, the daily risk of infection r_1 remains above 80%. In the second scenario, the candidate vaccine is introduced, and people who initially used a protection protocol now replace it with the vaccine, while those who have not used protection continue to do so. The median post-vaccine risk of infection r_2 is less than 80% in this case. However, the range of r_2 is wide ($0\% \leq r_2 \leq 97\%$), which implies a high volatility in the daily risk. In the third scenario, the ideal case of absolute vaccine uptake, the median per day-risk r_2 drops to 30%, ranging from 0 to 60%, a net decrease from the initial risk r_1 of 80% and a decrease in volatility. This indicates that a high rate of vaccine uptake would be required to continuously maintain the risk of infection below its current value.

Fig. 6 shows PRCCs of the parameters that affect r^*. For general vaccine uptake, the fraction of people who get vaccinated q_7 is the only variable that has a significant impact on r^* (Fig. 6(a)). When the vaccine uptake is high ($0.7 \leq q_7 \leq 1$), Fig. 6(b) shows that the transmission probability β and vaccine efficacy e_v affect r^* significantly. Fig. 7 shows that there is a threshold whereby the fraction of people who use the vaccine (q_7) is guaranteed to increase the risk is if it sufficiently low (<25%) but guaranteed to decrease the risk if it is sufficiently high (>70%), regardless of the protective behavior or lack thereof.

If a vaccine is introduced, it must have at least 50% efficacy, and at least 70% of people in the affected areas must receive it to start seeing an effective reduction in the risk of disease. To halve and control the risk of an Ebola outbreak, at least 80% of people need to be vaccinated with a vaccine that is at least 50% effective. Vaccine uptake has a stronger impact on disease control than vaccine efficacy.

Finally, we examined some possibilities for parameter ranges beyond the ranges given in Table 1. In particular, we constrained the eight pre-vaccination proportions as $0 \leq p_j \leq 0.125$ in order to consider all protection protocols equally. However,

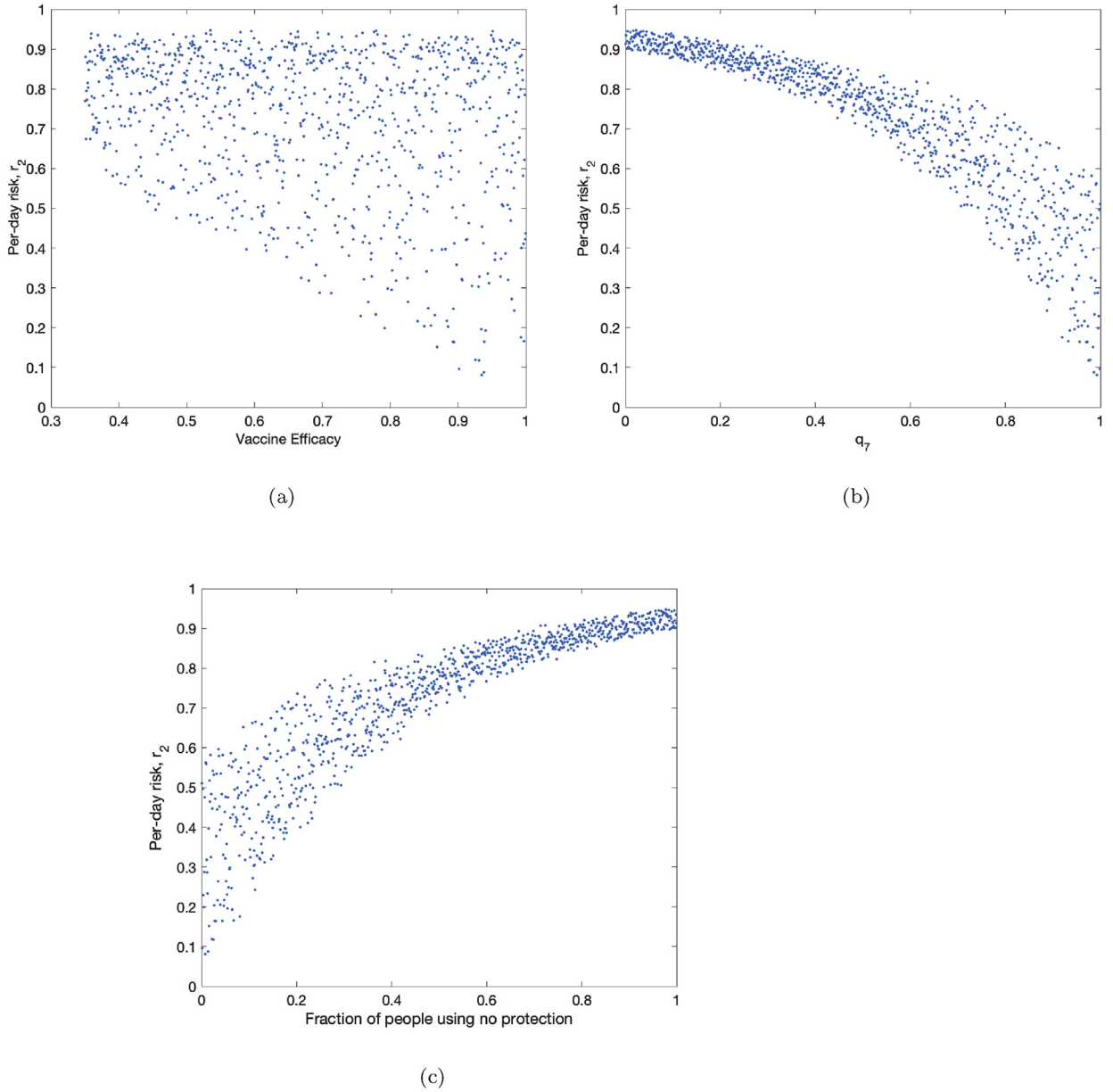


Fig. 3. Sensitivity of the daily risk of Ebola to the effectiveness of the vaccine e_v, its proportion of use q_7 and the fraction of people not using any protection. The proportional vaccine uptake q_7 varies from 0 to 1, and vaccination is the only available protection protocol. The transmission rate β is between 0.9 and 0.95.

in order to stress test this, we examined three potential scenarios: (a) in the absence of hazmat suits, (b) if contact with the living was unchanged and (c) if contact with the dead was unchanged. These possibilities may arise if hazmat suits are not available, if people fail to follow social distancing or if funeral practices are unchanged. Note that the absence of a protection protocol also implies its absence in any combination protocol. Thus, for (a), we not only have $p_2 = 0$ but also $p_4 = p_5 = p_6 = 0$, and we increased the range of the remaining protection protocols to $0 \leq p_0, p_1, p_3 \leq 0.333$.

The results are illustrated in Fig. 8. In the absence of hazmat suits, the most significant protocol is p_3, the fraction of people reducing contact with the infected living and dead bodies. The next most significant parameters are e_{c_l} and e_{c_D}, the effectiveness of contact reductions with the living and the dead, respectively. That is, in the absence of hazmat suits, the combination of remaining protection protocols becomes crucial. Likewise, if contact with the living is unchanged, then the most significant parameter is p_4, the fraction of people who use hazmat suits and reduce contact with the dead, followed by the efficacies of these two protection protocols. Finally, if contact with the dead is unchanged, then p_5, the fraction of people who

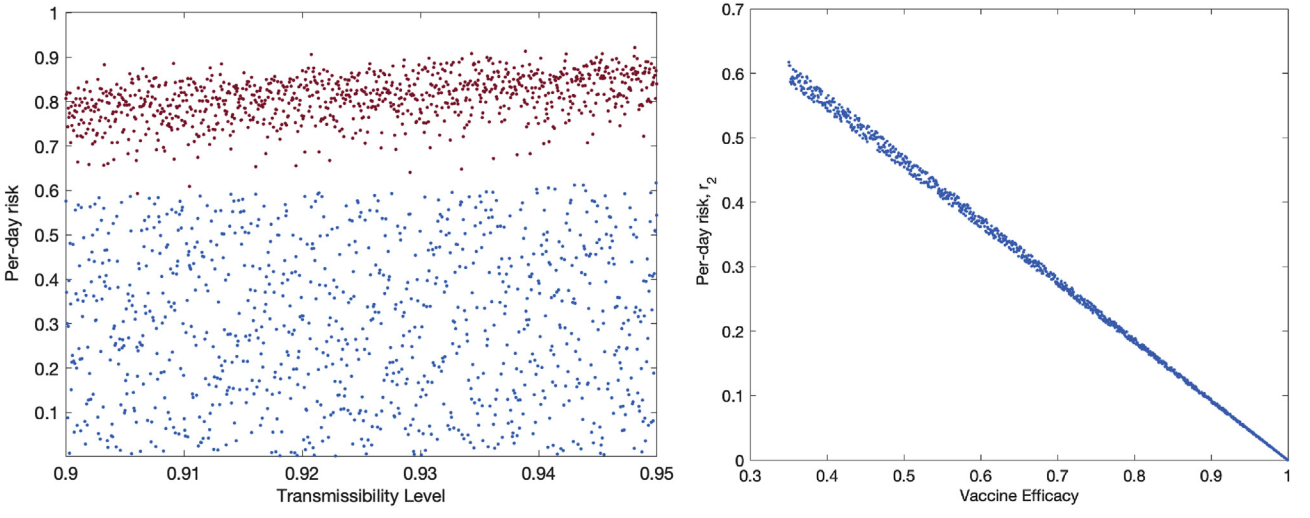
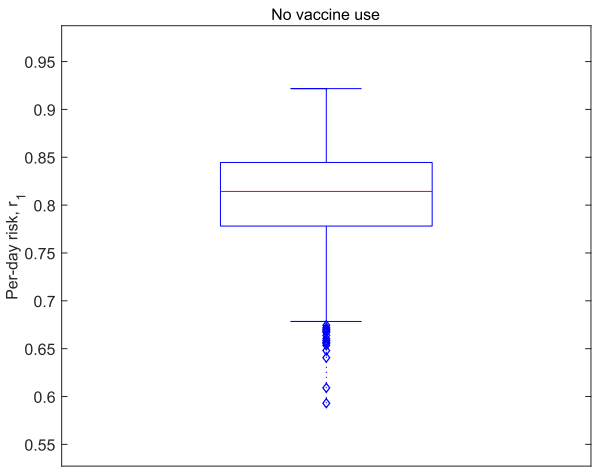
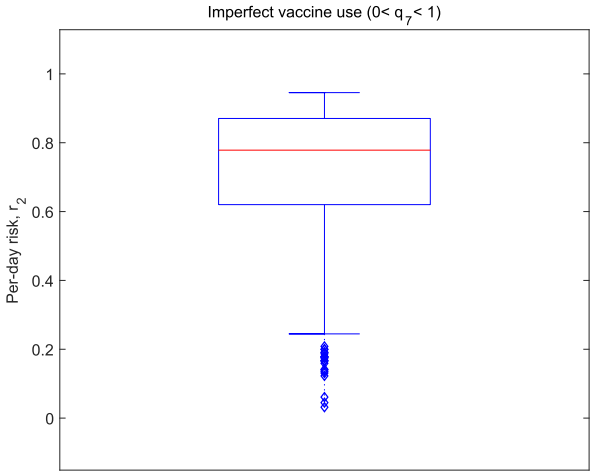


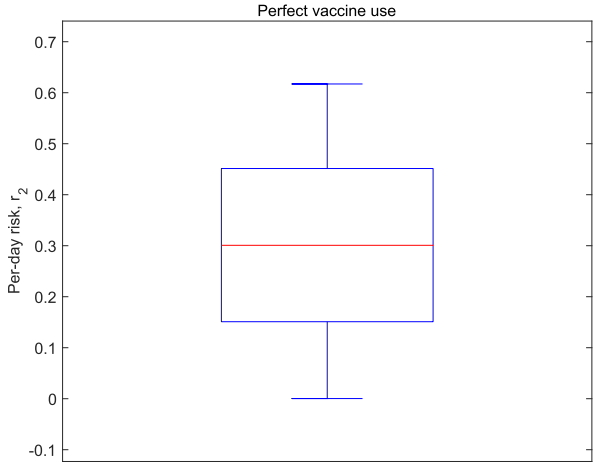
Fig. 4. Sensitivity of the daily risk of Ebola to transmission rates and vaccine efficacy when all susceptible individuals get vaccinated. The red dots represent the current risk of infection while the blue dots represent the post-vaccine risk of Ebola. This is an ideal case, and the proportion of use of the vaccine q_7 is set to 1. The transmission rate β is between 0.9 and 0.95.



(a)



(b)



(c)

Fig. 5. Boxplots of 1000 sampled values using the LHS ranges from Table 1. The horizontal red line indicates the median value. We present the daily risk of Ebola under three scenarios: before the vaccine, imperfect vaccine uptake ($0 < q_7 < 1$) and perfect vaccine use ($q_7 = 1$).

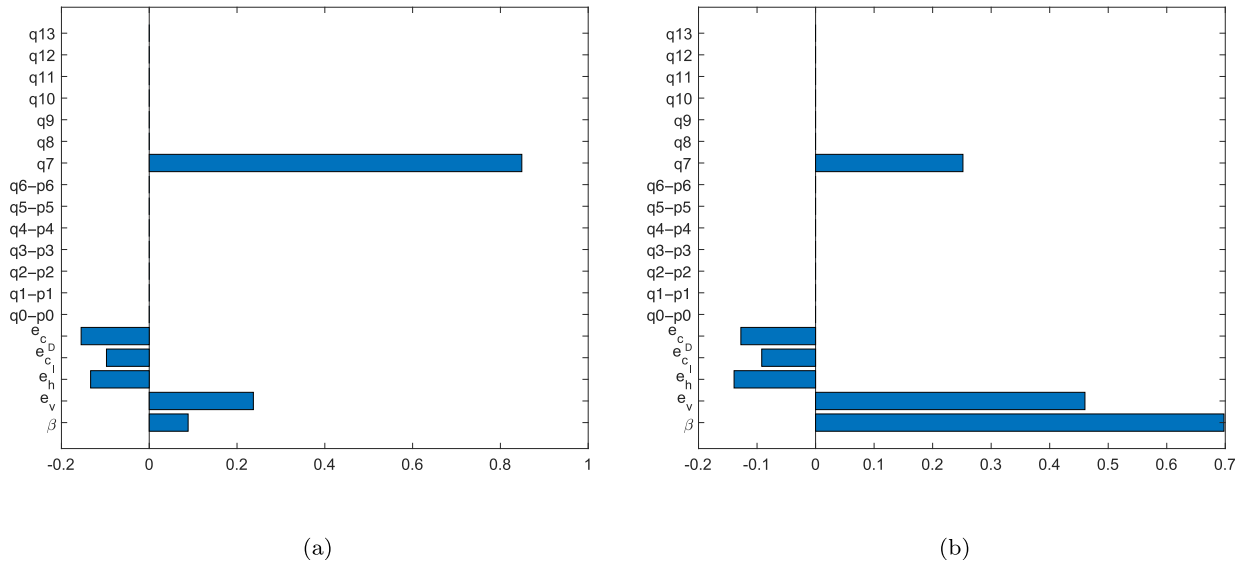


Fig. 6. PRCCs for parameters that affect r^*. (a) The case for general vaccine uptake ($0 < q_7 < 1$). (b) The case for high vaccine uptake ($0.7 < q_7 < 1$). The transmission rate β is between 0.5 and 1.

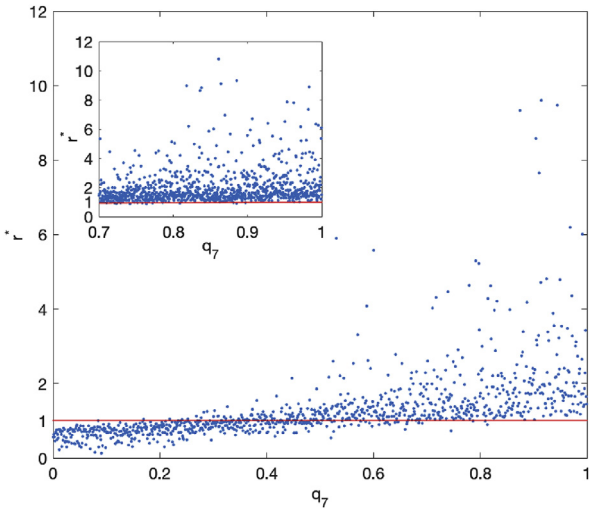


Fig. 7. Sensitivity of the threshold level r^* to (a) the fraction of people using the vaccine q_7 and (b) the fraction of people not using any protection. The transmission rate β is between 0.5 and 1. Inset: the range $q_7 > 70\%$ that guarantees risk reduction.

use hazmat suits and reduce contact with the living, becomes the most significant parameter, followed by the efficacies of these two protection protocols.

4. Discussion

According to our results, the parameters with the greatest effect on the Ebola epidemic are the transmission probability (β), the fraction of people using the vaccine (q_7), vaccine efficacy (e_v), reducing contact with dead bodies (e_{c_D}) and wearing hazmat suits (e_h). The increased risk due to dead bodies is likely due to the fact that infectious dead bodies remain infectious for up to a week after death (Prescott et al., 2015). Safe burial methods enforced by the US Centers for Disease Control (CDC) have proven useful in reducing case incidence rates and hence transmissibility (Nielsen et al., 2015). The transmission probability is the most influential parameter in our risk equations. Our results indicate that any efforts to reduce this transmission, such as a vaccine, would have a significant effect on reducing the overall epidemic if populations can be sufficiently educated about the necessity for high vaccine uptake. In the absence of a vaccine, we also showed that if

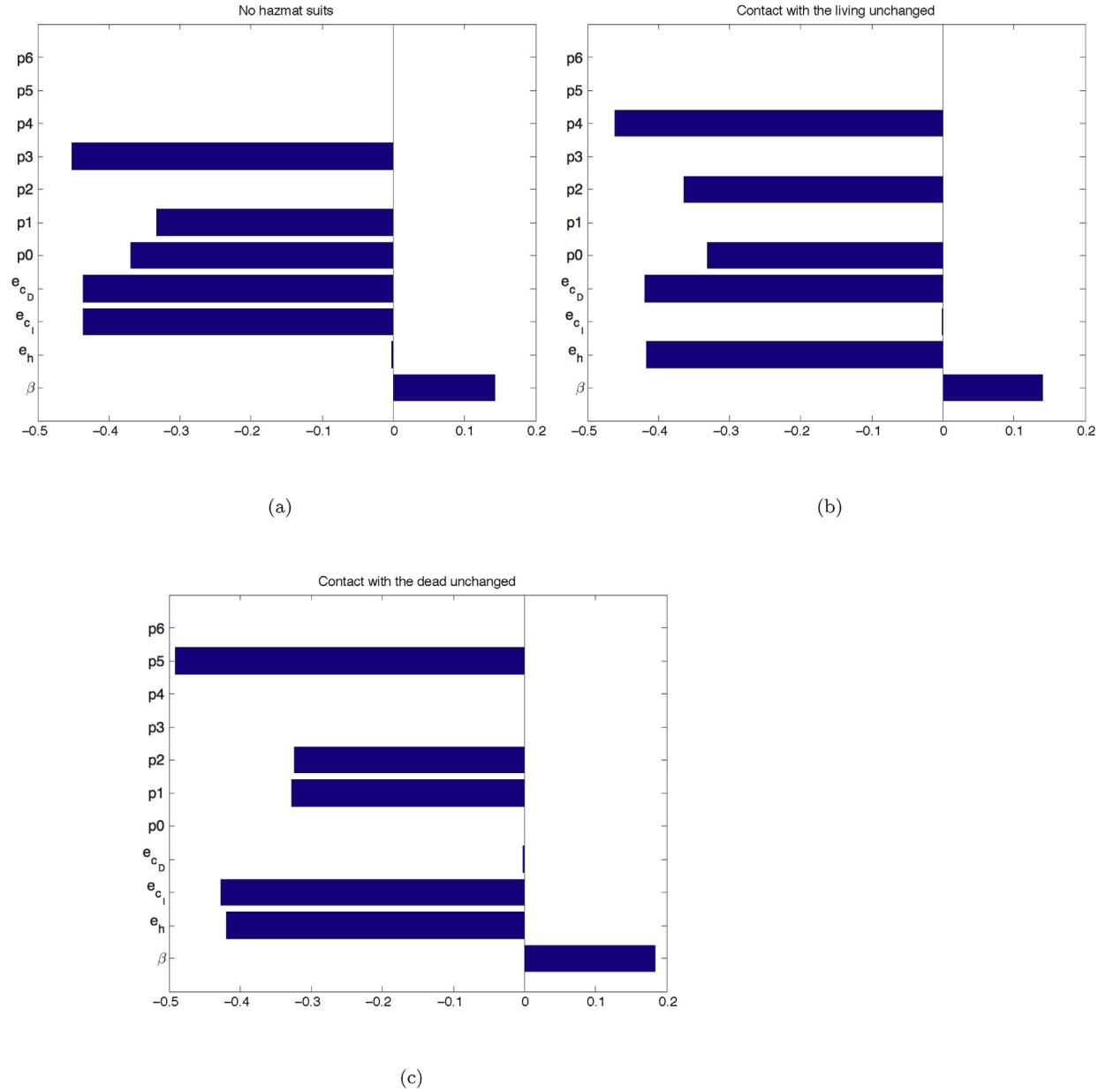


Fig. 8. PRCCs for some possibilities outside the ranges in Table 1: (a) the absence of hazmat suits, (b) when contact with the living infected is unchanged and (c) when contact with dead bodies is unchanged. In each case, the most significant influence on the outcome is the combination of the remaining protection protocols, followed by the efficacies of those remaining protection protocols.

one of the protection protocols is not followed, then the combination of the remaining protection protocols becomes crucial.

Several interventions have already been used to reduce the spread of Ebola including extensive awareness campaigns meant to educate susceptible individuals on transmission, symptoms and health risks of the disease. Quarantine of individuals found through aggressive contact tracing and isolation of infected individuals while they are treated have also been effective methods to reduce the daily risk of infection (Bausch et al., 2007). The CDC has employed safe burial teams, which are tasked with safely burying corpses (Nielsen et al., 2015). This results in less contact between susceptible individuals and infected dead bodies. There have been recent trials for an Ebola vaccine, some of which have been promising (Chowell & Nishiura, 2014). An excellent vaccine would reduce the case incidence rate; however, a reasonably good vaccine that can be administered to most people would likely lower the transmissibility and help to control disease spread.

Our model has several limitations, which should be acknowledged. Initially, before a vaccine is introduced, we assumed a uniform use of all protection protocols available, including using no protection, which may not hold as populations become more aware of the disease and adjust their protective behaviours. We assumed the same transmission probability for the living and dead, which may not be true.

After the recent outbreak in West Africa, efforts to develop an effective vaccine against the Ebola Virus Disease have increased. We have shown that a vaccine can control the epidemic, even when transmission rates are high (above 90%). We found that at a high transmission rate of Ebola, a large fraction of the population must be vaccinated (>80%) to achieve a 50% decrease in the daily risk of infection. If a vaccine is introduced, it must have at least 50% efficacy, and almost everyone in the affected areas must receive it to effectively control outbreaks of Ebola. These results indicate that a low-efficacy Ebola vaccine runs the risk of having vaccinated people be overconfident in a weak vaccine and hence the possibility of the vaccine making the situation worse, unless the population can be sufficiently educated about the necessity for high vaccination rates.

The question of how effective and widely distributed a vaccine needs to be to have a beneficial impact on public health extends far beyond the application to Ebola. Given the economic costs and personal inconvenience of the mitigation strategies in use for COVID-19, for example, many of the existing strategies may end once a vaccine becomes available. Hence, more modelling along these lines will provide further insights to other infectious diseases.

Declaration of competing interest

We have no conflict of interest.

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