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Vaccinating in disease-free regions: a vaccine model with application to yellow fever

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Concerns regarding natural or induced emergence of infectious diseases have raised a debate on the pros and cons of pre-emptive vaccination of populations under uncertain risk. In the absence of immediate risk, ethical issues arise because even smaller risks associated with the vaccine are greater than the immediate disease risk (which is zero). The model proposed here seeks to formalize the vaccination decision process looking from the perspective of the susceptible individual, and results are shown in the context of the emergence of urban yellow fever in Brazil. The model decomposes the individual's choice about vaccinating or not into uncertain components. The choice is modelled as a function of (i) the risk of a vaccine adverse event, (ii) the risk of an outbreak and (iii) the probability of receiving the vaccine or escaping serious disease given an outbreak. Additionally, we explore how this decision varies as a function of mass vaccination strategies of varying efficiency. If disease is considered possible but unlikely (risk of outbreak less than 0.1), delay vaccination is a good strategy if a reasonably efficient campaign is expected. The advantage of waiting increases as the rate of transmission is reduced (low R_0) suggesting that vector control programmes and emergency vaccination preparedness work together to favour this strategy. The opposing strategy, vaccinating pre-emptively, is favoured if the probability of yellow fever urbanization is high or if expected R_0 is high and emergency action is expected to be slow. In summary, our model highlights the nonlinear dependence of an individual's best strategy on the preparedness of a response to a yellow fever outbreak or other emergent infectious disease.

Keywords: emerging infectious diseases; decision analysis; yellow fever; Brazil

1. INTRODUCTION

Sylvatic yellow fever (SYF) is endemic in the north and central regions of Brazil where the transmission cycle is maintained between non-human primates and *Haemagogus* and *Sabethes* mosquitoes. Approximately 10% of infections with this *Flavivirus* are severe and result in haemorrhagic fever, with case fatality of 50% (Vasconcelos 2003). This virus can also be transmitted through an urban cycle, where the vector is the mosquito *Aedes aegypti*. The last urban yellow fever (UYF) epidemic in Rio de Janeiro occurred in 1929 (Vasconcelos 2003). However, given the re-introduction of *A. aegypti* and its spread throughout Brazil, the risk of UYF is questioned. It has been estimated that the risk of an UYF epidemic in Rio de Janeiro should vary with the endemic cycle of SYF and might reach an upper limit of 29% in epizootic years (Codeço *et al.* 2004).

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Yellow fever can be prevented through immunization. In Brazil, the vaccine 17DD has been used since the 1930s. It is estimated that approximately 95% of the population living in the endemic regions of Brazil has been vaccinated. In the transition zone, where epizootic activity of the disease is observed, vaccine coverage might reach a similar fraction. However, since the coastal region of Brazil, including Rio de Janeiro, has not been systematically vaccinated, vaccine coverage is expected to be minimal (Vasconcelos 2003).

In Brazil, yellow fever vaccine (YFV) has been associated with four fatalities in children and adults. Estimates of the expected risk of a fatal adverse event following vaccination have varied from 0.017 to 12 fatalities per one million doses *applied* (i.e. not discounting re-vaccination of the same individual; Struchiner *et al.* 2004). These fatalities are thought to result from an individual's enhanced immune response (Galler *et al.* 2001; Marchevsky *et al.* 2003). Serious viscerotropic disease has also been associated with the vaccine (Engel *et al.* 2006). A randomized controlled trial was recently conducted to determine the

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immunogenicity and reactogenicity of the vaccine (Camacho *et al.* 2004, 2005). Seroconversion rates upon vaccination were found to be over 98%. Using the placebo group as reference, the maximum risk differences for local and systemic adverse events were 2.5 and 7.4%, respectively.

The possibility of an UYF epidemic poses a dilemma for regions of the country where no SYF activity occurs: pre-emptively vaccinate or wait for an epidemic to occur to vaccinate? If vaccine is made available before an outbreak, there are two risks associated with pre-emptive vaccination for the individual. First, the direct risk of an adverse event following vaccination, which could be local, systemic or fatal. Second, an indirect risk of a vaccine scare through the possible occurrence of adverse events in other individuals. If the fear of taking the vaccine reached a significant proportion of the community, it could, in turn, result in low vaccine coverage. On the other hand, if the vaccination campaign is delayed until an outbreak, the time needed to curtail an epidemic through mass vaccination might result in greater disease mortality. In this scenario, overall mortality depends on the timeliness of epidemic detection and vaccine distribution.

Here, we approach the 'yellow fever vaccination problem' comparing the strategies mentioned above (pre-emptive and emergency vaccination), from the point of view of a rational individual deciding between taking a vaccine shot pre-emptively or delaying vaccination to an epidemic situation. We determine the vaccine strategy that minimizes adverse events from disease and vaccine. Massad *et al.* (2005) showed that the optimum vaccine coverage, when disease and vaccine adverse events are minimized in the community, might not be adequate to prevent a yellow fever outbreak. Here, we similarly try to minimize adverse events from disease and vaccine. However, we add another level of complexity to the problem: the uncertainty of the occurrence and the timing of events. The question is: what is the optimal strategy for a susceptible individual who moves to a disease-free city at-risk of yellow fever urbanization who can either vaccinate pre-emptively or in response to an outbreak.

2. MATERIAL AND METHODS

(*a*) *The vaccination decision rule*

An individual, seronegative to YF, is offered the vaccine. He is not currently at risk of getting yellow fever (he lives in a disease-free city), but is uncertain about his future risk. The individual must decide between getting vaccinated immediately (strategy V) or waiting until a situation of risk occurs (strategy W). Choosing V has the advantage of acquiring long-lasting protection against a serious disease, the disadvantage is the possibility of vaccine-associated adverse events. Choosing W has the advantage of not exposing himself to any risk immediately (since disease is not present), but has the disadvantage of losing control of his access to the vaccine in an emergency situation. In other words, during an outbreak, the probability of receiving a vaccine shot depends on the demand and the policy decisions regarding priorities. In other words, he must get in line.

The reward of choosing V is inversely related to the probability of adverse events from the vaccine (c_v). The reward of choosing strategy W depends on many uncertain variables: the probability of (i) an outbreak (u), (ii) getting infected if an outbreak occurs (π_i), (iii) getting vaccinated before the infection event (π_v) and (iv) serious disease given infection (r_i) and serious adverse events from the vaccine (c_v). Formally, we have

$$\text{Reward for strategy V}: R_V = 1 - c_v,$$
$$\text{Reward for strategy W}: R_W = 1 - u(\pi_i r_i + \pi_v c_v) = 1 - c_w.$$

We are interested in defining epidemiological situations where $r = R_V - R_W > 0$, i.e. situations where vaccinating immediately is advantageous from the individual perspective. That clearly depends on the risk of experiencing an outbreak (u), and upon occurrence, the probability of receiving the vaccine or escaping infection and disease.

(*b*) *Epidemiological scenarios*

(i) *Probability of urban emergence of yellow fever (u).* In Brazil, most cities in the coastal region have high abundance of the yellow fever urban vector, *A. aegypti*, which is a relatively competent vector under laboratory conditions (de Oliveira *et al.* 2002). Despite this observation, in Brazil, there is no evidence of yellow fever transmission by *A. aegypti* under natural conditions. Some argue that urban transmission is just a matter of time, others defend that somehow this mosquito is no longer adapted for transmission. Codeço *et al.* (2004) estimated the probability of an infected person arriving from SYF endemic region at Rio de Janeiro and triggering an outbreak (assuming the mosquito a competent vector). Considering various sources of uncertainty regarding mosquito competence and transmission dynamics, they estimated the risk of yellow fever urbanization per year, in the interval [0, 0.29] during the 1990s.

Here, we consider UYF emergence scenarios varying from $u=0$ (for example, our reference individual lives in an area where the vector is absent) to $u=1$ (UYF already occurred in another area, and it is just a matter of time until it reaches an area where our individual is located). Between these two extremes lies the situation described above, where the conditions for transmission exist, but an outbreak has not occurred yet due to chance.

(ii) *Probability of acquiring infection during an outbreak (π_i).* Without considering heterogeneities, the probability of someone becoming infected during an outbreak is retrospectively given by the total number of cases divided by the total population at risk. This is partially dependent on the reproductive number (R_0), i.e. a small R_0 implies a small number of cases (and consequently a small π_i). Massad *et al.* (2001) estimated what would be the R_0 of UYF outbreaks using data from epidemic curves of dengue fever (which is also transmitted by *A. aegypti*) in many cities of Sao Paulo, Brazil. The estimated R_0 ranges from 1.2 to 6.8. Thus, we assume that a yellow fever outbreak would have R_0 within the interval [1, 7].

To obtain estimates of π_i from different scenarios of disease spread, we used a mathematical model adapted from Codeço *et al.* (2004), which describes an outbreak triggered by the arrival of an infectious individual to a city with a population of one million. The index case arrives at the beginning of the summer, when mosquito density is at its peak. To represent the natural reduction in transmission due to mosquito density seasonality in tropical regions, we allow mosquito

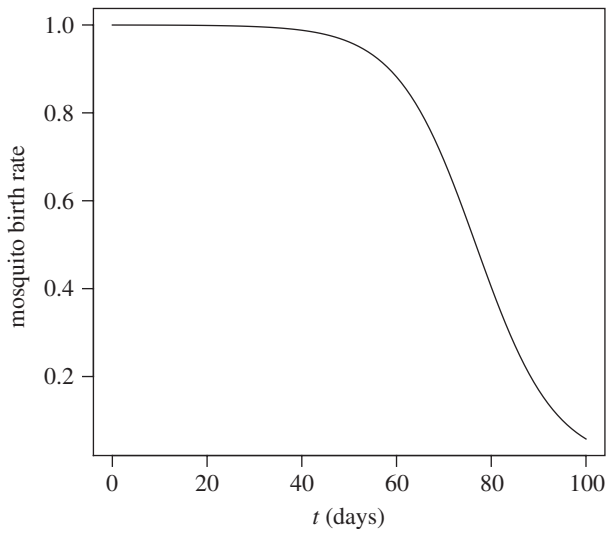

Figure 1. Variation in mosquito birth rate (n) during the 'disease season', which lasts approximately 90 days.

density to decrease and the disease season to end after 90 days (figure 1). Figure 2 shows a graphical representation of the model. Upon infection, individuals enter a latent stage (Lh), which lasts 3–6 days, and then progress to be infectious (Ih, for 3–4 days) to mosquitoes who take a blood meal from the individual. After 6–10 days of latency (Lm), mosquitoes become infectious for life (Im). The cycle closes as infectious mosquitoes bite susceptible humans (Sh), producing the second generation of human cases. This conceptual model is translated into a matrix population model (Caswell 2000). Parameters and their meanings are described in table 1.

$$\begin{pmatrix} Sh \\ Lh \\ Ih \\ Vh \\ Sm \\ Lm \\ Im \end{pmatrix}(t+1) = \begin{pmatrix} 1-ph & 0 & 0 & 0 & 0 & 0 & 0 \\ ph & 1-th & 0 & fph & 0 & 0 & 0 \\ 0 & th & 1-r & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 1-fph & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 1-pm-m & n & n \\ 0 & 0 & 0 & 0 & pm & 1-m-tm & 0 \\ 0 & 0 & 0 & 0 & 0 & tm & 1-m \end{pmatrix} \begin{pmatrix} Sh-v \\ Lh \\ Ih \\ Vh+v \\ Sm \\ Lm \\ Im \end{pmatrix}(t).$$

(iii) *Emergency mass vaccination campaigns.* Since the reward of waiting (R_W) varies with π_v (the probability of getting vaccinated in the emergency situation), a variety of scenarios of intervention was considered as well. We consider the following scenarios: (i) a delayed intervention scenario where emergency vaccination campaign starts only after the mosquito season has ended and an epidemic is ongoing. This scenario clearly favours V (ii) a more timely intervention scenario with mass vaccination of susceptibles, initiated t_v days after the arrival of the index case, with v doses per day (we assume no loss of vaccine effort by vaccinating individuals who are already immune).

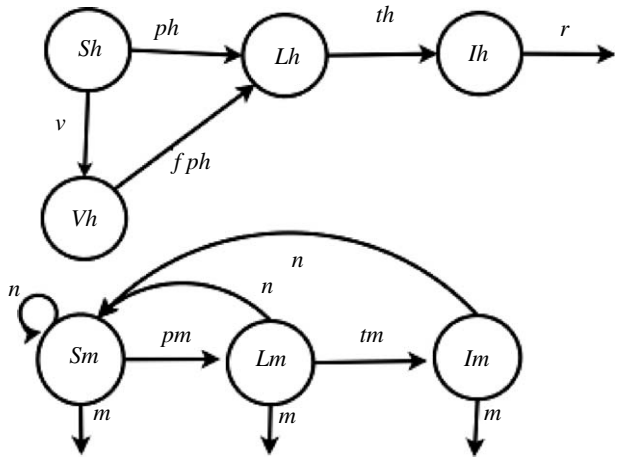

Figure 2. Yellow fever epidemic model.

(iv) *Model parameterization and simulation.* Any prediction regarding a future outbreak of UYF is inevitably uncertain. To reduce uncertainty, we need to consider all information available. We know: the transmission cycle of yellow fever (represented by the mathematical model); reasonable ranges for the parameters in the model (from the entomological literature); and a reasonable range for the reproductive ratio (Massad *et al.* 2001). However, the joint distribution of these parameters is unknown. To reconstruct the joint distribution, we used a restricted version of the Bayesian melding method (Poole & Raftery 2000). Briefly, we assigned prior distributions to each input parameter of the model (pre-model input priors), as listed in table 1. We also assigned a prior distribution to R_0, the output of the model (pre-model output prior). A random sample of 30 000 values from each one of the input prior distributions was taken. Using these sets of values as input for the model, we obtained 30 000 epidemic trajectories from which R_0 was calculated. This distribution of R_0 is said to be 'induced by the model' to distinguish it from the pre-model output prior. The melding procedure combines these two R_0 priors by means of logarithmic pooling (see electronic supplementary material), to produce a pooled prior which is coherent with both the model and the pre-model information. The next step is to find the values of input parameters that would generate such output. This is obtained by sampling (with replacement) 3000 values from the total of 30 000 sets of parameters, with probabilities given by the pooled distribution (using importance sampling algorithm). The final product is a post-model distribution for the input parameters that is coherent with the range of R_0 as defined originally. Figures in the electronic supplementary material show the priors and posteriors obtained with this approach.

Using these 3000 sets of input values, we ran simulations varying the pre-outbreak vaccine coverage (v_0), the daily vaccine effort during an outbreak (v) and the initiation date of the vaccination campaign (t_v). We recorded the total number of infected individuals and the total number of individuals vaccinated during the outbreak after 100 days. These values, divided by the initial susceptible population, provided 3000 estimates of π_i and π_v.

3. RESULTS

(*a*) *A collection of hypothetical outbreaks of urban yellow fever*

Consider the introduction of UYF in a completely susceptible population of one million, at the beginning

Table 1. Symbols in the mathematical model and their meanings. (The daily probability of a susceptible human becoming infected (*pm*) is 1 minus the probability of being bitten and not being infected. The number of bites received by a human per day is given by aM/H. The daily probability of a mosquito becoming infected (*ph*) is equal to 1 minus the probability of biting a number of times and not becoming infected, which depends on the proportion of infected humans and the efficacy of transmission.)

symbol	meaning	values
Sh	number of human susceptibles	
Lh	number of humans with latent infection	
Ih	number of infectious humans	
Vh	number of vaccinated humans	
Sm	number of susceptible mosquitoes	
Lm	number of exposed mosquitoes	
Im	number of infectious mosquitoes	
M	total mosquito population	$[0.12\text{–}11.2]\times H$
H	total human population	1×10^6
c	mosquito–human transmission efficiency	[0.01–0.3]
a	mosquito daily biting rate	[0.6, 1.2]
v_0	vaccine coverage before outbreak	[0, 0.2, 0.4, 0.6, 0.8]
v	vaccine effort (doses per day)	$[5, 10, 50, 100k]$
t_v	date of mass vaccination	[0, 7, 14, 21, 27, 35]
th	1/(infectious stage), humans	[1/6, 1/3]
f	probability of vaccine failure	0
r_i	probability of death by infection	0.05–0.1
r	rate of recovery in humans	[1/4, 1/3]
m	death rate of mosquitoes	[0.04–0.17]
n	birth rate of mosquitoes	$m\times(1-1/(1+10\,000\times\exp(-.12\times t)))$
b	human–mosquito transmission efficiency	[0.01–0.3]
tm	1/(infectious stage), mosquitoes	[1/10, 1/6]
ph	human force of infection	$1-(1-(bI_M/M)^{aM/H})$
pm	mosquito force of infection	$1-(1-(cI_H/H)^a)$

of the 'mosquito season'. In the absence of any intervention, the expected number of cases at the end of this hypothetical outbreak will vary from 1 individual (if R_0 is close to 1) up to 292 000 cases (if $R_0=7$). These numbers provide a range for $\pi_i=[1\times10^{-6}, 0.29]$. The distribution of π_i, however, is highly skewed to the right and dependent on R_0. As shown in figure 3, π_i exceeds 0.05 only when $R_0>5$.

For 'an average outbreak' (one with R_0 between 3 and 4), the expected chance of acquiring a yellow fever infection is 0.12% (ranging from 0.009 to 0.41%). For more extreme transmission scenarios (with R_0 between 5 and 7), the expected chance of acquiring infection jumps to 3.9% (interval=[0.08, 29.2%]). If 10% of the cases lead to death or serious complications, then we should expect 120 ([9, 410]) serious events during an average outbreak and 3900 ([80, 29 000]) severe cases, in an intense outbreak.

(i) *Comparing strategies, under different intervention scenarios.* Consider a susceptible individual, before an outbreak, that is deciding between getting a vaccine shot now (strategy V) or waiting until an epidemic occurs (strategy W). He knows that the cost of choosing strategy V is fixed, c_v. This cost is independent of the characteristics of the potentially coming outbreak. The cost of choosing strategy W, on the other hand, depends on the probability of (i) yellow fever urbanization (u), (ii) becoming infected (π_i) and (iii) receiving a vaccine shot during the outbreak (π_v), as defined by the reward functions above.

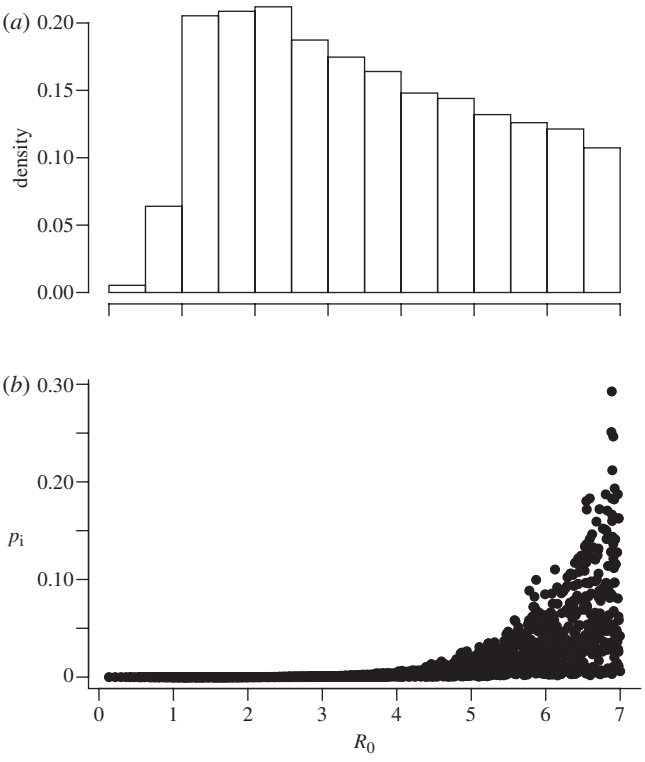

Figure 3. (*a*) Post-model distribution of R_0 representing our uncertainty regarding the expected reproductive ratio of an UYF outbreak. (*b*) Probability of getting infected during an UYF outbreak, in the absence of vaccination, as a function of R_0.

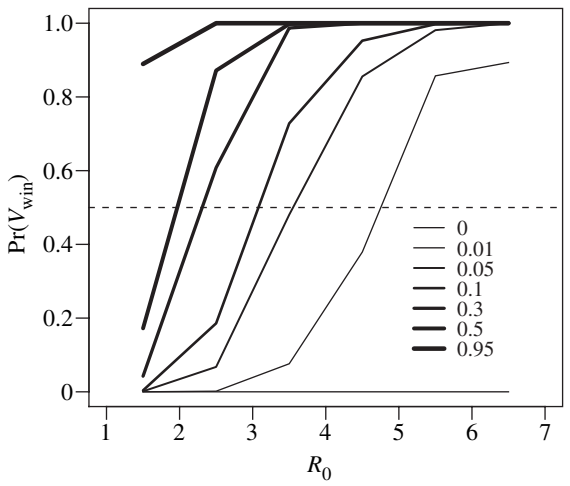

Figure 4. Proportion of epidemiological scenarios where vaccinating pre-emptively would be more rewardable than waiting until a transmission situation (i.e. $R_V > R_W$), assuming an extremely lazy mass vaccination campaign that starts only *after* the outbreak has ended. Thickness of lines indicates different levels of probability of urbanization. In other words, thin lines indicate unlikely urbanization, thick lines indicate probable urbanization. Horizontal line marks the 50% level, where strategy V wins half of the epidemiological scenarios. Above this line, V wins more often than W; below this line, W wins more often than V.

A delayed campaign. We first consider an extreme scenario favouring V, i.e. a scenario where an individual expects a slow emergency vaccination campaign in the case of a yellow fever urban outbreak, one that will start only after the mosquito season has ended. In other words, if an outbreak happens in the future, he will be vaccinated eventually but that will not protect him, or anybody else in the community, during the first yellow fever epidemic wave. As expected, if $u=0$ (the individual lives in an area free of the vector, for example), we find that waiting is always better than vaccinating now, since waiting implies never receiving the vaccine. At the other extreme, if $u=1$ (an outbreak is certain), V always wins (since the individual will get the vaccine anyway, it is better to get it before the outbreak than after). The situation becomes more interesting when one must consider the likelihood of an outbreak. Figure 4 shows that the best decision depends on the expected outbreak reproductive ratio, in a nonlinear way. If an outbreak is considered possible but unlikely ($u=0.01$), then strategy W wins more often, but only if $R_0<5$. In other words, if transmission is expected to be fast (for example, because mosquito abundance is very high), then V becomes more rewarding. As an outbreak is considered more probable, V becomes more rewardable even for a lower level of transmission. For $u>0.3$, waiting is better only if expected transmission is very low (R_0 below 2).

More timely campaigns. Now, let us suppose the individual knows that the public health system is conducting surveillance and is prepared to implement an emergency mass vaccination campaign in the case of a yellow fever outbreak. For the individual that implies a chance of receiving the vaccine during the outbreak in the case he decides for strategy W. Figure 5 shows the results for campaigns that vary in terms of effort (number of doses per day) and timing. As expected, if $u=0$ (an outbreak is not expected), strategy W always wins (after all, if an outbreak never occurs, the intervention has no benefit). At the other extreme ($u=0.95$: yellow fever urbanization is almost certain), then V wins in most epidemiological/intervention scenarios, except in the extreme case of a very efficient campaign (40 000 doses per day starting at day 0) and a less than average R_0 ($R_0<4$).

If yellow fever urbanization is considered possible but unlikely ($u<0.1$), waiting is a good strategy if a reasonably efficient campaign is expected (doses per day$>10\,000$ starting at day 30). The advantage of waiting also increases as rate of transmission is reduced (low R_0), suggesting that vector control programmes and emergency vaccination preparedness work together to favour W.

In general, these results suggest that if urban emergence of yellow fever is seen as an unlikely event ($u<0.3$), investments in vector control, surveillance and emergency preparedness make W an attractive strategy. Vaccinating pre-emptively, on the other hand, tends to be more attractive if the probability of yellow fever urbanization is high or if expected R_0 is high and emergency action is expected to be slow.

(*b*) *Facing a risk now or in the unknown future*

Another factor to be considered, when deciding between getting a vaccine shot now or later, is the balance between costs and benefits of facing a risk now (from the vaccine) versus a potentially higher cost from disease at some point in the future. One may think that it is worth to afford a greater risk if this risk is not faced now. That may be represented by an extra penalty for V, i.e. one may choose V only if

$$R_V - R_W > \epsilon,$$

where ϵ is the extra risk that the individual accepts when he decides not to get the vaccine now.

Figure 6 shows the impact of ϵ on the advantage of V in the scenario where emergency vaccination occurs only after the first epidemic wave. It is clear from this figure that even for a very small $\epsilon=0.001$, the balance shifts very rapidly towards W.

4. DISCUSSION

Concerns regarding natural or induced emergence of infectious diseases (as flu, smallpox and UYF) have raised a debate on the pros and cons of pre-emptive vaccination of populations under uncertain risk. In the absence of evidence of immediate risk, ethical issues arise because even small risks associated with the vaccine are greater than the immediate disease risk (which is zero). The model proposed here seeks to formalize the vaccination decision process looking from the perspective of the susceptible individual, and results are shown in the context of the emergence of UYF. In general, we found that the decision to *wait* tends to be the best strategy when the risk of an outbreak is perceived as low or the conditions for transmission are poor (low mosquito abundance). As a consequence, any intervention strategy

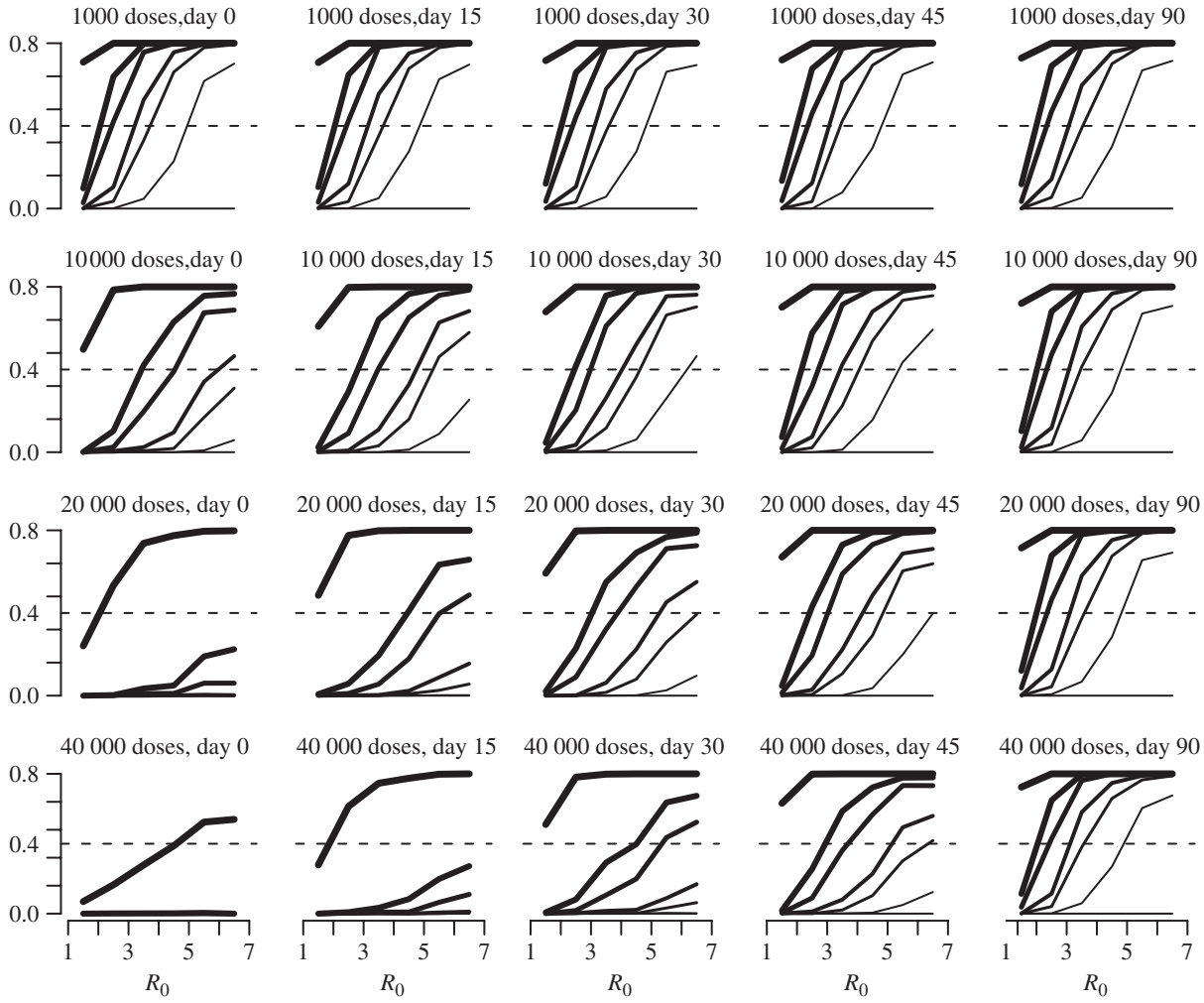

Figure 5. Same as figure 4, now considering more efficient emergency vaccination campaigns. At the top of each graph, there is a short description of the campaign: number of doses given per day and the day of start (counted from the arrival of the index case).

aiming at reducing both outbreak and transmission risks would increase the benefit of waiting. This is an important result, highlighting the importance of surveillance and preparedness. In addition, specifically for dengue endemic regions, this result brings to attention the interplay of different diseases that can be jointly prevented by one control measure.

If disease emergence is considered very likely and spread is expected to be fast, on the other hand, an individual's decision should balance towards pre-emptive vaccination since it is better to get the vaccine shot before the disease arrives. After an outbreak has begun, an unvaccinated individual will risk the chance of not receiving the vaccine before the infection occurs. We believe this result shows the importance of accurate estimation of UYF risk. Attempts have been made in order to explore the risk of yellow fever urbanization, but these suffer from uncertainties regarding vector competence measurements and human viral surveillance. Measures of competence of the present *A. aegypti* to the entire transmission cycle of the virus, i.e from human to mosquito and back to human, are extremely difficult (and unethical) to obtain. Adequate viral surveillance in humans would also be informative but, given the expected low prevalence of positive tests, would be extremely costly.

In our model, freedom to choose ends when the disease emerges. In other words, vaccination becomes compulsory. This scenario contrasts with previous work which assumes freedom of choice even during an outbreak (Massad *et al.* 2005). Under freedom of choice, YFV coverage that minimizes individual risks (from vaccine or disease) is lower than the vaccine coverage required to halt disease transmission (maximum population benefit; Massad *et al.* 2005). That occurs because a few non-vaccinated individuals would gain the indirect benefits of vaccine (herd immunity) without facing the (however small) vaccine risk (Salmon & Omer 2006). Such divergence between individual and collective interests poses a debate on the value of compulsory vaccination policies. Those against it argue that compulsory vaccination curtails individual autonomy. People defending compulsory vaccination base their argument on the concept of equity in society, since all members of the society share the risks and benefits of the vaccine (Salmon *et al.* 2006). We base our model definition in this latter principle.

To effectively implement a programme of mass vaccination, the great majority of the population must be willing to be vaccinated (Salmon *et al.* 2006). One extra benefit of preparedness compared to pre-emptive vaccination is to preserve the perception of vaccine

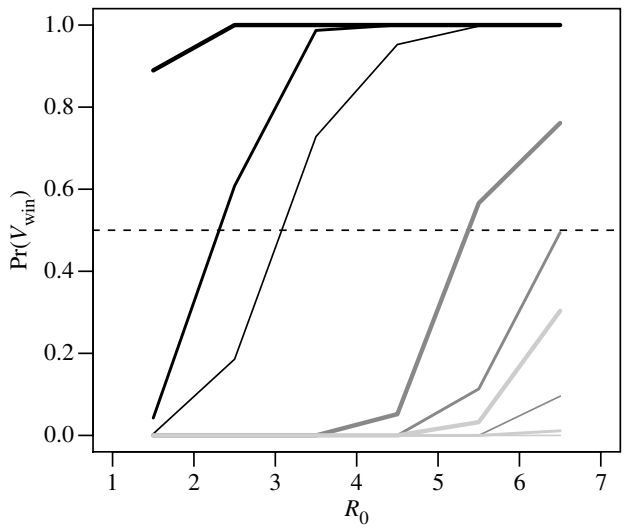

Figure 6. Proportion of epidemiological scenarios where the decision to vaccinate now (strategy V) wins, when V gets an extra penalty ϵ since it implies in taking risk now rather than later. Black lines show the situation where $\epsilon=0$, dark grey lines show $\epsilon=0.001$, light grey lines show $\epsilon=0.005$. Line thickness indicates levels of urbanization risk ($u=0.3$, 0.5 and 1 respectively). Dashed line marks the 50% level, where strategy V wins half of the epidemiological scenarios. Above this line, V wins more often than W; below this line, W wins more often than V. Entomological parameter values taken from Luz *et al.* (2003).

safety. The reason is that in a pre-emptive vaccination scenario, vaccine would be applied to a population of at least six million individuals (in Rio de Janeiro, for example). In such a setting, one to six fatal adverse events following vaccination would be expected (Struchiner *et al.* 2004). Although this number might seem small, even one event, if well disseminated by the media, may cause a refusal to get vaccinated by the whole population in future vaccinations. If an outbreak becomes 'almost certain', such scare may preclude rapid implementation of control measures.

In summary, our model highlights the nonlinear dependence of an individual's best strategy on the preparedness of a response to a yellow fever outbreak. Some limitations of the model include the assumption that the individual has complete knowledge of the risk of an UYF outbreak. This may not be the case. One may argue that if the risk of yellow fever urbanization is high, and knowledge of this risk within the community is low, the efficacy of a pre-emptive vaccination strategy is limited. Additionally, our model focuses on the individuals and their decisions in face of uncertainties associated with yellow fever urbanization. Further work should be devoted to find the best decisions at the public health level. For example, should managers stock vaccines based on a pre-emptive level of vaccine consumption or should they wait until the probability of urbanization goes above a certain threshold? What are the best strategies? Do they compete with the individual strategies? The questions are many and the present work is a step towards a better understanding of the current yellow fever dynamics in Brazil.

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