Available online at www.sciencedirect.com
SCIENCE DIRECT®
Vaccine 23 (2005) 3908–3914
Vaccine
www.elsevier.com/locate/vaccine

Yellow fever vaccination: How much is enough?

Eduardo Massad[a,b,*], Francisco Antonio Bezerra Coutinho[a], Marcelo Nascimento Burattini[a], Luis Fernandez Lopez[a], Cláudio José Struchiner[c]

[a] *School of Medicine, The University of São Paulo and LIM 01/HCFMUSP, Av. Dr. Arnaldo, 455, São Paulo CEP 01246-903, SP, Brazil*
[b] *London School of Hygiene and Tropical Medicine, London University, UK*
[c] *Program of Scientific Computation, Fundação Oswaldo Cruz-FIOCRUZ, Rio de Janeiro, Brazil*

Received 10 November 2004; accepted 9 March 2005
Available online 2 April 2005

Abstract

In recent years, a growing number of serious adverse events (including deaths) associated with the yellow fever (YF) vaccine has been reported. If YF vaccination were incorporated in routine programs, administered to children, the risk of deaths from this vaccine would be minimized provided that mortality of children vaccinated below 1 year were negligible. However, in affected areas the vaccine is administered to all age groups. This poses a dilemma to public health authorities – what proportion of a population subject to low risk of YF outbreaks should be vaccinated in order to minimize the total number of serious adverse events (including deaths) due both to natural infection and vaccination? In other words, how much vaccination is safe?

Our results suggest that, depending on the age-specific rates of developing vaccine-induced serious adverse events and the risk of yellow fever outbreaks, the optimum proportion to vaccinate may be lower than the proportion that would prevent an epidemics or even be zero. We also show that the vaccine should not be applied to individuals older than 60 years of age because the risk of serious adverse events (including deaths) is higher for that age class. Our work is instrumental to the discussion on the optimum strategy to vaccinate affected populations against yellow fever.

Therefore, the aim of this work is to estimate the optimum proportion to vaccinate against YF taking into account the risks of serious adverse events associated with both the vaccine and natural infection.

Keywords: Yellow fever; Vaccination; Adverse events

1. Introduction

Yellow fever (YF) was one of the most feared lethal diseases before the development of an elective vaccine [1]. Even today, according to WHO, some few hundred to a few thousand new cases are reported every year, although up to 200,000 new cases are estimated to occur based on serosurveys from tropical regions of Africa. The main reservoirs for the yellow fever virus are some species of monkeys, and transmission occurs through the bites of infected mosquitoes. In the sylvatic cycle of South America the main vectors are mosquitoes from the genera *Haemagogus* and *Sabethes*, whilst the urban cycle and the African sylvatic cycle involve mosquitoes of the genus *Aedes*, in particular *Aedes aegypti*. The bridge between the sylvatic and the urban cycles depends on humans that go to the sylvatic areas for leisure or work, eventually returning to the urban areas carrying the YF virus.

The disease can be prevented by a live attenuated vaccine prepared from the 17D strain of YF virus, that induces seroconversion in more than 95% of recipients and provides immunity for 30 years or longer [2]. Scattered YF vaccination occurs in some places of South America and in Africa, but coverage rates are low in both continents. In addition, the vaccine is not efficiently used in YF endemic countries for primary prevention, instead being used as an emergency response tool to control epidemics after they have been reported

* Corresponding author. Tel.: +55 11 30817717; fax: +55 11 30667382.
E-mail address: edmassad@usp.br (E. Massad).

0264-410X/$ – see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.vaccine.2005.03.002

[3]. However, in Brazil more than 90 million doses of YF vaccine were prevently administered, in the last decade [4]. Vaccination policies has ranged from preemptive mass vaccination to post-outbreak ring vaccination.

Unfortunately, in recent years, a growing number of serious adverse events, and even deaths, associated with the YF vaccine has been reported in the literature [4–7]. By serious adverse events we mean the life-threatening vaccine-associated viscerotropic and vaccine-associated neurotropic diseases. The rate of serious adverse effects increases with age but is rare in children [8,9]. In a recent publication Khromava et al. [10] studied the risk of serious adverse events of YF vaccine with respect to age. Their estimations ranged from 0 to 43 cases per million doses applied with the worst figures related to individuals older than 70 years. The risk of fatal adverse events associated with the 17DD yellow fever vaccine used in Brazil was estimated by Struchiner et al. [4]. Their estimation varied from 0.017 to 12.071 fatalities per million doses administered. If YF vaccination were incorporated in routine programs, administered to children, the risk of deaths from this vaccine would be minimized provided that mortality of children vaccinated below 1 year were negligible. However, data on the risk of serious adverse events for this age class is still unknown. In addition, in affected areas the vaccine is administered to all age groups.

Given that in affected areas the vaccine is administered to all age groups, those vaccine-associated serious adverse events rates poses a dilemma to public health authorities – what proportion of populations subject to low risk of YF outbreaks should be vaccinated in order to minimize the total number of deaths due both to natural infection and vaccination? In other words, how much vaccination is safe? The aim of this work is to estimate the optimum vaccinate coverage to protect against YF taking into account the risks of serious and/or fatal events associated with both the vaccine and natural infection.

2. Methods and results

The minimal proportion to be vaccinated, p_c, in order to control a given infection is related to the threshold for its establishment, T [11,12]. To understand how important T is, it suffices to say that in a city with $T < 1$, the arrival of an infective will not trigger an epidemic.

The relation between p_c and T is given by [12]:

$$p_c = 1 - \frac{1}{T} \tag{1}$$

In previous papers [13,14], we estimated the YF threshold for several cities in the state of São Paulo from estimations of T for dengue, T_{dengue}, taking advantage of the fact that both infections are transmitted by the same vector, viz, *A. aegypti*. We would like to stress that T_{dengue} is not directly observable and that the values actually used reflect our indirect estimates. The relationship between T for yellow fever, T_{yf}, and T for dengue, T_{dengue}, in a simplified form is given by:

$$T_{yf} = T_{dengue} \frac{\gamma_{dengue}}{\gamma_{yf}} e^{-\mu_M(\tau_{yf}-\tau_{dengue})} \tag{2}$$

where γ_i^{-1} (i, dengue; yf, yellow fever) are the average duration of viraemia in humans, μ_M the daily mortality rate of mosquitoes and τ_j (j, dengue; yf, yellow fever) is the extrinsic incubation periods of each virus [13].

Table 1
The 19 cities from the State of São Paulo, southeastern Brazil, to which the optimum proportion to preemptively vaccinate in order to avoid a yellow fever epidemic

City	Population size	T_{yf}	p_c	p_{gr}	Δ
Palm. Oeste	10126	2.07	0.52	0.47	0.05
Maracaí	12968	1.94	0.48	0.44	0.04
B. Bonita	35317	1.81	0.45	0.40	0.05
O. Cruz	29628	1.57	0.36	0.31	0.05
Borborema	13165	1.54	0.35	0.29	0.06
Valparaiso	18554	1.52	0.34	0.28	0.06
I. Solteira	23966	1.47	0.32	0.27	0.05
S. Sebastião	57595	1.47	0.32	0.27	0.05
Guarujá	264575	1.41	0.29	0.23	0.06
Jaboticabal	67306	1.39	0.28	0.22	0.06
Jardinópolis	30654	1.34	0.26	0.15	0.11
S. Vicente	302335	1.33	0.25	0.14	0.11
S.J.R. Preto	357052	1.31	0.24	0.13	0.11
Guaíra	34563	1.30	0.23	0.12	0.11
Mirassol	48327	1.27	0.21	0.11	0.10
Pinhal	40378	1.19	0.16	0.09	0.07
F. Prestes	5423	1.19	0.16	0.09	0.07
Igarapava	25891	1.18	0.15	0.08	0.07
Araraquara	180000	1.08	0.07	0.00	0.07

The values of T_{yf} and the critical proportion p_c for 19 cities in the State of São Paulo, for which T_{dengue} was estimated from the initial growing phase of the epidemics [13,14], are presented in Table 1 (see below). As mentioned before, those values represent a proportion of vaccination that prevents outbreaks of the infection that would occur in urban centers whenever an infective individual who caught the infection in the wild returns to his/hers home city, where *Aedes* density is high enough ($T_{yf} > 1$). These estimates do not consider neither additional mortality (or serious adverse events) induced by the vaccine nor the low risk of outbreaks occurrence.

However, the optimum proportion to vaccinate, i.e., that minimizes mortality or serious adverse events due to the vaccine and natural infection, should consider both the vaccine-induced mortality or serious adverse events and the probability of occurrence of an outbreak.

If p is the proportion of the population that is preemptively vaccinated in campaigns before outbreaks, we can express the expected total number of deaths or serious adverse events, $D(p)$, due to vaccination and potential yellow fever outbreaks as [15]:

$$D(p) = N_h\{pd_v + r(1-p)[(d_{yf} - d'_v)\pi_{yf}(p) + \pi_v(p)d'_v(p)]\} \tag{3}$$

where N_h is the size of the human population, d_v the probability of developing serious adverse events (including deaths) after being preemptively vaccinated, r the risk of an outbreak, d_{yf} the probability of dying of yellow fever, $\pi_{yf}(p)$ the probability of getting the infection if not vaccinated, $\pi_v(p)$ the probability of receiving the vaccine during the outbreak and $d'_v(p)$ is the probability of developing serious adverse events (including deaths) from the vaccine received during the outbreak. The quantities d_v and r were taken from [10,16], respectively, and the quantities $d_{yf}(p)$, $\pi_{yf}(p)$, $\pi_v(p)$ and $d'_v(p)$ were calculated through a dynamical system described in the appendix, where an analysis of the model's sensitivity to the parameters is also carried out. Therefore, we are considering the possibility of vaccination before and during an eventual outbreak.

Note that, the term $N_h p d_v$ in Eq. (3) is the number of serious adverse events (including deaths) of those individuals preemptively vaccinated in campaigns before outbreaks. The second term in Eq. (3), $N_h r(1-p)[(d_{yf}(p) - d'_v(p))\pi_{yf}(p) + \pi_v(p)d'_v(p)]$ is the number of serious adverse events (including deaths) after an outbreak, due to death by yellow fever infection and of serious adverse events (including deaths) due to vaccination during the outbreak.

We then minimize $D(p)$ on the unit interval ($0 \le p \le 1$) to determine the group optimum, p_{gr}, which is the coverage level that would have to be imposed to minimize the total expected number of serious adverse events (including deaths).

The results of the simulation of Eq. (3) is presented for several scenarios, taking into account:

(a) the age-related probability of developing serious adverse events from the vaccine, ranging from 0 to 43 per million doses, estimated according to [10] (Fig. 1); and
(b) the risk of vaccine-induced fatality rate of 2.5×10^{-6} doses^{-1} estimated by [16] with different values of T_{yf}, ranging from 1.08 to 2.07, assuming the same risk of vaccine-induced fatality rate of 2.5×10^{-6} doses^{-1} estimated by [16] (Fig. 2).

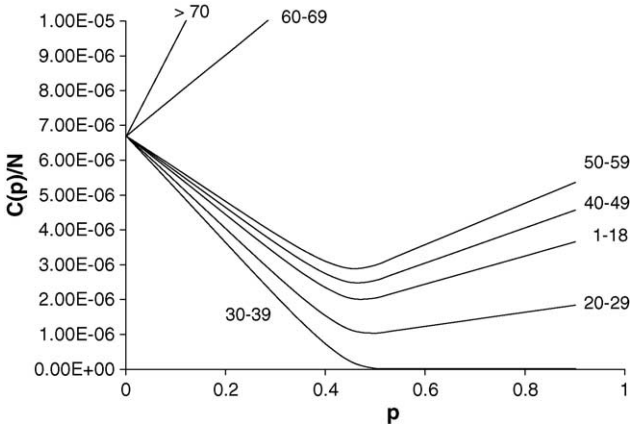

Fig. 1. Expected per capita number of deaths ($D(p)/N$) as a function of the proportion of preemptively vaccinated individuals (p) and the age-dependent risk of developing serious adverse events (including deaths).

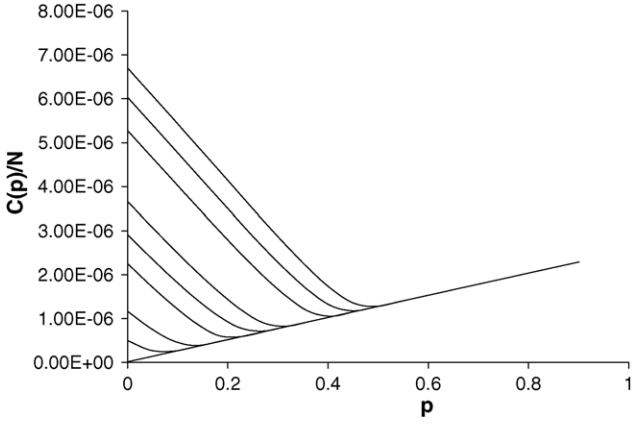

Fig. 2. Expected per capita number of deaths ($D(p)/N$) as a function of the proportion of preemptively vaccinated individuals (p) and the threshold condition T_{yf}, ranging from 2.07 (uppermost line) to 1.08 (botton line).

In Fig. 1, we show the result of the simulation of Eq. (3) varying the risk of serious adverse events stratified according to age. Those risks were estimated by [10] and were based on 722 adverse events reported after yellow fever vaccination and were submitted to the U.S. Vaccine Event Reporting Systems in 1990–2002. The age-related risks of vaccine-induced serious adverse events (including deaths) estimated by [10] were: 1–18 years, 4×10^{-6} doses^{-1}; 19–29 years, 2×10^{-6} doses^{-1}; 30–39 years, 0 doses^{-1}; 40–49 years, 5×10^{-6} doses^{-1}; 50–59 years, 6×10^{-6} doses^{-1}; 60–69 years, 27×10^{-6} doses^{-1}; and >70 years, 43×10^{-6} doses^{-1}. We can see from the figure that for that age class without any risk of vaccine-induced serious adverse event (30–39 years) the optimum proportion to vaccinate is the same as the critical proportion estimated from Eq. (1). For the other four age classes until 59 years, the optimum proportion to vaccinate, that is, the one that minimizes the per capita number of serious adverse events, is slightly below of the critical proportion estimated from Eq. (1). For the elder groups, above 60 years of age, vaccination is always contraindicated, according to our calculations, since the minimum per capita number of serious adverse events is obtained with no vaccination at all.

In Fig. 2, we show the simulations of Eq. (3) in which we carried out the calculations of the optimum proportion, p_{gr}, to vaccinate for the 19 cities from Table 1, assuming a risk of vaccine-induced fatality rate of 2.5×10^{-6} doses^{-1} estimated by [4] and a risk of outbreak of 2×10^{-4}, estimated from data described in [16]. In the figure, we show only some of the cities with the one with the highest T_{yf} (Palmeira D'Oeste, which estimated T_{yf} was used in simulations of Fig. 1) in the uppermost line and that with the lowest T_{yf} in the bottom line. We can note that there is a linear relationship between T_{yf} and the optimum proportion to vaccinate against yellow fever. We can see that for the city with the lowest T_{yf} (1.08) the optimum strategy is not to vaccinate ($p = 0$).

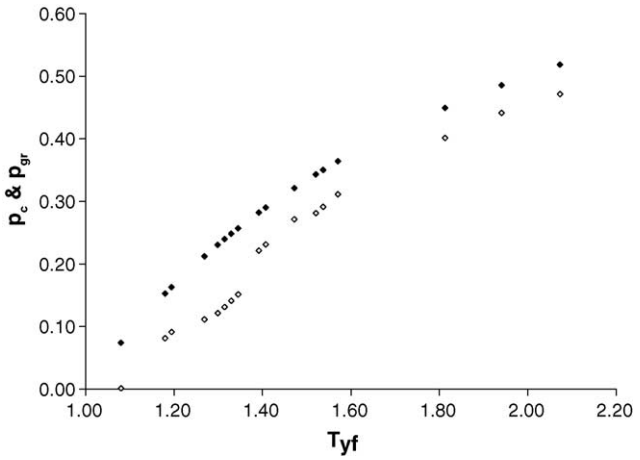

Fig. 3. The differences between the critical proportion to vaccinate, estimated by T_{yf}-only (black diamonds), and the optimum proportion corrected by the risk of outbreak and vaccine lethality (white diamonds).

Table 1 shows the values of T_{yf}, the critical proportion to vaccinate considering only the T_{yf}, p_c, the optimized proportion to vaccinate taking into account the risk of outbreaks and the vaccine related mortality, p_{gr}, and the difference between these two proportions, Δ, for 19 cities of the state of São Paulo with $T_{yf} > 1$ in 2001 (T_{yf} varying from 1.08 to 2.07). Fig. 3 shows the graphical representation of the T_{yf}-related differences between the critical, p_c, and the optimum, p_{gr}, proportions to vaccinate against yellow fever for the same 19 cities.

3. Conclusions

It has been traditionally accepted that the critical proportion to vaccinate is related to the threshold for establishment of a given infection in an affected population [12,15]. However, this approach does not allow for corrections of the optimal vaccine coverage that simultaneously take into account the risk of outbreaks and of severe adverse effects of the vaccine.

In this paper we were able to show that it is possible to foster estimates of vaccine coverage of a population at risk for yellow fever by considering the occurrence of serious adverse events due to the vaccine and the risk of outbreaks of yellow fever. Therefore, for a seasonal risk of yellow fever outbreak of the order of 2×10^{-4} and a vaccine lethality of 2.5 per million doses, the optimum proportion to preemptively vaccinate a population at risk, that is, the proportion that minimizes the total number of serious adverse events (including deaths) is always lower than the critical proportion calculated according to the threshold condition T_{yf}. Also, when we stratified the risk of vaccine-associated serious adverse events by age we demonstrated that there is an optimum proportion to vaccinate that minimizes the total number of serious adverse events that is equal or slightly below the critical proportion calculated according to T_{yf} for ages lower than 60 years and that the vaccine is contraindicated above that age.

Finally, the age-dependent analysis we carried out suggests that administering yellow vaccine in the immunization programs of affected areas would minimize both the risk of outbreaks and minimize the risk of serious adverse events.

Acknowledgements

This work was supported by grant from LIM01-HDFMUSP, CNPq and FAPESP.

Appendix A

A.1. The dynamical system

In order to calculate the proportion of cases and serious adverse events (including deaths) after a YF outbreak, as well as the proportion of people vaccinated during the outbreak, we modeled the epidemic with a dynamical system, described by the following system of differential equations:

$$\frac{dM_s}{dt} = \frac{-caM_sH_i}{N_h} + (\alpha_M + \mu_M)M_i$$

$$\frac{dM_i}{dt} = \frac{ca\exp(-\mu_M\tau)M_s(t-\tau)H_i(t-\tau)}{N_h} - (\alpha_M + \mu_M)M_i$$

$$\frac{dH'_s}{dt} = \frac{-baM_iH'_s}{N_h} - (\nu_h + \mu_h)H'_s$$

$$\frac{dH''_s}{dt} = -(\mu_\nu + \mu_h)H''_s$$

$$\frac{dH_i}{dt} = baM_iH'_s/N_h - (\gamma_h + \mu_h + \alpha_h)H_i$$

$$\frac{dH_v}{dt} = \nu_hH'_s - (\mu_h + \mu_\nu)H_v$$

$$\frac{dH_r}{dt} = \gamma_hH_i - \mu_hH_r \quad (4)$$

We now briefly describe some features of the system. Consider first the mosquito population, described by the first two equations of system (4). When a susceptible (without the infection) mosquito bites an infected person it may become (with a certain probability) infected. If it survives for a period of time τ (the extrinsic incubation period) it becomes infective, that is, if it bites a human it may transmit (with a certain probability) the infection. We are not interested in infected but not yet infective mosquitoes, but rather we consider only susceptible mosquitoes, M_s, and infective mosquitoes, M_i. The first two equations of the system above describe the dynamics of those two populations. Consider the first equation. We denote by a the biting rate of mosquitoes. So aM_s is the number of bites the susceptible mosquitoes inflict on humans per unit of time. Of those, only a proportion H_i/N_h will be on infected humans and of those only a proportion c will result in infected mosquitoes. We are aware that mosquitoes susceptibility to

Table 2
Initial conditions and parameters used in the numerical simulation of the dynamical system

Parameter/initial conditions	Biological meaning	Values	Source
$H_s'(0)$	Initial condition of susceptible humans	$(1-p)N_h$	Variable according to the city
$H_s''(0)$	Initial condition of preemptively vaccinated humans	pN_h	Variable according to the city
$H_i(0)$	Initial condition of infected humans	1	Assumed
$H_v(0)$	Initial condition of humans vaccinated in the outbreak	0	Assumed
$M_s(0)$	Initial condition of susceptible mosquitoes	N_M	Estimated for each city
$M_i(0)$	Initial condition of infected mosquitoes	0	Assumed
μ_h	Natural mortality rate of humans	3.9×10^{-5} days^{-1}	Demographic data for Brazil
γ_η	Recovery rate from viraemia	0.14 days^{-1}	Ref. [18]
α_h	Mortality rate of yellow fever	10^{-2} days^{-1}	Ref. [18]
ν_η	Post-outbreak vaccination rate	10^{-5} days^{-1}	Chosen to make $d_v'(p) = d_v(p)$ (see main text)
μ_ν	Mortality rate of YF vaccine	10^{-10} days^{-1}	Ref. [8]
a	Average daily biting rate of *Aedes*	1.2 days^{-1}	Ref. [17]
b	Host susceptibility	1	Ref. [21]
c	Vector infection probability	1.0	Assumed
α_M	Infected mosquitoes additional mortality rate	0	Ref. [19]
μ_M	Natural mortality rate of mosquitoes	0.15 days^{-1}	Ref. [19]
τ	Extrinsic incubation period	12 days	Ref. [19]

infection varies geographically. However, this parameter, as well as all other shown in Table 2 are estimated averages. Susceptible mosquitoes are assumed to die at a rate μ_M. The first term of the second equation describes the number of mosquitoes that became infected τ units of time earlier, survived a time interval τ and now became infective. The infective mosquitoes are assumed to die at a rate $\alpha_M + \mu_M$.

Let's now consider the human population. Humans are divided into those who were preemptively vaccinated, denoted H_s'', and those who did not receive the vaccine and are, therefore, truly susceptible, denoted H_s'. The latter acquired the infection from infective mosquitoes through the bites aM_iH_s'/N_h, a fraction of which, b, generates a new infection, although it is known that for *Aedes* mosquitoes this fraction is believed to be high [21]. They may be vaccinated during an outbreak, with a rate ν_h, or dye by natural causes, with a rate μ_h. The value of the rate ν_h was chosen in order to obtain the probability of dying by vaccination, $d_v'(p)$ as equal to that estimated for real populations, $d_v(p)$ The individuals preemptively vaccinated, H_s'', dye with rates μ_ν (by the effect of the vaccine) and μ_h, the natural mortality rate of humans. Once infected, H_i, individuals can either recover from the infection, with rate γ_h, or dye with rates α_h (the mortality rate of yellow fever) or μ_h, the natural mortality rate of humans. The mortality rate quoted above, α_h, does not take into account the possible modulating effects of heterotypic flavivirus antibodies since there are no available quantitative data on this ectect. Individuals vaccinated during the outbreaks, H_v, can dye by natural causes, or by the vaccine, with rates μ_h, and μ_ν, respectively. Depending on the case the rate μ_ν also represent the rate of developing vaccine-induced serious adverse events. Those recovered from the infection, H_r, dye only by natural causes.

From the system (4), it is possible to calculate the threshold for the establishment of an epidemic in the absence of vaccination, resulting in

$$T = \frac{N_m}{N_h} \frac{a^2 bc\, e^{-\mu_m \tau}}{(\gamma + \mu_h + \alpha_h)(\mu_m + \alpha_m)} \tag{5}$$

Expression (5) is the threshold as defined by Macdonald [20]. Its numerical value can also be estimated through the analysis of the initial phase of an epidemics [11].

We calculate the values of T_{dengue} for 19 cities in the State of São Paulo, through the initial phase of the epidemic, as described by [14,17]. Then, we calculate T_{yf}, by using Eq. (2) of the main text. Next, we calculated the size of the mosquito population for each city analyzed, by the relation:

$$N_m = \frac{N_h}{T_{yf}} \frac{(\gamma + \mu_h + \alpha_h)(\mu_m + \alpha_m)}{a^2 bc\, e^{-\mu_m \tau}} \tag{6}$$

since N_h is known and the other parameters were assumed to be the same for all the 19 cities analyzed because they are all in the same microclimatic region of the State of São Paulo.

Using the parameters and initial conditions described in Table 2, we numerically solved the system (4) in order to obtain the quantities necessary to estimate the optimum proportion to vaccinate, p_{gr}, that minimizes the total number of serious adverse events (including deaths):

$$\begin{aligned}
\pi_{yf}(p) &= \frac{\int_0^\infty baM_iH_s'/N_h\, dt}{(1-p)N_h} \\
d_{yf}(p) &= \frac{\int_0^\infty (\mu_h + \alpha_h)H_i\, dt}{(1-p)N_h} \\
\pi_\nu(p) &= \frac{\int_0^\infty \nu_h H_s'\, dt}{(1-p)N_h} \\
d_v'(p) &= \frac{\int_0^\infty \mu_\nu H_v\, dt}{(1-p)N_h}
\end{aligned} \tag{7}$$

where p is the proportion of the population preemptively vaccinated, as described in the main text.

A.2. Model's sensitivity to the parameters

In this subsection we analyze the model's sensitivity to some of the parameters presented in Table 2. Among all the parameters used in the simulations some are relatively well known from the literature, some are dependent on the environmental conditions, in particular the temperature and some are not very well known. The relatively well know parameters are the human mortality rate, μ_h, the recovery rate from the disease, γ, the mortality rate of yellow fever, α_h, the rate of developing vaccine induced serious adverse events (including deaths), μ_v, and the average daily biting rate of the *Aedes*, a. The less well known parameters used are the probability that a susceptible mosquito biting a viremic patient gets the infection, c, and the probability that an infected mosquito biting a susceptible human generates a new infection, b. However, considering the high levels of viraemia presented by yellow fever patients, it is reasonable to assume the parameter c as equal to 1, although one should keep in mind that this is highly variable because geographic populations of *A. aegypti* vary in their susceptibility to infection. Also, it is well known that *Aedes* mosquitos are highly efficient vectors of yellow fever. Sabin [21] showed 60 years ago that infection with a single dengue virion will cause infections in a susceptible human and, therefore, we considered this parameter as equal to 1. The parameters that depend on the environmental conditions are the mosquito daily mortality rate μ_M and the extrinsic incubation period, τ. We, therefore, ranged the values of those parameters, from 0.15 to 0.30 days^{-1} for μ_M, and from 7 to 14 days for τ. The results can be seen in Fig. 4, in which we simulated Eq. (3) for the same conditions used for the city with the highest T_{yf} (Palmeira D'Oeste, 2:07).

We can see from the figure that the results are qualitatively similar to that obtained in Fig. 2 and the model is more sensitive to variations in the extrinsic incubation period τ, than to the mosquito daily mortality rate, μ_M, for the range of variations analyzed.

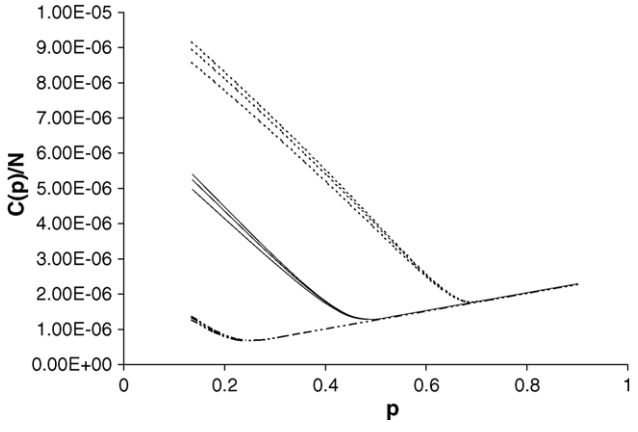

Fig. 4. Sensitivity of the model to mosquito daily mortality rates, μ_M, and yellow fever virus extrinsic incubation period, τ. Dotted lines represent $\tau = 7$ days with three values of μ_M (0.15, 0.23 and 0.30 days^{-1}) from bottom-up, respectively. Continuous line represent the same mosquitoes mortality rates but $\tau = 12$ days. Double dots-trace lines as above with $\tau = 14$ days.

References

[1] Monath TP. Yellow fever: an update. Lancet Infectious Diseases 2001;1:11–20.
[2] Poland JD, Calisher CH, Monath TP, Downs WG, Murphy K. Persistence of neutralizing antibody 30–35 years after immunization with 17D yellow fever vaccine. Bull World Org 1981;59(6):895–900.
[3] Gubler DJ. The changing epidemiology of yellow fever and dengue, 1900 to 2003: full circle? Comparative Immunol, Microbiol Infect Dis 2004;27(5):319–30.
[4] Struchiner CJ, Luz PM, Dourado I, Sato HK, Aguiar SG, Ribeiro JGL, et al. Risk of fatal adverse events associated with 17DD yellow fever vaccine. Epidemiol Infect 2004.
[5] Martin M, Tsaib TF, Croppb B, Changb G-JJ, Holmesb DA, Tsengb J, et al. Fever and multisystem organ failure associated with 17D-204 yellow fever vaccination: a report of four cases. Lancet 2001;358:98–104.
[6] Vasconcelos PFC, The Brazilian Yellow Fever Vaccine Evaluation Group. Serious adverse events associated with yellow fever 17DD vaccine in Brazil: a report of two cases. Lancet 2001;358:91–7.
[7] Chan RC, Penney DJ, Little D, Carter IW, Roberts JA, Rawlinson WD. Hepatitis and death following vaccination with 17D-204 yellow fever vaccine. Lancet 2001;358:121–2.
[8] CDC. Adverse events associated with 17D-derived yellow fever vaccination. United States, 2000–2002. MMWR 2002;51(44):989–93.
[9] Martin M, Weld LH, Tsai TF, Mootrey GT, Chen RT, Niu M, et al. Advanced age a risk factor for illness temporally associated with yellow fever vaccination emerging infectious diseases. Emerging Infect Dis 2001;7(6):945–51.
[10] Khromava AY, Eidex RB, Weld LH, Kohl KS, Bradshaw RD, Chen RT, et al. Yellow fever vaccine: an updated assessment of advanced age as a risk factor for serious adverse events. Vaccine 2005;23:3256–63.
[11] Lopez LF, Coutinho FAB, Burattini MN, Massad E. Threshold conditions for infection persistence in complex host-vectors interactions. Comptes Rendus Biologies Académie des Sciences Paris 2002;325:1073–84.
[12] Dietz K. The estimation of the basic reproduction number for infectious diseases. Stat Methods Med Res 1993;2:23–41.
[13] Massad E, Coutinho FAB, Burattini MN, Lopez LF. The risk of yellow fever in a dengue infested area. Trans Roy Soc Trop Med 2001;95(3):370–4.
[14] Massad E, Burattini MN, Coutinho FAB, Lopez LF. Dengue and the risk of urban yellow fever reintroduction in São Paulo, Brazil. Revista de Saúde Pública 2003;37(4):477–84.
[15] Bauch CT, Galvani AP, Earn DJD. Group interest versus self-interest in smallpox vaccination policy. Proc Natl Acad Sci USA 2003;100:10564–7.
[16] Codeço CT, Luz PM, Struchiner CJ. Risk assessment of yellow fever urbanization in Rio de Janeiro, Brazil. Trans Roy Soc Trop Med Hygiene 2004;98(12):702–10.
[17] Anderson RM, May RM. Infectious diseases of humans: dynamics and control. Oxford: Oxford University Press; 1991.

[18] Monath TP. Yellow fever. In: Warren KS, Mahmoud AAF, editors. Tropical and geographical medicine. New York: McGraw-Hill Information Services Company; 1990. p. 661–74.
[19] Gubler DJ, Kuno G. Dengue and dengue hemorrhagic fever. Wallingford: CABI Publishing; 1997.
[20] Macdonald G. The analysis of equilibrium in malaria. Trop Dis Bull 1952;49:813–28.
[21] Hauck Center for the Albert B. Sabin Archives, Box 12, file 5. http://sabin.uc.edu/dengue.ucm; 2005.