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The Potential Impact of Using Vaccination and Insect Repellent to Control the Spread of Yellow Fever

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Abstract

Yellow fever is a viral hemorrhagic fever transmitted by the *Aedes aegypti* mosquito. It has historically caused thousands of deaths throughout Africa, the Americas, Europe, and the Caribbean and continues to pose threats in Africa and Central and South America. The disease is most detrimental in densely populated areas with warmer climates where individuals have limited access to health care facilities. These conditions are exemplified by the yellow fever epidemic of 1878 in Memphis, Tennessee. The limited medical knowledge, warm climate, and densely populated urban areas greatly contributed to the magnitude of the epidemic that killed thousands. We have developed an ordinary differential equations model to simulate the dynamics of human and mosquito populations during a yellow fever outbreak using historical data. Additionally, we examined the use of insect repellent and vaccination as methods to reduce the severity of the outbreak. We examined the conditions under which the disease-free equilibria are stable for the complete model. We also used uncertainty and sensitivity analyses to quantify the reduction in cumulative infections and deaths due to the use of insect repellent and vaccination among humans.

Keywords: yellow fever, ordinary differential equations model, Memphis, vector-borne disease

1 Introduction

Yellow fever is a viral hemorrhagic fever transmitted by the *Aedes aegypti* mosquito. It is estimated this disease evolved in Africa and spread to the western hemisphere through transcontinental slave trade [5, 8]. In humans, yellow fever has an incubation period that lasts 3–6 days, during which humans are asymptomatic and non-infectious. Once the incubation period is complete, the virus enters the blood stream, causing fever, myalgia, nausea, and vomiting [2]. Shortly after becoming symptomatic, some see an improvement in symptoms mimicking recovery, but the disease may then worsen, causing jaundice, internal bleeding, and death in some individuals [2].

During the early 1800s, when the field of medicine was still in its infancy and the link between yellow fever and mosquitoes had not yet been discovered, the United States had several devastating yellow fever outbreaks that resulted in the deaths of thousands. Memphis, Tennessee had its first yellow fever outbreak in 1828, which spread upstream from New Orleans [7, 11]. In 1878, Memphis had its worst outbreak, totaling 17,000 cases and approximately 5,000 deaths [7, 11]; the daily death toll due to yellow fever during the outbreak is shown in Figure 1.

While yellow fever is no longer a major concern in the United States, there has recently been a resurgence of the disease throughout tropical regions of Africa, as well as Central and South America [2]. There is no known cure for yellow fever, and individuals visiting high risk areas are encouraged to take precautionary measures to avoid contracting the disease, such as vaccination [6]. The first vaccine was developed in 1938, well after the deadliest Memphis outbreak, by using an isolated viral strain from a yellow fever survivor [17]. The attenuated vaccine is very successful in preventing the spread of yellow fever because it provides susceptible individuals effective, lifelong immunity from the yellow fever virus [17]. However, immunity is only achieved after an incubation period during which individuals are still at risk of contracting the disease, though at a lower rate than unvaccinated individuals [1].

Some limitations exist for vaccination in individuals without access to reliable health care, individuals whose beliefs do not support vaccinations, immunodeficient individuals, small children, and women who are pregnant. Other control methods exist to prevent the outbreak of yellow fever, including the use of insect repellent to decrease the number of mosquito-to-human interactions that spread yellow fever. Insect repellent is readily available and may be used by many individuals who cannot receive vaccinations. The Centers for Disease Control and Prevention (CDC) specifically recommends consis-

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tent use of N,N-Diethyl-meta-toluamide insect repellent (DEET) to avoid vector-born illnesses like yellow fever [6]. Memphis dwellers hoping to quell yellow fever in the 1878 outbreak did not use any form of insect repellent as a control measure because it was not discovered until the early 1900s that mosquitoes are the vector of yellow fever transmission [7, 17].

To our knowledge, there have been no other publications that study the combined effects of insect repellent and vaccination on yellow fever epidemics using mathematical modeling. However, Kiszewski and Darling used a static probability model to study the effectiveness of insect repellent as a control measure against malaria, another disease carried by the *Aedes aegypti* [12]. Their findings indicate that a very high degree of repellent efficacy is necessary to suppress malaria infection rates more than by using bed nets [12]. The Kiszewski & Darling model assumes a constant proportion of the population wearing insect repellent and a constant efficacy of the repellent. We use a different approach, proposing a dynamical systems model which simulates the waning effects of insect repellent over time and human's propensity to reapply repellent. Other differential equation models have also looked at insect bite prevention strategies, such as insect repellent and bed nets, coupled with additional control measures to reduce the intensity of vector-borne outbreaks of Zika virus and malaria [9, 14]. Similarly, we hope to quantify the individual use of both insect repellent and vaccination, as well as their combined use, as control measures during a yellow fever outbreak.

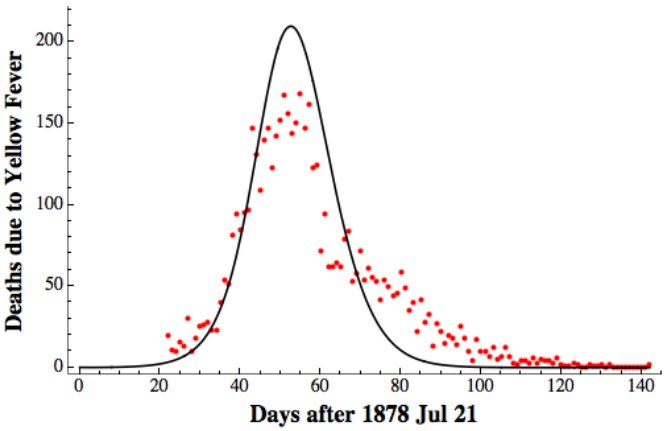


Figure 1: Deaths in Memphis, TN during the 1878 epidemic due to yellow fever, represented by the red data points [11]. The solid black line is generated by the model in System (1) with initial condition $S_H(0) = 17{,}000$, $I_H(0) = 2$, $R_H(0) = 5{,}000$, $S_M(0) = 950{,}000$, $I_M(0) = 100$, and all other states initialized to zero. The human and mosquito parameter values used are given in Table 1, and all control parameters were set to zero.

2 The Model

The SEIR model depicts the dynamics of an infectious disease spreading within a population by modeling the change in the number of susceptible (S), exposed (E), infectious (I), and recovered (R) individuals over time. The SEIR model is used to simulate infectious diseases with an incubation period. An individual in the exposed state is infected but not yet contagious and is usually asymptomatic, while an individual in the infectious state is contagious and symptomatic. We adapt the SEIR model to simulate the transmission dynamics of yellow fever between a human population and a mosquito population, denoted by subscripts H and M, respectively. Only the susceptible, exposed, and infectious states are used for the mosquito population since mosquitoes remain infected with yellow fever until their death.

We assume the human and mosquito populations are well mixed, and that yellow fever is only transmitted between *Aedes aegypti* and humans, without accounting for vertical transmission in mosquitoes or yellow fever being transmitted to non-human primates. Since the time scale of a few months is marginal compared with the average human life span, we assume changes to the total human population through birth or background deaths are negligible and thus excluded from the model. Interactions between mosquitoes and humans are reduced by the use of insect repellent. Thus, our model includes additional states for humans wearing repellent as a control measure, denoted by subscript R. Since the use of insect repellent decreases human to mosquito interactions, the probability of transmission is lower between infectious humans and mosquitoes. We assume a waning effectiveness of repellent and that humans reapply repellent at a rate dependent on the severity of the epidemic.

Humans can also avoid infection by receiving a vaccination [6]. In our model, humans that have received a vaccination are denoted by subscript V. Individuals who have been vaccinated move to the S_V class where they remain susceptible but have a lower probability of becoming infected with yellow fever from interactions with infected mosquitoes. Individuals in the S_V class who apply repellent move to the S_{RV} class, and have increased protection from yellow fever than if they were in the S_V class. However, we do not include vaccination of individuals wearing repellent since the period of repellent effectiveness is short, so they are unlikely to be vaccinated during this time. If an individual in the S_V class becomes infected with yellow fever, the disease progresses typically, following the same incubation period and progression rates as unvaccinated classes. After approximately 10 days, an individual who has been vaccinated becomes immune to infection from yellow fever and moves to the R_V class [6].

A flow diagram depicting the transition between states

is given in Figure 2. The model is given by the following system of equations:

Humans without Repellent or Vaccine

$$S_H' = -\beta_H S_H I_M - \big(\gamma_S A + \rho_s\big) S_H + \sigma S_R - \alpha\omega S_H \tag{1.1}$$

$$E_H' = \beta_H S_H I_M - \kappa_H E_H - \big(\gamma_S A + \rho_s\big) E_H + \sigma E_R + \beta_V S_V I_M \tag{1.2}$$

$$I_H' = \kappa_H E_H - \nu_H I_H - \big(\gamma_I A + \rho_I\big) I_H + \sigma I_R \tag{1.3}$$

$$R_H' = (1-\delta)\nu_H I_H + (1-\delta)\nu_H I_R \tag{1.4}$$

Humans with repellent, but no vaccine

$$S_R' = -q\beta_H S_R I_M + \big(\gamma_S A + \rho_s\big) S_H - \sigma S_R \tag{1.5}$$

$$E_R' = q\beta_H S_R I_M - \kappa_H E_R + \big(\gamma_S A + \rho_s\big) E_H - \sigma E_R + q\beta_V S_{RV} I_M \tag{1.6}$$

$$I_R' = \kappa_H E_R - \nu_H I_R + \big(\gamma_I A + \rho_I\big) I_H - \sigma I_R \tag{1.7}$$

Humans who have been vaccinated

$$S_V' = \alpha\omega S_H - \beta_V S_V I_M - \big(\gamma_V A + \rho_V\big) S_V + \sigma S_{RV} - \chi S_V \tag{1.8}$$

$$S_{RV}' = -q\beta_V S_{RV} I_M + \big(\gamma_V A + \rho_V\big) S_V - \sigma S_{RV} \tag{1.9}$$

$$R_V' = \chi S_V \tag{1.10}$$

Mosquitoes

$$S_M' = \Omega_M - \beta_M S_M I_H - q\beta_M S_M I_R - \mu_M S_M \tag{1.11}$$

$$E_M' = \beta_M S_M I_H + q\beta_M S_M I_R - (\mu_M + \kappa_M) E_M \tag{1.12}$$

$$I_M' = \kappa_M E_M - \mu_M I_M, \tag{1.13}$$

where $A = \frac{I_H + I_R}{N_H}$, and N_H is the size of the total human population. The definitions, values, and units of all parameters can be found in Table 1.

Application of Repellent · We include three parameters (σ, ρ, and γ) to simulate the movement of individuals between states with and without repellent. The parameter σ denotes the rate at which repellent becomes ineffective due to wearing off over time. The parameter ρ represents the baseline rate of repellent application when humans are not considering the severity of the epidemic when choosing to apply repellent. The parameter γ denotes the rate of reapplication above the baseline due to the presence of infectious humans. The parameters ρ and γ are different for asymptomatic individuals, unvaccinated and symptomatic individuals, and vaccinated individuals, denoted by parameter subscripts S, I, and V, respectively. The variation is due to the assumption that asymptomatic individuals are more likely to increase repellent use to avoid contracting yellow fever, while vaccinated and symptomatic individuals are less likely to increase repellent use as the severity of an epidemic increases. Additionally, we assume the rate at which humans reapply repellent is dependent on the severity of the outbreak at the time, thus the rate of reapplication is the product of γ and the proportion of infectious individuals within the entire human population, i.e. $A = \frac{I_H + I_R}{N_H}$.

Empirical data on the application rates of repellent among humans is scarce. Thus, these parameters ranges have been estimated using a wide range of reapplication rates. The recommendation of the CDC to travelers visiting countries with mosquito-borne diseases is to reapply repellent as protection wanes and mosquitoes start to bite [6]. The rate of repellent waning, σ, was estimated using packaging information for repellent containing 40% DEET repellent, which guarantees over eight hours of protection. Allowing for four hours of increased or decreased longevity, we assume the repellent lasts between 4 and 12 hours. For each of the baseline application parameters, ρ, we assume that the maximum number of applications is six per day when epidemic severity is not taken into consideration and that every person is applying repellent at least once every seven days. We assume that susceptible and exposed (asymptomatic) individuals have the highest rate of repellent reapplication, followed by vaccinated and then infectious individuals. The values of γ were calculated based on assumptions of repellent application when 80% of the population is symptomatic, and the baseline is assumed to be its highest value in these calculations. Therefore,

$$\gamma = \frac{\big|\text{time between application} - \text{baseline}\big|}{0.8}.$$

We assume that asymptomatic, unvaccinated individuals (S & E) are the most likely to apply repellent, so these individuals will apply between one and six times a day as a baseline, an average of 3.5 times daily, and increase application to twice a day on average when 80% of the population is symptomatic. We also assume that symptomatic individuals (I) are the least likely to apply repellent due to epidemic severity since they are not concerned about becoming infected, applying between once per day and once every seven days, and they will increase application to every three days on average when the epidemic worsens. Lastly, we assume that vaccinated individuals (V) are less likely to apply than unvaccinated, so they apply repellent between four times per day and once per week and will increase application to every 3 days on average. Each ρ and γ parameter was assigned a unique range of values (shown in Table 1) wherein the parameter value varies in uncertainty and sensitivity analyses (see Section 3).

Table 1: Model parameter units, values, and definitions.

	Parameter	Units	Value	Ref	Definition
Humans	β_H	$1/(\text{mosq} \cdot \text{days})$	$3.69 \cdot 10^{-7}$	§ 3	Transmission rate in humans
	$1/\kappa_H$	days	4.3	[10]	Intrinsic incubation period
	$1/\nu_H$	days	3.875	[1]	Recovery time of humans
	δ	—	0.303	[11]	Proportion of infected individuals who die
Mosquitoes	β_M	$1/(\text{ppl} \cdot \text{days})$	$9.69 \cdot 10^{-5}$	§ 3	Transmission rate in mosquitoes
	$1/\mu_M$	days	33.3	[20]	Lifespan of mosquitoes
	Ω_M	mosq/day	28,500	[20]	Birth rate of mosquitoes
	$1/\kappa_M$	days	10	[10]	Extrinsic incubation period
Parameters for control measures	β_V	$1/(\text{mosq} \cdot \text{days})$	$\beta_H/2$		Transmission rate during vaccine incubation period
	q	—	0.4	[18]	Effectiveness of insect repellent
	α	1/days	0.01–0.05		Vaccination rate
	ω	—	0.99	[13]	Vaccine efficacy
	χ	1/days	0.9/10	[6]	Incubation rate for yellow fever vaccine in humans
	$1/\sigma$	days	0.083–0.25	[19]	Period of repellent effectiveness
					Time between ...
	$1/\rho_S$	days	0.16–2		Base repellent application for susceptible/exposed humans
	$1/\rho_I$	days	1–7		Base repellent application for infectious humans
	$1/\rho_V$	days	0.167–7		Base repellent application for vaccinated humans
	$1/\gamma_S$	days	0–0.625		Repellent application for susceptible/exposed humans above baseline
	$1/\gamma_I$	days	0–8.750		Repellent application for infected humans above baseline
	$1/\gamma_V$	days	0–5.000		Repellent application for vaccinated humans above baseline

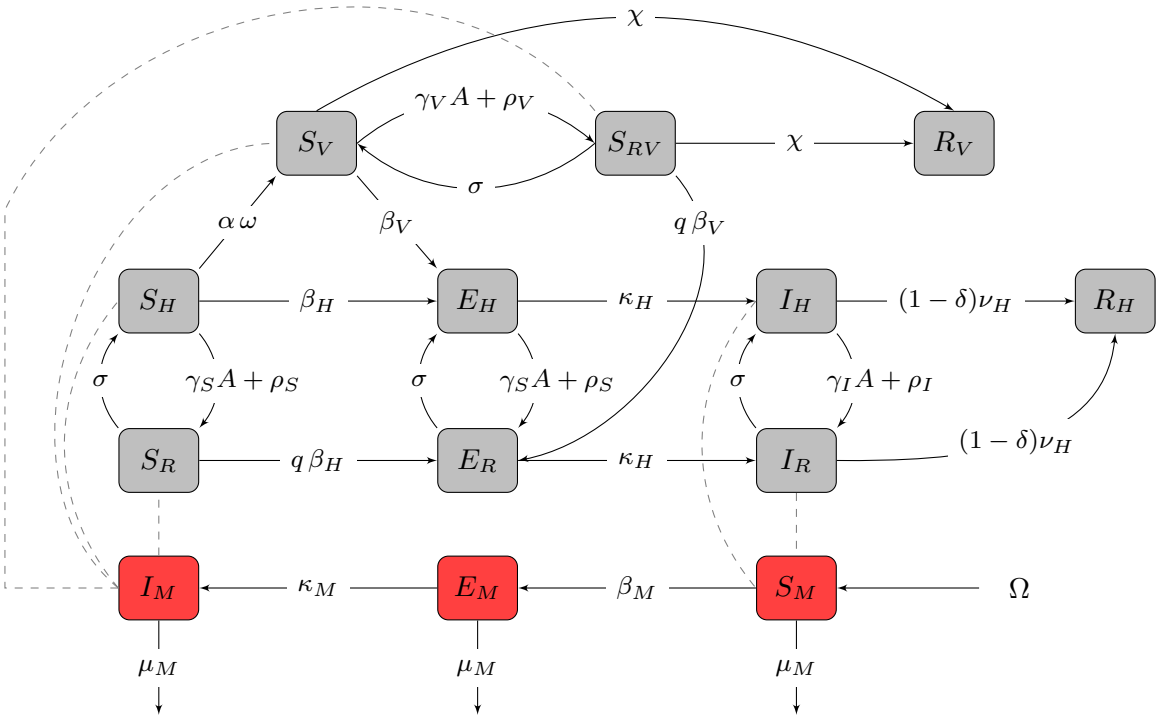


Figure 2: Flow diagram of the model given by System (1), where $A = \frac{I_H + I_R}{N_H}$ and N_H denotes the total human population. Gray and red boxes represent human and mosquito states, respectively. Solid arrows represent movement of individuals between states, while dashed arrows represent interactions between individuals.

Vaccination · The control parameters for vaccination are based on empirical data. Values for the efficiency and efficacy of yellow fever vaccination inherently have a range of reasonable possibilities depending on host characteristics, vaccine characteristics, and differential access to healthcare. From person to person, vaccine efficacy, ω, can depend on the age of the host, comorbidity, and the host's prior exposure to the disease [16]. Efficacy can also be influenced by the method of delivery and storage of the vaccine prior to its injection in the host [16]. For example, the yellow fever vaccine is most effective when stored and transported at temperatures between 2°C and 8°C, and when the reconstituted vaccine is used within one hour [13]. However, in most cases, the efficacy rate is shown to be very high, so we assume a constant vaccine efficacy of 0.99 [13].

Variation in vaccination rate, α, depends on a multitude of factors including the accessibility of healthcare in the community, the availability of the vaccine, and proportion of the population that can reasonably be vaccinated daily due to these constraints. Thus, we explore various vaccination rates in model simulations. We also simulate the use of vaccination campaigns, where varying proportions of the population are vaccinated prior to the onset of the epidemic.

The yellow fever vaccine has a short incubation period before it can provide effective immunity as the antibodies build up within the immune system [1]. The production of antibodies is a continuous process, where zero antibodies exist in the system prior to vaccination, and immunity occurs after a certain threshold of antibodies have been produced to allow the body to fight off infection. Therefore, we estimate the value of the transmission rate for vaccinated individuals during the vaccine incubation period, β_V, to be half of the transmission rate of unvaccinated individuals; thus, $\beta_V = \beta_H/2$.

Disease-Free Equilibria · The disease-free equilibrium of the model without vaccination ($\alpha = 0$) is given by

$$\begin{aligned} E_H^* &= E_R^* = I_H^* = I_R^* = S_V^* = S_{RV}^* = 0 \\ E_M^* &= I_M^* = 0 \\ S_M^* &= \frac{\Omega_M}{\mu_M} \\ S_H^* &= N_H\big(1 + \frac{\sigma}{\rho_S}\big) \\ S_R^* &= \frac{N_H}{1 + \frac{\sigma}{\rho_S}} \\ R_V^* &= 0. \end{aligned} \tag{2}$$

Note that without vaccination, the proportion of the population that remains susceptible to yellow fever (S_H) depends on the rate of repellent application via parameters σ and ρ. The disease-free equilibrium of the model with vaccination ($\alpha \neq 0$) is given by

$$\begin{aligned} E_H* &= E_R* = I_H* = I_R* = S_V* = S_{RV}* = 0 \\ E_M* &= I_M* = 0 \\ S_H* &= S_R* = 0 \\ S_M* &= \frac{\Omega_M}{\mu_M} \\ R_V* &= N_H. \end{aligned} \tag{3}$$

For the disease-free equilibrium with vaccination, the entire human population is in the fully vaccinated class (R_V).

3 Methods

Using Historical Data to Estimate Transmission Parameters · Historical data of the daily count from the 1878 epidemic in Memphis, TN were used to estimate model transmission rates, β_H and β_M. The total number of deaths due to yellow fever each day from 21 July to 10 December was calculated using data from J. Keating's *A History of the Yellow Fever* and are shown as the red data points in Figure 1 [11]. Using the parameter fitting method described in [4], Latin hypercube sampling (LHS) was used to create sets of parameters (β_M, β_H) over a wide range of potential transmission rate values. LHS is a sampling method used to create unique parameter sets spanning the entire parameter space without testing every possible combination of parameter values. See [3, 15] for a detailed description and examples of LHS. Both β_H and β_M were sampled over uniform distributions by dividing each parameter range into 1,000 equally probable values. Using LHS, 1,000 unique parameter combinations were generated spanning the entirety of the (β_M, β_H) parameter space. The model was then simulated for each of these parameter combinations (using the values given in Table 1 for all other parameter values). Using the model solution, the number of deaths per day was calculated for each simulation. The weighted error of the daily death count for each parameter set was calculated using

$$\text{error} = \frac{1}{n}\sqrt{\sum_{t\in\mathbf{T}}\Big(D(t) - D_t\Big)^2}, \tag{4}$$

where $\mathbf{T}$ is the set of times at which a data point exists, n is the total number of data points, $D(t)$ is the total deaths due to yellow fever on day t predicted by the model, and D_t represents the deaths due to yellow fever on day t as given by the data [11]. The set of transmission parameters giving the lowest error value was used for further model simulations and are given in Table 1.

Uncertainty Analysis of Vaccination & Repellent Parameters · If the values of model parameters are imprecisely known, it is necessary to perform an uncertainty analysis to predict the variation in model outcomes due to uncertainty in model parameters. To examine the range of epidemic outcomes given a range of vaccination and repellent parameters (see Table 1 for ranges), uncertainty analysis was utilized. Each of the eight parameters (σ, ρ_S, ρ_I, ρ_V, γ_S, γ_I, γ_V, and α) was sampled without replacement over uniform distributions within the ranges given in Table 1, and LHS was used to generate 1,000 unique parameter combinations which spanned the 8-dimensional parameter space. The model was simulated for each parameter combination, producing a range of model outcomes as parameters varied.

Sensitivity Analysis of Vaccination & Repellent Parameters · Model outcomes may be more sensitive to changes in certain parameters. Sensitivity analyses are used to determine how sensitive model outcomes are to changes in uncertain parameters. We modeled 40 different vaccination scenarios (in the absence of the use of insect repellent) using eight different vaccination rates over five different time periods prior to the introduction of the first infected human into the population. For each scenario we calculated the cumulative number of infections and deaths and the peak day of infection.

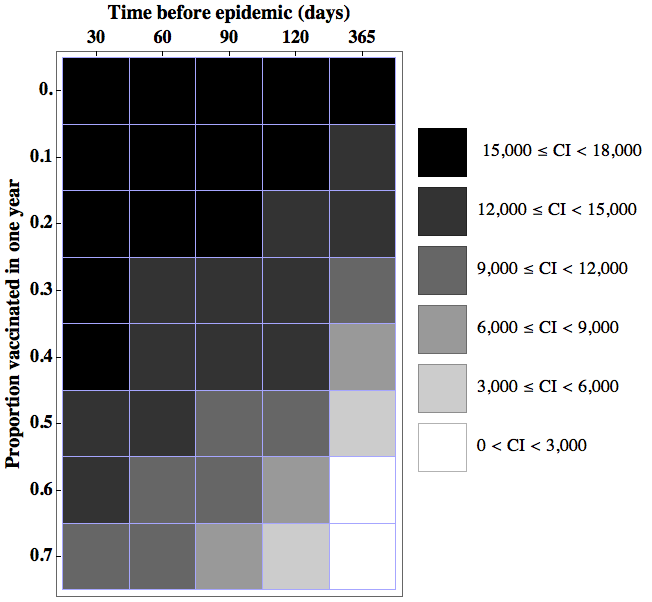
4 Numerical Results

A Yellow Fever Outbreak without Control Measures · The parameters denoting the transmission rates of yellow fever, β_H and β_M were fitted using the data from the 1878 epidemic in Memphis (see red points in Figure 1). The transmission rates with the lowest error values (see Equation 4) were $\beta_H = 3.92 \times 10^{-7}$ and $\beta_M = 9.25 \times 10^{-5}$. In the fitted model simulation where no control methods are implemented (see black curve in Figure 1), the model aligns closely to the data until approximately day 50. At this point, the model overestimates the number of deaths per day until approximately day 65. The model then underestimates the tail of the epidemic from days 65 to 100. The combined over approximation and under approximation between days 50 and 100 allows the number of cumulative deaths to be consistent with the data from the 1878 epidemic, predicting 5,150 total deaths.

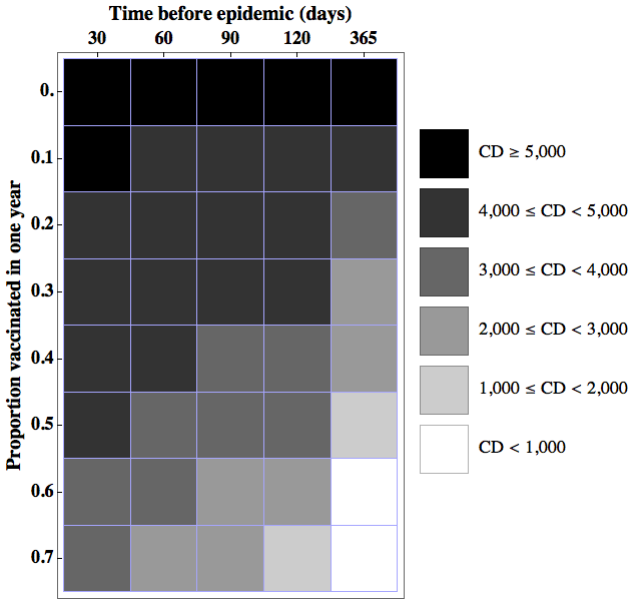
Use of vaccination alone · Different vaccination programs can be implemented to decrease the number of susceptible humans in a population over time. Programs may consider vaccinating during colder months in order to increase the number of immune individuals in the population before *Aedes aegypti* activity reaches its peak in warmer months. To model this, vaccination scenarios were simulated for vaccination occurring in a disease-free population for 30, 60, 90, 120, and 365 days prior to the introduction of the first infected human into the population. Additionally, eight different vaccination rates were simulated for each scenario to account for different vaccination program intensities. Vaccination rates were chosen such that 10, 20, 30, 40, 50, 60, and 70 percent of the human population would be completely immune (i.e. in the R_V class) after 1 year of vaccination at that rate. The number of cumulative infections and deaths and the peak day of infection were calculated for each of these vaccination programs, and are shown in the matrix plots of Figure 3.

As expected, when the vaccination rate and the period of vaccination prior to the introduction of the first infectious human increase, the number of cumulative infections and deaths decreases. The cumulative infections and cumulative deaths matrix plots, shown in Figures 3a and 3b, show that beginning vaccination, even at low rates, at least a year prior to the epidemic can greatly decrease the severity of the epidemic by reducing the cumulative number of infections and deaths. Furthermore, as the vaccination rate and vaccination period increase, so does the peak day of infection (see Figure 3c). The higher peak day of infection indicates that the epidemic is being pushed forward in time, increasing the amount of time between the onset of the epidemic and its peak. Thus, an aggressive vaccination campaign over a longer period of time could result in a small but more prolonged epidemic.

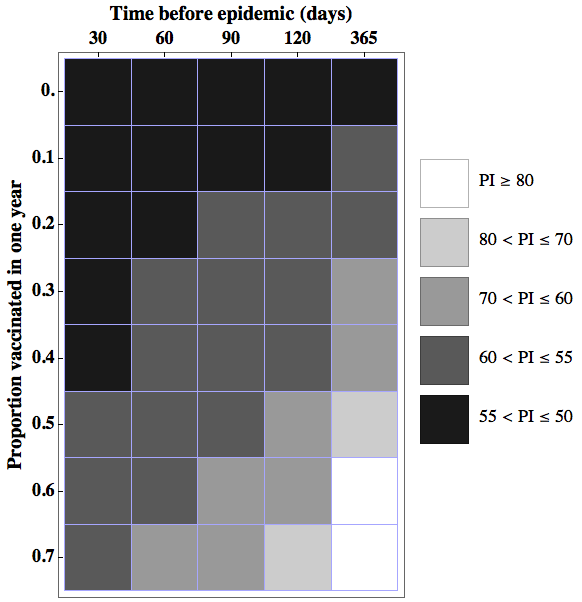
Use of insect repellent alone · In order to examine the effects of insect repellent on epidemic severity without the advantages of vaccination, all vaccine parameters were set to zero. Repellent control parameters were varied within their respective ranges using LHS. Figure 4a shows the variation in cumulative deaths when only repellent is used as a control measure. The model was simulated 1,000 times with unique parameter sets spanning the 6-dimensional space of repellent control parameters. The entire range of output over all 1,000 simulations are shown by the gray shading between the thick black lines. The interquartile range (the middle 50% of simulations) are shown in the red shaded region between the dashed red lines; the solid red line within the interquartile region shows the median over all 1,000 simulations. The use of repellent within the ranges given has little effect on the total number of deaths occurring throughout the epidemic, as all simulation results appear to approach 5,150 deaths. However, even modest use of insect repellent does have a dampening effect on epidemic progression, pushing the onset of infection forward in time and allowing for a slower accumulation of deaths over time.



(a) Cumulative infections

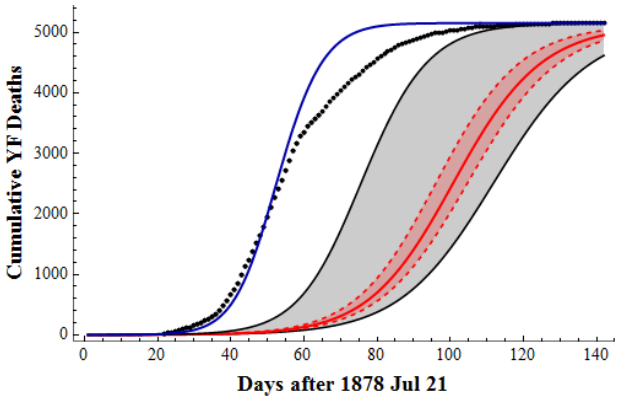


(b) Cumulative deaths

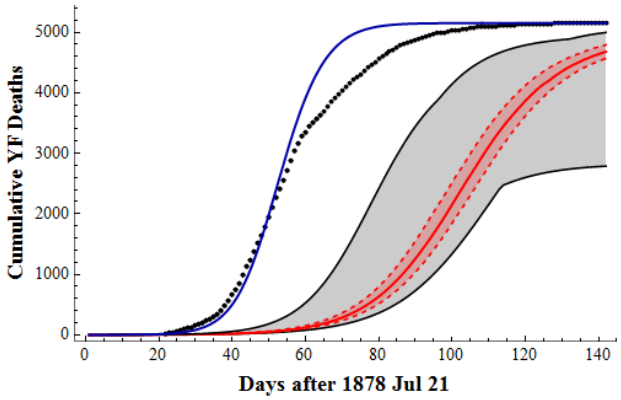


(c) Peak day of infection

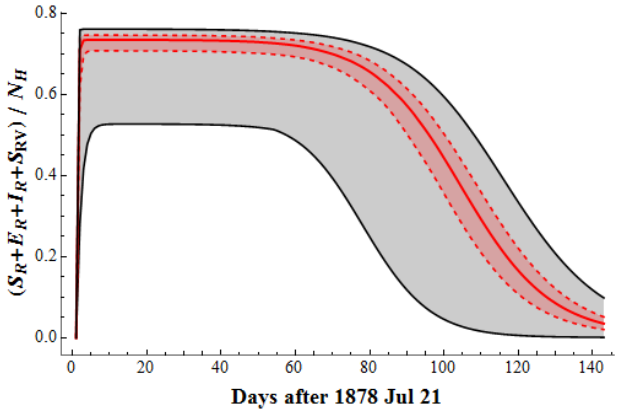
Figure 3: Cumulative infections (a), cumulative deaths (b), and peak day of infections (c) for 40 different vaccination scenarios. The darker colors represent increased severity of the epidemic, while the lighter colors represent decreased epidemic severity.



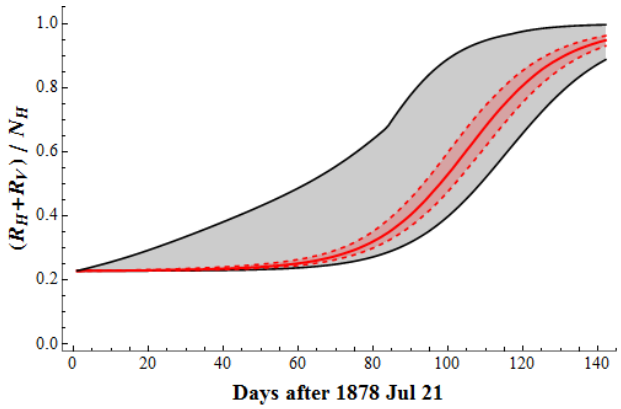
(a) Cumulative deaths; repellent only



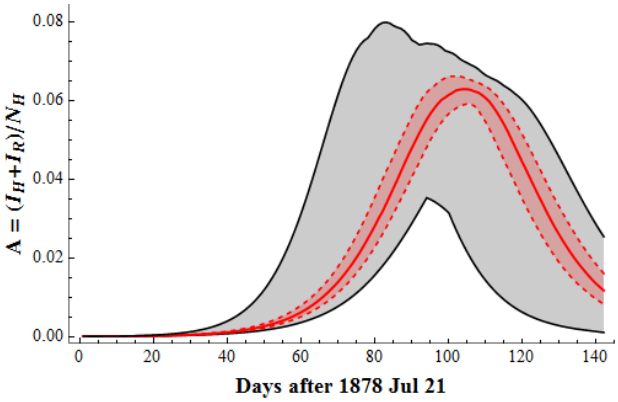
(b) Cumulative deaths; vaccination & repellent



(c) Proportion of human population wearing repellent, $(S_R + E_R + I_R + S_{RV})/N_H$



(d) Proportion of human population immune to yellow fever, $(R_H + R_V)/N_H$



(e) Proportion of human population infectious with yellow fever, $A = (I_H + I_R)/N_H$

Figure 4: Variation in model outcomes given uncertainty in model repellent parameters only (Figure (a)), and vaccination and repellent parameters (Figures (b–e)). The upper and lower solid black curves denote maximum and minimum simulation results, respectively. The red dashed curves represent the first and third quartile, and the red solid curve represents the median. Cumulative death data from the 1878 epidemic is shown by the black data points for comparison in Figures (a & b), while the no control simulation is shown by a dark blue curve.

Use of vaccination & insect repellent · Uncertainty in the control parameters for vaccination (α) and use of insect repellent (σ, ρ_S, ρ_I, ρ_V, γ_S, γ_I, and γ_V) leads to variation in model outcomes, as shown in Figure 4. Each graph in Figure 4 shows the results of 1,000 simulations generated with unique parameter combinations which span the 8-dimensional parameter space for vaccination and insect repellent parameters. The full range of output over all 1,000 simulations are shown in the shaded region between the thick black lines, while the interquartile range are shown in the red shaded region between the dashed red lines; the solid red line within the interquartile region shows the median over all 1,000 simulations. Variation in model output is shown for cumulative deaths (Figure 4b); proportion of humans wearing repellent, $(S_R + E_R + I_R + S_{RV})/N_H$ (Figure 4c); proportion of humans with immunity to yellow fever, $(R_H + R_V)/N_H$ (Figure 4d), and the proportion of the human population which is infectious, $A = (I_H + I_R)/N_H$ (Figure 4e).

Figure 4b also shows the cumulative deaths due to yellow fever from the 1878 Memphis epidemic data as a basis of comparison. Notice that the epidemic is delayed in every simulation in Figure 4b, indicating that even a small amount of control use can postpone the epidemic. However, the use of vaccination and insect repellent as control measures at the onset of the epidemic did not completely eradicate the epidemic in any simulation. Furthermore, the upper end of the range of cumulative deaths approach the cumulative death data, i.e. the cumulative deaths accumulated when no vaccination and repellent are used; these simulations correspond to low vaccination rates in conjunction with low repellent reapplication rates and a short period of effectiveness of insect repellent.

Figure 4d shows that when vaccination and insect repellent are used as control measures, the majority of humans who survived the epidemic are immune to yellow fever by $t_f = 142$ days because they were either vaccinated and ended up in the R_V class or because they became infected with yellow fever and recovered, ending up in the R_H class. Furthermore, since the model assumes that immune individuals do not wear repellent, Figure 4c shows that very few humans are wearing repellent by $t_f = 142$ days across all simulations, and that the proportion of humans wearing repellent decreases over the course of the epidemic as individuals move into one of the immune classes.

Lastly, Figure 4e shows the proportion of the human population that is infectious with yellow fever over the course of the epidemic. As expected, increased levels of control can decrease the number of infections over time. However, note that the day of peak infection is shifted between simulations, occurring early in the epidemic, approximately 70 days after the onset, when modest control measures are applied (upper black line). When very high control parameters are used (lower black line), the peak day of infection is pushed back to approximately 95 days after the onset of the epidemic. The median control use (red line) shows the peak day of infection being pushed back to approximately 105 days after the onset.

5 Conclusions

We used historical epidemic records to parameterize a novel yellow fever model and then examined the impact of vaccination and insect repellent on the dynamics and outcomes of a yellow fever outbreak. Our results show that the preventative measure of vaccination is most effective when implemented prior to the onset of the epidemic. The longer a vaccination campaign is in place before the start of an outbreak, the more likely it is to quell the epidemic completely. Our results also showed that the use of disease prevention programs may delay the progression of the epidemic, while not preventing it all together. This is especially important in climates with seasonality where mosquito activity decreases in colder seasons. In these regions, delaying the epidemic offers another level of control.

Since vaccines are not readily available or easily accessible in all areas affected by yellow fever, the use of repellent to avoid human-to-mosquito contact can further prevent the spread of an epidemic. The habitual application of insect repellent is important after the onset of the epidemic due to the waning effectiveness of repellent. Our results show that the use of insect repellent along with vaccination starting at the beginning of an outbreak can be effective in significantly reducing the number of cumulative infections and deaths over the course of the epidemic. However, this control strategy is unable to completely prevent the epidemic. Repellent alone can also be used to slow the progression of an epidemic but is not effective to prevent the spread of infection when it is the sole control measure used.

The use of historical medical records to model yellow fever can provide great insight as to how we control yellow fever epidemics today. While medicine has seen significant advancements since 1878, there are still many parts of the world affected by yellow fever with limited access to medical care. The model results of vaccination and insect repellent as control measures can be applied to yellow fever epidemics in these areas today. This model could also be adapted for other vector-borne diseases such as Dengue, West Nile, Malaria, and Zika by redefining disease-specific parameters and refitting transmission parameters. The model could then be used to estimate the vaccine efficacy, vaccination rate, and repellent application strategies needed to prevent outbreaks of these diseases.

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