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Dengue vaccination modulates the dengue-Zika viral system via immunogenic cross-talk

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To my parents, Drs. Denise A. Leonardi and Dario D. Silva

"$e^{i\pi} + 1 = 0$" – *Leonhard Euler*

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ABSTRACT

A vaccine for dengue, a viral disease which is a major driver of morbidity and mortality in tropical and subtropical regions, has recently been approved by eleven countries. While vaccination has the potential to reduce disease burden, the approved vaccine faces challenges due to the interactions between the four serotypes of dengue virus (DENV1-4) and the potential interactions with Zika virus (ZIKV), a related flavivirus. In this study, we propose a mathematical model incorporating both DENV and ZIKV in order to investigate the effects of viral competition on dengue vaccine performance, the potential for change in incidence of Zika due to dengue vaccination, and the change in incidence of secondary flavivirus infections following vaccine implementation. Our model predicts that dengue vaccine performance will be modulated by the presence of ZIKV and that dengue vaccination could lead to an increase in incidence of Zika secondary to dengue. Additionally, we predict vaccination before the introduction of ZIKV has the potential to cause future increases in incidence of

secondary dengue. Our study highlights the importance of understanding the interplay between DENV and ZIKV for policy decisions regarding the implementation of the dengue vaccine.

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Chapter 1

Introduction

Dengue is a mosquito-borne viral disease of public health significance affecting tropical and sub-tropical regions. Recent studies estimate that there are approximately 390 million cases of dengue per year, and 3.9 billion people at risk in 128 countries [4, 6]. Dengue has a wide range of clinical presentations, ranging from dengue fever, an acute febrile illness, to the severe manifestation of the disease, including dengue shock syndrome (DSS) and dengue hemorrhagic fever (DHF), characterized by plasma leakage and possibly hemorrhaging [66]. The whole spectrum of disease presentation contributes significantly to morbidity and mortality in endemic regions [66].

The dengue virus serocomplex is comprised of four serotypes (DENV1-4) that circulate throughout at-risk regions [42, 66]. The co-circulation of multiple serotypes in a region is important because of the potential for immune-modulated enhancement of disease; secondary dengue infections are much more likely to result in DSS/DHF [23]. One possible explanation for this increase in the likelihood of severe disease is antibody-dependent enhancement (ADE) [26]. ADE is hypothesized to occur because of how the immune system reacts to an infection with heterotypic

serotypes. Immediately after infection, the immune system produces a large amount of serotype-specific and cross-reactive antibodies that protect against homologous and heterotypic dengue serotypes. Longer after infection, the concentration and/or the avidity of the antibodies for heterotypic serotypes is lower. At lower concentrations or affinities, these antibodies do not neutralize the virus but rather facilitate viral entry into host cells [48], which fosters the replication of DENV *in vivo* [54]. Downstream, an immune cascade is thought to lead to enhanced severity of disease [24].

Even as recently as 2009, the only approved control measures for dengue centered around controlling vectors or limiting the contact between vectors and hosts [66]. More recently, and after many years of research and clinical trials, a dengue vaccine has been developed and approved. ADE and the multi-serotype nature of dengue presented significant hurdles for vaccine development [58]. For a vaccine to be effective, it must protect against all serotypes, in order to not inadvertently cause increased risk of disease for non-protected serotypes. From December 2015 through today, 11 countries have approved the use of Dengvaxia® (Mexico, The Philippines, Brazil, El Salvador, Costa Rica, Paraguay, Guatemala, Peru, Indonesia, Thailand and Singapore) [68]. In April 2016, the Philippines began a vaccination campaign for school-aged children over the age of 9 [52], followed by a campaign in Brazil in August 2016 [50], and Mexico began deployment in private clinics in September 2016 [51].

Unfortunately, the efficacy of the vaccine seems to be associated with whether or not a person has had a previous dengue infection [25]. In phase III trials in Southeast Asia, children 2-5 years of age had a higher risk of severe infection after vaccination [8, 25, 27]. Because it is not fully protective, the vaccine is hypothesized to "prime" the immune system, much like a primary natural infection. Therefore, any breakthrough infections, i.e. infections after vaccination, mimicked a secondary

natural infection by increasing the risk of hospitalization. Consequently, vaccination strategy, especially age at vaccination, plays an important role in vaccine performance and disease reduction, and Dengvaxia® is currently only approved for use in 9-45 year olds [18].

Another potential issue with the vaccine is the recent emergence of Zika (ZIKV), another flavivirus. *In vitro* studies have shown that DENV-positive serum exhibits both cross-protective and ADE effects for ZIKV [11, 13, 56]. Additionally, ZIKV-positive serum exhibits both cross-protective and ADE effects for DENV [15, 28]. This means individuals with previous ZIKV infections might experience a period of cross-immunity against DENV and later be susceptible to ADE, and vice versa. This theory of immunogenic cross-talk between dengue and Zika is enhanced by recent studies showing the genetic relatedness of the viruses, and the structural basis of cross-neutralization, which involves similarities in the viral protein coat [3]. Herein, immunogenic cross-talk refers to the production of cross-reactive, neutralizing and non-neutralizing antibodies between the DENV serocomplex and ZIKV.

Furthermore, dengue and Zika share a primary mosquito vector, *Aedes aegypti* [33], which guarantees overlap in their potential distributions. Because of the small flight range and short lifespan of the vector [60], the introduction of novel viruses to a region is primarily caused by human movement [47]. In 2014, Zika virus was introduced into Easter Island, Chile [59] and onto the South American continent in 2015 [7]. Originating in Africa, Zika caused outbreaks in the Pacific in 2007 and 2013 [29, 39]. It is hypothesized that the Brazilian outbreak in 2015-2016 was caused by a Zika strain from French Polynesia [38]. The resulting epidemic in 2015-2016 was declared a Public Health Emergency of International Concern by the WHO because of severe fetal deformities due to Zika infection during pregnancy [69]. The potential for ecological and immunological interactions amongst the different viruses leads us to model the DENV virus serocomplex and ZIKV together, treating them

as a dengue-Zika viral system. By doing so, we seek to understand the effects of viral competition on pathogen community dynamics.

Mathematical modeling has allowed insight into these effects in dengue and other diseases. For instance, models of influenza have demonstrated that short-term cross-immunity between strains is key to explaining how subtypes of influenza evolve and go extinct, and the partial competitive exclusion seen in influenza epidemics [19]. Further work has shown that for enough influenza subtypes, cross-immunity between strains alone can produce temporal segregation of subtypes, as has been observed in flu epidemics [31]. Pneumococcus diversity, with over 90 serotypes, can be partially explained by immune-mediated competition between the various serotypes. Modeling predicts that the large number of serotypes arises from weak serotype-specific immunity (to a serotype that an individual has previously contracted), leading to a higher chance of reinfection, and non-specific immunity that reduces viral fitness differences [10]. Viral competition through cross-immunity has also been shown to be important in explaining the epidemiology of dengue outbreaks in hyper-endemic areas with multiple serotypes [1, 40, 65].

Many multi-serotype models of dengue are based off of a two-strain influenza model first described by Andreasen [2]. Two or more competing strains of dengue have been shown to produce temporal oscillations in prevalence, leading to switches in the dominant strain [17]. Cross-immunity to heterologous serotypes after infection plays an important role in understanding dengue epidemic dynamics, and the periodicity they exhibit [5, 17]. Wearing and Rohani showed that single serotypes can exhibit ten-year cycles, while the overall period for dengue epidemics was between three and four years [65]. In addition, studies have shown that models that include cross-immunity fit data better than models without [46].

Modeling efforts following phase III trials for Dengvaxia® have offered insights into its effects, by examining the population-level consequences of the results of

phase III trials. Some efforts have focused on optimal deployment [18], which have helped dictate the guidelines for the vaccine, i.e. being approved for 9-45 year olds. Others have attempted to use our current understanding of the vaccine to model future impact [20], indicating that implementation of the vaccine in moderate-high endemic regions will have the most beneficial effects, with potential downsides in low endemic regions. Still others have looked into vaccination effects on ZIKV [57], although unlike the current study, they focused on co-infection of Zika and dengue rather than immunogenic cross-talk. Although this study did not include temporary cross-immunity between dengue and Zika, they found that dengue vaccination had the potential to increase the incidence of Zika. What the models and data agree on is that the vaccine protects against both severe and non-severe infection when used in high endemic areas, and deployed for the correct age group [8, 18, 20, 27].

In this thesis, we develop a model that incorporates the transmission of both dengue and ZIKV, as well as vaccination against dengue, to test our hypotheses and answer three main questions about dengue vaccination and Zika introduction into dengue-endemic populations:

1. What are the anticipated effects of viral competition on vaccine performance?
   We hypothesize that ZIKV will enhance dengue vaccine performance because it will compete for both vectors and hosts. In particular, infection with ZIKV will make hosts briefly cross-immune to dengue, resulting in fewer dengue infections. Implementation strategy will also play a role in vaccine performance. For example, vaccinating a larger portion of the population should lead to a larger decrease in dengue burden.

2. How will vaccination for dengue affect the incidence of ZIKV?
   Vaccination for dengue should allow for competitive release of ZIKV, because it will expand its range as dengue becomes less prevalent. However, dengue

outbreaks will still occur and thus, under certain circumstances, ZIKV may not always be more prevalent in the presence of the vaccine.

3. What are the potential effects of immunogenic cross-talk on the levels of severe disease?

   We anticipate that levels of severe disease might increase in response to the presence of both dengue and ZIKV. There should be more chances for severe disease to occur via secondary infections, because Zika will provide another avenue for secondary dengue infections to occur. If dengue vaccination increases the incidence of ZIKV, we expect more Zika infections to occur after a primary dengue infection, so-called "secondary Zika", which might lead to a higher burden of severe Zika infections. On the other hand, vaccination is expected to decrease dengue disease burden overall, which would imply that the level of severe dengue should decrease overall as well.

Chapter 2

Methods

Model Description

To address our questions, we propose a deterministic, host-vector compartmental model described by a system of ordinary differential equations. It is based off of a SEIR-type model developed for four serotypes with temporary cross-immunity described by Wearing and Rohani [65]. In a traditional SEIR model the host population is divided into four compartments: S for susceptible, E for exposed, I for infectious, and R for recovered. In this model, each of these compartments is further subdivided according to the infection history of the hosts. Tracking the infection history allows us to differentiate between primary, secondary, and tertiary infections, which becomes important for hypothesizing levels of severe disease. We do not limit the number of infections an individual can experience, other than by natural or vaccine induced immunity, because of the importance of non-apparent and non-severe infections [9]. A summary of the model is presented in Figure 2.1. After hosts become recovered and enter an R compartment, they eventually pass back into another S (susceptible) compartment for heterologous serotypes (simulating the loss of cross-immunity). The specific S compartment depends on which infections the host has

had previously, because the model assumes lifelong homologous immunity. The total number of sub-compartments for each of the SEIR compartments is related to the total number of serotypes present at a given time. For example, a population with two serotypes co-circulating would have three susceptible compartments, four exposed compartments, four infectious compartments, four temporarily recovered compartments, and one susceptible compartment to the serotypes not-present that would serve as a "completely recovered" compartment, for each age group. The vector population is divided into S, E, and I compartments based on the assumption that vectors die before recovery, because of studies showing viral persistence well beyond the average lifespan of the vector [64]. Vectors are assumed to only be infected with one serotype at a time.

The host population is also divided into three age groups depending on vaccination status. These age groups are based on the guidelines set by Sanofi-Pasteur for Dengvaxia® and phase III trials. The three age groups correspond to pre-vaccination age, vaccination age (when individuals receive the vaccine), and post-vaccination age. Two age structures are examined. For both age structures the pre-vaccination age group is ages 0-8 y.o. The vaccination age group is set to either 9-15 y.o. or 9-45y.o. Finally the post-vaccination age group is >15 y.o. or >45 y.o., respectively. All births are assumed to be completely susceptible to all four serotypes of dengue, as well as Zika, in the model. We assume symmetry for infections parameters, including transmission rate, intrinsic/extrinsic incubation period, recovery rate, and cross-immunity period. A summary of variables and parameters used in the model can be found in Table 2.1 and 2.2.

Vaccination is implemented in the S and R compartments of the second age group. Vaccination does not occur in E and I compartments because the time spent in the E and I compartments is negligible compared to the time spent in the S and R compartments. Individuals can be vaccinated while naïve to all serotypes of dengue,

DENV1-4, vaccinated after infection with only one previous serotype, or vaccinated after infection with two or more serotypes. Individuals who are vaccinated after no or one previous infection have a chance to be infected again if the vaccine fails, whereas individuals vaccinated after two or more infections are assumed to be completely immune. Vaccine failure is modeled as an all-or-nothingness in vaccination. This means that the vaccine either succeeds completely or fails for a specific serotype immediately. If the vaccine fails for a previously acquired serotype, the life-long immunity caused by previous infection still protects against that serotype, effectively increasing vaccine efficacy for previously infected individuals. Once successfully vaccinated, the immunity is lifelong and perfect. The vaccine is set to only fail for one serotype at a time, as there is no current evidence for two subsequent infections after vaccination.

Population	Description
N^H	Total host population
$S_m^{H^x,a}$	Susceptible host population, with vaccination status x, in age group a, with infection history $\{m\}$
$E_{m,k}^{H^x,a}$	Exposed host population, with vaccination status x, in age group a, currently infected with virus $\{k\}$, with $\{m\}$ previous infections.
$I_{m,k}^{H^x,a}$	Infectious host population, with vaccination status x, in age group a, currently infectious for virus $\{k\}$, with $\{m\}$ previous infections.
$R_{m,k}^{H^x,a}$	Recovered host population, with vaccination status x, in age group a, recovered from virus $\{k\}$, with $\{m\}$ previous infections.
S^V	Susceptible vector population
E_k^V	Exposed vector population for virus k
I_k^V	Infectious vector population for virus k

Table 2.1: Definition of variables representing populations in the model. For these populations: $a \in \{1, 2, 3\}$ represents the three age groups; $x \in \{\emptyset, vn, vo, vt\}$ represents unvaccinated, vaccinated while naïve, vaccinated after one infection, and vaccinated after two or more infections, respectively; $m \subseteq \{1, 2, 3, 4, Z\}$ represents the infection history; and $k \in \{1, 2, 3, 4, Z\}$ represents the current infection being experienced by the host or vector, with $k \notin m$.

Model Equations

For the full complement of model equations, see "Model Equations" in the supplemental materials. Here we present a vignette that describes a small subset of compartments and follows one individual as they move through compartments in the model.

Model Equation Vignette

Consider a host in the 9-15 year old age group who has previously been exposed to DENV2. The first compartment they would be in is described by

$$\frac{dS_2^{H,2}}{dt} = \overbrace{\rho^1 S_2^{H,2}}^{\text{Age-In}} + \underbrace{\sigma^H R_2^{H,2}}_{\text{Enter via recovery}} - \overbrace{\sum_{j\in\{1,3,4,Z\}} S_2^{H,2}\frac{\beta_j^V I_j^V}{N^H}}^{\text{Leave via infection}} \tag{2.1}$$
$$- S_2^{H,2}(\underbrace{\mu_d^H}_{\text{Death}} + \overbrace{\rho^2}^{\text{Age-out}} + \underbrace{\boxed{\sum_{k\in v}\nu_k}}_{\text{Vaccination}})$$

where $v = \{1, 2, 3, 4, \emptyset\}$.

While in this age group this individual becomes vaccinated, but the vaccine fails for DENV1. The compartment they are now in is described by

$$\frac{dS_{\{2,3,4\}}^{H^{vo},2}}{dt} = \overbrace{\boxed{\sum_{i\in\{2,3,4\}}\nu_1 S_i^{H,2}}}^{\text{In}} - \sum_{j\in\{1,Z\}} S_{\{2,3,4\}}^{H^{vo},2}\frac{\beta_j^V I_j^V}{N^H} - S_{\{2,3,4\}}^{H^{vo},2}(\mu_d^H + \underbrace{\boxed{\rho^2}}_{\text{Out}}). \tag{2.2}$$

If this individual experiences no infection for a given period of time this individual

ages out of this compartment and into the third age group, as described by

$$\frac{dS^{H^{vo},3}_{\{2,3,4\}}}{dt} = \overbrace{\boxed{\rho^2 S^{H^{vo},2}_{\{2,3,4\}}}}^{\text{In}} - \underbrace{\boxed{\sum_{j\in\{1,Z\}} S^{H^{vo},3}_{\{2,3,4\}} \frac{\beta^V_j I^V_j}{N^H}}}_{\text{Out}} - \mu^H_d S^{H^{vo},3}_{\{2,3,4\}}. \tag{2.3}$$

At this point, the individual contracts DENV1, and enters into an exposed compartment described by

$$\frac{dE^{H^{vo},3}_{\{m,1\}}}{dt} = \overbrace{\boxed{S^{H^{vo},3}_{\{m\}} \frac{\beta^V_1 I^V_1}{N^H}}}^{\text{In}} - \underbrace{\boxed{\alpha^H_1 E^{H^{vo},3}_{\{m,1\}}}}_{\text{Out}} - \mu^H_d E^{H^{vo},3}_{\{m,1\}} \tag{2.4}$$

$$m = \{2,3,4\}.$$

As the disease progresses, they enter an infectious compartment

$$\frac{dI^{H^{vo},3}_{\{m,1\}}}{dt} = \overbrace{\boxed{\alpha^H_1 E^{H^{vo},3}_{\{m,1\}}}}^{\text{In}} - \underbrace{\boxed{\gamma_1 I^{H^{vo},3}_{m,1}}}_{\text{Out}} - \mu^H_d I^{H^{vo},3}_{\{m,1\}} \tag{2.5}$$

$$m = \{2,3,4\}.$$

And they finally enter into a recovered compartment for all serotypes of dengue

$$\frac{dR^{H^{vo},3}_{\{1,2,3,4\}}}{dt} = \rho^2 R^{H^{vo},2}_{\{1,2,3,4\}} + \overbrace{\boxed{\sum_{i=1}^{4} \gamma_i I^{H^{vo},3}_{n,i}}}^{\text{In}} - R^{H^{vo},3}_{\{1,2,3,4\}}(\mu^H_d + \underbrace{\boxed{\sigma^H}}_{\text{Out}}) \tag{2.6}$$

$$n = \{1,2,3,4\} \setminus i.$$

After a period of cross-immunity, they enter into a compartment that is only susceptible to Zika, as described by

$$\frac{dS^{H^{vo},3}_{\{1,2,3,4\}}}{dt} = \rho^2 S^{H^{vo},2}_{\{1,2,3,4\}} + \overbrace{\boxed{\sigma^H R^{H^{vo},3}_{\{1,2,3,4\}}}}^{\text{In}} - S^{H^{vo},3}_{\{1,2,3,4\}} \frac{\beta^V_Z I^V_Z}{N^H} - \mu^H_d S^{H^{vo},3}_{\{1,2,3,4\}}. \tag{2.7}$$

Simulation Description

"Run-in" Period

For each simulation, a 105 year "run-in" period is simulated to establish an endemic population. An endemic population is important for experimentation because of the transient dynamics that occur immediately after a serotype is introduced into a population. This "run-in" period establishes stable oscillations of the various serotypes in the model output. To accomplish this, the desired number of serotypes for a simulation is introduced into a naïve population and the viruses are allowed to "run their course." Thus, when we begin the measurements on our various simulations, the population is not completely naïve. Rather, individuals in the population have experienced a wide range of outcomes, from being completely naïve, to having already experienced four infections. This is important to our modeling efforts because of the variable vaccine efficacy seen at different serostatuses.

Vaccine performance

Vaccine performance is assessed as the proportion of cases averted. We measure yearly incidence of dengue for vaccination only, vaccination and Zika introduction, and no vaccination scenarios. These incidences are transformed via the formula $1-\frac{\#\text{ of cases under vaccination}}{\#\text{ of cases under no vaccination}}$ to obtain the proportion of cases averted compared to the scenario where no vaccination or Zika is present. The subsequent curves are plotted in Figure 3.1. The closer this value is to 1, the better the vaccine performs. If the proportion of cases averted is between 0 and 1, the vaccine is preventing cases, but not perfectly. If this value goes below zero, this indicates an increase in the number of dengue cases being experienced by the population that is being vaccinated.

We examine four strategies: 80% vaccination of 9-15 year olds ($\epsilon = 0.00242$), 80% vaccination of 9-45 year olds ($\epsilon = 0.00242$), vaccination of 9-45 year olds to achieve

the same proportion of the total population vaccinated as vaccinating 80% of 9-15 year olds over 25 years ($\epsilon = 0.0001059$), and 50% of 9-15 year olds ($\epsilon = 0.00056$), which are plotted in Figure 3.1A-D, respectively. For all of these strategies, the target vaccination percentage is reached within ten years. The first case approximates the phase III trials in Latin America [63] with a realistic vaccination proportion. The second case is using a realistic vaccination proportion on the entire age group for which the vaccine is indicated. In the third case, there is enough vaccine to vaccinate 80% of 9-15 year olds but instead of deploying it in the 9-15 age group the vaccine is deployed to individuals aged 9-45. The fourth case represents a scenario where less vaccine is available, but it is being deployed in school-aged children.

For each of these strategies, we model both the vaccine performance when Zika is present and the vaccine performance when Zika is absent. Zika and vaccination are introduced simultaneously and yearly incidence of dengue is recorded.

Vaccine performance can exhibit slight variations based on the seroprevalence in the population at any given time. Because of the oscillatory nature of seroprevalence, to determine vaccine performance we run our model 30 times, with slightly different initial seroprevalence profiles. We obtain these seroprevalence profiles by modifying the "run-in" period for each run. Since the transmission cycle of a single serotype is on the order of 10 years, we add between 0 and 3000 days to explore the majority of the variability. Once we calculate the 25-year proportion of cases averted for each simulation, we take an average and use that average to plot vaccine performance.

Effects of vaccination on Zika

The change in incidence of ZIKV in a vaccinated versus an unvaccinated population can be measured as a fraction: $\frac{\text{Cases With Vaccine}}{\text{Cases Without Vaccine}}$. The initial conditions are obtained from the end of the "run-in" period, but in this case we manipulate the amount of time Zika has been in the population before introducing a vaccine. Since

South America has only recently had an outbreak of Zika and the dengue vaccine has not had wide-scale deployment, Zika introduction occurs before dengue vaccine implementation in the simulations. We model Zika introduction 1-25 years prior to vaccine introduction, and measure the change in incidence over 25 years as the log-transform of the proportion incidence ($\log_{10} \frac{\text{Cases With Vaccine}}{\text{Cases Without Vaccine}}$). Each Zika introduction scenario is stacked on a heat map in Figure 3.2 with year 0 indicating the beginning of the vaccine campaign.

In this heat map, white squares indicate that the model predicts less than one case in both the vaccination and the no vaccination scenarios. Color-filled squares indicate years that are predicted to have an increase in cases when vaccination is present. Grey squares indicate years in which the vaccination scenario is predicted to have less incidence of Zika than with no vaccination.

For each of these simulations, vaccination rate is set at 80% of 9-15 year olds, simulating a vaccination campaign aimed at school-aged children.

Vaccination effects of severe disease

Following our modeling of the effects of dengue vaccination on Zika incidence, we also examine the effects of dengue vaccination on secondary Zika incidence. Using a method similar to that in the previous section, we calculate the proportion increase in secondary Zika infections by calculating the fraction: $\frac{\text{Secondary Zika Cases With Vaccine}}{\text{Secondary Zika Cases Without Vaccine}}$. This simulation is repeated for between one and four serotypes. The log-transformed incidence proportions are presented in Figure 3.3.

The greatest risk for severe disease from dengue occurs in secondary dengue infections. Thus we keep track of secondary infections much like in the previous section. We measure the proportion change in incidence of secondary dengue infections using the fraction: $\frac{\text{Secondary Dengue Cases With Vaccine}}{\text{Secondary Dengue Cases Without Vaccine}}$. Here we model two different scenarios:

one where Zika is introduced to a population 1-25 years before a vaccination campaign is begun (Figure 3.4), and one where a vaccine campaign is begun 1-25 years before Zika is introduced to a population (Figure 3.5).

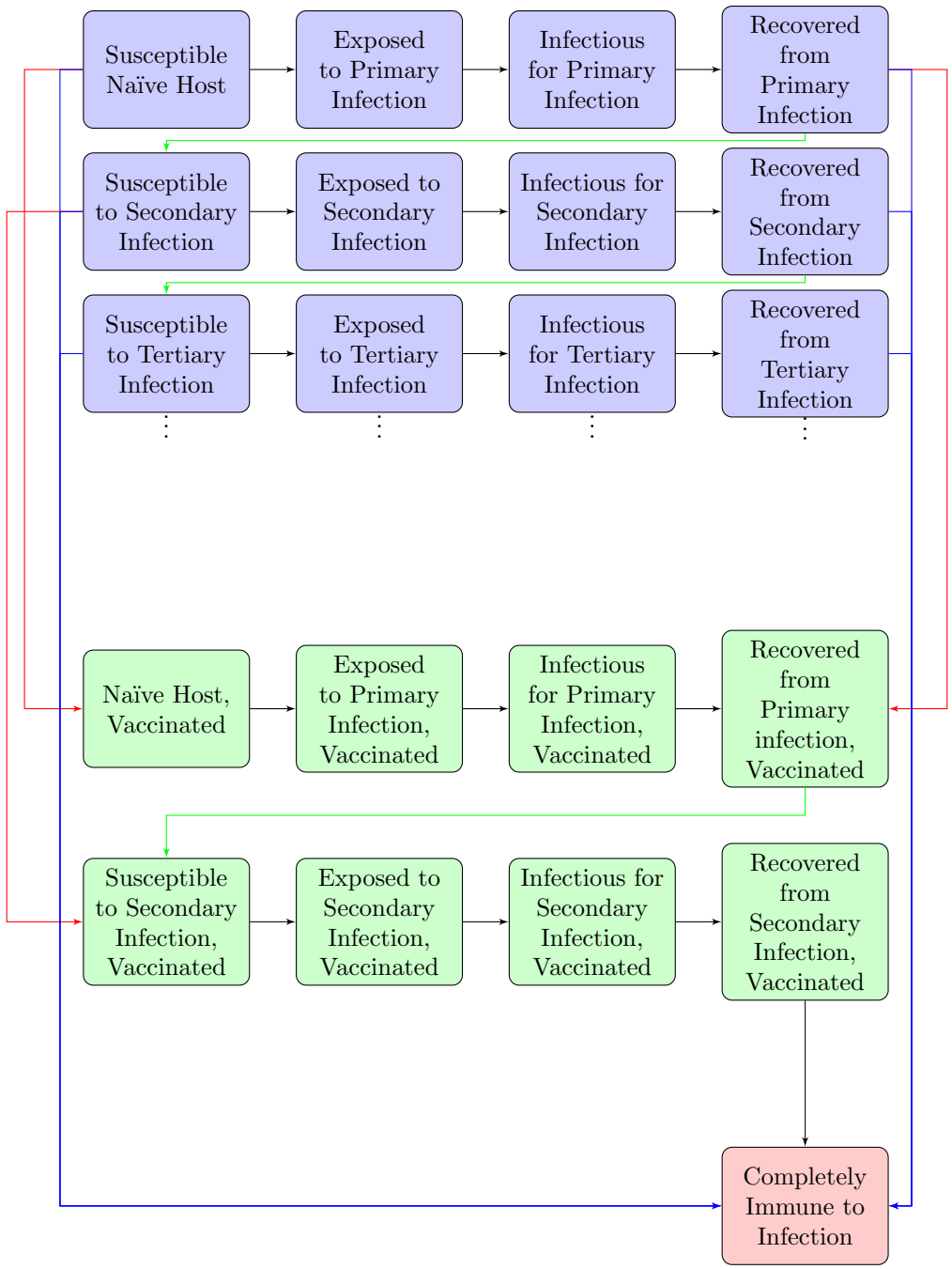

Figure 2.1: A simplified diagram of the disease model describing how hosts move through primary, secondary and tertiary infections in the second age group. Vectors are not shown. "Naïve host" means that the host has not experienced any infection. "Primary Infection" represents the first infection an individual in that compartment has ever experienced. "Tertiary Infections" are any infections occurring after an individual has already experienced two infections. The green arrows represent loss of cross-immunity to heterologous serotypes ending. The blue arrows represent vaccination success. The red arrows represent vaccine failure.

Parameter	Description	Default Value and Source
β_i^H	Transmission rate for hosts for virus i	0.247 day^{-1} [41, 43]
$1/\alpha_i^H$	Average host intrinsic incubation period for virus i	5 days [49, 55]
$1/\gamma_i$	Average host infectious period for virus i	6 days [22, 61]
$1/\sigma^H$	Average host temporary cross-immunity period	100 days [49]
ϵ	Vaccination rate	Differs by scenario. For vaccinating 9-15 y.o.s at 80% $\epsilon = 0.00242$
$\nu_\emptyset$	Vaccination success rate: the product of vaccination rate and the rate at which the vaccine protects perfectly	0.6ϵ [25]
ν_v	Vaccination failure rate: the product of vaccination rate and vaccine failure rate for each dengue serotype. v is the dengue serotype for which the vaccine fails	0.1ϵ [the vaccine is assumed to fail equally for each serotype]
ρ^a	Aging rate for age group a	Depends on age structure
β_i^V	Transmission rate for vectors for virus i	0.247 day^{-1} [41, 43]
$1/\alpha_i^V$	Average vector extrinsic incubation period for virus i	10 days [55, 64]
$\mu_b^{H,a}$	Birth rate for hosts in age group a	Depends on age structure. See supplemental materials.
$\mu_d^{H,a}$	Death rate for hosts in age group a	Depends on age structure. See supplemental materials.
$1/\mu^V$	Average lifespan of Mosquito	14 days [60]

Table 2.2: Parameters used in the model, their description, their default values, and their sources. Here $i \in \{1, 2, 3, 4, Z\}$ represents all viruses in the model, $v \in \{1, 2, 3, 4, \emptyset\}$ represents all vaccine outcomes, and $a \in \{1, 2, 3\}$ represents the three age classes.

Chapter 3

Results

What are the anticipated effects of viral competition on vaccine performance?

We investigated the impacts of viral competition on vaccine performance by considering four different strategies. Strategy A (Figure 3.1A) represents vaccination at a rate that leads to 80% of 9-15 year olds being vaccinated. Strategy B (Figure 3.1B) represents 80% of 9-45 year olds being vaccinated. Strategy C (Figure 3.1C) represents vaccination of 9-45 year olds at a rate that leads to the same fraction of the total population being vaccinated as in strategy A. Finally, strategy D (Figure 3.1D) shows vaccination at a rate leading to 50% of 9-15 year olds being vaccinated. For all strategies, the vaccination campaign and the introduction of Zika occur simultaneously. We measure the vaccine performance by calculating the proportion of cases averted as described in the methods.

Vaccine performance depends on vaccine strategy. The vaccine is predicted to initially perform better when ZIKV is present, as seen in the early years of Figures 3.1A-D. This could be due to Zika competing for hosts and vectors, as well as affording temporary cross-protection. However, this increase in performance is transient, and between six (Figure 3.1C) and ten (Figure 3.1A) years later vaccination with

Zika present performs worse than vaccination alone.

In strategy A, we see an increase in the effectiveness of the vaccine when ZIKV is first introduced. This is possibly explained by the Zika epidemic having run its course and thereby reducing the number of dengue infections due to the cross-protective effects of ZIKV for dengue infections, as well as viral competition for hosts and vectors. This competition decreases the number of individuals being infected by DENV and therefore effectively increases vaccine performance. Eventually, the competition allows a sufficient number of dengue susceptible individuals to accumulate, which leads to a situation in which a dengue epidemic can occur. Also, these simulations are run in a hyper-endemic setting where four serotypes are present. Because of competition among dengue serotypes, any one serotype may not have been prevalent for many years. This reinforces the build-up of susceptible individuals for certain serotypes, which could lead to a larger dengue epidemic and consequently worse vaccine performance.

Overall, vaccination strategy A works well for this level of transmission, corresponding to a basic reproductive number (R_0) of 3, well within the estimated range of R_0 for dengue [34, 35]. Because we are measuring proportion cases averted for the whole population, even in the later years when Zika is present the vaccination campaign is preventing a large amount of cases. However, for higher transmission rates, resulting in a R_0 of 4.5, this vaccination strategy becomes much less effective, as seen in Figure B.1. Vaccination strategy A performs worse with most years having less than 80% of their dengue cases averted, although it still serves to decrease the total number of dengue cases.

Strategy B leads to much higher vaccine performance, as shown in Figure 3.1B, as the proportion of the total population vaccinated reaches a high level. With a large proportion of the population becoming protected, we would expect to see near perfect performance, since herd immunity protects those that are not vaccinated. Over

a longer time scale we expect that there will be a slight drop in performance, as enough vaccine failures accumulate to cause an epidemic to occur. This would mark the end of the honeymoon period first described by McLean & Anderson [36], during which vaccination delays the build-up of a large enough pool of susceptible individuals. Once a sufficiently large enough pool of susceptible individuals accumulates, we predict an epidemic could occur.

For strategy C, shown in Figure 3.1C, vaccine performance is similar to that resulting from strategy A in the first few years, but after this period, performance is much lower. This occurs even as the same proportion of the total population receives the vaccine as in strategy A. Because of the serial nature of infections, and the immunity that natural infections confer, older individuals are more likely to have had prior infections (with more serotypes). When the age group being vaccinated is not young enough, some vaccine is going towards those who are already naturally protected. Additionally, because of the serial nature of infections, older individuals may not be susceptible to the dominant dengue serotypes in an area for many years. In strategy C, instead of vaccinating mostly naïve individuals, or individuals who have experienced only one infection, much of the vaccine will be going to people who have experienced two or more infections. While this will provide complete protection to those vaccinated individuals, fewer individuals with no or only one prior infection will be protected.

For strategy D, shown in Figure 3.1D, vaccine performance is similar to strategy C (Figure 3.1C), in that there is a transient increase in initial performance after the introduction of Zika. After this initial increase, vaccine performance with Zika is lower than without Zika, but there are oscillations in this trend; around year 18 vaccination with Zika starts to outperform vaccination without Zika. Because a much lower percentage of people are being vaccinated, the force of infection is not lowered as much as in strategy A. The strategy does produce mostly positive proportions of

cases averted, implying the strategy is still beneficial overall. The one exception is between years 19 and 21, when more cases are predicted than would normally occur, possibly explained by the aforementioned build-up of dengue susceptible individuals. For both strategies C and D, a larger transmission rate exaggerates this build-up and subsequent epidemic cycle, thereby causing predicted increases in incidence, as shown in Figure B.1C and D.

How will vaccination for dengue affect the incidence of ZIKV?

ZIKV will compete with DENV for hosts and vectors. Introducing a vaccine will lower the competitive fitness of DENV and potentially lead to competitive release: the depression of dengue as a competitor allowing Zika to proliferate. This competitive release does not occur immediately in all cases as shown in Figure 3.2A-D.

Figure 3.2A-D compares the yearly incidence of Zika under dengue vaccination versus no vaccination. For no vaccination, Zika was introduced into the population between 1-25 years before we began measurement of Zika cases. We utilized this same protocol for studying cases when the vaccine was introduced at measurement year 0. In Figure 3.2, we present the change in proportion incidence in the population with the vaccine relative to no vaccine. We show this in relationship to the time since vaccination introduction (horizontal axis) and the number of years Zika was introduced prior to the vaccination campaign (vertical axis).

Our model predicts Zika to mostly be silent following its initial outbreak, with an increase in incidence not happening for more than 20 years after initial introduction of Zika. These increases in incidence are as high as 10^5 times more infections than without the vaccine being present. The decreases in incidence, on the order of 10^5 times fewer Zika infections occurring, indicate that total Zika cases will remain the same, and these increases are a result of shifting the same epidemic in time.

On a longer time scale, there is a slight increase in incidence of Zika with dengue vaccination. With a higher transmission rate, leading to a higher force of infection, these effects are accelerated and our model projects large scale outbreaks about 20 years after Zika is first introduced, following the beginning of a vaccination campaign (Figure B.2).

Interestingly, the number of dengue serotypes that are co-circulating in a population with ZIKV is related to the severity of subsequent Zika epidemics after the initial outbreak. As such, Figure 3.2A shows more years with a higher maximum increase in Zika incidence than Figure 3.2D, once increases start occurring. This implies that, in the presence of dengue vaccination, areas that have experienced more serotypes in the past would have a more severe Zika epidemic than an area that has experienced fewer dengue serotypes.

What are the potential effects of immunogenic cross-talk on the levels of severe disease?

Secondary infections with DENV generally lead to a higher chance of developing severe disease. Recent work has also shown that Zika displays a similar dynamic *in vitro* [44]. The current model tracks the infection history of each compartment, allowing for analysis of secondary infections.

Because of the potential immunogenic-enhancement of disease caused by dengue sero-positivity on Zika infection (or what we will refer to as secondary Zika), Zika infections occurring after a dengue infection are postulated to be more severe. Therefore, we measured the increase in Zika infections secondary to a single dengue infection or vaccination. Similar to the increase we observed in Figure 3.2, Zika infections secondary to dengue infection (or vaccination) increase, and the magnitude of the increase is correlated with the number of dengue serotypes co-circulating in the population. This is demonstrated by the result that the maximum magnitude

of increase with four serotypes co-circulating with Zika, on the order of 10^5, (Figure 3.3A) is larger than the maximum magnitude of increase when only one serotype is co-circulating with Zika, on the order of 10^3 (Figure 3.3D). These maximum magnitudes are predicted to take place during the same year, 25 years after vaccine introduction, when Zika was introduced 15 years before the vaccine was introduced.

Comparing all Zika infections to secondary Zika infections (Figure 3.2 and Figure 3.3, respectively), there is a high degree of similarity between how secondary Zika cases will increase and how Zika cases will increase as a whole, under dengue vaccination. However, for secondary Zika infections, the magnitude of the increase in infections is predicted to be greater under dengue vaccination than without vaccination. Vaccination opens another pathway for a secondary Zika infection to occur, enhancing the outbreak sizes. Since the population is already highly susceptible to ZIKV, from having no previous exposure, more secondary Zika infections occur and the increases are not offset by similar decreases, implying more secondary infection overall. This effect is on the same 20+ year time-scale shown for all Zika cases (Figure 3.2) but it is sensitive to the transmission rate and occurs on shorter time scales when the transmission rate is increased (Figure B.3).

Without vaccination, Zika infections will be depressed by the cross-immunity that infection with DENV might provide. This competition between Zika and dengue without vaccination will not completely exclude Zika, as seen by the large Zika epidemic that occurred in South America in 2015-2016, but it could serve to depress levels of Zika in hyper-endemic settings. Also, in a setting with two or more serotypes, no vaccination will lead to individuals being more likely to have been infected with multiple serotypes before being infected with ZIKV. With vaccination, secondary Zika infections will be increased in three ways: first the competitive release of ZIKV allowing for more Zika infections; second, with a decrease in dengue infections, less people will have been infected two or more times; third, a Zika infection after suc-

cessful vaccination might increase the amount of secondary Zika infections. This will provide a larger population of hosts who have only been infected with one dengue serotype prior to infections with Zika.

Secondary dengue infections are predicted to decrease when ZIKV is introduced into a population before the start of a vaccination campaign, shown in Figure 3.4. Some years will have a slight increase in secondary dengue infections, under certain sero-profiles, with a maximum increase in secondary dengue occurring when only one serotype is present, and only in certain years (Figure 3.4D). Secondary infections are decreased in large part by the fact that the total number of dengue infections is decreased. This is consistent with previous studies that have shown that vaccination leads to a decrease in overall dengue, as well as a decrease in severe dengue [8, 25]. While in most years the model predicts a decrease in the amount of secondary dengue, and therefore potentially severe dengue, there are still years that will have as many, or more, cases of severe dengue in the presence of ZIKV and dengue vaccination. This is caused by temporal shifts in the epidemics and does not indicate an overall increase in infection. Instead, it is a signal that without dengue vaccination and Zika, those years would have had normally very low infection rates, but now as the epidemic has shifted, more infections than normal would occur during that time frame. At a higher transmission rate, there are more years with an increase in the number of secondary dengue infections, as seen in Figure B.4. Increased infection years occur more frequently in populations with one or two serotypes co-circulating with ZIKV, and the maximum increases are predicted to be an order of magnitude higher than at lower transmission levels. Still, the vaccine will lower the overall incidence of secondary dengue as these increases are offset by larger decreases in other years.

If dengue vaccination is begun before ZIKV is introduced into a population, there is a period of increased secondary dengue infections a few years after the introduction of Zika (shown in Figure 3.5). This increased incidence of secondary dengue

can persist for many years (see Figure 3.5A), or can be nearly nonexistent, as in the case with two serotypes (Figure 3.5C). When Zika is first introduced, the number of dengue infections drops dramatically, shown as the dark grey area in years 1-3 in Figure 3.5. This drop in dengue infections allows dengue susceptible individuals to accumulate, providing the necessary conditions for a dengue outbreak. Four serotypes co-circulating with ZIKV offers the longest sustained increases in secondary dengue incidence for the largest range of starting conditions. This is interesting because the model predicts that after a short period of decreased secondary dengue a long period of secondary dengue at or above non-vaccination levels will occur (Figure 3.5A). For two or three serotypes co-circulating with Zika (Figure 3.5C and Figure 3.5B, respectively), our model predicts little to no increase in secondary dengue. For one serotype co-circulating with Zika, the model predicts outcomes with the largest increase in secondary dengue to occur when the vaccine is introduced shortly before Zika enters the population (Figure 3.5A). If only one serotype is present in a population, dengue vaccination and Zika introduction offer the only way for secondary cases to arise. If dengue vaccination is begun early enough before the introduction of Zika in a population, the vaccine will be effective in preventing more secondary dengue cases to occur by lowering the force of infection. If it is introduced only shortly before ZIKV enters a population, two novel ways of obtaining a secondary infection drive an increase in secondary infections in the population. Increased levels of transmission affect the timing of the increase in secondary dengue, but the magnitude of the increase is similar, as seen in Figure B.5. The increased levels of transmission also shorten the periods of increased secondary dengue for four serotypes co-circulating with Zika (Figure B.5A), and cause increases in secondary dengue infections for two and three serotypes co-circulating (Figure B.5C and Figure B.5B, respectively).

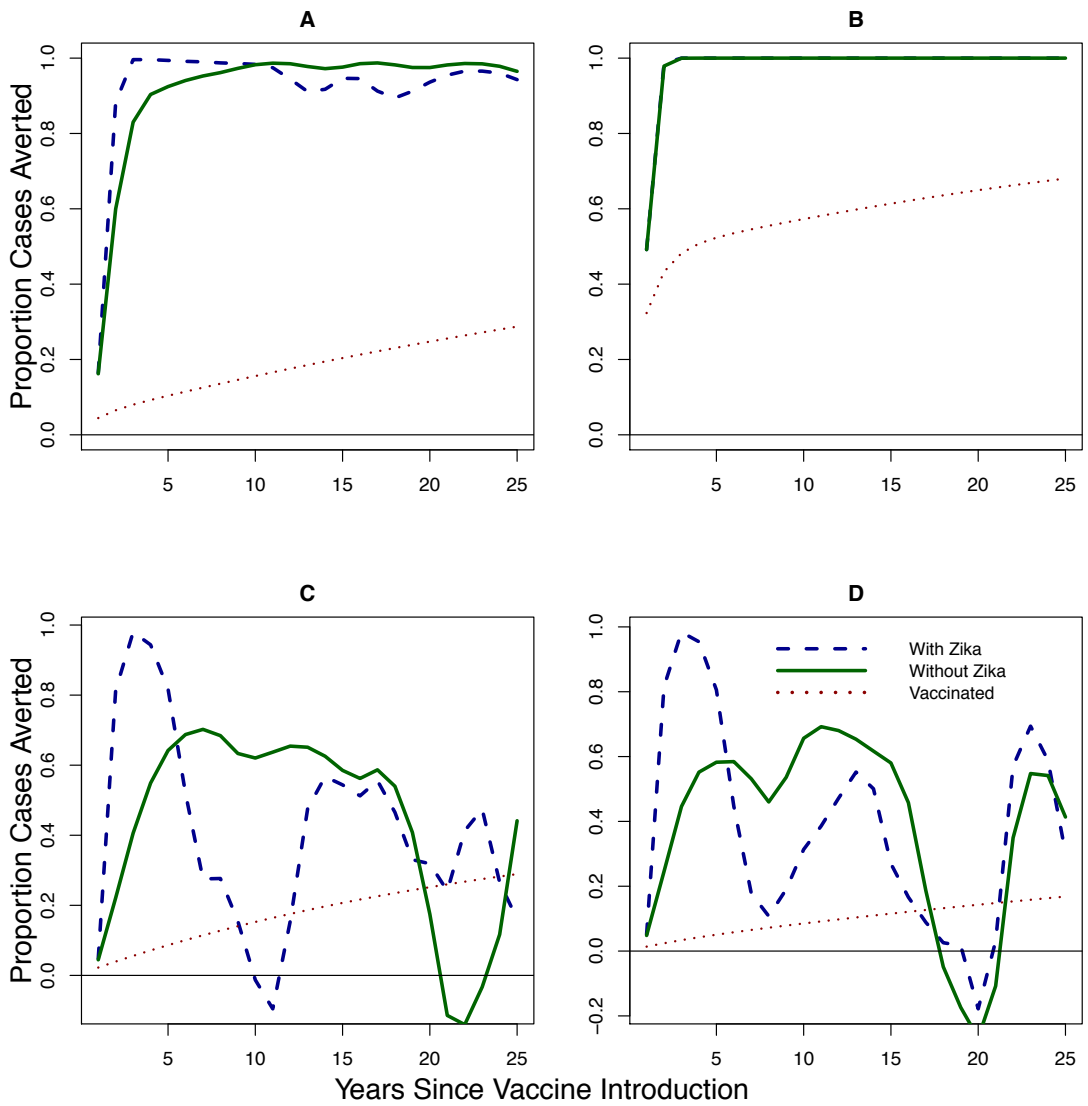

Figure 3.1: Average proportion of cases averted through vaccination in the presence and absence of ZIKV over 25 years. The graphs also show the proportion of the total population that is vaccinated in each case (represented by the dotted red line). (A) Vaccination of 80% of 9-15 year olds. (B) Vaccination of 80% of 9-45 year olds. (C) The same proportion of the total population vaccinated as in 3.1A, but the vaccination age group is 9-45 y.o. (D) Vaccination of 50% of 9-15 year olds.

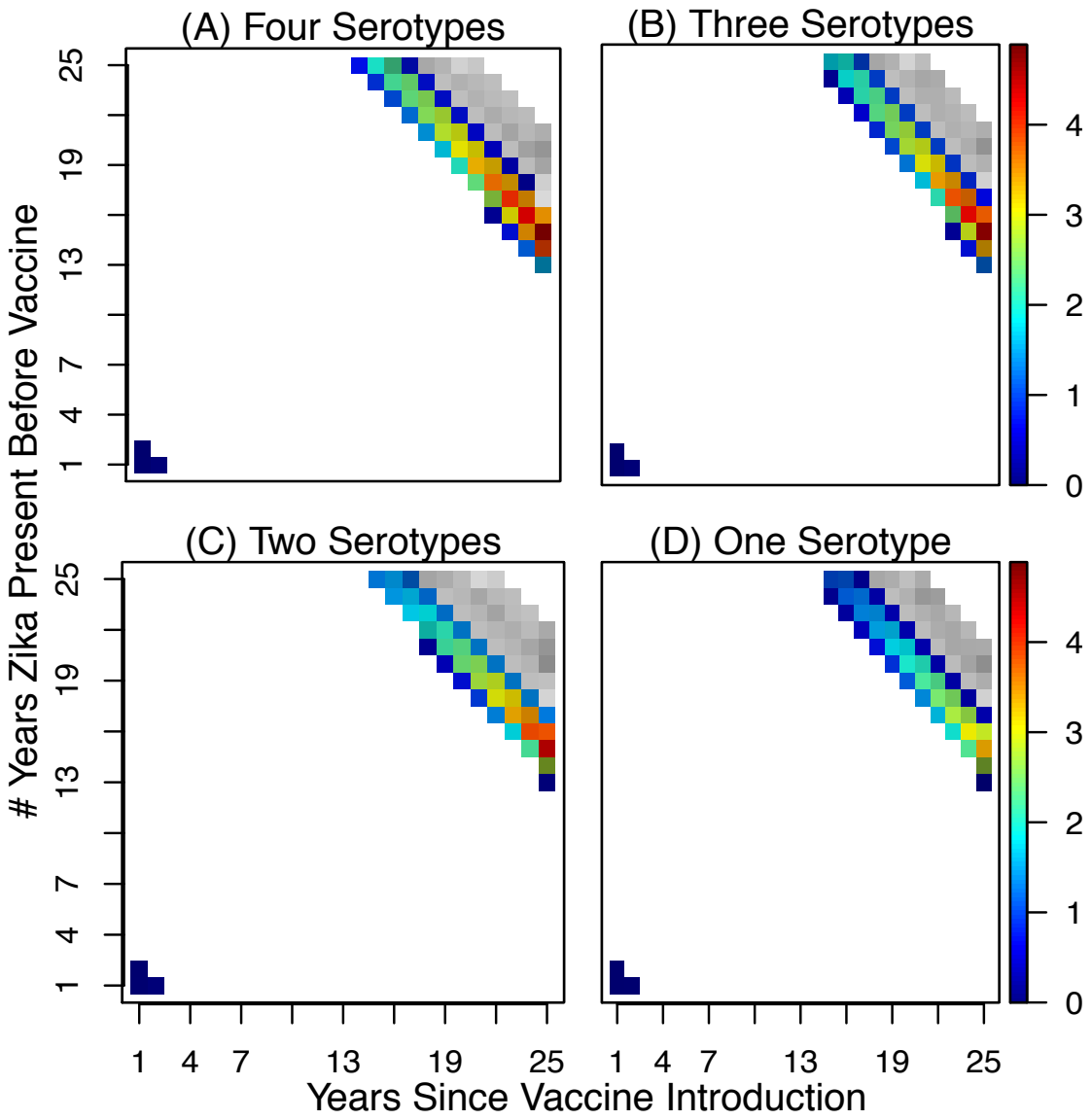

Figure 3.2: Change in Zika incidence due to dengue vaccination over time, relative to timing of vaccine deployment. Each panel represents model output where a different number of dengue serotypes co-circulate with Zika. The x-axis represents how many years have elapsed since the vaccine was introduced. Each row along the y-axis corresponds to a different scenario in which the number of years that ZIKV was present before the vaccine was implemented is varied. The colors correspond to the log of the proportion change in incidence (i.e. $\log_{10}(\frac{\text{Cases with vaccine}}{\text{Cases without vaccine}})$), e.g. a value of one represents a year in which there were ten times more cases in the presence of the vaccine. Grey-scale squares represent years that would see a decrease in Zika infections in the presence of dengue vaccine. White squares indicate that the model predicts less than one case in both the vaccine and no vaccine scenarios.

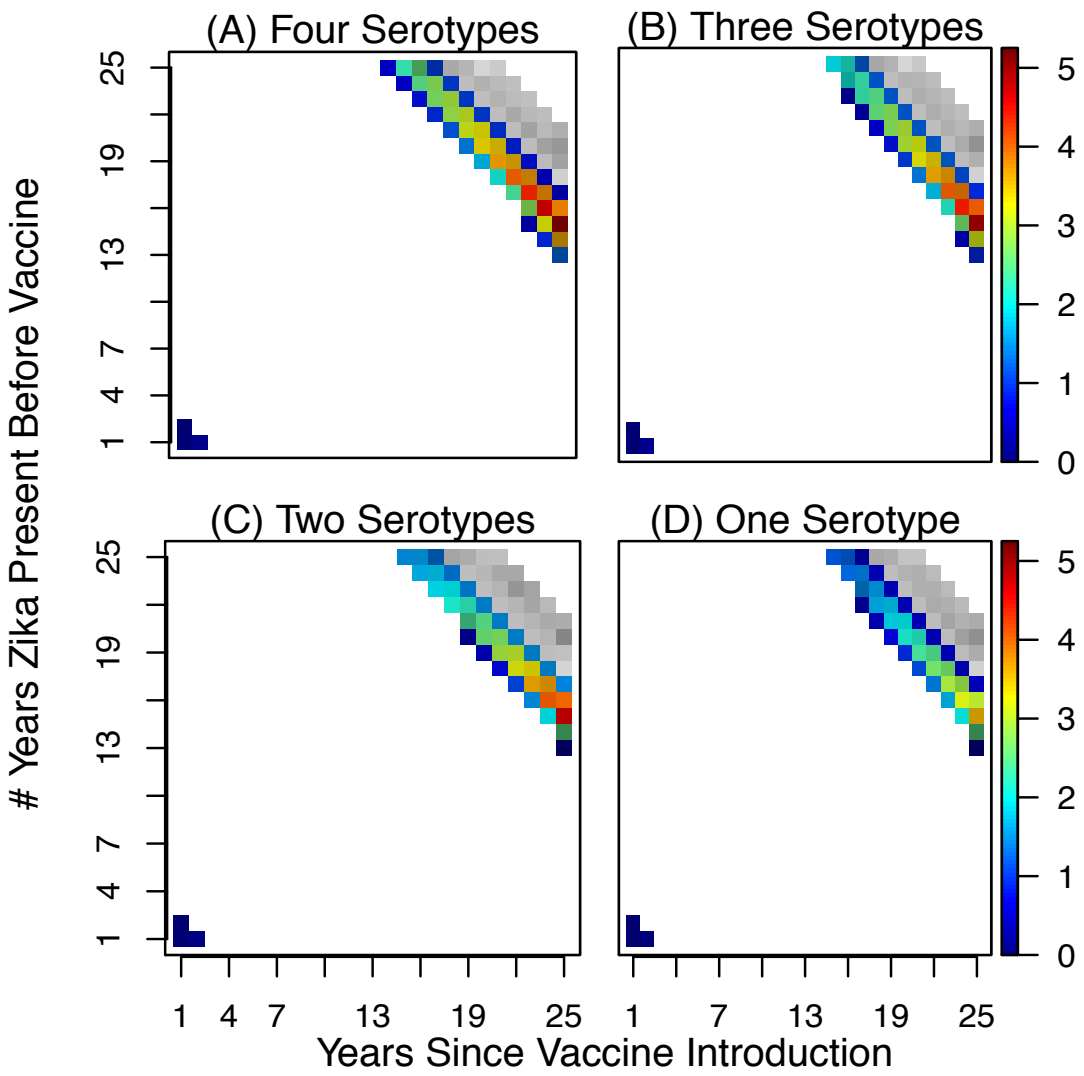

Figure 3.3: Change in secondary Zika incidence due to dengue vaccination over time, relative to timing of vaccine deployment. Each panel represents model output where a different number of dengue serotypes co-circulate with Zika. The x-axis represents how many years have elapsed since the vaccine was introduced. Each row along the y-axis corresponds to a different scenario in which the number of years that ZIKV was present before the vaccine was implemented is varied. The colors correspond to the log of the proportion change in incidence (i.e. $\log_{10}(\frac{\text{Cases with vaccine}}{\text{Cases without vaccine}})$), e.g. a value of one represents a year in which there were ten times more cases in the presence of the vaccine. Grey-scale squares represent years that would see a decrease in Zika infections in the presence of dengue vaccine. White squares indicate that the model predicts less than one case in both the vaccine and no vaccine scenarios.

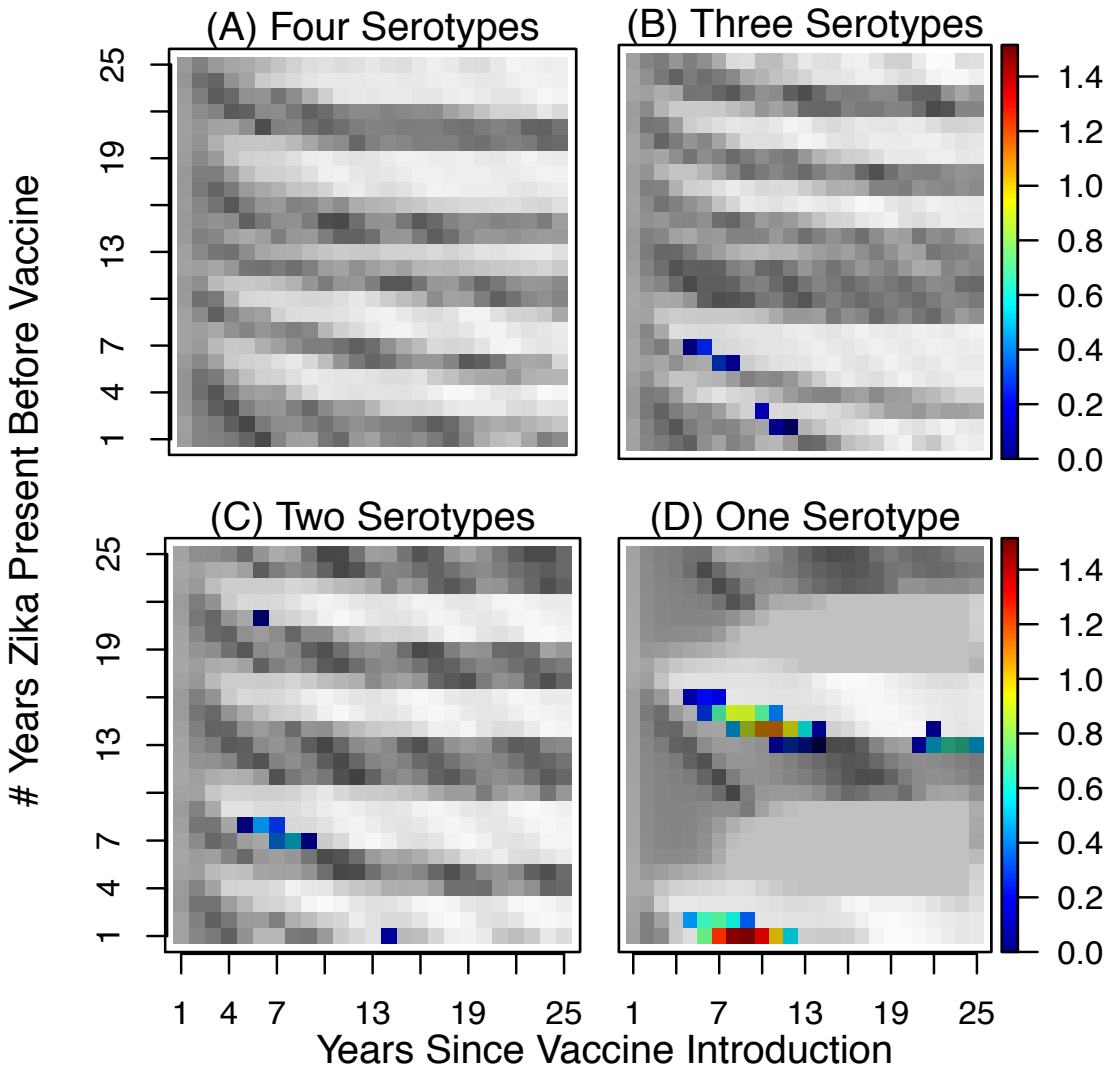

Figure 3.4: Change in secondary dengue due to dengue vaccination over time, relative to timing of Zika introduction. Each panel represents model output where a different number of dengue serotypes co-circulate with Zika. The x-axis represents how many years have elapsed since the vaccine was introduced. Each row along the y-axis corresponds to a different scenario in which the number of years that ZIKV was present before the vaccine was implemented is varied. The colors correspond to the log of the proportion change in incidence (i.e. $\log_{10}(\frac{\text{Cases with vaccine}}{\text{Cases without vaccine}})$), e.g. a value of one represents a year in which there were ten times more cases in the presence of the vaccine. Grey-scale squares represent years that would see a decrease in Zika infections in the presence of dengue vaccine. White squares indicate that the model predicts less than one case in both the vaccine and no vaccine scenarios.

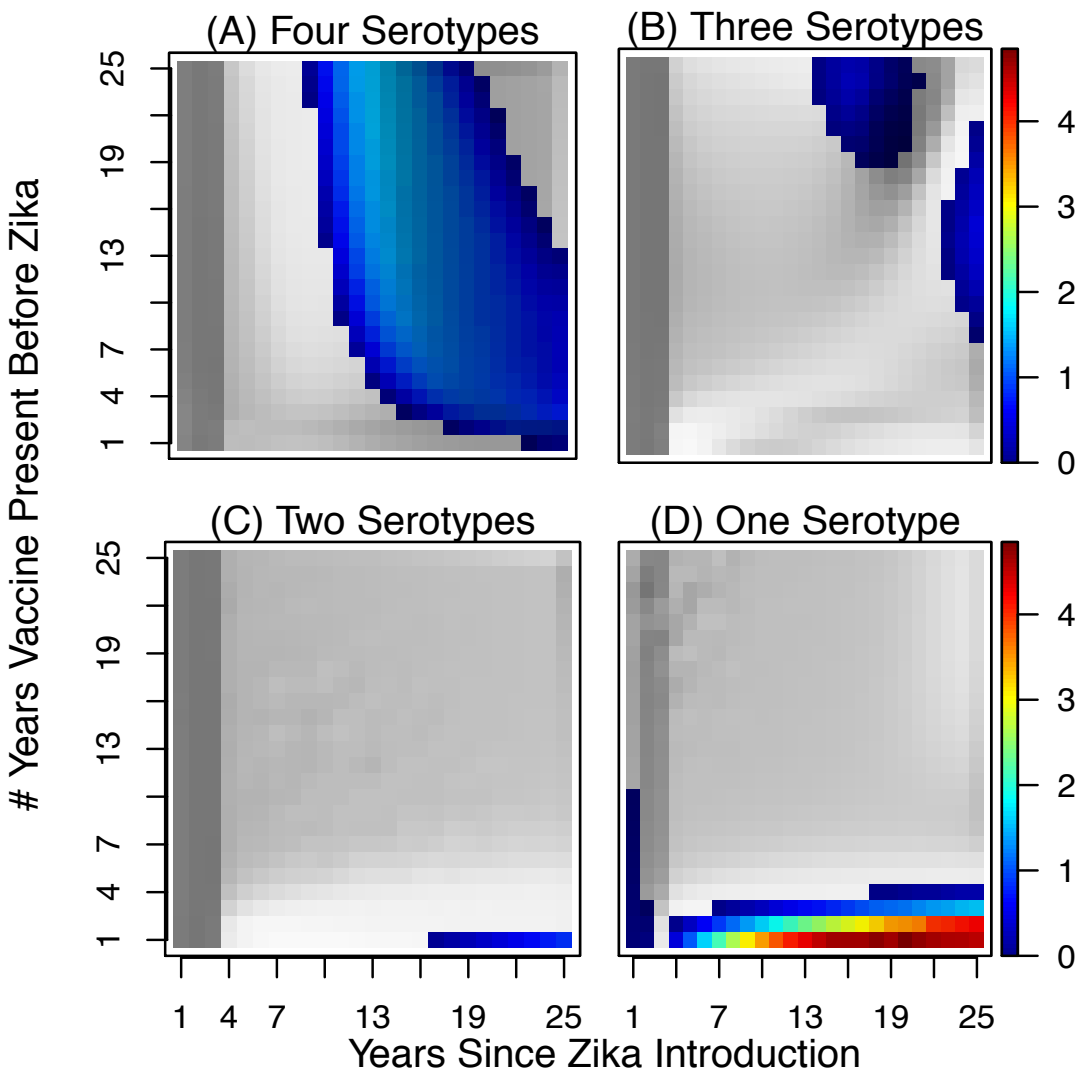

Figure 3.5: Change in secondary dengue due to dengue vaccination over time, relative to timing of Zika introduction. Note: here vaccination is begun before Zika is introduced into a population. Each panel represents model output where a different number of dengue serotypes co-circulate with Zika. The x-axis represents how many years have elapsed since ZIKV was introduced. Each row along the y-axis corresponds to a different scenario in which the number of years that vaccination was occurring before the Zika was introduced is varied. The colors correspond to the log of the proportion change in incidence (i.e. $\log_{10}(\frac{\text{Cases with vaccine}}{\text{Cases without vaccine}})$), e.g. a value of one represents a year in which there were ten times more cases in the presence of the vaccine. Grey-scale squares represent years that would see a decrease in Zika infections in the presence of dengue vaccine. White squares indicate that the model predicts less than one case in both the vaccine and no vaccine scenarios.

Chapter 4

Discussion

Vaccination against dengue has the potential to reduce the number of dengue cases by millions in tropical and subtropical regions. But this potential reduction in disease burden carries with it potential risks. The same immunological forces that hindered vaccine development have the potential to hinder effective vaccine deployment. Understanding not only the risks posed by DENV, but also the potential for cross-reactivity with other flaviviruses, will be important for further development of vaccines and subsequent control strategies. Competition amongst viruses plays a role in establishing the ecology of the viral community in the host and vector populations, and understanding how control measures affect that competition will allow safer, more effective policy decisions to be made.

A key result of our modeling is that there is the potential for enhancement of secondary Zika incidence, as a consequence of dengue vaccination. If the *in vitro* results of enhanced infectivity hold true *in vivo*, it is possible that Zika and dengue will interact through ADE and temporary cross-immunity. Because of this potential immunogenic cross-talk, our model predicts the possibility of an increase in the amount of secondary Zika infections, possibly leading to a higher level of severe Zika, as a consequence of dengue vaccination. While our model does not predict an immediate threat of an increased Zika epidemic, as seen in Figure 3.2, the dynamics

of when another epidemic will occur are sensitive to the transmission rates and basic reproductive number of both dengue and Zika, and thus could occur much sooner, as seen in Figure B.2. Any increases in infectivity or mosquito population size and distribution, potentially caused by changes in temperature, precipitation, or humidity, could lead to a large epidemic sooner.

Secondary dengue incidence, and therefore the chance for severe dengue, will likely decrease if vaccination is begun before Zika introduction, as seen under all simulations in Figure 3.4, in the vaccine trials, and in other modeling efforts [8, 18, 25, 27] . While the overall trend shows a lowering of secondary infections, the drop is not linear over time. Fewer secondary infections are predicted to occur overall, but we still predict years with greater-than-expected secondary cases of dengue with the vaccine, if less than four serotypes are co-circulating with Zika, versus no vaccine. While this is not an ideal outcome of vaccination, the overall reduction helps meet the WHO's goals of dengue morbidity and mortality reductions [67]. If dengue vaccination is introduced before Zika introduction, the potential for increase in secondary dengue is much higher. Our results indicate that if the vaccine is deployed before Zika is introduced into a population, there is a potential for sustained increases in secondary dengue infections for both one and four serotypes co-circulating with Zika (Figure 3.5). This might indicate that while the vaccine does perform well in most hyper-endemic settings, there are certain population sero-profiles that could cause the vaccine to enhance the level of secondary infection. More sensitivity analysis on sero-profiles that lead to enhanced secondary dengue is needed.

Our modeling results are consistent with previous work that showa that the vaccine, at a high enough vaccination rate will lead to a reduction in dengue disease burden, exemplified in Figure 3.1B [18, 20]. When the same proportion of the total population is vaccinated, our model predicts that a higher proportion of dengue cases will be averted if the dengue vaccination campaign is directed at a school-aged group,

with or without the presence of Zika, at various transmission rates (See Figure 3.1 and Figure B.1). The potential temporary cross-immunity induced by Zika modeled here will allow dengue susceptible individuals to accumulate. Because of this, our model predicts a temporary increase in vaccine performance, regardless of the age group of vaccination. The same factors causing this temporary increase in performance also create the potential for a dengue outbreak, which potentially causes a decrease in vaccine performance. This effect is magnified even further if the limited amount of dengue vaccine is distributed among a larger range of ages, 9-45 y.o.s, as shown in Figure 3.1C.

The Philippines have already implemented a large scale dengue vaccination campaign for school-aged children [52]. The Philippines have also recently experienced an outbreak of Zika, which is ongoing [69]. If our model predictions are correct, there are risks to this vaccination campaign, and others like it, because of the co-circulation of Zika. Understanding these risks is key to making informed and impactful policy decisions. Because the implementation of the vaccine and introduction of Zika are concurrent, there is the potential for lower vaccine performance if vaccination rates are not high enough in schools (Figure 3.1C), future long-term increases in the amount of secondary Zika (Figure 3.3), and possible long term increases in secondary dengue (Figure 3.5).

Our model, of course, has limitations. We assume symmetry in infection parameters across all viruses, though there is evidence of some strains of dengue being more virulent than others [45]. Varying these parameters might lead to more complicated interactions but more consensus evidence on the variance in virulence between serotypes is needed. By using pseudo-stratified age groupings, some nuance of how age groups interact with the viruses is lost. Because of the variable efficacy of the vaccine according to serostatus at vaccination, using a more stratified model with yearly age groups would help to better understand the dynamics of age-at-first-

infection. Understanding how the age-at-first-infection might shift and its impacts on Zika transmission could also be important because of the consequences of Zika infection for pregnant women [37, 53]. If secondary Zika is to blame for the high rate of severe manifestations of prenatal Zika, shifting the average age of infection into reproductive age could have dire consequences. More analysis is also needed to measure the relative importance of limiting co-infection in hosts and possibly vectors. While co-infection seems rare, there have been documented cases in 2014 and 2015 [16, 62].

While the model presented here does not allow forecasting, per se, it can help interpret general trends and make testable hypotheses as new data become available. Our model also assumes only vector-borne transmission of Zika, ignoring the role of sexual transmission [21, 38], although in a hyper-endemic setting we expect the main driver of Zika transmission to be mosquito-borne. The vaccine in this model is considered an all-or-nothing vaccine, implying it works perfectly or not at all. While breakthrough infections were seen very early in phase III trials, the exact mechanism of vaccine failure seen in Dengvaxia® is not known. Further study and analysis of vaccine performance can lead to a better understanding of exactly how the vaccine is failing. Also, while Dengvaxia® was the first vaccine approved, it is not the only one that has made it to late phase trials [12]. A more efficacious vaccine would be predicted to alter the dynamics of the viral interactions, and potentially not have the unintended consequences of a less perfect vaccine.

Seasonality also plays an important role in the burden of dengue, Zika, and other arthropod-borne viruses. *Aedes aegypti* is sensitive to moisture levels and temperature which in turn affects the transmission cycle of dengue [14, 32]. Because these effects are cyclic, the long-term trends that our model predicts should be robust to the addition of seasonality, but yearly variance would likely be different if seasonality was included.

Despite these limitations, our analysis offers insight into the effects of ZIKV introduction and dengue vaccination on a population. Dengue vaccine performance has the potential to be changed by a competing virus, such as Zika, not protected by the vaccine. While a Zika vaccine is in the pipeline, we may experience another Zika epidemic before the vaccine is approved and deployed [30]. A Zika vaccine, along with a dengue vaccine that is more effective among seronegative individuals, would present an opportunity to reduce morbidity and mortality by flaviviruses in tropical and sub-tropical regions. Without the deployment of both, however, the relatedness of the viruses and subsequent immunogenic cross-talk, raises concerns. Future studies should look at surveillance data that is becoming available in states being affected by DENV and ZIKV to examine their relationship and look for indications of cross-immunity. With more data becoming available about ZIKV, vaccine performance, and the relationship between ZIKV and DENV, further analyses can help predict the future of epidemics caused by the dengue-Zika viral system.

Appendices

Appendix A

Full Model Equations

Pre-Vaccination Age (Age Group 1)

Susceptible naïve hosts in the first age group increase by births and leave by death, infection, or aging into the next age group

$$\frac{dS_{\emptyset}^{H,1}}{dt} = \sum_{a} \mu_b^{H,a} N^{H,a} - \mu_d^{H,1} S_{\emptyset}^{H,1} - \sum_{j \in n} S_{\emptyset}^{H,1} \frac{\beta_j^H I_j^V}{N^H} - \rho^1 S_{\emptyset}^{H,1} \tag{A.1}$$

where $n = \{1, 2, 3, 4, Z\}$ and $a \in \{2, 3\}$.

After a host has experienced a first, second, third or fourth infection, individuals will have an infection history m referring to all previous serotypes they have acquired. The equations for these compartments are described by

$$\forall m \in \{\{w\}, \{w, x\}, \{w, x, y\}, \{w, x, y, u\}\}$$

$$w, x, y, u \in \{1, 2, 3, 4, Z\}, w \neq x \neq y \neq u$$

$$\frac{dS_m^{H,1}}{dt} = R_m^{H,1} \sigma^H - \mu_d^{H,1} S_m^{H,1} - \sum_{j \in i} S_m^{H,1} \frac{\beta_j^H I_j^V}{N^H} - \rho^1 S_m^{H,1} \tag{A.2}$$

where $i = \{1, 2, 3, 4, Z\} \setminus \{m\}$

e.g. If $m = \{1, 3, Z\} \rightarrow i = \{2, 4\}$.

After exiting the susceptible compartment, hosts pass into an exposed compartment depending on their prior serostatus. From the exposed compartment, they pass into an infectious compartment, where they can infect vectors, and then pass to a recovered compartment. In these equations, the "infection history" of the hosts is $\{m\}$, and the current infection they are experiencing is i. The set of equations for these compartments is as follows

$$\begin{aligned}
&\forall i \in \{1,2,3,4,Z\} \\
&\forall m \subseteq \{1,2,3,4,Z\} \setminus i \\
\frac{dE^{H,1}_{m,i}}{dt} &= S^{H,1}_{m}\frac{\beta^H_i I^V_i}{N^H} - E^{H,1}_{m,i}(\mu^{H,1}_d + \alpha^{H,1}_i + \rho^1) && \text{(A.3)} \\
\frac{dI^{H,1}_{m,i}}{dt} &= E^{H,1}_{m,i}\alpha^{H,1}_i - I^{H,1}_{m,i}(\mu^{H,1}_d + \gamma^{H,1}_i + \rho^1) && \text{(A.4)} \\
\frac{dR^{H,1}_{m,i}}{dt} &= I^{H,1}_{m,i} - R^{H,1}_{m,i}(\mu^{H,1}_d + \sigma^H + \rho^1). && \text{(A.5)}
\end{aligned}$$

Vaccination Age (Age group 2)

Age group two, $a = 2$, represents the age group during which hosts are vaccinated. As vaccination occurs, this age group is split into four sets of compartments: unvaccinated, vaccinated with no prior-exposure, vaccinated after being infected with one previous serotype, and vaccinated after being infected with two or more previous serotypes.

All individuals pass through the unvaccinated compartment before becoming vaccinated because we treat vaccination as a continuous process, rather than an instantaneous occurrance.

Dengue naïve hosts: The dengue naïve hosts are comprised of two compartments and they receive individuals from the first age class and lose individuals via death, infection, aging out, or vaccination. For those who have never been exposed

to Zika, the equation is

$$\frac{dS_{\emptyset}^{H,2}}{dt} = \rho^1 S_{\emptyset}^{H,1} - \mu_d^{H,2} S_{\emptyset}^{H,2} - \sum_{j \in n} S_{\emptyset}^{H,2} \frac{\beta_j^H I_j^V}{N^H} - \rho^2 S_{\emptyset}^{H,2} - \epsilon S_{\emptyset}^{H,2} \tag{A.6}$$

where $n = \{1, 2, 3, 4, Z\}$ and $v \in \{1, 2, 3, 4, \emptyset\}$.

For those who have experienced a prior Zika infection, the equation is

$$\frac{dS_{Z}^{H,2}}{dt} = \rho^1 S_{Z}^{H,1} - \mu_d^{H,2} S_{Z}^{H,2} - \sum_{j \in n} S_{Z}^{H,2} \frac{\beta_j^H I_j^V}{N^H} - \rho^2 S_{Z}^{H,2} - \epsilon S_{Z}^{H,2} \tag{A.7}$$

where $n = \{1, 2, 3, 4\}$ and $v \in \{1, 2, 3, 4, \emptyset\}$.

Since the vaccine can fail in four ways, eight compartments are needed to represent those who are vaccinated, but not fully protected, while naïve to dengue: four for those who have never been exposed to Zika, and four for those who have been exposed to Zika previously. These eight compartments are described by

$$\begin{gathered} \forall m = \{w, x, y\} \text{ and } \forall m = \{w, x, y, Z\} \\ w, x, y \in \{1, 2, 3, 4\}, w \neq x \neq y \\ \frac{dS_{m}^{H^{vn},2}}{dt} = \nu_{\{i \setminus Z\}} S_0^{H,2} - \mu_d^{H,2} S_m^{H^{vn},2} - \sum_{j \in i} S_m^{H^{vn},2} \frac{\beta_j^H I_j^V}{N^H} - \rho^2 S_m^{H^{vn},2} \end{gathered} \tag{A.8}$$

where $i \in \{1, 2, 3, 4, Z\} \setminus m$.

Depending on their previous exposure to Zika, those individuals who are fully protected by the vaccine enter into one of two compartments. For no previous Zika infection, the equation is as follows

$$\begin{gathered} m = \{1, 2, 3, 4\} \\ \frac{dS_{m}^{H^{vn},2}}{dt} = \sigma^H R_m^{H^{vn},2} + \nu_{\emptyset} S_0^{H,2} - \mu_d^{H,2} S_m^{H^{vn},2} - S_m^{H^{vn},2} \frac{\beta_Z^H I_Z^V}{N^H} - \rho^2 S_m^{H^{vn},2}. \end{gathered} \tag{A.9}$$

If they have been previously infected with ZIKV, or recovered from an infection after vaccination, they enter into a fully recovered compartment

$$\begin{aligned} m &= \{1,2,3,4,Z\} \\ \frac{dR_m^{H^{vn},2}}{dt} &= \sum_{i\in m}\gamma_i I_{n,i}^{H^{vn},2} + \nu_\emptyset S_Z^{H,2} - \mu_d^{H,2} R_m^{H^{vn},2} - \rho^2 R_m^{Hvn,2} \\ \text{where } n &= m \setminus i. \end{aligned} \tag{A.10}$$

One previous dengue infection: For those who have had one dengue infection prior to vaccination, their equations follow from those of the first age group, Equation A.2, with the vaccination term added:

$$\begin{aligned} \forall m &= \{w\} \text{ and } \forall m = \{w,Z\} \\ w &\in \{1,2,3,4\} \\ \frac{dS_m^{H,2}}{dt} &= \sigma^H R_m^{H,2} - \mu_d^{H,2} S_m^{H,2} - \sum_{j\in i} S_m^{H,2}\frac{\beta_j^H I_j^V}{N^H} - \rho^2 S_m^{H,2} - \epsilon S_m^{H,2} \\ \text{where } i &= \{1,2,3,4,Z\} \setminus m. \end{aligned} \tag{A.11}$$

After vaccination, this group of individuals enters into a second set of compartments much like those of the naïve individuals, except that vaccine failure for a previously acquired serotype leads to complete immunity. There are still eight compartments, one for each vaccine failure for Zika naïve individuals, and one for each vaccine failure for those who have been previously infected with Zika. The former four compartments are described by

$$\begin{aligned} \forall m &= \{w,x,y\} \\ w,x,y &\in \{1,2,3,4\}, w \neq x \neq y \\ \frac{dS_m^{H^{vo},2}}{dt} &= \sum_{k\in m}\nu_i S_k^{H,2} - \mu_d^{H,2} S_m^{H^{vo},2} - \sum_{j\in\{i,Z\}} S_m^{H^{vo},2}\frac{\beta_j^H I_j^V}{N^H} - \rho^2 S_m^{H^{vo},2} \\ \text{where } \ i &= \{1,2,3,4\} \setminus m. \end{aligned} \tag{A.12}$$

Appendix A. Full Model Equations

The latter four compartments are described by

$$\begin{aligned} \forall m &= \{w, x, y, Z\} \\ w, x, y &\in \{1, 2, 3, 4\}, w \neq x \neq y \\ \frac{dS_m^{H^{vo},2}}{dt} &= \sum_{k \in m \setminus Z} [\nu_i (S_{k,Z}^{H,2} + S_{Z,k}^{H,2})] - \mu_d^{H,2} S_m^{H^{vo},2} - \sum_{j \in \{i\}} S_m^{H^{vo},2} \frac{\beta_j^H I_j^V}{N^H} - \rho^2 S_m^{H^{vo},2} \end{aligned} \tag{A.13}$$

where $i = \{1, 2, 3, 4, Z\} \setminus m$.

Depending on their previous exposure to Zika, those who are fully protected by the vaccine, either by perfect vaccination or vaccine failure for a previously acquired serotype, enter into one of two compartments. For no previous Zika infection, the equation describing those only susceptible to Zika is as follows

$$\begin{aligned} m &= \{1, 2, 3, 4\} \\ \frac{dS_m^{H^{vo},2}}{dt} &= \sigma^H R_m^{H^{vo},2} + \sum_{i=1}^{4} [(\nu_\emptyset + \nu_i) S_i^{H,2}] - \mu_d^{H,2} S_m^{H^{vo},2} - S_m^{H^{vo},2} \frac{\beta_Z^H I_Z^V}{N^H} \\ &\quad - \rho^2 S_m^{H^{vo},2}. \end{aligned} \tag{A.14}$$

Individuals who have had previous exposure to Zika enter into a fully recovered compartment, $R_{1,2,3,4,Z}^{H^{vo},2}$, described by

$$\begin{aligned} m &= \{1, 2, 3, 4, Z\} \\ \frac{dR_m^{H^{vo},2}}{dt} &= \sum_{i=1}^{4} [(\nu_i + \nu_\emptyset)(S_{Z,i}^{H,2} + R_{Z,i}^{H,2})] + \sum_{i \in m} \gamma_i I_{n,i}^{H^{vo},2} - \mu_d^{H,2} R_m^{H^{vo},2} - \rho^2 R_m^{H^{vo},2} \end{aligned} \tag{A.15}$$

where $n = m \setminus i$.

Two or more previous infections: For those who have had two or more prior infections, the vaccine is assumed to work perfectly, providing complete protection

against all serotypes of DENV:

$$\begin{aligned}
&\forall m \in \{\{w,x\},\{w,x,y\},\{w,x,y,u\}\} \text{ and} \\
&\forall m \in \{\{w,x,Z\},\{w,x,y,Z\},\{w,x,y,u,Z\}\} \\
&w,x,y,u \in \{1,2,3,4\}, w \neq x \neq y \neq u \\
&\frac{dS_m^{H,2}}{dt} = \sigma^H R_m^{H,2} - \mu_d^{H,2} S_m^{H,2} - \sum_{j\in i} S_m^{H,2} \frac{\beta_j^H I_j^V}{N^H} - \rho^2 S_m^{H,2} - \epsilon S_m^{H,2} \\
&\text{where } i \in \{1,2,3,4,Z\} \setminus m.
\end{aligned} \tag{A.16}$$

After vaccination, individuals can enter into two compartments. The first is still susceptible to Zika, and is described by

$$\begin{aligned}
&m = \{1,2,3,4\} \\
&\frac{dS_m^{H^{vt},2}}{dt} = \sigma^H R_m^{H^{vt},2} + \sum_i \nu_\emptyset S_i^{H,2} - \mu_d^{H,2} S_Z^{H^{vt},2} - S_Z^{H^{vt},2} \frac{\beta_Z^H I_Z^V}{N^H} - \rho^2 S_Z^{H^{vt},2} \\
&\text{where } i \in \{\{w,x\},\{w,x,y\},\{w,x,y,u\}\} \\
&w,x,y,u \in \{1,2,3,4\}, w \neq x \neq y \neq u.
\end{aligned} \tag{A.17}$$

If they have been previously infected with ZIKV, they enter into a fully recovered compartment described by

$$\begin{aligned}
&m = \{1,2,3,4,Z\} \\
&\frac{dR_m^{H^{vt},2}}{dt} = \sum_{i\in m} \gamma_i I_{n,i}^{H^{vt},2} + \sum_i [\nu_\emptyset (S_i^{H,2} + R_i^{H,2})] - \mu_d^{H,2} R_m^{H^{vt},2} - \rho^2 R_m^{H^{vt},2} \\
&\text{where } i \in \{\{w,x,Z\},\{w,x,y,Z\},\{w,x,y,u,Z\}\} \\
&w,x,y,u \in \{1,2,3,4\}, w \neq x \neq y \neq u \\
&n = m \setminus i.
\end{aligned} \tag{A.18}$$

Infected individuals in this age group pass through the E and I compartments

much as the pre-vaccination age group does in Equations A.3 and A.4, except that there is no aging into the vaccinated compartments.

$$\forall i \in \{1, 2, 3, 4, Z\}$$

$$\forall m \subseteq \{1, 2, 3, 4, Z\} \setminus i$$

$$\frac{dE^{H,2}_{m,i}}{dt} = \rho^1 E^{H,1}_{m,i} + S^{H,2}_m \frac{\beta^H_i I^V_i}{N^H} - E^{H,2}_{m,i}(\mu^{H,1}_d + \alpha^H_i + \rho^2) \tag{A.19}$$

$$\frac{dI^{H,2}_{m,i}}{dt} = \rho^1 I^{H,1}_{m,i} + E^{H,2}_{m,i}\alpha^H_i - I^{H,2}_{m,i}(\mu^{H,2}_d + \gamma^H_i + \rho^2) \tag{A.20}$$

$$\frac{dE^{H^{vn},2}_{m,i}}{dt} = S^{H^{vn},2}_m \frac{\beta^H_i I^V_i}{N^H} - E^{H^{vn},2}_{m,i}(\mu^{H,2}_d + \alpha^H_i + \rho^2) \tag{A.21}$$

$$\frac{dI^{H^{vn},2}_{m,i}}{dt} = E^{H^{vn},2}_{m,i}\alpha^H_i - I^{H^{vn},2}_{m,i}(\mu^{H,2}_d + \gamma^H_i + \rho^2) \tag{A.22}$$

$$\frac{dE^{H^{vo},2}_{m,i}}{dt} = S^{H^{vo},2}_m \frac{\beta^H_i I^V_i}{N^H} - E^{H^{vo},2}_{m,i}(\mu^{H,2}_d + \alpha^H_i + \rho^2) \tag{A.23}$$

$$\frac{dI^{H^{vo},2}_{m,i}}{dt} = E^{H^{vo},2}_{m,i}\alpha^H_i - I^{H^{vo},2}_{m,i}(\mu^{H,2}_d + \gamma^H_i + \rho^2) \tag{A.24}$$

$$\frac{dE^{H^{vt},2}_{m,i}}{dt} = S^{H^{vt},2}_m \frac{\beta^H_i I^V_i}{N^H} - E^{H^{vt},2}_{m,i}(\mu^{H,2}_d + \alpha^H_i + \rho^2) \tag{A.25}$$

$$\frac{dI^{H^{vt},2}_{m,i}}{dt} = E^{H^{vt},2}_{m,i}\alpha^H_i - I^{H^{vt},2}_{m,i}(\mu^{H,2}_d + \gamma^H_i + \rho^2) \tag{A.26}$$

Here m is the infection history of the compartment and i is the current infection that hosts in that compartment are experiencing.

Because of the length of time spent in the recovered class, vaccination also occurs in this compartment and has to be accounted for, much as in the susceptible compartments in this age group. For unvaccinated individuals in the second age group

who are recovering from their first dengue infection, the equations are as follows

$$\begin{aligned}
\forall m = \{w\} \text{ and } \forall m = \{w, Z\} \\
w \in \{1, 2, 3, 4\} \\
\frac{dR_m^{H,2}}{dt} = \rho^1 R_m^{H,1} + \sum_{i \in m} \gamma_i I_{n,i}^{H,2} - \mu_d^{H,2} R_m^{H,2} - R_m^{H,2}(\rho^2 + \sigma^H + \epsilon) \qquad \text{(A.27)} \\
\text{where } n = m \setminus i.
\end{aligned}$$

For those who are recovering from their second, third, or fourth dengue infection, the equations are

$$\begin{aligned}
\forall m \in \{\{w, x\}, \{w, x, y\}, \{w, x, y, u\}, \\
\{w, x, Z\}, \{w, x, y, Z\}, \{w, x, y, u, Z\}\} \\
w, x, y, u \in \{1, 2, 3, 4\}, w \neq x \neq y \neq u \\
\frac{dR_m^{H,2}}{dt} = \rho^1 R_m^{H,1} + \sum_{i \in m} \gamma_i I_{n,i}^{H,2} - \mu_d^{H,2} R_m^{H,2} - R_m^{H,2}(\rho^2 + \sigma^H + \epsilon) \qquad \text{(A.28)} \\
\text{where } n = m \setminus i.
\end{aligned}$$

If this is an individual's first dengue infection, they enter into the H^{vo} group. If this is their second or greater infection, they will enter into the H^{vt} compartment and be completely immune to all dengue serotypes, and only susceptible to Zika if they have not experienced a Zika infection before. Those who are recovering from their first infection and had a vaccine failure are described by eight compartments, based on whether or not they had a previous Zika infection. For those who have

never been exposed to Zika these compartments are described by

$$\begin{aligned} \forall m &= \{w, x, y\} \\ w, x, y &\in \{1, 2, 3, 4\}, w \neq x \neq y \\ \frac{dR_m^{H^{vo},2}}{dt} &= \sum_{k \in m} \nu_i R_k^{H,2} - R_m^{H^{vo},2}(\mu_d^{H,2} + \rho^2 + \sigma^H) \\ \text{where} \quad i &\in \{1, 2, 3, 4\} \setminus m. \end{aligned} \tag{A.29}$$

For those with previous Zika exposure the set of compartments is described by

$$\begin{aligned} \forall m &= \{w, x, y, Z\} \\ w, x, y &\in \{1, 2, 3, 4\}, w \neq x \neq y \\ \frac{dR_m^{H^{vo},2}}{dt} &= \sum_{k \in m \setminus Z} [\nu_i (R_{Z,k}^{H,2} + R_{k,Z}^{H,2})] - R_m^{H^{vo},2}(\mu_d^{H,2} + \rho^2 + \sigma^H) \\ \text{where} \quad i &\in \{1, 2, 3, 4, Z\} \setminus m. \end{aligned} \tag{A.30}$$

If the vaccination is perfect they enter into one of two compartments. For individuals who have never experienced a Zika infection:

$$\begin{aligned} m &= \{1, 2, 3, 4\} \\ \frac{dR_m^{H^{vo},2}}{dt} &= \sum_{i=1}^{4} [(\nu_i + \nu_\emptyset)(S_i^{H,2} + R_i^{H,2})] + \sum_{i \in m} \gamma_i I_{n,i}^{H^{vo},2} - R_m^{H^{vo},2}(\mu_d^{H,2} + \rho^2 + \sigma^H) \\ \text{where } n &= m \setminus i. \end{aligned} \tag{A.31}$$

If they have experienced a previous Zika infection, they enter into the $R_{1,2,3,4,Z}^{H^{vo},2}$ compartment as described in Equation A.15.

If vaccination occurs during recovery from a second, third, or fourth dengue infection, individuals pass to a compartment that is completely immune or temporarily immune to Zika, depending on whether or not they have experienced a Zika infection.

Appendix A. Full Model Equations

For those who have never experienced a Zika infection

$$m = \{1, 2, 3, 4\}$$
$$\frac{dR_m^{H^{vt},2}}{dt} = \sum_{k \subseteq m} [\epsilon(S_k^{H,2} + R_k^{H,2})] - R_m^{H^{vt},2}(\mu_d^{H,2} + \rho^2 + \sigma^H). \tag{A.32}$$

Note: in this case k always has two or more elements.

If they have experienced a previous Zika infection, they enter into the $R_{1,2,3,4,Z}^{H^{vt},2}$ compartment as described in Equation A.18.

Post-Vaccination Age Group (Age Group 3)

Finally, the vaccination age group ages into the post-vaccination age group, which can experience infections according to their susceptibility, and can die. The post-vaccine age group remains categorized into four different sets of compartments: unvaccinated, vaccinated while dengue naïve, vaccinated after one dengue infection, vaccinated after two or more infections. For simplicity we present them all together as age group $\{H, 3\}$. This simplification is possible because although the groups are separated, they are also symmetrical, e.g. $S_1^{H,3}$ behaves similarly to $S_1^{H^{vo},3}$, because no vaccination is occurring in this compartment.

For those individuals in age group three who are naïve to dengue

$$\frac{dS_\emptyset^{H,3}}{dt} = \rho^2 S_\emptyset^{H,3} - \mu_d^{H,3} S_\emptyset^{H,3} - \sum_{j \in i} S_\emptyset^{H,3} \frac{\beta_h^H I_h^V}{N^H} \tag{A.33}$$

where $i = \{1, 2, 3, 4, Z\}$.

After a host has experienced a primary infection, they eventually pass to a compartment susceptible to a second or greater infection as described by

$$\begin{aligned} &\forall m \subseteq \{1,2,3,4,Z\} \\ &\frac{dS_m^{H,3}}{dt} = \rho^2 S_m^{H,3} + \sigma^H R_m^{H,3} - \mu_d^{H,3} S_i^{H,3} - \sum_{j\in i} S_m^{H,3} \frac{\beta_j^H I_j^V}{N^H} \\ &\quad \text{where } i = \{1,2,3,4,Z\} \setminus \{m\}. \end{aligned} \tag{A.34}$$

Similar to hosts in the first age group, once individuals in these compartments are infected, they pass through exposed, infectious, and recovered compartments before either returning to a different susceptible compartment, or becoming completely recovered for all viruses in the model. Recall that m represents the infection history of individuals in the compartment, and i is the most recent infection individuals in that compartment have experienced.

$$\begin{aligned} &\forall i \in \{1,2,3,4,Z\} \\ &\forall m \subseteq \{1,2,3,4,Z\} \setminus i \\ &\frac{dE_{m,i}^{H,3}}{dt} = \rho^2 E_{m,i}^{H,2} + S_m^{H,3} \frac{\beta_i^H I_i^V}{N^H} - E_{m,i}^{H,3}(\mu_d^{H,3} + \alpha_i^{H,3}) \end{aligned} \tag{A.35}$$

$$\frac{dI_{m,i}^{H,3}}{dt} = \rho^2 I_{m,i}^{H,2} + \alpha_i^{H,3} E_{m,i}^{H,3} - I_{m,i}^{H,3}(\mu_d^{H,3} + \gamma_i^{H,3}) \tag{A.36}$$

$$\frac{dR_n^{H,3}}{dt} = \rho^2 R_n^{H,2} + \sum_{i\in n} \gamma_i^H I_{m,i}^{H,3} - R_n^{H,3}(\mu_d^{H,3} + \sigma^H) \tag{A.37}$$

where $n = m \cup i$.

As they become infected with every serotype and Zika, hosts enter into the fully recovered compartment $R_{\{1,2,3,4,Z\}}^{H,3}$ where they will remain until death.

$$\begin{aligned} &n = \{1,2,3,4,Z\} \\ &\frac{dR_n^{H,3}}{dt} = \rho^2 R_n^{H,2} + \sum_{i\in n} \gamma_i I_{m,i} - \mu_d^{H,3} R_n^{H,3} \end{aligned} \tag{A.38}$$

where $m = n \setminus i$.

Appendix B

Supplementary Figures

Appendix B. Supplementary Figures

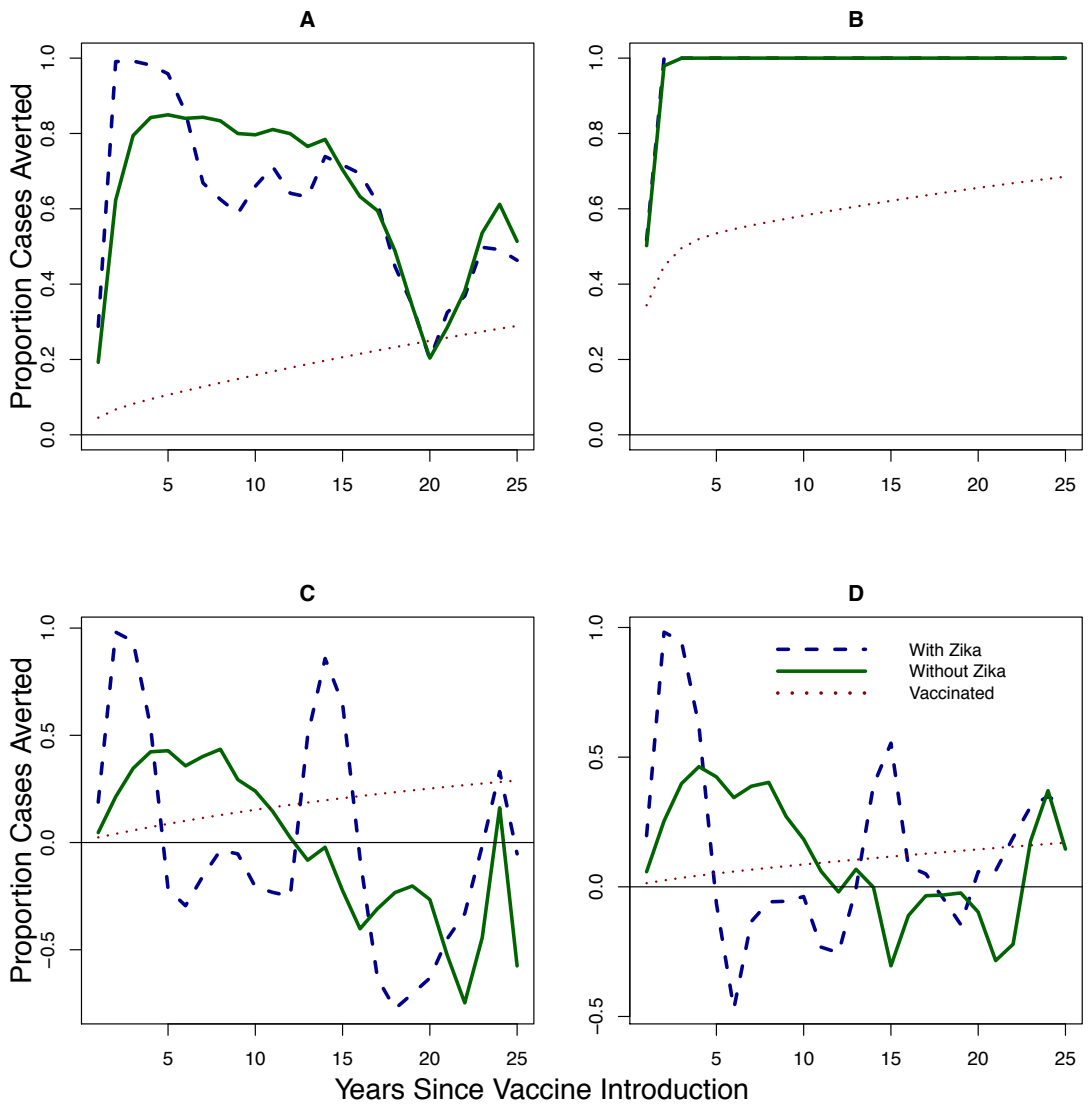

Figure B.1: Average proportion of cases averted through vaccination in the presence and absence of ZIKV over 25 years (when $\beta^H = \beta^V = 0.303$, $R_0 \approx 4.5$). The graphs also show the proportion of the total population that is vaccinated in each case (represented by the dotted red line). (A) Vaccination of 80% of 9-15 year olds. (B) Vaccination of 80% of 9-45 year olds. (C) The same proportion of the total population vaccinated as in 3.1A, but the vaccination age group is 9-45 y.o. (D) Vaccination of 50% of 9-15 year olds.

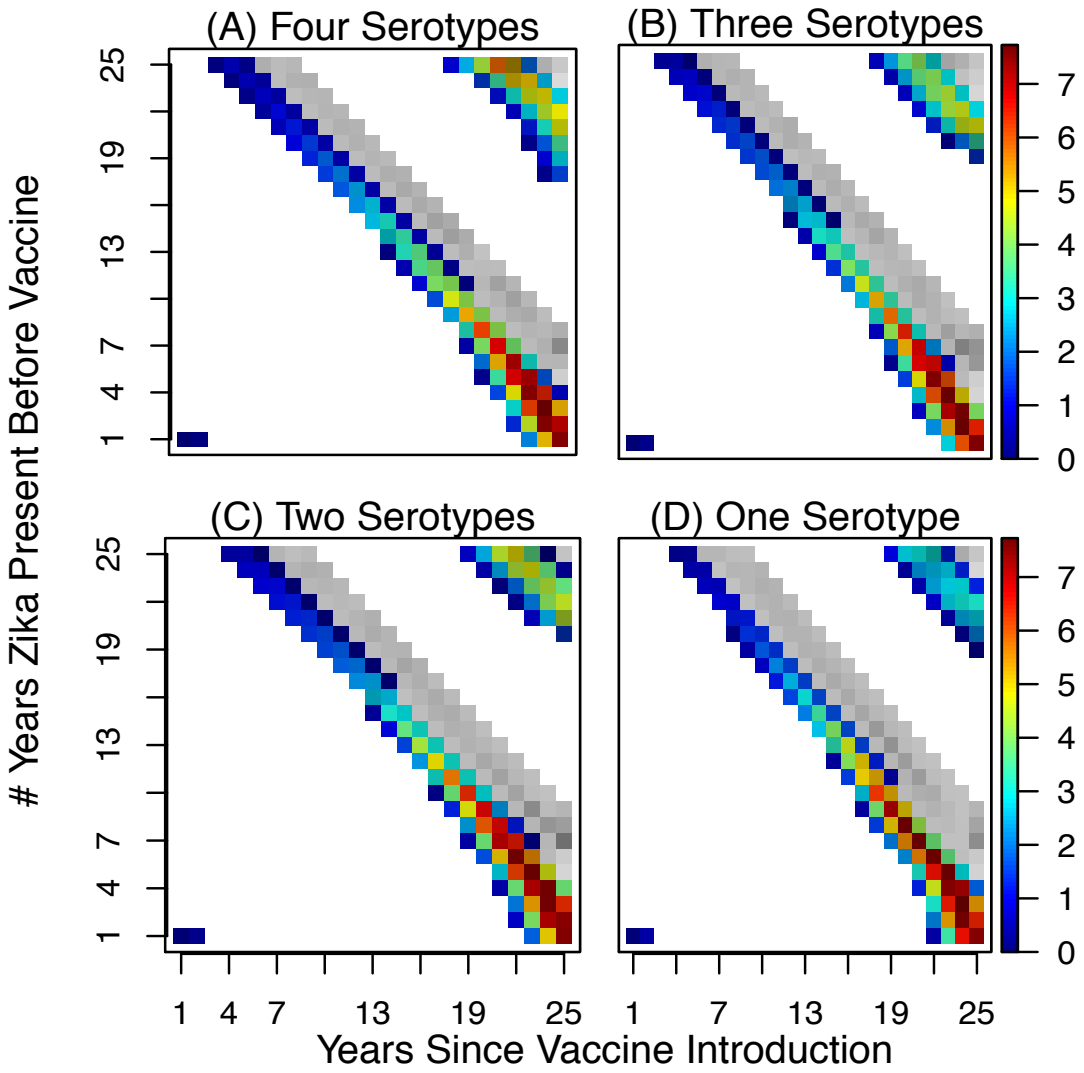

Figure B.2: Change in Zika incidence due to dengue vaccination over time, relative to timing of vaccine deployment (when $\beta^H = \beta^V = 0.303$, $R_0 \approx 4.5$). Each panel represents model output where a different number of dengue serotypes co-circulate with Zika. The x-axis represents how many years have elapsed since the vaccine was introduced. Each row along the y-axis corresponds to a different scenario in which the number of years that ZIKV was present before the vaccine was implemented is varied. The colors correspond to the log of the proportion change in incidence (i.e. $\log_{10}(\frac{\text{Cases with vaccine}}{\text{Cases without vaccine}})$), e.g. a value of one represents a year in which there were ten times more cases in the presence of the vaccine. Grey-scale squares represent years that would see a decrease in Zika infections in the presence of dengue vaccine. White squares indicate that the model predicts less than one case in both the vaccine and no vaccine scenarios.

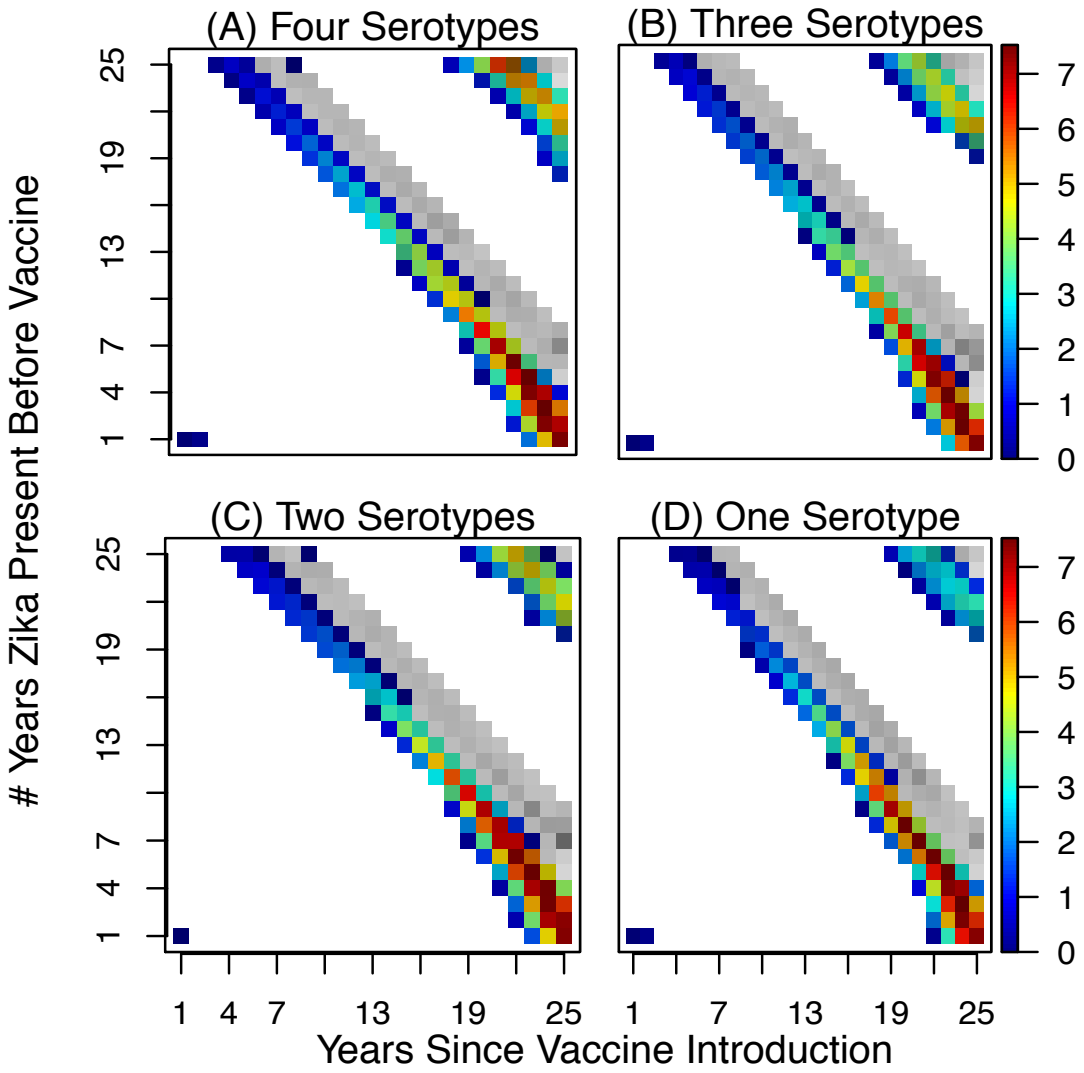

Figure B.3: Change in secondary Zika incidence due to dengue vaccination over time, relative to timing of vaccine deployment (when $\beta^H = \beta^V = 0.303, R_0 \approx 4.5$). Each panel represents model output where a different number of dengue serotypes co-circulate with Zika. The x-axis represents how many years have elapsed since the vaccine was introduced. Each row along the y-axis corresponds to a different scenario in which the number of years that ZIKV was present before the vaccine was implemented is varied. The colors correspond to the log of the proportion change in incidence (i.e. $\log_{10}(\frac{\text{Cases with vaccine}}{\text{Cases without vaccine}})$), e.g. a value of one represents a year in which there were ten times more cases in the presence of the vaccine. Grey-scale squares represent years that would see a decrease in Zika infections in the presence of dengue vaccine. White squares indicate that the model predicts less than one case in both the vaccine and no vaccine scenarios.

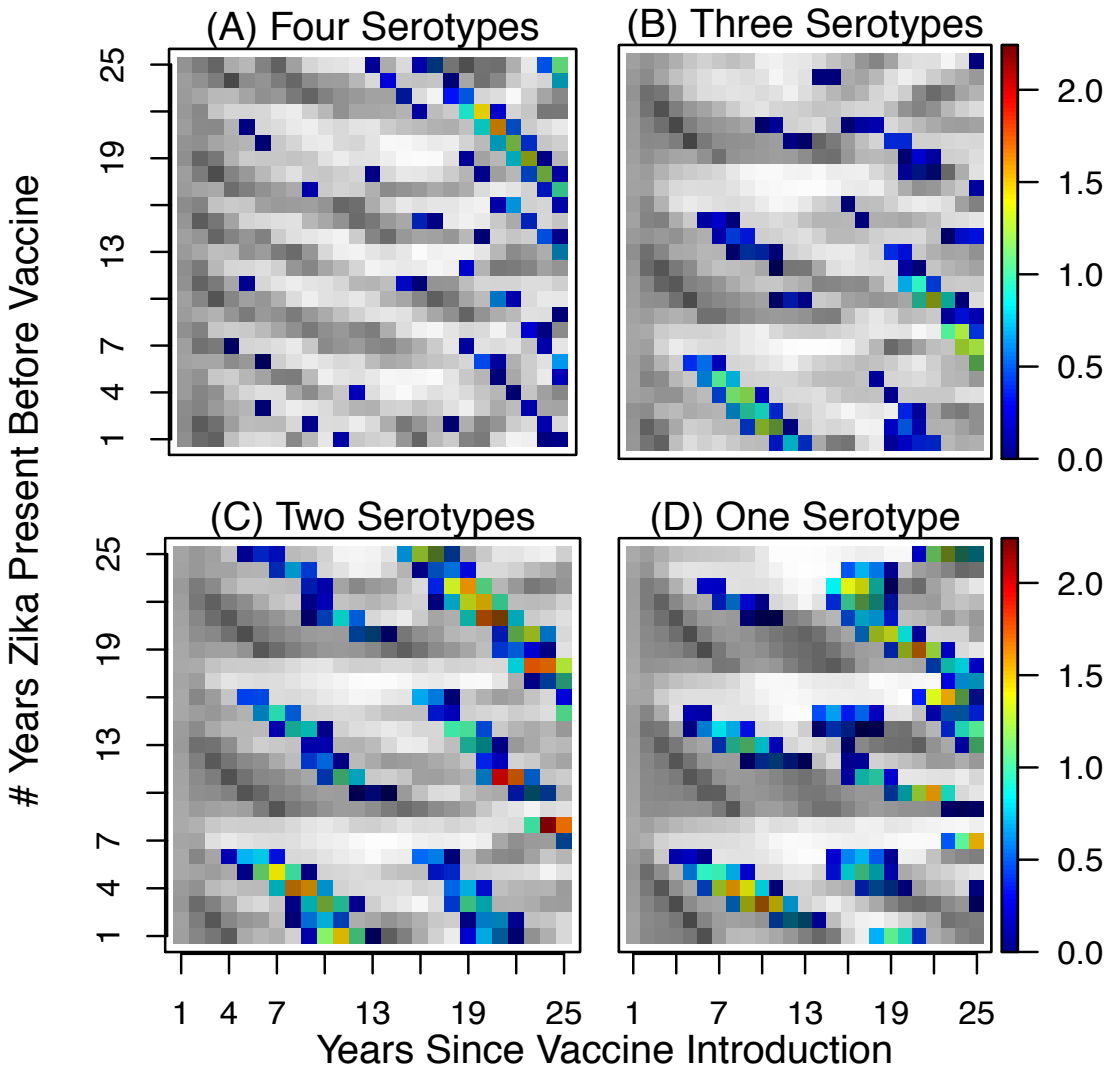

Figure B.4: Change in secondary dengue due to dengue vaccination over time, relative to timing of vaccine deployment (when $\beta^H = \beta^V = 0.303$, $R_0 \approx 4.5$). Each panel represents model output where a different number of dengue serotypes co-circulate with Zika. The x-axis represents how many years have elapsed since the vaccine was introduced. Each row along the y-axis corresponds to a different scenario in which the number of years that ZIKV was present before the vaccine was implemented is varied. The colors correspond to the log of the proportion change in incidence (i.e. $\log_{10}(\frac{\text{Cases with vaccine}}{\text{Cases without vaccine}})$), e.g. a value of one represents a year in which there were ten times more cases in the presence of the vaccine. Grey-scale squares represent years that would see a decrease in Zika infections in the presence of dengue vaccine. White squares indicate that the model predicts less than one case in both the vaccine and no vaccine scenarios.

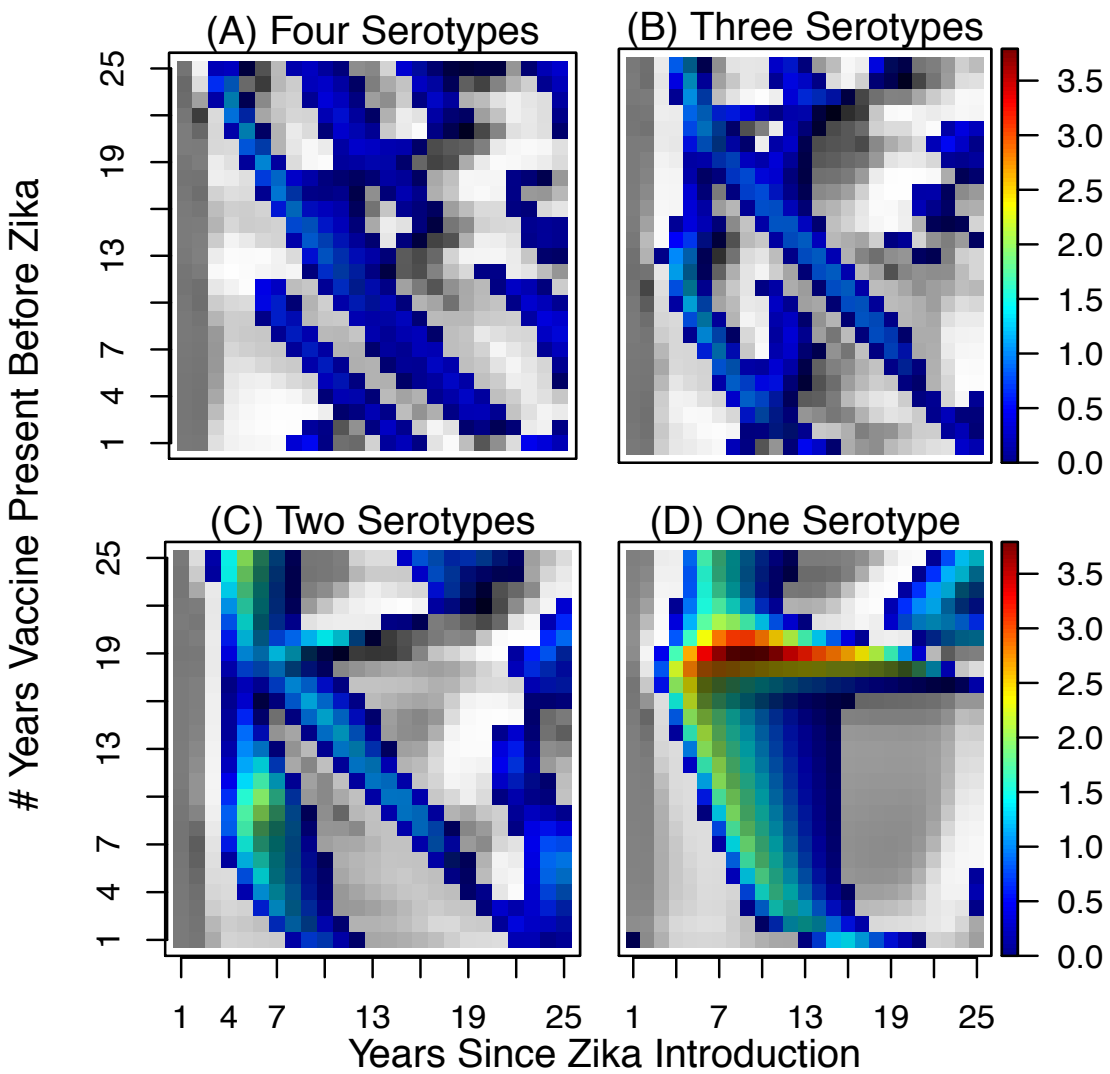

Figure B.5: Change in secondary dengue due to dengue vaccination over time, relative to timing of Zika introduction (when $\beta^H = \beta^V = 0.303$, $R_0 \approx 4.5$). Note: here vaccination is begun before Zika is introduced into a population. Each panel represents model output where a different number of dengue serotypes co-circulate with Zika. The x-axis represents how many years have elapsed since ZIKV was introduced. Each row along the y-axis corresponds to a different scenario in which the number of years that vaccination was occurring before the Zika was introduced is varied. The colors correspond to the log of the proportion change in incidence (i.e. $\log_{10}(\frac{\text{Cases with vaccine}}{\text{Cases without vaccine}})$), e.g. a value of one represents a year in which there were ten times more cases in the presence of the vaccine. Grey-scale squares represent years that would see a decrease in Zika infections in the presence of dengue vaccine. White squares indicate that the model predicts less than one case in both the vaccine and no vaccine scenarios.

Appendix C

Demography Table

Age Group	Percent of Total Population	Birth rate	Death rate
0-8	16.4%	0	0.00004479452 day^{-1}
9-15	8.3%	0	0.00001687671 day^{-1}
$\geq$16	75.3%	0.0000603 day^{-1}	0.0000443562 day^{-1}
0-8	16.4%	0	0.00004479452 day^{-1}
9-45	54.9%	0.0000853 day^{-1}	0.00000872603 day^{-1}
$\geq$45	28.7%	0.000013 day^{-1}	0.0000843562 day^{-1}

Table C.1: Initial population parameters. Adapted from CIA World Fact Book for Brazil: https://www.cia.gov/library/publications/the-world-factbook/geos/br.html

Appendix D

Calculation of Basic Reproductive Number

Wearing & Rohani 2006 [65] pose a formula for calculating the basic reproductive number for a multi-serotype model of dengue. The original formula is:

$$R_{0i} = \frac{kp_i q_i b^2 \sigma_H \sigma_V}{\mu_v(\gamma_i + \mu_H)(\sigma_H + \mu_H)(\sigma_V + \mu_V)} \tag{D.1}$$

where k is the Vector/Host ratio, $q_i b = p_i b$ is the transmission rate, $\frac{1}{\sigma_H}$ is the intrinsic incubation period, $\frac{1}{\sigma_V}$ is the extrinsic incubation period, μ_v is the vector recruitment rate, $\frac{1}{\gamma_i}$ is the infectious period for hosts, and μ_H is the recruitment rate for hosts.

Which in the current model translates to

$$R_{0i} = \frac{\beta_i^H \beta_i^V \alpha_i^H \alpha_i^V}{\mu_V(\gamma_i^H + \mu_d^H)(\alpha_i^H + \mu_b^H)(\alpha_i^V + \mu_V)}. \tag{D.2}$$

Rearranging this formula yields

$$\beta_i^H \beta_i^V = R_{0i} \frac{\mu_V(\gamma_i^H + \mu_d^H)(\alpha_i^H + \mu_b^H)(\alpha_i^V + \mu_V)}{\alpha_i^H \alpha_i^V}. \tag{D.3}$$

Appendix D. Calculation of Basic Reproductive Number

Assuming $\beta_i^H = \beta_i^V$ gives

$$\beta_i^H = \sqrt{R_{0i} \frac{\mu_V(\gamma_i^H + \mu_d^H)(\alpha_i^H + \mu_b^H)(\alpha_i^V + \mu_V)}{\alpha_i^H \alpha_i^V}}. \tag{D.4}$$

So for $R_0 = 3$

$$\beta_i^H = 0.247$$

and for $R_0 = 4.5$

$$\beta_i^H = 0.303.$$

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