Impact of tetravalent dengue vaccination with screening, ADE, and altered infectivity on single-serotype dengue and Zika transmission

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December 28, 2022

Abstract

Acquired immunity to a dengue virus serotype (whether by infection or the only licensed dengue vaccine) can produce antibody-dependent enhancement (ADE) in later infections with another dengue serotype, resulting in higher viral loads and more severe symptoms such as dengue hemorrhagic fever, unless the person already has immunity to multiple dengue serotypes. Screening to confirm dengue seropositivity is therefore recommended before vaccination. Recent studies suggest that the closely-related Zika virus may also interact with dengue through ADE. This study uses a mathematical model to evaluate the likely impact of imperfect screening and dengue vaccination on the spread of both viruses in a population where only one dengue serotype circulates, although the vaccine may take against any or all of the four recognized serotypes. Analysis focuses on the reproductive numbers of the viruses. Results indicate that vaccination increases the spread of Zika through induced ADE, while its impact on the spread of dengue depends on screening specificity and serotype-specific vaccine efficacies, as well as the intensity of ADE. Numerical analysis identifies the roles played by age-in and catch-up vaccination as well as screening characteristics and prior dengue exposure.

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Keywords: antibody-dependent enhancement, serotype-specific efficacy, invasion reproductive number, dual outbreak, dynamical systems model

MSC2020: 92D30

Acknowledgments

CK acknowledges travel support from his home institution.

This is a peer reviewed, accepted author manuscript of the following research article: Kribs, C., & Greenhalgh, D. (Accepted/In press - 02 April 2023). Impact of tetravalent dengue vaccination with screening, ADE and altered infectivity on single-serotype dengue and Zika transmission. *Journal of Mathematical Biology*.

1 Introduction

More than half the population of the world is at risk for mosquito-borne diseases. Vector-borne diseases cause more than 700,000 deaths each year, and factors such as climate change and rapid urbanization in developing countries are causing their incidence to rise dramatically. The dengue virus alone accounts for an estimated 100 million cases per year, with nearly 4 billion people in over 120 countries at risk of contracting it [3, 30]. Dengue is carried primarily by the mosquito *Aedes aegypti*, which also transmits chikungunya, yellow fever and Zika viruses. Acute infection with these viruses causes some symptoms common to respiratory infections, but more severe cases of dengue fever (DF) can develop into *dengue hemorrhagic fever* (DHF) or *dengue shock syndrome* (DSS), which can be fatal. Zika can cause serious complications such as Guillain-Barré syndrome and congenital Zika syndrome typically involving microcephaly [4, 31]. Since no direct treatment has been known for these infections (an antiviral treatment for dengue is currently in development), the main focus in limiting the spread of these neglected tropical diseases has historically been vector control, as was the case with malaria over a century ago.

In many places, several of these viruses circulate together, and coinfection is not uncommon (e.g., [22, 26]). A phenomenon known as antibody-dependent enhancement (ADE) has recently been identified as a primary factor causing interplay between the infection history of a person and his susceptibility to infection by a different virus. Upon recovery from infection with one of these viruses, the immune system of a person continues to produce antibodies granting immunity against reinfection by the same serotype. However, these same antibodies have the effect of facilitating later infection by related viruses; this is a well-known problem with dengue, for which four different serotypes (Dengue virus, DENV-1 through 4) are known to infect humans. ADE causes the viral load of a person to multiply faster and more easily. Secondary dengue infections are therefore often more severe, requiring hospitalization and leading to DHF. In recent years, ADE has also been verified (*in vitro*, and *in vivo* in mice and macaques) between dengue and Zika (see [26] and references therein), which are closely related viruses. Recovery from a secondary dengue infection typically broadens the immune response enough that a third or fourth dengue infection is generally minor. An effect similar to ADE has also been observed in mosquitoes coinfected with dengue and either Zika or chikungunya, within which direct interactions between viruses produce altered viral loads, affecting infectivity (see [5, 17] and references therein). Specifically, Chaves et al. observed a higher dengue viral load and a reduced Zika viral load in coinfected mosquitoes.

A vaccine recently developed for dengue, CYD-TDV (Dengvaxia produced by Sanofi-Pasteur), has shown varying efficacies against the four subtypes [2, 28], but also has the effect of acting like a "silent infection" [14], advancing the immunological count of dengue infections of a person by one. Thus seronegative individuals (i.e., never exposed to dengue) who become vaccinated then act immunologically like those infected once; if the vaccine fails, the resulting infection may be severe. Individuals seropositive to one type, meanwhile, have their immune counts raised to two by vaccination which is successful against at least one other serotype, making any subsequent infections (vaccine failure) typically minor. This news has led to much debate regarding the use of Dengvaxia, especially since, in high-transmission regions, seronegative individuals are often the very young. Immunological screening is now recommended prior to vaccination [23], but such tests are not yet readily accessible in many affected areas. In regions of high dengue endemicity where universal screening for prior exposure is not possible, it has been recommended to vaccinate only above a certain cutoff age, typically age 9, by which point individuals are likely to have had exposure. The effects of ADE also mean that Dengvaxia (like a prior dengue infection) can affect the risk of a person for infection by Zika.

A few mathematical modeling studies have already studied the impact of dengue vaccination

without screening on the cocirculation of dengue and Zika [19, 24, 25, 29]. Tang et al. found that under a high mosquito birth rate, dengue vaccination (incorporated through initial conditions) led to higher Zika prevalence and a higher, earlier peak prevalence [24]. They also found that when simultaneous dengue-Zika coinfection is possible, low levels of dengue vaccination should reduce Zika incidence because, by reducing dengue infections in the vaccinated, it prevents some unvaccinated individuals from developing dengue infections which would later produce ADE [25]. Okuneye et al. considered a different scenario with a dengue-chikungunya-Zika superinfection hierarchy in which dengue vaccination also offers some protection against Zika infection, and ADE increases the susceptibility to Zika infection of those recovered from dengue [19]. Their analysis focuses on seasonal temperatures that maximize transmission. Wang and Zhao similarly considered ADE to affect susceptibility rather than infectivity, and vectors not to be able to be coinfected [29]. They also considered perfect vaccine efficacy. They then found the basic reproductive number (BRN) of Zika to increase monotonically with the vaccination rate. All of these studies also considered only one dengue serotype, but even in settings where only one serotype is circulating, it is important to consider the other serotypes when evaluating vaccine "take". (For instance, Tang et al. [25] did not consider the ADE induced in secondary dengue infections by prior primary dengue infections by a different serotype.) The two which considered ongoing vaccination also considered implicitly that individuals in whom the vaccine failed remained equally likely to seek vaccination again.

España et al. instead used an agent-based model to study the impact of (imperfect) screening and vaccination on dengue transmission alone [8]. In addition to numerous additional individual-level details such as body size and spatial location, they considered age- and serostatus-dependent vaccine efficacy for a "leaky" vaccine with per-exposure protection applied at age nine. They observed that screening specificity is important in low-transmission settings, while screening sensitivity is most important in high-transmission settings. They also estimated cost-effectiveness and found that screening and vaccination are only cost-effective in areas with high dengue transmission and GDP and where screening and vaccination are cheap.

The present study aims to integrate these different factors in order to measure how the WHO-recommended screening prior to dengue vaccination impacts the transmission of both dengue and Zika virus (ZIKV). Imperfect screening and vaccination, the tetravalence of the vaccine, coinfection in both hosts and vectors, and bidirectional ADE in hosts as well as altered infectivity in coinfected mosquitoes all play important roles here. We consider a setting with ZIKV and one DENV serotype cocirculating, where both ADE in hosts and viral interactions within vectors affect the infectivities of hosts and vectors with secondary infections (from either virus), and where screening for dengue seropositivity is required prior to vaccination. In such a setting, does a tetravalent vaccine (considering "take" separately for each serotype) like Dengvaxia increase or decrease the combined ability of the two viruses to spread? We address this question through a mathematical model which takes into account the effects of a tetravalent vaccine which may "take" against one or more noncirculating DENV serotypes. Reproductive numbers provide one way to measure and compare the ability of pathogens to spread, and also in this case the role played (for both viruses) by altered infectivity due to ADE in hosts or viral interactions within vectors.

2 Model development

We consider a deterministic compartmental model which classifies host and vectors by infection status for both dengue and Zika and also classifies hosts by vaccination status: vaccine "take" (development of protective antibodies) is evaluated independently for each dengue serotype, and individuals who (after screening as seropositive) receive a vaccine do not seek vaccination again

regardless of the outcome (which they are assumed not to know), while individuals identified (correctly or not) as seronegative by screening may try again later. Only one dengue serotype (DENV-j for a given $j \in \{1, 2, 3, 4\}$) is assumed to circulate locally. We use an SIR structure for hosts and an SI structure for vectors, for both pathogens, allowing coinfection.

This produces four compartments for vectors and, in conjunction with vaccination status (unvaccinated, vaccinated without "take" against a noncirculating serotype, or with "take" against a noncirculating serotype) twenty-seven compartments for hosts (in this regard it is an extension of the structure in [24]). Note that nine pairs of human classes are distinguishable only by whether they have received a vaccine, not by immune status; vaccinated individuals will not seek further vaccination. Vaccine protection against a noncirculating dengue serotype is relevant because it advances the immune count of the body by one and can thus either cause ADE in a subsequent infection or (in conjunction with immunity against the circulating serotype) prevent it in hypothetical subsequent dengue infections. Numerical subscripts in compartment names indicate the number of (dengue) serotypes against which individuals in a given class have developed antibodies: "1" refers to the circulating serotype DENV-j, "2" means two or more (assumed enough to prevent further clinical infection by any DENV serotype), and ω refers to any single noncirculating serotype. Definitions for each compartment are given in Table 1, and a flow chart in Figure 1.

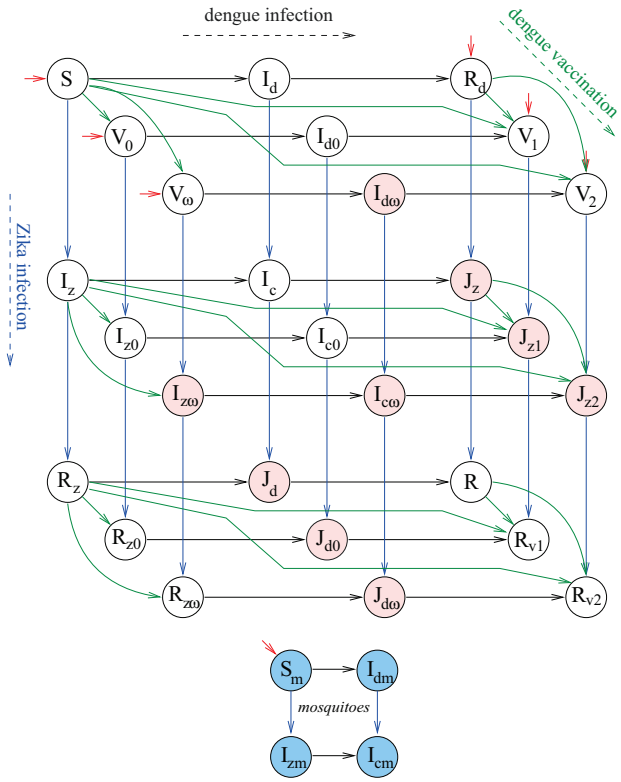

Figure 1: Transitions in the compartmental model. Transitions to the right (black) within each grid represent dengue infection and recovery. Transitions downward (blue) represent Zika infection and recovery. Diagonal (green) transitions represent vaccination results; short (red) arrows denote entry into the study population. For simplicity, mortality (departure from the study population) in each class is not shown.

We next outline the primary assumptions underlying the model.

- Humans enter the study population (at age nine) with a fixed dengue seropositivity rate α (for

Variable	Definition
unvaccinated individuals	
S	susceptible, unvaccinated population
I_d	unvaccinated DENV-j infectives who have not had Zika
R_d	unvaccinated, recovered from DENV-j, have not had Zika
I_z	unvaccinated Zika infectives who have not had dengue
I_c	unvaccinated coinfectives (DENV-j and Zika)
J_z	unvaccinated Zika infectives, recovered from DENV-j †
R_z	unvaccinated, recovered from Zika, have not had dengue
J_d	unvaccinated DENV-j infectives, recovered from Zika †
R	unvaccinated, recovered from both DENV-j and Zika
vaccinated individuals unprotected against nonlocal serotypes	
V_0	susceptibles in whom the vaccine completely failed to take ("unprotected")
I_{d0}	unprotected vaccinated DENV-j infectives who have not had Zika
V_1	vaccinated, and recovered or protected only from DENV-j, have not had Zika
I_{z0}	unprotected vaccinated Zika infectives who have not had dengue
I_{c0}	unprotected vaccinated coinfectives (DENV-j and Zika)
J_{z1}	vaccinated Zika infectives, recovered or protected only from DENV-j †
R_{z0}	unprotected vaccinated, recovered from Zika, have not had dengue
J_{d0}	unprotected vaccinated DENV-j infectives, recovered from Zika †
R_{v1}	vaccinated, recovered or protected from both DENV-j and Zika
vaccinated individuals protected against one or more nonlocal serotypes	
V_ω	susceptibles in whom vaccination took against one nonlocal serotype
$I_{d\omega}$	vaccinated DENV-j infectives (protected vs. one nonlocal serotype) who are Zika-naïve †
V_2	vaccinated, protected against two or more serotypes, have not had Zika
$I_{z\omega}$	vaccinated Zika infectives (protected vs. one nonlocal serotype) who are dengue-naïve †
$I_{c\omega}$	vaccinated coinfectives (DENV-j and Zika) protected vs. one nonlocal serotype †
J_{z2}	vaccinated Zika infectives, protected against two or more serotypes †
$R_{z\omega}$	vaccinated, recovered from Zika, protected against one nonlocal serotype
$J_{d\omega}$	vaccinated DENV-j infectives, protected vs. one nonlocal serotype, recovered from Zika †
R_{v2}	vaccinated, recovered from Zika and protected against two or more serotypes
mosquitoes	
S_m	uninfected (female adult) mosquitoes
I_{dm}	mosquitoes carrying DENV-j
I_{zm}	mosquitoes carrying Zika virus
I_{cm}	mosquitoes carrying DENV-j and Zika

Table 1: State variables. Variables refer to human populations except as noted. "Serotype" refers to DENV. DENV-j refers to the circulating serotype. † denotes populations experiencing ADE.

the circulating serotype). No one enters the study population infected (individuals infected on their ninth birthdays should be considered to enter the study population before or after the infection, since doing otherwise interferes with model analysis) or Zika-seropositive (since Zika is assumed not to be endemic to the area).

- Recovery from natural infection confers permanent immunity to that pathogen/serotype, but also causes ADE with regard to any other closely related pathogen(s) not yet encountered. ADE and primary immunity only arise following recovery from a given pathogen (or vacci-

nation), so do not affect secondary infections (coinfections) before recovery from the primary infection.

- ADE occurs when an individual with dengue "immune count" of 1 becomes infected (with a serotype against which she or he has no immunity). Any positive dengue "immune count" causes ADE of Zika. Recovery from Zika causes ADE of dengue for those with "immune count" 0 or 1.

- ADE is assumed to increase infectivity (upon subsequent infection) but not susceptibility to infection.

- Vaccination may confer (complete) protection against a given dengue serotype by "taking" (inducing the production of serotype-specific antibodies) in a given individual. Whether a vaccination "takes" for one serotype in that individual is independent of whether it "takes" for other serotypes. Each "take" advances the "immune count" of the body to dengue by one (unless the individual was already immune to that serotype) and is assumed to provide complete protection against infection by the given serotype (so-called "all-or-nothing" vaccination) identical to that provided by natural recovery.

- Vaccination after screening can occur either upon entry into the age range of the study (a proportion p seek it) or on an ongoing basis (at rate ϕ among the nine unvaccinated classes). Individuals recovered from dengue may still be vaccinated, as the vaccine is tetravalent. We assume that 100% of vaccinees comply with the full vaccination schedule of three doses over 12 months.

- Anyone seeking vaccination must first be screened for dengue seropositivity. Dengue screening (with a given sensitivity ψ and specificity χ) may involve a combination of antigen (e.g. NS1) and antibody (e.g. IgM) tests and is not serotype-specific. Screening can thus detect active dengue infections, even when asymptomatic (but no Zika infections). Only individuals who screen as dengue-seropositive without active infections will be vaccinated. Individuals with active Zika infections who pass dengue screening can be vaccinated and develop protective antibodies.

- Vaccination does not change the infection-related behaviour (or infectivity) of an individual. Vaccinated individuals do not seek re-vaccination. Individuals do not know their infection history except through screening (they may know they have been sick, but not what it was). Vaccinated status is assumed permanent (no waning). Vaccination has no other therapeutic effect.

- The incubation period in both humans and mosquitoes prior to becoming infectious is ignored, to focus the complexity on immune interactions in hosts.

- Vectors are assumed to be permanent carriers of any pathogen they acquire (no clearance).

- Vectors carrying both pathogens are assumed to have altered viral loads: specifically, a higher dengue viral load and a reduced Zika viral load.

- To simplify, sexual transmission of Zika is not considered.

- Since dengue and Zika have case fatality ratios of well under 1% (mostly under 0.1% for dengue in 2022, e.g., [9], and under 0.01% for Zika), disease-related deaths do not significantly affect infectious contact rates (other than removal of the deceased from infectious classes) or

population size. Disease-related deaths are therefore neglected to maintain model tractability: with births and deaths equal, host and vector populations are constant.

The resulting dynamical system is given by a system of ordinary differential equations which include the following five types of terms:

Ongoing screening and vaccination at rate ϕ, for unvaccinated hosts. Only those screened as dengue-seropositive (which depends on sensitivity ψ for seropositives and on specificity *failure* $1-\chi$ for seronegatives) go on to be vaccinated, and the results of vaccination depend on the "take" proportions η_i $(i = 1, ..., 4)$: Vaccinated seronegatives receive no protection in proportion $a_0 = \prod_{i=1}^{4}(1-\eta_i)$, protection against only the local serotype j in proportion $a_1 = \eta_j \prod_{i\neq j}(1-\eta_i)$, protection against only one nonlocal serotype in proportion $a_\omega = \sum_{k\neq j}\eta_k \prod_{i\neq k}(1-\eta_i)$, and protection against two or more serotypes in proportion $a_2 = 1-a_0-a_1-a_\omega$. Vaccinated seropositives receive no new protection in proportion $b_1 = \prod_{i\neq j}(1-\eta_i)$ and protection against at least one nonlocal serotype in proportion $b_2 = 1-b_1$.

Entry into the study population. Children are assumed to become eligible for dengue vaccination (thus entering the study population) at age nine, at which point they may be either seronegative or seropositive to dengue. A routine dengue vaccination program divides new hosts among six compartments $(S, R_d, V_0, V_1, V_\omega, V_2)$ in proportions c_i $(i = 1, ..., 6)$ reflecting screening and vaccination outcomes. $c_1 = (1-\alpha)(1-p(1-\chi))$ includes those entering seronegatives who either do not seek screening or are correctly screened (and thus refused vaccination), $c_2 = \alpha(1-p\psi)$ gives those seropositives who either do not seek screening or are incorrectly screened (and thus refused vaccination), $c_3 = (1-\alpha)p(1-\chi)a_0$ gives those seronegatives who are incorrectly screened and then vaccinated, but the vaccine fails to take against each of the four serotypes, $c_4 = (1-\alpha)p(1-\chi)a_1+\alpha p\psi b_1$ gives those seronegatives incorrectly screened in whom the vaccine takes only against the local (circulating) serotype *and* also seropositives in whom the vaccine fails to take against all three nonlocal serotypes, $c_5 = (1-\alpha)p(1-\chi)a_\omega$ gives those seronegatives incorrectly screened in whom the vaccine takes against only one nonlocal serotype, and finally $c_6 = (1-\alpha)p(1-\chi)a_2 + \alpha p\psi b_2$ gives those seronegatives incorrectly screened in whom the vaccine takes against two or more serotypes *and* those seropositives in whom the vaccine takes against at least one nonlocal serotype.

Natural death, at rates μ_h for hosts and μ_m for vectors. Since both total populations (N_h and N_m) are assumed to be at demographic equilibrium, the total birth rate ($\mu_h N_h$ or $\mu_m N_m$) is equal to the total death rate. For simplicity (and to focus analysis on the vaccination structure) the case fatality ratio (CFR) for both diseases is assumed to be low enough not to affect significantly the population sizes or disease transmissions.

Infection by dengue or Zika, for those hosts or vectors susceptible to it. New infections in hosts occur at rate β_{hd} or β_{hz} multiplied by the proportion of hosts from each of the nine compartments susceptible to that infection and the number of vectors carrying the pathogen, with the infectivity of coinfected mosquitoes adjusted by a factor $(\nu_d > 1, \nu_z < 1)$ reflecting the within-vector interactions between viruses [5]. New infections in vectors occur at rate β_{md} or β_{mz} multiplied by the number of mosquitoes not carrying the given pathogen and the effective proportion T_d/N_h or T_z/N_h of hosts infected with the given pathogen, where

$$T_d = I_d + I_{d0} + I_c + I_{c0} + k_d(J_d + J_{d0} + I_{d\omega} + I_{c\omega} + J_{d\omega}),$$
$$T_z = I_z + I_{z0} + I_c + I_{c0} + k_z(J_z + J_{z1} + I_{z\omega} + I_{c\omega} + J_{z2}),$$

and k_d and k_z reflect increased infectivity from ADE.

Recovery from dengue or Zika, for infected hosts, at per capita rates γ_d and γ_z.

The system is given by the following equations, collectively system (1). Table 2 summarizes parameter definitions.

$$
\begin{aligned}
S' &= c_1\mu_h N_h - \beta_{hd}\frac{S}{N_h}(I_{dm}+\nu_d I_{cm}) - \beta_{hz}\frac{S}{N_h}(I_{zm}+\nu_z I_{cm}) - \phi(1-\chi)S - \mu_h S,\\
I_d' &= \beta_{hd}\frac{S}{N_h}(I_{dm}+\nu_d I_{cm}) - \beta_{hz}\frac{I_d}{N_h}(I_{zm}+\nu_z I_{cm}) - \gamma_d I_d - \mu_h I_d,\\
R_d' &= c_2\mu_h N_h + \gamma_d I_d - \beta_{hz}\frac{R_d}{N_h}(I_{zm}+\nu_z I_{cm}) - \phi\psi R_d - \mu_h R_d,\\
I_z' &= \beta_{hz}\frac{S}{N_h}(I_{zm}+\nu_z I_{cm}) - \beta_{hd}\frac{I_z}{N_h}(I_{dm}+\nu_d I_{cm}) - \gamma_z I_z - \phi(1-\chi)I_z - \mu_h I_z,\\
I_c' &= \beta_{hz}\frac{I_d}{N_h}(I_{zm}+\nu_z I_{cm}) + \beta_{hd}\frac{I_z}{N_h}(I_{dm}+\nu_d I_{cm}) - \gamma_z I_c - \gamma_d I_c - \mu_h I_c,\\
J_z' &= \beta_{hz}\frac{R_d}{N_h}(I_{zm}+\nu_z I_{cm}) + \gamma_d I_c - \gamma_z J_z - \phi\psi J_z - \mu_h J_z,\\
R_z' &= \gamma_z I_z - \beta_{hd}\frac{R_z}{N_h}(I_{dm}+\nu_d I_{cm}) - \phi(1-\chi)R_z - \mu_h R_z,\\
J_d' &= \beta_{hd}\frac{R_z}{N_h}(I_{dm}+\nu_d I_{cm}) + \gamma_z I_c - \gamma_d J_d - \mu_h J_d,\\
R' &= \gamma_z J_z + \gamma_d J_d - \phi\psi R - \mu_h R,\\
V_0' &= c_3\mu_h N_h + \phi(1-\chi)a_0 S - \beta_{hd}\frac{V_0}{N_h}(I_{dm}+\nu_d I_{cm}) - \beta_{hz}\frac{V_0}{N_h}(I_{zm}+\nu_z I_{cm}) - \mu_h V_0,\\
I_{d0}' &= \beta_{hd}\frac{V_0}{N_h}(I_{dm}+\nu_d I_{cm}) - \beta_{hz}\frac{I_{d0}}{N_h}(I_{zm}+\nu_z I_{cm}) - \gamma_d I_{d0} - \mu_h I_{d0},\\
V_1' &= c_4\mu_h N_h + \phi(1-\chi)a_1 S + \phi\psi b_1 R_d + \gamma_d I_{d0} - \beta_{hz}\frac{V_1}{N_h}(I_{zm}+\nu_z I_{cm}) - \mu_h V_1,\\
I_{z0}' &= \phi(1-\chi)a_0 I_z + \beta_{hz}\frac{V_0}{N_h}(I_{zm}+\nu_z I_{cm}) - \beta_{hd}\frac{I_{z0}}{N_h}(I_{dm}+\nu_d I_{cm}) - \gamma_z I_{z0} - \mu_h I_{z0},\\
I_{c0}' &= \beta_{hz}\frac{I_{d0}}{N_h}(I_{zm}+\nu_z I_{cm}) + \beta_{hd}\frac{I_{z0}}{N_h}(I_{dm}+\nu_d I_{cm}) - \gamma_z I_{c0} - \gamma_d I_{c0} - \mu_h I_{c0},\\
J_{z1}' &= \phi(1-\chi)a_1 I_z + \phi\psi b_1 J_z + \beta_{hz}\frac{V_1}{N_h}(I_{zm}+\nu_z I_{cm}) + \gamma_d I_{c0} - \gamma_z J_{z1} - \mu_h J_{z1},\\
R_{z0}' &= \phi(1-\chi)a_0 R_z + \gamma_z I_{z0} - \beta_{hd}\frac{R_{z0}}{N_h}(I_{dm}+\nu_d I_{cm}) - \mu_h R_{z0},\\
J_{d0}' &= \beta_{hd}\frac{R_{z0}}{N_h}(I_{dm}+\nu_d I_{cm}) + \gamma_z I_{c0} - \gamma_d J_{d0} - \mu_h J_{d0},\\
R_{v1}' &= \phi(1-\chi)a_1 R_z + \phi\psi b_1 R + \gamma_z J_{z1} + \gamma_d J_{d0} - \mu_h R_{v1},\\
V_\omega' &= c_5\mu_h N_h + \phi(1-\chi)a_\omega S - \beta_{hd}\frac{V_\omega}{N_h}(I_{dm}+\nu_d I_{cm}) - \beta_{hz}\frac{V_\omega}{N_h}(I_{zm}+\nu_z I_{cm}) - \mu_h V_\omega,\\
I_{d\omega}' &= \beta_{hd}\frac{V_\omega}{N_h}(I_{dm}+\nu_d I_{cm}) - \beta_{hz}\frac{I_{d\omega}}{N_h}(I_{zm}+\nu_z I_{cm}) - \gamma_d I_{d\omega} - \mu_h I_{d\omega},\\
V_2' &= c_6\mu_h N_h + \gamma_d I_{d\omega} + \phi(1-\chi)a_2 S + \phi\psi b_2 R_d - \beta_{hz}\frac{V_2}{N_h}(I_{zm}+\nu_z I_{cm}) - \mu_h V_2,\\
I_{z\omega}' &= \phi(1-\chi)a_\omega I_z + \beta_{hz}\frac{V_\omega}{N_h}(I_{zm}+\nu_z I_{cm}) - \beta_{hd}\frac{I_{z\omega}}{N_h}(I_{dm}+\nu_d I_{cm}) - \gamma_z I_{z\omega} - \mu_h I_{z\omega},\\
I_{c\omega}' &= \beta_{hz}\frac{I_{d\omega}}{N_h}(I_{zm}+\nu_z I_{cm}) + \beta_{hd}\frac{I_{z\omega}}{N_h}(I_{dm}+\nu_d I_{cm}) - \gamma_z I_{c\omega} - \gamma_d I_{c\omega} - \mu_h I_{c\omega},
\end{aligned}
\tag{1}
$$

Parameter	Definition
α	proportion of entering population who are type-j seropositive
p	proportion of incoming population who seek vaccination upon eligibility
ϕ	rate at which unvaccinated, uninfected individuals seek screening for vaccination
χ	screening specificity (proportion of seronegative individuals who screen negative)
ψ	screening sensitivity (proportion of seropositive individuals who screen positive)
η_i	proportion of vaccinated individuals in whom the vaccine "takes" for serotype i
μ_h, μ_m	human and mosquito death rates
β_{hd}, β_{hz}	rates at which mosquitoes infect hosts with dengue or Zika
β_{md}, β_{mz}	rates at which mosquitoes acquire dengue or Zika from hosts
γ_d, γ_z	recovery rate from DENV-j or Zika
k_d, k_z	relative host infectivity for DENV-j or Zika due to ADE
ν_d, ν_z	infectivity adjustment factors for coinfected mosquitoes
N_h, N_m	total human and mosquito population sizes
a_0	proportion of vaccinations which provide no protection
a_1	proportion of vaccinations which "take" against only the circulating serotype j
a_ω	proportion of vaccinations which "take" against only one nonlocal serotype
a_2	proportion of vaccinations which "take" against two or more serotypes
c_1	proportion of entering population dengue-seronegative and unvaccinated
c_2	proportion of entering population dengue-seropositive and unvaccinated
c_3	prop. of entering pop. dengue-seronegative and vaccinated but unprotected
c_4	prop. of entering pop. protected only against the circulating serotype
c_5	prop. of entering pop. protected only against one nonlocal serotype
c_6	prop. of entering pop. protected against two or more serotypes

Table 2: Model parameters, primary and then derived

$$
\begin{aligned}
J'_{z2} &= \phi(1-\chi)a_2 I_z + \phi\psi b_2 J_z + \beta_{hz}\frac{V_2}{N_h}(I_{zm} + \nu_z I_{cm}) + \gamma_d I_{c\omega} - \gamma_z J_{z2} - \mu_h J_{z2},\\
R'_{z\omega} &= \gamma_z I_{z\omega} + \phi(1-\chi)a_\omega R_z - \beta_{hd}\frac{R_{z\omega}}{N_h}(I_{dm} + \nu_d I_{cm}) - \mu_h R_{z\omega},\\
J'_{d\omega} &= \beta_{hd}\frac{R_{z\omega}}{N_h}(I_{dm} + \nu_d I_{cm}) + \gamma_z I_{c\omega} - \gamma_d J_{d\omega} - \mu_h J_{d\omega},\\
R'_{v2} &= \gamma_z J_{z2} + \gamma_d J_{d\omega} + \phi(1-\chi)a_2 R_z + \phi\psi b_2 R - \mu_h R_{v2};\\
S'_m &= \mu_m N_m - \beta_{md}\frac{S_m}{N_h}T_d - \beta_{mz}\frac{S_m}{N_h}T_z - \mu_m S_m,\\
I'_{dm} &= \beta_{md}\frac{S_m}{N_h}T_d - \beta_{mz}\frac{I_{dm}}{N_h}T_z - \mu_m I_{dm},\\
I'_{zm} &= \beta_{mz}\frac{S_m}{N_h}T_z - \beta_{md}\frac{I_{zm}}{N_h}T_d - \mu_m I_{zm},\\
I'_{cm} &= \beta_{mz}\frac{I_{dm}}{N_h}T_z + \beta_{md}\frac{I_{zm}}{N_h}T_d - \mu_m I_{cm}.
\end{aligned}
$$

3 Qualitative analysis

3.1 Reproduction numbers

Following common practice, we begin model analysis by deriving the relevant reproduction numbers, measures of the abilities of the pathogens to spread in various environments. This also requires explicit calculation of various equilibria. Our choice to focus analysis on reproduction numbers and equilibrium values is considered: it permits the identification of qualitative trends—whether certain parameters increase or decrease the spread of the pathogens—in ways that a purely quantitative analysis cannot. We first derive the *control reproductive numbers* (CRNs) for dengue and Zika, identifying the impact of dengue screening and vaccination on the spread of both pathogens. Setting the vaccination parameters p and ϕ to 0 gives the *basic reproductive numbers* (BRNs) as special cases of the CRNs, measuring the abilities of the pathogens to spread in the absence of vaccination. Finally, in cases where the pathogens are able to invade individually, we derive their *invasion reproductive numbers* (IRNs), which measure their abilities to spread in a setting (a single-pathogen endemic equilibrium) where the other pathogen is already resident. To develop these expressions we apply next-generation methods (e.g., [7, 27]), adapting them as necessary (e.g., [18]). Standard references (cited) for these methods tie each reproduction number to the local asymptotic stability of an equilibrium: for the overall CRN of the system (the maximum of the two single-pathogen CRNs) it is the disease-free equilibrium (DFE), while for the IRN of each pathogen it is the equilibrium at which only the other pathogen is endemic. The DFE is locally asymptotically stable (LAS) if and only if the overall CRN is less than 1. As will be shown below, the solo endemic equilibrium of each pathogen exists if and only if the CRN of that pathogen exceeds 1; in this case that equilibrium is LAS if and only if the IRN of the other pathogen is less than 1. No claims regarding global stability are made here, although numerical analysis (omitted here) and the absence of mechanisms (such as fixed delays or nonlinear relapse) known capable of preventing global stability suggest that any given LAS equilibrium is in fact globally stable.

Derivation of the CRN for system (1) begins by identifying the DFE. Setting $I^*_{dm} = I^*_{zm} = 0$ in the equilibrium conditions for system (1) leads to the DFE

$$\frac{S^*}{N_h} = c_1 \frac{\mu_h}{\mu_h + \phi(1-\chi)},\ \frac{R^*_d}{N_h} = c_2 \frac{\mu_h}{\mu_h + \phi\psi},\ \frac{V^*_0}{N_h} = c_1 \frac{\phi(1-\chi)}{\mu_h + \phi(1-\chi)}\, a_0 + c_3,$$

$$\frac{V^*_1}{N_h} = c_1 \frac{\phi(1-\chi)}{\mu_h + \phi(1-\chi)}\, a_1 + c_2 \frac{\phi\psi}{\mu_h + \phi\psi}\, b_1 + c_4,\ \frac{V^*_\omega}{N_h} = c_1 \frac{\phi(1-\chi)}{\mu_h + \phi(1-\chi)}\, a_\omega + c_5,$$

$$\frac{V^*_2}{N_h} = c_1 \frac{\phi(1-\chi)}{\mu_h + \phi(1-\chi)}\, a_2 + c_2 \frac{\phi\psi}{\mu_h + \phi\psi}\, b_2 + c_6,\ S^*_m = N_m,$$

and all other state variables 0, including the Zika recovered classes $R^*_z, R^*, R^*_{z0}, R^*_{v1}, R^*_{z\omega}, R^*_{v2}$ since we assume no one enters the population Zika-seropositive (or infective). Note that in the absence of an ongoing vaccination program ($\phi = 0$), the equilibrium proportions above reduce to the c_i.

The next step is to derive the next-generation matrix (NGM) of the system. This involves forming a vector $\mathbf{x}$ that includes all the infected compartments, and then (to use the notation of van den Driessche and Watmough [27]) separating $d\mathbf{x}/dt$ into two vectors $\mathcal{F}$ and $\mathcal{V}$ such that $\mathcal{F}$ contains all new infection terms entering each class, $\mathcal{V}$ contains all other transitions, and $d\mathbf{x}/dt = \mathcal{F} - \mathcal{V}$. One then defines the matrices $F = d\mathcal{F}/d\mathbf{x}$ and $V = d\mathcal{V}/d\mathbf{x}$, and computes the NGM as FV^{-1}. For system 1 there are eighteen infected classes (fifteen human and three mosquito), leading to an 18×18 NGM. However, substituting in the DFE zeroes out seven of the rows: the four corresponding to the coinfected classes, since without simultaneous coinfection events, the compartments from

which coinfected classes draw are empty at the DFE; and the three corresponding to the J_{d*} classes (infected with dengue, recovered from Zika), since those draw from either coinfected classes or Zika-recovered classes–of which there are assumed to be none at the DFE. Details of the computation are shown in Appendix A.1.

The CRN of the system is then the dominant eigenvalue of the NGM, namely $\mathcal{R}_c = \max(\mathcal{R}_d, \mathcal{R}_z)$, where

$$\mathcal{R}_d = \sqrt{\frac{\beta_{hd}\frac{N_m}{N_h}}{\mu_h+\gamma_d}\,\frac{\beta_{md}}{\mu_m}\,\frac{S^*+V_0^*+k_dV_\omega^*}{N_h}} = \sqrt{\frac{\beta_{hd}\frac{N_m}{N_h}}{\mu_h+\gamma_d}\,\frac{\beta_{md}}{\mu_m}\left[c_1\frac{\mu_h+\phi(1-\chi)(a_0+k_da_\omega)}{\mu_h+\phi(1-\chi)}+c_3+k_dc_5\right]},$$

$$\mathcal{R}_z = \sqrt{\frac{\beta_{hz}\frac{N_m}{N_h}}{\mu_h+\gamma_z}\,\frac{\beta_{mz}}{\mu_m}\,\frac{q_0S^*+V_0^*+k_z(R_d^*+V_1^*+V_\omega^*+V_2^*)}{N_h}},$$

$$\text{and } q_0 = \frac{\mu_h+\gamma_z}{\mu_h+\gamma_z+\phi(1-\chi)} + \frac{\phi(1-\chi)}{\mu_h+\gamma_z+\phi(1-\chi)}\left[a_0+k_z(1-a_0)\right].$$

Here $\mathcal{R}_d$ and $\mathcal{R}_z$ are the CRNs for dengue and Zika individually, and q_0 is the average relative Zika-infectivity (RZI) of an individual who is in the S class at the DFE. As can be seen in the form of q_0, for most such individuals this RZI is 1, but a proportion (the coefficient of k_z in q_0) develop dengue seropositivity through vaccination (prior to Zika recovery), which causes ADE of Zika and thus an RZI of k_z. In general the last fraction inside each of the reproductive numbers gives the average relative infectivity of an individual (monoinfected) at the DFE, where the relative infectivity of each class is 1 without ADE, k with ADE, and 0 if that class is immune to infection by the given pathogen. (If Zika were assumed endemic in the entering population, then V_ω^* in the expression for $\mathcal{R}_d$ would be replaced by $(V_\omega^* + R_z^* + R_{z0}^* + R_{z\omega}^*)$.)

To obtain the corresponding BRNs, we set $p = \phi = 0$ and find that q_0 simplifies to 1, and $\mathcal{R}_0 = \max(\mathcal{R}_{0d}, \mathcal{R}_{0z})$, where

$$\mathcal{R}_{0d} = \sqrt{\frac{\beta_{hd}\frac{N_m}{N_h}}{\mu_h+\gamma_d}\,\frac{\beta_{md}}{\mu_m}\,(1-\alpha)},\quad \mathcal{R}_{0z} = \sqrt{\frac{\beta_{hz}\frac{N_m}{N_h}}{\mu_h+\gamma_z}\,\frac{\beta_{mz}}{\mu_m}\,[(1-\alpha)+k_z\,\alpha]}.$$

Here the average relative dengue infectivity at the DFE is a weighted average of 1 for the $(1-\alpha)$ seronegative part of the population and 0 for the α seropositive proportion of the population (who are dengue-immune). The average relative Zika infectivity at the DFE is a weighted average of 1 for the $(1-\alpha)$ seronegative part of the population and k_z for the α seropositive proportion of the population (who would have ADE if infected).

Deriving the IRNs is more complicated since they are defined at endemic equilibria. $\tilde{\mathcal{R}}_z$, the IRN for Zika invading a dengue-endemic setting, is defined at the dengue-endemic equilibrium (DEE), which presupposes that $\mathcal{R}_d > 1$. To find the DEE, we set $I_{zm}^* = 0$ in the equilibrium conditions for system (1) and factor out and discard the solution where $I_{dm}^* = 0$. After simplification, this leaves the following nonzero equilibrium components:

$$\frac{S^*}{N_h} = c_1\frac{\mu_h}{\mu_h+\phi(1-\chi)+\beta_{hd}I_{dm}^*/N_h},\quad \frac{I_d^*}{N_h} = c_1\frac{\beta_{hd}I_{dm}^*/N_h}{\mu_h+\phi(1-\chi)+\beta_{hd}I_{dm}^*/N_h}\,\frac{\mu_h}{\mu_h+\gamma_d},$$

$$\frac{R_d^*}{N_h} = \left(c_1\frac{\beta_{hd}I_{dm}^*/N_h}{\mu_h+\phi(1-\chi)+\beta_{hd}I_{dm}^*/N_h}\,\frac{\gamma_d}{\mu_h+\gamma_d}+c_2\right)\frac{\mu_h}{\mu_h+\phi\psi},$$

$$\frac{V_0^*}{N_h} = \left(c_1\frac{\phi(1-\chi)}{\mu_h+\phi(1-\chi)+\beta_{hd}I_{dm}^*/N_h}\,a_0+c_3\right)\frac{\mu_h}{\mu_h+\beta_{hd}I_{dm}^*/N_h},$$

$$\frac{I_{d0}^*}{N_h} = \left(c_1\frac{\phi(1-\chi)}{\mu_h+\phi(1-\chi)+\beta_{hd}I_{dm}^*/N_h}\,a_0+c_3\right)\frac{\beta_{hd}I_{dm}^*/N_h}{\mu_h+\beta_{hd}I_{dm}^*/N_h}\,\frac{\mu_h}{\mu_h+\gamma_d},$$

$$
\begin{aligned}
\frac{V_1^*}{N_h} &= c_1 \frac{\phi(1-\chi)\,a_1}{\mu_h+\phi(1-\chi)+\beta_{hd}I_{dm}^*/N_h} + \left(c_1 \frac{\beta_{hd}I_{dm}^*/N_h}{\mu_h+\phi(1-\chi)+\beta_{hd}I_{dm}^*/N_h}\,\frac{\gamma_d}{\mu_h+\gamma_d} + c_2\right)\frac{\phi\psi\,b_1}{\mu_h+\phi\psi} \\
&\quad + \left(c_1 \frac{\phi(1-\chi)}{\mu_h+\phi(1-\chi)+\beta_{hd}I_{dm}^*/N_h}\,a_0 + c_3\right)\frac{\beta_{hd}I_{dm}^*/N_h}{\mu_h+\beta_{hd}I_{dm}^*/N_h}\,\frac{\gamma_d}{\mu_h+\gamma_d} + c_4, \\
\frac{V_\omega^*}{N_h} &= \left(c_1 \frac{\phi(1-\chi)}{\mu_h+\phi(1-\chi)+\beta_{hd}I_{dm}^*/N_h}\,a_\omega + c_5\right)\frac{\mu_h}{\mu_h+\beta_{hd}I_{dm}^*/N_h}, \\
\frac{I_{d\omega}^*}{N_h} &= \left(c_1 \frac{\phi(1-\chi)}{\mu_h+\phi(1-\chi)+\beta_{hd}I_{dm}^*/N_h}\,a_\omega + c_5\right)\frac{\beta_{hd}I_{dm}^*/N_h}{\mu_h+\beta_{hd}I_{dm}^*/N_h}\,\frac{\mu_h}{\mu_h+\gamma_d}, \\
\frac{V_2^*}{N_h} &= c_1 \frac{\phi(1-\chi)\,a_2}{\mu_h+\phi(1-\chi)+\beta_{hd}I_{dm}^*/N_h} + \left(c_1 \frac{\beta_{hd}I_{dm}^*/N_h}{\mu_h+\phi(1-\chi)+\beta_{hd}I_{dm}^*/N_h}\,\frac{\gamma_d}{\mu_h+\gamma_d} + c_2\right)\frac{\phi\psi\,b_2}{\mu_h+\phi\psi} \\
&\quad + \left(c_1 \frac{\phi(1-\chi)}{\mu_h+\phi(1-\chi)+\beta_{hd}I_{dm}^*/N_h}\,a_\omega + c_5\right)\frac{\beta_{hd}I_{dm}^*/N_h}{\mu_h+\beta_{hd}I_{dm}^*/N_h}\,\frac{\gamma_d}{\mu_h+\gamma_d} + c_6, \\
S_{dm}^* &= N_m - I_{dm}^*,
\end{aligned}
$$

and I_{dm}^* such that

$$
\begin{aligned}
&\left[\mu_m + \beta_{md}\,\frac{\mu_h}{\mu_h+\gamma_d}(c_1+c_3+k_dc_5)\right]\left(\beta_{hd}\frac{I_{dm}^*}{N_h}\right)^2 \\
&+\left\{\mu_m[2\mu_h+\phi(1-\chi)] + \beta_{md}\,\tfrac{\mu_h}{\mu_h+\gamma_d}\Big[c_1(\mu_h+\phi(1-\chi)(a_0+k_da_\omega)) + (c_3+k_dc_5)(\mu_h+\phi(1-\chi))\right. \\
&\quad\left.-\beta_{hd}\,\frac{N_m}{N_h}(c_1+c_3+k_dc_5)\Big]\right\}\left(\beta_{hd}\frac{I_{dm}^*}{N_h}\right) + \mu_h[\mu_h+\phi(1-\chi)]\mu_m(1-\mathcal{R}_d^2) = 0.
\end{aligned}
$$

This last equation has the form $f(x) = Ax^2 + Bx + C = 0$ where $A > 0$, and $C > 0$ if and only if $\mathcal{R}_d < 1$. Thus there is a unique positive root when $\mathcal{R}_d > 1$. It is straightforward (but tedious) to show that $B^2 - 4AC > 0$, and that $C > 0$ implies $B > 0$, which together imply that f has no positive roots (i.e., there is no DEE) when $\mathcal{R}_d < 1$. See Appendix A.2 for details.

With the DEE thus defined, the NGM for $\tilde{\mathcal{R}}_z$ is computed using only the eleven Zika-infective classes (nine human and two mosquito). Then we substitute in the DEE (instead of the DFE) and take the spectral radius of the NGM, its largest eigenvalue (see Appendix A.3 for details). The result is

$$
\tilde{\mathcal{R}}_z = \sqrt{\frac{\beta_{hz}}{\mu_h+\gamma_z}\,\frac{\beta_{mz}}{\mu_m}\,\frac{N_m}{N_h}\left[\frac{\mu_m+\beta_{md}t_d^*\nu_z}{\mu_m+\beta_{md}t_d^*}\,\frac{S_{dm}^*}{N_m} + \nu_z\,\frac{I_{dm}^*}{N_m}\right]\frac{q_dS^* + d_i(I_d^*+I_{d0}^*) + d_vV_0^* + k_zA_z^*}{N_h}},
$$

where: $t_d^* = T_d^*/N_h$, $S_{dm}^* = S_m^*$, I_{dm}^*, and the nine Zika-seronegative human classes in the last term, including $A_z^* = R_d^* + V_1^* + V_\omega^* + I_{d\omega}^* + V_2^*$, are all evaluated at the DEE; and

$$
\begin{aligned}
q_d &= \frac{\mu_h+\gamma_z+d_i\beta_{hd}I_{dm}^*/N_h}{\mu_h+\gamma_z+\phi(1-\chi)+\beta_{hd}I_{dm}^*/N_h} + \frac{\phi(1-\chi)\,[d_va_0 + k_z(a_1+a_\omega+a_2)]}{\mu_h+\gamma_z+\phi(1-\chi)+\beta_{hd}I_{dm}^*/N_h}, \\
d_i &= \frac{\mu_h+\gamma_z+\gamma_dk_z}{\mu_h+\gamma_z+\gamma_d}, \text{ and } d_v = \frac{\mu_h+\gamma_z+d_i\beta_{hd}I_{dm}^*/N_h}{\mu_h+\gamma_z+\beta_{hd}I_{dm}^*/N_h}.
\end{aligned}
$$

The term in square brackets is the average relative Zika infectivity of mosquitoes, whether or not they carry dengue at the time of Zika exposure (a weighted average of 1 and $\nu_z < 1$, thus less than 1), and the final fraction in $\tilde{\mathcal{R}}_z$ is the average relative Zika infectivity of humans, at the DEE. This form makes possible a comparison to $\mathcal{R}_z$. (Note if $k_z > 1$ then $1 < d_v < d_i < k_z$, since d_i is a

weighted average of 1 and k_z, and d_v is a weighted average of 1 and d_i.) q_d is the average relative Zika infectivity of a person infected out of the S class at the DEE; it can be written as a weighted average of d_v and k_z,

$$q_d = \frac{[\mu_h + \gamma_z + \beta_{hd} I^*_{dm}/N_h + \phi(1-\chi)a_0]d_v + \phi(1-\chi)(1-a_0)k_z}{\mu_h + \gamma_z + \beta_{hd} I^*_{dm}/N_h + \phi(1-\chi)},$$

so also falls between d_v and k_z. d_i, d_v, and k_z are the average relative Zika infectivities at the DEE of the other Zika-infectable human classes as shown, so the last term in the IRN, representing the overall RZI of humans at the DEE, is also bounded between d_v and k_z.

Finally, even though we do not consider Zika to be endemic, it is worthwhile to compute the IRN for dengue in a Zika-endemic setting because it gives a measure of how the presence of Zika (however temporary) affects the spread of dengue. The dengue IRN $\tilde{\mathcal{R}}_d$ is defined about the Zika-endemic equilibrium (ZEE), which can be identified by setting $I^*_{dm} = 0$ in the equilibrium conditions for system (1) and discarding the solution where $I^*_{zm} = 0$. After simplification, the ZEE has nonzero components

$$\frac{S^*}{N_h} = c_1 \frac{\mu_h}{\mu_h + \phi(1-\chi) + \beta_{hz} I^*_{zm}/N_h}, \quad \frac{I^*_z}{N_h} = c_1 \frac{\beta_{hz} I^*_{zm}/N_h}{\mu_h + \phi(1-\chi) + \beta_{hz} I^*_{zm}/N_h} \frac{\mu_h}{\mu_h + \gamma_z + \phi(1-\chi)},$$

$$\frac{R^*_d}{N_h} = c_2 \frac{\mu_h}{\mu_h + \phi\psi + \beta_{hz} I^*_{zm}/N_h}, \quad \frac{J^*_z}{N_h} = c_2 \frac{\beta_{hz} I^*_{zm}/N_h}{\mu_h + \phi\psi + \beta_{hz} I^*_{zm}/N_h} \frac{\mu_h}{\mu_h + \gamma_z + \phi\psi},$$

$$\frac{R^*_z}{N_h} = c_1 \frac{\beta_{hz} I^*_{zm}/N_h}{\mu_h + \phi(1-\chi) + \beta_{hz} I^*_{zm}/N_h} \frac{\gamma_z}{\mu_h + \gamma_z + \phi(1-\chi)} \frac{\mu_h}{\mu_h + \phi(1-\chi)},$$

$$\frac{R^*}{N_h} = c_2 \frac{\beta_{hz} I^*_{zm}/N_h}{\mu_h + \phi\psi + \beta_{hz} I^*_{zm}/N_h} \frac{\gamma_z}{\mu_h + \gamma_z + \phi\psi} \frac{\mu_h}{\mu_h + \phi\psi},$$

$$\frac{V^*_0}{N_h} = \left(c_1 \frac{\phi(1-\chi)}{\mu_h + \phi(1-\chi) + \beta_{hz} I^*_{zm}/N_h} a_0 + c_3 \right) \frac{\mu_h}{\mu_h + \beta_{hz} I^*_{zm}/N_h},$$

$$\frac{V^*_1}{N_h} = \left(c_1 \frac{\phi(1-\chi)}{\mu_h + \phi(1-\chi) + \beta_{hz} I^*_{zm}/N_h} a_1 + c_2 \frac{\phi\psi}{\mu_h + \phi\psi + \beta_{hz} I^*_{zm}/N_h} b_1 + c_4 \right) \frac{\mu_h}{\mu_h + \beta_{hz} I^*_{zm}/N_h},$$

$$\begin{aligned} \frac{I^*_{z0}}{N_h} = &\left[c_1 \frac{\beta_{hz} I^*_{zm}/N_h}{\mu_h + \phi(1-\chi) + \beta_{hz} I^*_{zm}/N_h} \frac{\phi(1-\chi)}{\mu_h + \gamma_z + \phi(1-\chi)} a_0 \right. \\ &\left. + \left(c_1 \frac{\phi(1-\chi)}{\mu_h + \phi(1-\chi) + \beta_{hz} I^*_{zm}/N_h} a_0 + c_3 \right) \frac{\beta_{hz} I^*_{zm}/N_h}{\mu_h + \beta_{hz} I^*_{zm}/N_h} \right] \frac{\mu_h}{\mu_h + \gamma_z}, \end{aligned}$$

$$\begin{aligned} \frac{J^*_{z1}}{N_h} = &\left[c_1 \frac{\beta_{hz} I^*_{zm}/N_h}{\mu_h + \phi(1-\chi) + \beta_{hz} I^*_{zm}/N_h} \frac{\phi(1-\chi)\, a_1}{\mu_h + \gamma_z + \phi(1-\chi)} + c_2 \frac{\beta_{hz} I^*_{zm}/N_h}{\mu_h + \phi\psi + \beta_{hz} I^*_{zm}/N_h} \frac{\phi\psi\, b_1}{\mu_h + \gamma_z + \phi\psi} \right. \\ &\left. + \left(c_1 \frac{\phi(1-\chi)\, a_1}{\mu_h + \phi(1-\chi) + \beta_{hz} I^*_{zm}/N_h} + c_2 \frac{\phi\psi\, b_1}{\mu_h + \phi\psi + \beta_{hz} I^*_{zm}/N_h} + c_4 \right) \frac{\beta_{hz} I^*_{zm}/N_h}{\mu_h + \beta_{hz} I^*_{zm}/N_h} \right] \frac{\mu_h}{\mu_h + \gamma_z}, \end{aligned}$$

$$\begin{aligned} \frac{R^*_{z0}}{N_h} = &\, c_1 \frac{\beta_{hz} I^*_{zm}/N_h}{\mu_h + \phi(1-\chi) + \beta_{hz} I^*_{zm}/N_h} \frac{\gamma_z}{\mu_h + \gamma_z + \phi(1-\chi)} \frac{\phi(1-\chi)}{\mu_h + \phi(1-\chi)} a_0 \\ &+ \left[c_1 \left(\frac{\beta_{hz} I^*_{zm}/N_h}{\mu_h + \phi(1-\chi) + \beta_{hz} I^*_{zm}/N_h} \frac{\phi(1-\chi)}{\mu_h + \gamma_z + \phi(1-\chi)} a_0 \right. \right. \\ &\left. \left. + \frac{\phi(1-\chi)}{\mu_h + \phi(1-\chi) + \beta_{hz} I^*_{zm}/N_h} a_0 \frac{\beta_{hz} I^*_{zm}/N_h}{\mu_h + \beta_{hz} I^*_{zm}/N_h} \right) + c_3 \frac{\beta_{hz} I^*_{zm}/N_h}{\mu_h + \beta_{hz} I^*_{zm}/N_h} \right] \frac{\gamma_z}{\mu_h + \gamma_z}, \end{aligned}$$

$$\begin{aligned} \frac{R^*_{v1}}{N_h} = &\, c_1 \frac{\beta_{hz} I^*_{zm}/N_h}{\mu_h + \phi(1-\chi) + \beta_{hz} I^*_{zm}/N_h} \frac{\gamma_z}{\mu_h + \gamma_z + \phi(1-\chi)} \frac{\phi(1-\chi)}{\mu_h + \phi(1-\chi)} a_1 \\ &+ c_2 \frac{\beta_{hz} I^*_{zm}/N_h}{\mu_h + \phi\psi + \beta_{hz} I^*_{zm}/N_h} \frac{\gamma_z}{\mu_h + \gamma_z + \phi\psi} \frac{\phi\psi}{\mu_h + \phi\psi} b_1 \end{aligned}$$

$$
\begin{aligned}
&+\left[c_1\,\frac{\beta_{hz}I^*_{zm}/N_h}{\mu_h+\phi(1-\chi)+\beta_{hz}I^*_{zm}/N_h}\,\frac{\phi(1-\chi)\,a_1}{\mu_h+\gamma_z+\phi(1-\chi)}+c_2\,\frac{\beta_{hz}I^*_{zm}/N_h}{\mu_h+\phi\psi+\beta_{hz}I^*_{zm}/N_h}\,\frac{\phi\psi\,b_1}{\mu_h+\gamma_z+\phi\psi}\right.\\
&\left.+\left(c_1\,\frac{\phi(1-\chi)\,a_1}{\mu_h+\phi(1-\chi)+\beta_{hz}I^*_{zm}/N_h}+c_2\,\frac{\phi\psi\,b_1}{\mu_h+\phi\psi+\beta_{hz}I^*_{zm}/N_h}+c_4\right)\frac{\beta_{hz}I^*_{zm}/N_h}{\mu_h+\beta_{hz}I^*_{zm}/N_h}\right]\frac{\gamma_z}{\mu_h+\gamma_z},\\
\frac{V^*_\omega}{N_h}&=\left(c_1\,\frac{\phi(1-\chi)}{\mu_h+\phi(1-\chi)+\beta_{hz}I^*_{zm}/N_h}\,a_\omega+c_5\right)\frac{\mu_h}{\mu_h+\beta_{hz}I^*_{zm}/N_h},\\
\frac{V^*_2}{N_h}&=\left(c_1\,\frac{\phi(1-\chi)}{\mu_h+\phi(1-\chi)+\beta_{hz}I^*_{zm}/N_h}\,a_2+c_2\,\frac{\phi\psi}{\mu_h+\phi\psi+\beta_{hz}I^*_{zm}/N_h}\,b_2+c_6\right)\frac{\mu_h}{\mu_h+\beta_{hz}I^*_{zm}/N_h},\\
\frac{I^*_{z\omega}}{N_h}&=\left[c_1\,\frac{\beta_{hz}I^*_{zm}/N_h}{\mu_h+\phi(1-\chi)+\beta_{hz}I^*_{zm}/N_h}\,\frac{\phi(1-\chi)}{\mu_h+\gamma_z+\phi(1-\chi)}\,a_\omega\right.\\
&\left.+\left(c_1\,\frac{\phi(1-\chi)}{\mu_h+\phi(1-\chi)+\beta_{hz}I^*_{zm}/N_h}\,a_\omega+c_5\right)\frac{\beta_{hz}I^*_{zm}/N_h}{\mu_h+\beta_{hz}I^*_{zm}/N_h}\right]\frac{\mu_h}{\mu_h+\gamma_z},\\
\frac{J^*_{z2}}{N_h}&=\left[c_1\,\frac{\beta_{hz}I^*_{zm}/N_h}{\mu_h+\phi(1-\chi)+\beta_{hz}I^*_{zm}/N_h}\,\frac{\phi(1-\chi)\,a_2}{\mu_h+\gamma_z+\phi(1-\chi)}+c_2\,\frac{\beta_{hz}I^*_{zm}/N_h}{\mu_h+\phi\psi+\beta_{hz}I^*_{zm}/N_h}\,\frac{\phi\psi\,b_2}{\mu_h+\gamma_z+\phi\psi}\right.\\
&\left.+\left(c_1\,\frac{\phi(1-\chi)\,a_2}{\mu_h+\phi(1-\chi)+\beta_{hz}I^*_{zm}/N_h}+c_2\,\frac{\phi\psi\,b_2}{\mu_h+\phi\psi+\beta_{hz}I^*_{zm}/N_h}+c_6\right)\frac{\beta_{hz}I^*_{zm}/N_h}{\mu_h+\beta_{hz}I^*_{zm}/N_h}\right]\frac{\mu_h}{\mu_h+\gamma_z},\\
\frac{R^*_{z\omega}}{N_h}&=c_1\,\frac{\beta_{hz}I^*_{zm}/N_h}{\mu_h+\phi(1-\chi)+\beta_{hz}I^*_{zm}/N_h}\,\frac{\gamma_z}{\mu_h+\gamma_z+\phi(1-\chi)}\,\frac{\phi(1-\chi)}{\mu_h+\phi(1-\chi)}\,a_\omega\\
&+\left[c_1\,\frac{\beta_{hz}I^*_{zm}/N_h}{\mu_h+\phi(1-\chi)+\beta_{hz}I^*_{zm}/N_h}\,\frac{\phi(1-\chi)}{\mu_h+\gamma_z+\phi(1-\chi)}\,a_\omega\right.\\
&\left.+\left(c_1\,\frac{\phi(1-\chi)}{\mu_h+\phi(1-\chi)+\beta_{hz}I^*_{zm}/N_h}\,a_\omega+c_5\right)\frac{\beta_{hz}I^*_{zm}/N_h}{\mu_h+\beta_{hz}I^*_{zm}/N_h}\right]\frac{\gamma_z}{\mu_h+\gamma_z},\\
\frac{R^*_{v2}}{N_h}&=\left[c_1\,\frac{\beta_{hz}I^*_{zm}/N_h}{\mu_h+\phi(1-\chi)+\beta_{hz}I^*_{zm}/N_h}\,\frac{\phi(1-\chi)}{\mu_h+\gamma_z+\phi(1-\chi)}\,a_2\right.\\
&+c_2\,\frac{\beta_{hz}I^*_{zm}/N_h}{\mu_h+\phi\psi+\beta_{hz}I^*_{zm}/N_h}\,\frac{\phi\psi}{\mu_h+\gamma_z+\phi\psi}\,b_2\\
&\left.+\left(c_1\,\frac{\phi(1-\chi)\,a_2}{\mu_h+\phi(1-\chi)+\beta_{hz}I^*_{zm}/N_h}+c_2\,\frac{\phi\psi\,b_2}{\mu_h+\phi\psi+\beta_{hz}I^*_{zm}/N_h}+c_6\right)\frac{\beta_{hz}I^*_{zm}/N_h}{\mu_h+\beta_{hz}I^*_{zm}/N_h}\right]\frac{\gamma_z}{\mu_h+\gamma_z}\\
&+c_1\,\frac{\beta_{hz}I^*_{zm}/N_h}{\mu_h+\phi(1-\chi)+\beta_{hz}I^*_{zm}/N_h}\,\frac{\gamma_z}{\mu_h+\gamma_z+\phi(1-\chi)}\,\frac{\phi(1-\chi)}{\mu_h+\phi(1-\chi)}\,a_2\\
&+c_2\,\frac{\beta_{hz}I^*_{zm}/N_h}{\mu_h+\phi\psi+\beta_{hz}I^*_{zm}/N_h}\,\frac{\gamma_z}{\mu_h+\gamma_z+\phi\psi}\,\frac{\phi\psi}{\mu_h+\phi\psi}\,b_2,\\
S^*_{zm}&=N_m-I^*_{zm},
\end{aligned}
$$

and I^*_{zm} such that

$$\frac{\beta_{mz}}{\mu_m}\left(\frac{N_m-I^*_{zm}}{N_h}\right)\frac{[I^*_z+I^*_{z0}+k_z(I^*_{z\omega}+J^*_z+J^*_{z1}+J^*_{z2})]}{I^*_{zm}}=1. \tag{2}$$

By inspection of the expressions above for the six equilibrium values in square brackets in (2), their quotients with I^*_{zm} are clearly all monotone decreasing in I^*_{zm}, as is the term $N_m-I^*_{zm}$. Thus the left-hand side of (2) is monotone decreasing in I^*_{zm}, so (2) has at most one solution.

Substituting the expressions for the six equilibrium values in square brackets (as functions of I^*_{zm}) into (2) reduces the left side to a function of a single variable. Multiplying through by

$$(\mu_h+\beta_{hz}I^*_{zm}/N_h)(\mu_h+\phi(1-\chi)+\beta_{hz}I^*_{zm}/N_h)(\mu_h+\phi\psi+\beta_{hz}I^*_{zm}/N_h)$$

makes the equation cubic in I^*_{zm}, say $f(I^*_{zm}/N_m) = 0$. With positive lead (cubic) coefficient, the constant coefficient $f(0)$ can be shown to be a positive multiple of $1 - \mathcal{R}_z^2$, while $f(1) > 0$. This result, together with the one in the previous paragraph, proves that a unique ZEE exists if and only if $\mathcal{R}_z > 1$.

To compute $\tilde{\mathcal{R}}_d$ requires next deriving the NGM using only the eleven dengue-infective classes, and substituting the ZEE values. Details are given in Appendix A.4. The resulting IRN is

$$\tilde{\mathcal{R}}_d = \sqrt{\frac{\beta_{hd}}{\mu_h + \gamma_d} \frac{\beta_{md}}{\mu_m} \frac{N_m}{N_h} \left[\frac{\mu_m + \beta_{mz} t_z^* \nu_d}{\mu_m + \beta_{mz} t_z^*} \frac{S^*_{zm}}{N_m} + \nu_d \frac{I^*_{zm}}{N_m} \right] \frac{q_z(S^* + V_0^*) + z_i(I_z^* + I_{z0}^*) + k_d A_d^*}{N_h}},$$

where: $t_z^* = T_z^*/N_h$, $S^*_{zm} = S^*_m$, I^*_{zm}, and the nine Zika-seronegative human classes in the last term, including $A_d^* = R_z^* + R_{z0}^* + V_\omega^* + I_{z\omega}^* + R_{z\omega}^*$, are all evaluated at the ZEE;

$$q_z = \frac{\mu_h + \gamma_d}{\mu_h + \gamma_d + \beta_{hz} I^*_{zm}/N_h} + \frac{\beta_{hz} I^*_{zm}/N_h}{\mu_h + \gamma_d + \beta_{hz} I^*_{zm}/N_h} z_i; \text{ and } z_i = \frac{\mu_h + \gamma_d + \gamma_z k_d}{\mu_h + \gamma_d + \gamma_z}.$$

The term in square brackets is the average relative dengue infectivity of mosquitoes, and the final fraction in $\tilde{\mathcal{R}}_d$ is the average relative dengue infectivity of humans, at the ZEE. q_z gives the average relative Zika infectivity of individuals infected out of S and V_0, z_i the average relative Zika infectivity of individuals infected from I_z and I_{z0}, and k_d the relative dengue infectivity of all classes with ADE (A_d). Note that z_i is a weighted average of 1 and $k_d > 1$, while q_z is a weighted average of 1 and z_i, so $1 < q_z < z_i < k_d$.

3.2 Comparisons

These reproductive numbers can be used to study the overall effect of screening and dengue vaccination on the spread of the two viruses. First, we compare $\mathcal{R}_d$ to $\mathcal{R}_{0d}$. Substituting the definitions of the c_i into the expression for $\mathcal{R}_d$, we find that we can write $\mathcal{R}_d = \mathcal{R}_{0d}\sqrt{\sigma_d}$, where

$$\sigma_d = p(1-\chi)u_d + [1 - p(1-\chi)] \frac{\mu_h + \phi(1-\chi)u_d}{\mu_h + \phi(1-\chi)}, \quad u_d \equiv a_0 + k_d a_\omega.$$

We observe first that if $\chi = 1$ then $\sigma_d = 1$, so the only reason why vaccination of identified seropositives affects the ability of the same serotype to invade an uninfected population is that screening specificity failure misidentifies some of the seronegative population as seropositive and they receive the vaccine. These "misvaccinated" remain susceptible to infection if the vaccine fails to take against the locally circulating serotype and also fails to take against at least two serotypes, which occurs in proportion $a_0 + a_\omega$. In the latter (a_ω) case, taking only against one nonlocal serotype then also produces ADE, amplifying the eventual infectivity of the individual (for the local serotype) by a factor of k_d. Indeed, this leads to a second observation, that $\sigma_d < 1$ if and only if $u_d < 1$, regardless of the properties of the screening and vaccination procedures χ, p, ϕ. That is, although screening rates p and ϕ and specificity χ affect the *magnitude* of the deviation of σ_d from 1, it is only vaccine efficacy and ADE amplitude $a_0 + k_d a_\omega$ that determine whether vaccinating decreases or increases the overall ability of dengue to spread. This provides a simple measure by which to gauge whether vaccination reduces the spread of a single dengue serotype overall in the absence of Zika.

In the case that $\mathcal{R}_d > 1$, this same measure determines whether vaccination reduces dengue prevalence at the DEE. We can see this by observing that the equation which determines I^*_{dm} comes from setting two different expressions for t_d^* equal. From the equilibrium condition for I'_{dm} in system (1), we have $t_d^* = \mu_m I^*_{dm}/\beta_{md}(N_m - I^*_{dm})$. By definition, meanwhile, at the DEE we

have $t_d^* = (I_d^* + I_{d0}^* + k_d I_{d\omega}^*)/N_h$. Substituting first the equilibrium values at the DEE and then the definitions of the c_i, this latter expression becomes

$$t_d^* = \frac{(1-\alpha)\beta_{hd}\frac{I_{dm}^*}{N_h}}{\mu_h + \beta_{hd}\frac{I_{dm}^*}{N_h}} \frac{\mu_h}{\mu_h + \gamma_d} \left\{ p(1-\chi)u_d + [1-p(1-\chi)] \frac{\mu_h + \beta_{hd}\frac{I_{dm}^*}{N_h} + \phi(1-\chi)u_d}{\mu_h + \beta_{hd}\frac{I_{dm}^*}{N_h} + \phi(1-\chi)} \right\}.$$

Setting the two expressions for t_d^* equal and dividing out the zero (DFE) solution leaves the equation $f_{dL}(I_{dm}^*) = f_{dR}(I_{dm}^*)$, where $f_{dL}(x) = \mu_m/\beta_{md}(N_m - x)$ is a positive, increasing function of x on $[0, N_m)$ and

$$\begin{aligned} f_{dR}(x) &= \frac{(1-\alpha)\beta_{hd}/N_h}{\mu_h + \beta_{hd}\frac{x}{N_h}} \frac{\mu_h}{\mu_h + \gamma_d} \left\{ p(1-\chi)u_d + [1-p(1-\chi)] \frac{\mu_h + \beta_{hd}\frac{x}{N_h} + \phi(1-\chi)u_d}{\mu_h + \beta_{hd}\frac{x}{N_h} + \phi(1-\chi)} \right\} \\ &= \frac{\beta_{hd}}{N_h} \frac{(1-\alpha)\mu_h}{\mu_h + \gamma_d} \left\{ \frac{p(1-\chi)u_d}{\mu_h + \beta_{hd}\frac{x}{N_h}} + \frac{1-p(1-\chi)}{\mu_h + \beta_{hd}\frac{x}{N_h} + \phi(1-\chi)} \right. \\ &\qquad \left. + \frac{[1-p(1-\chi)]\phi(1-\chi)u_d}{(\mu_h + \beta_{hd}\frac{x}{N_h})(\mu_h + \beta_{hd}\frac{x}{N_h} + \phi(1-\chi))} \right\} \end{aligned}$$

is a positive, decreasing function of x on $[0, N_m)$. Thus they cross precisely once in $(0, N_m)$, iff $f_{dL}(0) < f_{dR}(0)$. Further algebra shows that $f_{dR}(0)/f_{dL}(0) = \mathcal{R}_d^2$, so this latter condition is equivalent to $\mathcal{R}_d > 1$.

After a significant amount of algebra, the expression in curly braces can be rewritten:

$$f_{dR}(x) = \frac{(1-\alpha)\beta_{hd}/N_h}{\mu_h + \beta_{hd}\frac{x}{N_h}} \frac{\mu_h}{\mu_h + \gamma_d} \left\{ 1 + [(a_0 + k_d a_\omega) - 1] \frac{p(1-\chi)[\mu_h + \beta_{hd}\frac{x}{N_h}] + \phi(1-\chi)}{\mu_h + \beta_{hd}\frac{x}{N_h} + \phi(1-\chi)} \right\}.$$

If either $\chi = 1$ or $p = \phi = 0$, then f_{dR} simplifies to $\frac{(1-\alpha)\beta_{hd}/N_h}{\mu_h + \beta_{hd}\frac{x}{N_h}} \frac{\mu_h}{\mu_h + \gamma_d}$. Otherwise, we observe that $f_{dR}(x) < \frac{(1-\alpha)\beta_{hd}/N_h}{\mu_h + \beta_{hd}\frac{x}{N_h}} \frac{\mu_h}{\mu_h + \gamma_d}$ for each value of x if and only if $a_0 + k_d a_\omega < 1$. Since $f_{dL}(x)$ is increasing, a lower value of $f_{dR}(x)$ moves the intersection point to the left; thus, vaccination (with $\chi < 1$) decreases I_{dm}^* if and only if $a_0 + k_d a_\omega < 1$. Recalling that $t_d^* = \mu_m I_{dm}^*/\beta_{md}(N_m - I_{dm}^*)$, we observe that decreasing dengue prevalence in mosquitoes I_{dm}^*/N_m also decreases the effective dengue prevalence in humans t_d^*. The true dengue prevalence in humans is $I_{dm}^* f_{dR}(I_{dm}^*)$ with $k_d = 1$, which simplifies to

$$\frac{(1-\alpha)\beta_{hd}\frac{x}{N_h}}{\mu_h + \beta_{hd}\frac{x}{N_h}} \frac{\mu_h}{\mu_h + \gamma_d} \left\{ 1 + [(a_0 + a_\omega) - 1] \frac{p(1-\chi)[\mu_h + \beta_{hd}\frac{x}{N_h}] + \phi(1-\chi)}{\mu_h + \beta_{hd}\frac{x}{N_h} + \phi(1-\chi)} \right\},$$

which is clearly increasing in I_{dm}^* and thus follows the same trend.

Under the assumption that dengue vaccination leads to ADE in subsequent Zika infections, there is no doubt that $\mathcal{R}_z > \mathcal{R}_{0z}$, but the expression showing the degree of change is more involved. Substituting the values for the DFE and the definitions of the c_i into the expression for $\mathcal{R}_z$, we can, with some work, rewrite $\mathcal{R}_z = \mathcal{R}_{0z}\sqrt{\sigma_z}$, where

$$\sigma_z = \frac{(1-\alpha)\left\{[1-p(1-\chi)]\sigma_{z1} + p(1-\chi)[a_0 + (1-a_0)k_z]\right\} + \alpha k_z}{(1-\alpha) + \alpha k_z},$$

$$\sigma_{z1} = \frac{\mu_h}{\mu_h + \phi(1-\chi)} \frac{\mu_h + \gamma_z + \phi(1-\chi)[a_0 + (1-a_0)k_z]}{\mu_h + \gamma_z + \phi(1-\chi)} + \frac{\phi(1-\chi)[a_0 + (1-a_0)k_z]}{\mu_h + \phi(1-\chi)}.$$

σ_{z1} is a weighted average of 1 and $k_z > 1$, so $\sigma_{z1} > 1$ also. Then the coefficient (in curly braces) of $(1-\alpha)$ in the numerator of σ_z is a weighted average of 1, σ_{z1}, and k_z, thus also greater than 1. With its numerator greater than its denominator, then, $\sigma_z > 1$ also, proving that $\mathcal{R}_z > \mathcal{R}_{0z}$. It is perhaps surprising that here, too, perfect specificity in screening $\chi = 1$ makes $\sigma_z = 1$, that is, keeps dengue vaccination from increasing the ability of Zika to spread, but under perfectly specific screening, only those individuals who are already dengue-seropositive (and thus would have ADE of any Zika infection) receive the vaccine, so vaccination then does not cause later ADE of Zika in anyone who was not already immunologically primed to have it. This highlights the importance of screening specificity.

Dengue vaccination also increases (through ADE) the Zika prevalences I^*_{zm}/N_m and $t^*_z|_{k_z=1}$ at the ZEE, as well as the effective prevalence in humans t^*_z, in the case where $\mathcal{R}_z > 1$. The proof is similar to that given above for the DEE but more complex; details are given in Appendix B.

The impact of dengue vaccination following imperfect screening on the invasion reproductive number of Zika depends on changes in the RZIs of humans and mosquitoes. As for humans, the population at the DEE can be divided into three groups: the seropositive population α, the seronegatives who do not get vaccinated, $(1-\alpha)g_N$, and the seronegatives who do get vaccinated, $(1-\alpha)g_Y$, where

$$g_N = [1 - p(1-\chi)]\frac{\mu_h + \beta_{hd} I^*_{dm}/N_h}{\mu_h + \beta_{hd} I^*_{dm}/N_h + \phi(1-\chi)},\ g_Y = p(1-\chi) + \frac{[1-p(1-\chi)]\,\phi(1-\chi)}{\mu_h + \beta_{hd} I^*_{dm}/N_h + \phi(1-\chi)}.$$

The RZI of seropositives is k_z whether they become vaccinated or not. The quantity

$$\zeta = \frac{\mu_h}{\mu_h + \beta_{hd} I^*_{dm}/N_h}\, d_v + \frac{\beta_{hd} I^*_{dm}/N_h}{\mu_h + \beta_{hd} I^*_{dm}/N_h}\left(\frac{\mu_h}{\mu_h + \gamma_d}\, d_i + \frac{\gamma_d}{\mu_h + \gamma_d}\, k_z\right)$$

gives the average relative Zika infectivity of the seronegatives $1-\alpha$ when there is no vaccination or (equivalently) screening with perfect specificity, because q_d simplifies to d_v in this case. (ζ is a weighted average over those who never get infected, those who get infected and die before recovery, and those who recover.) When vaccination with imperfect screening occurs, some (g_Y) of the seronegatives get vaccinated; their average relative Zika infectivity becomes $a_0\zeta + (1-a_0)k_z$, which is higher than ζ because $\zeta < k_z$. Those seronegatives who do not get vaccinated (g_N) then have average relative Zika infectivity in which the d_v in ζ is replaced with $q_d > d_v$, so for this group also, infectivity increases with vaccination parameters p, ϕ. However, dengue vaccination also affects I^*_{dm}, as seen earlier in this section, and d_v and ζ are both increasing functions of I^*_{dm}. If vaccination increases I^*_{dm} then d_v and ζ increase also, and the overall average Zika infectivity of seronegatives (and thus the population as a whole) is increased as well.

Meanwhile the average relative Zika infectivity of mosquitoes (a weighted average of 1 and ν_z) follows the reverse trend. If dengue vaccination increases dengue prevalence, then it increases the weight of $\nu_z < 1$ (and correspondingly decreases the weight of 1), thereby reducing the RZI of mosquitoes because more coinfected mosquitoes means more of the consequent reduced Zika viral loads inside them. If dengue vaccination decreases dengue prevalence, then the RZI of mosquitoes increases because fewer mosquitoes will carry both. Since the IRN of Zika depends on the product of the two RZIs, vaccination may in theory raise or lower $\tilde{\mathcal{R}}_z$, though in practice it appears that the increases caused by raising p and ϕ outweigh the more moderate changes from I^*_{dm} and ν_z (see section 4).

Subpopulation	RDI	Weight without vaccination	Weight with universal vaccination
dengue-immune	0	α	$\alpha + (1-\alpha)(a_1 + a_2)$
fully seronegative	q_z	$(1-\alpha)\frac{\mu_h}{\mu_h+\beta_{hz}I^*_{zm}/N_h}$	$(1-\alpha)\frac{\mu_h}{\mu_h+\beta_{hz}I^*_{zm}/N_h}\,a_0$
Zika-infected	z_i	$(1-\alpha)\frac{\beta_{hz}I^*_{zm}/N_h}{\mu_h+\beta_{hz}I^*_{zm}/N_h}\,\frac{\mu_h}{\mu_h+\gamma_z}$	$(1-\alpha)\frac{\beta_{hz}I^*_{zm}/N_h}{\mu_h+\beta_{hz}I^*_{zm}/N_h}\,\frac{\mu_h}{\mu_h+\gamma_z}\,a_0$
Zika-recovered	k_d	$(1-\alpha)\frac{\beta_{hz}I^*_{zm}/N_h}{\mu_h+\beta_{hz}I^*_{zm}/N_h}\,\frac{\gamma_z}{\mu_h+\gamma_z}$	$(1-\alpha)\left[\frac{\beta_{hz}I^*_{zm}/N_h}{\mu_h+\beta_{hz}I^*_{zm}/N_h}\,\frac{\gamma_z}{\mu_h+\gamma_z}\,a_0 + a_\omega\right]$

Table 3: Relative dengue infectivity by human subpopulation at the ZEE, when each group is either fully unvaccinated ($p, \phi = 0$) or fully vaccinated ($p = 1$ or $\phi \to \infty$, and $\chi = 0, \psi = 1$), under the assumption that all prior dengue seropositivity involves the serotype currently circulating. Note that I^*_{zm} is higher with vaccination than without, and consequently so is q_z.

As was the case with the CRN and BRN of dengue, the impact of screening and vaccination on $\tilde{\mathcal{R}}_d$ (the ability of dengue to spread in the presence of Zika) depends on the characteristics of the vaccine as well as the magnitude of ADE caused by prior exposure to Zika or dengue (including partly successful vaccination). In the expression for $\tilde{\mathcal{R}}_d$, it is straightforward to see that the average relative dengue infectivity (RDI) of vectors is increased by vaccination: it is a weighted average,

$$\mathrm{RDI}_m = \frac{\mu_m + \beta_{mz}t^*_z\nu_d}{\mu_m + \beta_{mz}t^*_z}\,\frac{S^*_{zm}}{N_m} + \nu_d\,\frac{I^*_{zm}}{N_m} = \frac{\mu_m}{\mu_m + \beta_{mz}t^*_z}\,\frac{S^*_{zm}}{N_m}\cdot 1 + \left[\frac{\beta_{mz}t^*_z}{\mu_m + \beta_{mz}t^*_z}\,\frac{S^*_{zm}}{N_m} + \frac{I^*_{zm}}{N_m}\right]\nu_d,$$

of 1 and $\nu_d > 1$; dengue vaccination increases Zika prevalence, t^*_z and I^*_{zm}/N_m; so the weight $\frac{\mu_m}{\mu_m+\beta_{mz}t^*_z}\,S^*_{zm}/N_m$ of 1 decreases with vaccination (with corresponding increase in the complementary weight of ν_d); and thus so does the overall weighted average. However, the average RDI of humans may increase or decrease under vaccination, as can be seen by comparing the weights of the RDIs of various subpopulations with and without universal vaccination, shown in Table 3. Therefore, focusing on the average RDI of seronegatives, the IRN of dengue in the presence of Zika infection is reduced by screening and vaccination if and only if

$$\mathrm{RDI}_m\left[a_0\left(\frac{\mu_h\,q_z + \beta_{hz}\frac{I^*_{zm}}{N_h}\,\frac{\mu_h\,z_i+\gamma_z\,k_d}{\mu_h+\gamma_z}}{\mu_h + \beta_{hz}I^*_{zm}/N_h}\right) + k_d a_\omega\right]\Bigg|_{p=\psi=1,\chi=0} < \mathrm{RDI}_m\,\frac{\mu_h\,q_z + \beta_{hz}\frac{I^*_{zm}}{N_h}\,\frac{\mu_h\,z_i+\gamma_z\,k_d}{\mu_h+\gamma_z}}{\mu_h + \beta_{hz}I^*_{zm}/N_h}\Bigg|_{p,\phi=0}. \quad (3)$$

3.3 Seropositivity to a different dengue serotype

One limitation of the model as conceived is that it addresses the effect of vaccination only when the serotype circulating is the same as the one to which some of the population have seropositivity from prior exposure. This is indeed the case in many areas, but underestimates the utility of dengue vaccination since then any seropositives who receive the vaccine are already immune to the circulating serotype, and the whole aim of vaccination is to prevent future dengue infection. It is worth noting that this (treatment of dengue as a single serotype) is also true of prior deterministic models for dengue vaccination and dengue and Zika transmission, but the issue is not as evident without pre-vaccination screening.

One way to incorporate prior exposure to a different dengue serotype is through initial conditions, adjusting the numbers starting in each class of dengue immunities (indeed, some authors

have modeled vaccination exclusively through initial conditions), but initial conditions are not reflected in reproduction numbers, so this approach limits the ability of a model to measure how such prior exposure affects the spread of the circulating pathogens (especially analytically). Since the reproduction numbers defined in this study measure transmission within a specific epidemiological landscape, we instead propose to reflect a shift in the serotype of dengue seropositivity through the equilibria at which the reproduction numbers are defined, so that the prior exposure of incoming individuals (seropositivity α) is to a different dengue serotype (say k) rather than the one currently circulating (say j, $j \neq k$). This changes the distribution of incoming seropositives as follows: there are no incoming seropositives immune only to the circulating serotype j (in c_2), and no seropositives without immunity to at least one nonlocal serotype (in c_4); instead, seropositives who either do not receive the vaccine or have it fail to take in any serotypes besides their prior exposure contribute to c_5, and the rest (seropositives in whom the vaccine takes in at least one additional serotype) contribute to c_6. This redistribution of the incoming population's serostatus leaves c_1 and c_3 unchanged but adjusts the others as follows: $c_2 = 0$ and

$$c_4 = (1-\alpha)p(1-\chi)a_1,\ c_5 = \alpha(1-p\psi b_4) + (1-\alpha)p(1-\chi)a_\omega,\ c_6 = \alpha p\psi b_4 + (1-\alpha)p(1-\chi)a_2,$$

where

$$b_3 = \prod_{i\neq k}(1-\eta_i) \text{ and } b_4 = 1-b_3$$

are the proportions of vaccinated seropositives, respectively, who receive no additional immunities from vaccination (besides their existing immunity to serotype k) and who do receive at least one additional serotype immunity.

Under these adjustments, all the reproduction numbers remain the same in terms of the c_i, but their elaborations in terms of the primitive parameters of the model may change. The Zika BRN and CRN remain unaffected, and its IRN is affected only to the extent that vaccine efficacy and ADE vary by dengue serotype, since those affect the DEE. The (amplifying) effects of vaccination on Zika transmission derived in the previous subsection therefore also still hold. The DFE and $\mathcal{R}_d$ are correct as originally given, but now the BRN for dengue is elaborated as follows. Without vaccination, we have $c_1 = 1-\alpha$, $c_2 = 0$, $c_5 = \alpha$, $S^*/N_h = c_1$, $V_\omega^*/N_h = c_5$, so

$$\mathcal{R}_{0d} = \sqrt{\frac{\beta_{hd}\frac{N_m}{N_h}}{\mu_h+\gamma_d}\frac{\beta_{md}}{\mu_m}\left[(1-\alpha)+k_d\alpha\right]},$$

exactly paralleling $\mathcal{R}_{0z}$.

To replicate the comparisons of the previous subsection under this new hypothesis for the dengue reproduction numbers, we substitute the new incoming distributions c_i into the expressions for $\mathcal{R}_d$ and $\tilde{\mathcal{R}}_d$. We find first that $\mathcal{R}_d = \mathcal{R}_{0d}\sqrt{\sigma_{d1}}$, where

$$\sigma_{d1} = \frac{(1-\alpha)\sigma_d + \alpha k_d(1-p\psi b_4)}{(1-\alpha)+\alpha k_d},$$

with σ_d as previously defined. It remains true that $\sigma_d < 1$ if and only if $a_0 + k_d a_\omega < 1$, so $a_0 + k_d a_\omega < 1$ still implies that $\mathcal{R}_d < \mathcal{R}_{0d}$, but this is no longer a necessary condition (in fact, σ_{d1} can be seen to be a weighted average of σ_d and $(1-p\psi b_4)$, so lies between them). Now, instead, the seropositivity level matters, and the more seropositivity there is, the more likely that vaccination and screening reduce the ability of dengue to spread. Furthermore, the quality of screening (ψ and χ) can affect whether this happens, which was not true when the prior and current serotypes were the same. Indeed, some algebra shows that

$$\sigma_{d1} < 1 \Leftrightarrow (1-\alpha)(\sigma_d - 1) < \alpha p\psi b_4 k_d,$$

so for a high enough seropositivity level, vaccination in this scenario is guaranteed to reduce the spread of dengue.

The change in c_5 adds an additional term $+\frac{\beta_{hd}/N_h}{\mu_h+\beta_{hd}\frac{x}{N_h}}\frac{\mu_h}{\mu_h+\gamma_d}\,\alpha(1-p\psi b_4)k_d$ to $f_{dR}(x)$. As this term is decreasing in x, it does not affect the existence and uniqueness argument for the DEE (t_d^* and true dengue prevalence in humans also still increase in I_{dm}^*). The condition that vaccination reduce $f_{dR}(x)$ (and thus I_{dm}^*) adds a single term involving x, becoming

$$\sigma_{d3} \equiv \frac{(1-\alpha)\sigma_{d2} + \alpha(1-p\psi b_4)k_d}{(1-\alpha)+\alpha k_d} < 1, \tag{4}$$

where

$$\sigma_{d2} = p(1-\chi)u_d + [1-p(1-\chi)]\,\frac{\mu_h + \beta_{hd}\frac{x}{N_h} + \phi(1-\chi)u_d}{\mu_h + \beta_{hd}\frac{x}{N_h} + \phi(1-\chi)}.$$

By inspection σ_{d2} simplifies to σ_d when $x = 0$; otherwise σ_{d2} lies between σ_d and 1, so (like σ_d) $\sigma_{d2} < 1$ if and only if $u_d < 1$. Thus, as with the condition $\sigma_{d1} < 1$, for $\sigma_{d3} < 1$ it is sufficient but not necessary that $u_d < 1$. In the case where $u_d > 1$, $\sigma_{d3} < \sigma_{d1}$, so $\sigma_{d3} > 1$ implies $\sigma_{d1} > 1$.

For the invasion reproductive number $\tilde{\mathcal{R}}_d$ of dengue, the RDI of mosquitoes increases under vaccination as before, while the RDI of humans is more complex. Employing the same technique as in section 3.2, we assemble a weighted average over each of the four groups represented in the expression for $\tilde{\mathcal{R}}_d$. The RDIs in Table 3 change only as regards the seropositive (α) terms in the first and last lines: the immune subgroup with RDI 0 has weight 0 without vaccination and $\alpha b_4 + (1-\alpha)(a_1+a_2)$ under universal vaccination, while the Zika-recovered group with RDI k_d has an additional weight of α without vaccination, and an additional weight of αb_3 under universal vaccination. Thus the average human RDI decreases under vaccination iff

$$\alpha b_3 k_d + (1-\alpha)\left[a_0\cdot \mathrm{RDI}_0 + k_d a_\omega\right]\Big|_{p=\psi=1,\chi=0} < \alpha k_d + (1-\alpha)\mathrm{RDI}_0\Big|_{p,\phi=0}, \tag{5}$$

where

$$\mathrm{RDI}_0 = \frac{\mu_h\, q_z + \beta_{hz}\frac{I_{zm}^*}{N_h}\frac{\mu_h\, z_i + \gamma_z\, k_d}{\mu_h+\gamma_z}}{\mu_h + \beta_{hz}I_{zm}^*/N_h} < k_d$$

gives the average RDI of seronegative humans with no additional immunity from vaccination. This condition can be simplified slightly to

$$(1-\alpha)\left[a_0\cdot \mathrm{RDI}_0 + k_d a_\omega\right]\Big|_{p=\psi=1,\chi=0} < \alpha b_4 k_d + (1-\alpha)\mathrm{RDI}_0\Big|_{p,\phi=0},$$

from which we can see that once again a high enough seropositivity level α ensures the condition holds. For example, since $\mathrm{RDI}_0 < k_d$, the whole left side is less than $(1-\alpha)(a_0+a_\omega)k_d$, and using just the α term on the right, we see that the condition $(1-\alpha)(a_0+a_\omega) < \alpha b_4$ is sufficient to make the average human RDI (RDI_h) decrease under vaccination. Nevertheless, since vaccination still drives up the average mosquito RDI (RDI_m) at the ZEE, the overall condition for vaccination to reduce the spread of dengue in the presence of Zika remains complex,

$$\mathrm{RDI}_m\cdot\mathrm{RDI}_h\big|_{p=\psi=1,\chi=0} < \mathrm{RDI}_m\cdot\mathrm{RDI}_h\big|_{p,\phi=0}. \tag{6}$$

Comparing (3) with (5), it is clear here also that the condition above is easier to fulfill. That is, whether in the absence or presence of Zika transmission, it is (as expected) easier for dengue screening and vaccination to reduce dengue spread when seropositivity through prior exposure involves a different serotype than the one in circulation, than when it involves the same serotype.

Parameter	Value	Source
α	0.72	[2]
p	0.15	this study
ϕ	0.01/day	this study
χ	0.98	[23]
ψ	0.91	[23]
η_i	0.584, 0.471, 0.736, 0.832	[12]
μ_h	0.0000365/day	this study
μ_m	(1/28)/day	[13]
N_m/N_h	0.5	[21, 16]

Parameter	Value	Source
β_{hd}	0.4489 $\frac{\text{people}}{\text{vector day}}$	[15, 13]
β_{md}	0.6164/day	[15, 13]
γ_d	(1/5.32)/day	[1]
k_d	1.0,1.3,1.1,1.1	[6]
ν_d	12	[5]
β_{hz}	0.1675 $\frac{\text{people}}{\text{vector day}}$	[15], this study
β_{mz}	0.201/day	[15, 6]
γ_z	(1/7)/day	[10]
k_z	1.1	this study
ν_z	0.11	[5]

Table 4: Sample parameter values used in the numerical analysis. Citation of multiple sources for a single value indicates assembly from multiple component terms. Values generated for this study represent sample values from the ranges appearing in literature (for the most closely related quantity available, when direct estimates were not available from primary sources). In all cases, parameters are meant as illustrative, not definitive. The authors recommend use of primary sources.

4 Numerical analysis

To illustrate the computations and comparisons of the previous section, we perform some elementary numerical analysis using sample parameter values taken from the literature. Table 4 gives a set of values for the model parameters; the values are taken from literature as much as possible for realism, but are not intended to be definitive (especially given the wide variation by region and season). Future work already under way entails a more detailed review of primary sources in the literature to document these and other values for the given parameters. The two vaccination parameters p and ϕ are, of course, hypothetical.

We begin by observing the resulting values of key threshold quantities, primarily the reproductive numbers. Most vaccinations ($a_2 = 89\%$) result in successful "takes" against two or more serotypes and thus (by assumption) protection against any symptomatic dengue infection. The RDI of a vaccinated individual, $u_d = a_0 + k_d a_\omega$, takes on a value between 0.064 and 0.126 depending on serotype; in any case it is much less than 1, so vaccination does reduce $\mathcal{R}_d$ and the prevalence at the DEE. Of the six classes into which incoming hosts (9-year-olds becoming eligible for dengue vaccination) enter the study population, a majority ($c_2 = 62\%$) are unvaccinated seropositives in the original scenario where dengue seropositivity represents prior exposure to the same serotype currently circulating, and most of the rest ($c_1 = 28\%$) are unvaccinated seronegatives. The resulting dengue reproductive numbers are $\mathcal{R}_{0d} = 2.4$, with $\mathcal{R}_d$ between 1.1 and 1.2, and $\tilde{\mathcal{R}}_d$ between 1.96 and 1.99, depending on circulating serotype. Meanwhile, $\mathcal{R}_{0z} = 1.88$, $\mathcal{R}_z = 1.900$, and $\tilde{\mathcal{R}}_z = 1.901$. Thus both pathogens should co-persist in this constant environment, each boosted by the other, but dengue clearly affected more by Zika than vice versa.

In the alternative scenario where prior dengue exposure was to a different serotype than the one now circulating, dengue reproductive numbers are much higher with no natural immunity (seropositivity) to the circulating serotype. Instead, infected seropositives exhibit ADE and spread the infection k_d times as fast. $\mathcal{R}_{0d}$ varies between 4.5 and 5 depending on which serotypes are prior and current; $\mathcal{R}_d$ likewise varies between 3.77 and 4.28. ($\mathcal{R}_{0z}$ and $\mathcal{R}_z$ are unaffected.)

If we examine the effects of the vaccination parameters p and ϕ in both scenarios, we find (computations not shown) that in the original scenario (section 3.2), ϕ affects the reproductive

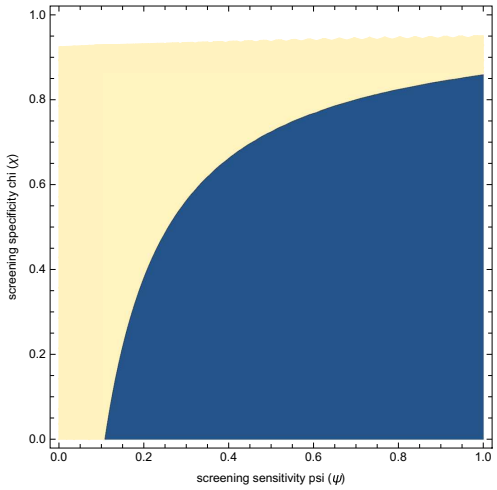

Figure 2: The dark shaded region indicates values of screening sensitivity ψ and specificity χ for which $\mathcal{R}_d < 1$, when initial dengue seropositivity involves a noncirculating serotype. Other parameter values are as given in Table 4 except $\alpha = 0.125$ and $1/\mu_m = 7$ days.

numbers far more than p does: Even with a value of ϕ so low that it takes 55 years to get vaccinated on average, ϕ reduces $\mathcal{R}_d$ more than p does. However, in the alternative scenario (section 3.3), the reverse holds: p affects $\mathcal{R}_d$ and $\tilde{\mathcal{R}}_d$ much more than ϕ. The reason for this difference is the change in seropositivity strain coupled with the high initial seropositivity level. In the original scenario, most people are seropositive to the circulating strain, which means initial onetime screening produces no additional immunity to the same serotype (except by false positives $1-\chi$), but repeated screening of the unvaccinated eventually catches most people for $\phi >> \mu_h$. In the alternative scenario, no one starts out seropositive to the circulating serotype, so initial onetime screening immunizes nearly everyone (many true positives ψ, plus a few false positives $1-\chi$), leaving little work for catch-up screening to do. From this contrast, we may conclude that vaccination of incoming individuals at age nine (henceforth age-in vaccination) is important when no one is already immune to the circulating serotype, but catch-up vaccination is important when most people are already immune to the circulating serotype.

Finally, we turn our attention to the effects and characteristics of pre-vaccination screening, a novel and key feature of our model. In the original scenario, numerical analysis shows both $\mathcal{R}_d$ and $\tilde{\mathcal{R}}_d$ highly sensitive to screening specificity χ. In fact, using the default parameters, both $\mathcal{R}_d$ and $\tilde{\mathcal{R}}_d$ drop below 1 as χ drops past a threshold value somewhere between 0.94 and 0.97 depending on the serotype. On the other hand, $\mathcal{R}_d$ is completely independent of screening sensitivity ψ, and ψ's effect on $\tilde{\mathcal{R}}_d$ is negligible. This makes sense since in this scenario the sensitivity of screening only affects how many seropositives are vaccinated, and seropositives are already assumed immune to repeat infection by the same dengue serotype. With $a_2 = 89\%$, however, nearly all vaccinations of seronegatives provide full protection against symptomatic infection, so (perhaps counterintuitively) lowering the specificity of the screening significantly reduces $\mathcal{R}_d$ and $\tilde{\mathcal{R}}_d$, because false positives lead to vaccinations, and vaccination is largely effective.

In the alternative scenario, where initial seropositivity is to a different serotype than the one circulating, the effects are nearly reversed: sensitivity ψ has a much larger impact than χ on both $\mathcal{R}_d$ and $\tilde{\mathcal{R}}_d$. Any seropositives are highly vulnerable (at first) to the circulating serotype due to ADE, so increasing ψ (with high seropositivity) reduces the reproductive numbers of dengue much more than χ except close to $\chi = 1$, where small specificity failures affect what proportion

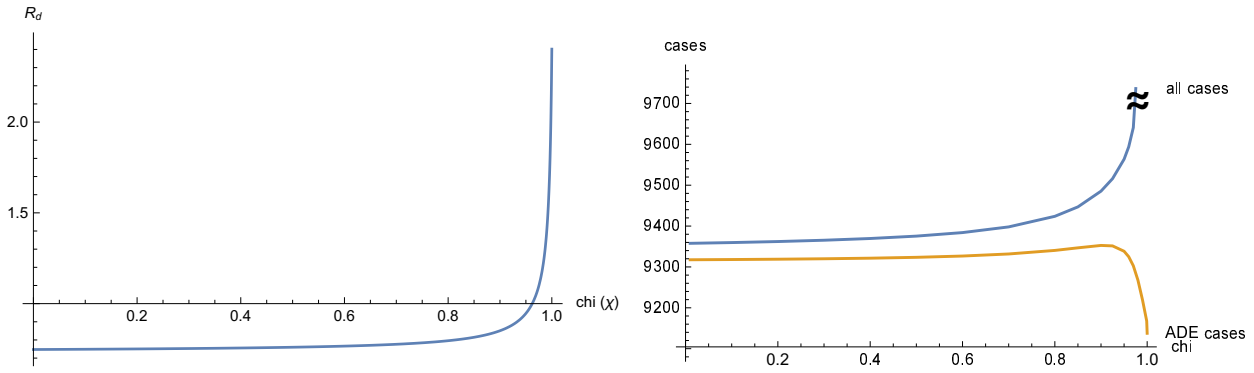

Figure 3: (a) Left, $\mathcal{R}_d$ for serotype DENV-1 as a function of screening specificity χ, using default parameters and initial seropositivity α to the circulating serotype. (b) Right, total dengue and Zika cases (upper curve) and total cases with ADE (lower curve) as functions of χ, using default parameters and initial seropositivity α to the circulating serotype. Note the "all cases" upper curve actually reaches approximately 12,000 cases for $\chi = 1$; plot range is restricted here in order to better show the curve shapes.

of seronegatives are eventually vaccinated. Under the default parameters, however, changes in screening quality cannot make the dengue reproductive numbers cross 1. Plausible changes in two of the parameters, however, can make this happen: Figure 2 shows values of ψ and χ for which $\mathcal{R}_d < 1$ when 1/8 of the human population is seropositive to a noncirculating dengue serotype and adult mosquitoes live only a week on average ($1/\mu_m = 7$ days). Both of these values are well within the ranges reported in the literature. In the figure, screening with high sensitivity and low specificity leads to enough vaccination to eradicate dengue. Here again we see the perhaps surprising result that less than perfect specificity χ reduces the spread of dengue.

However, reduced specificity in screening is at best a mixed blessing. As seen in Figure 3(a), a drop in χ from 1 to 0.9 reduces $\mathcal{R}_d$ from 2.4 to 0.85 (using default parameter values), by a factor of almost 3 and enough to eradicate the disease, because vaccinating seronegatives helps more people than it hurts, but it does hurt some people. As seen in Figure 3(b), using the default parameter values, lowering χ from 1 to 0.9 saves about 2,500 total cases (dengue and Zika combined, from a maximum of about 12,000, see note in figure caption) in a population of 10,000 but increases by about 220 the number of total cases which involve ADE (which are the most severe, with risk of death). This difference of just 10% in screening specificity has a huge impact both positive (reducing cases by 21%) and negative (increasing ADE cases by 2.4%). Ethically one cannot recommend using screening with low specificity because of the dangers posed to the individual by a false positive, but this example illustrates the complexity underlying public health recommendations, connected here to the idea known popularly as "the tragedy of the commons."

5 Discussion

This study has examined the impact of tetravalent dengue vaccination (patterned after Dengvaxia), following screening for prior exposure, on a joint outbreak of dengue (one serotype) and Zika viruses, through the lens of a compartmental dynamical system classifying individuals by infection status for each pathogen and (for hosts) immunization status. To our knowledge this is the first modeling study of dengue vaccination and Zika which distinguishes (a) seropositivity to circulating vs. noncirculating DENV serotypes and (b) seropositivity following prior exposure vs. age-in and

catch-up vaccination programs (α, p, ϕ respectively).

We derived and compared the reproductive numbers (control and invasion) for each virus with and without vaccination, in order to examine and compare the impact of not only age-in and catch-up vaccination programs and prior exposure (seropositivity) for dengue, but screening characteristics (sensitivity and specificity). The simplest expressions, for the basic reproductive numbers, matched those of the control reproductive numbers in Tang et al. [25], but with prior dengue seropositivity where they had vaccination proportions, which highlights the role of immunity prior to entering the system (our more complex expressions identify separate roles for the two types of vaccination parameters). Analysis also produced a simple measure, the average relative dengue infectivity (RDI) $u_d = a_0 + k_d a_\omega$ of vaccinated individuals, to determine whether vaccination reduces $\mathcal{R}_d$, as well as endemic dengue prevalence if $\mathcal{R}_d > 1$, and a more complex criterion (3) for the reduction of $\tilde{\mathcal{R}}_d$. Note that u_d is independent of screening characteristics. Analysis further showed that, even with screening, vaccination still increases $\mathcal{R}_z$, endemic Zika prevalence if $\mathcal{R}_z > 1$, and, for the parameter values used here, $\tilde{\mathcal{R}}_z$ as well. In the case where prior dengue seropositivity involves a different serotype than the one in circulation, there are less restrictive criteria (4) ($\sigma_{d3} < 1$) and (6) to reduce dengue prevalence and $\tilde{\mathcal{R}}_d$, since such alternative seropositivity makes it more likely that vaccination and screening will help (by preventing ADE).

Numerical analysis demonstrated that age-in vaccination (here, at age nine) is important when no one is already immune to the circulating dengue serotype, but catch-up vaccination (of older individuals) is important when most people are already immune to the circulating serotype. It also illustrated the impact of screening quality: sensitivity only affects transmission when there is significant seropositivity to a noncirculating serotype, while small failures in specificity drastically increase the number of seronegatives vaccinated due to false positive screenings, which reduces the total number of cases but increases the number of ADE cases.

Of course, this study has limitations, many of them involving simplifications in modeling. For instance, Dengvaxia is a three-dose vaccine. Our model effectively simplifies this to one. (One would need data on partially vaccinated people to address this.) We also assumed no direct adverse effects of (i.e., reactions to) vaccination, which is largely consistent with literature. Third, to limit model complexity and thus derive reproduction numbers, we assumed only one circulating dengue serotype, with possible prior exposure to a different serotype, such as observed in Cuba in 1981 and 1997 (e.g., [11]). We hope to consider multiple co-circulating serotypes in a future study. In a setting where multiple dengue serotypes have high incidence, ADE will be more common regardless of vaccination, so the potential negative effects of vaccination in this regard will be lessened. Fourth, for simplicity we have omitted age structure beyond the threshold for vaccination eligibility. There may be significant heterogeneities in the attack rate for different age groups; our model considers an average across all vaccine-eligible ages.

Finally, again to maintain model tractability, we have ignored the latent or incubation period for both hosts and vectors. This has the effect of overestimating each pathogen's ability to spread. A latent period typically reduces a pathogen's CRN by a factor $\rho/(\rho + \mu)$, where $1/\rho$ is the mean incubation period and μ accounts for removal from the infected population. Since we assume that vaccination cannot interrupt an incubating infection, the only relevant factor here is mortality. For vector-borne infections like dengue and Zika, this factor is averaged geometrically over the host and vector populations. In humans, the incubation period is negligible compared to the mean lifespan, $\rho >> \mu$, so this factor is very close to 1, but for mosquitoes the incubation period may be a significant proportion of the mean adult lifespan, so it may be important to take this factor into consideration. This factor should not, however, impact the type of effect (positive vs. negative) that a given vaccination-related parameter has on pathogen spread.

There also remains further work to do on the question posed here. We have focused analysis

here on reproduction numbers and equilibria since their closed-form expressions allow identification of trends independent of specific parameter values. Numerical analysis can show how those effects may vary over the course of an outbreak but requires careful estimation of the many parameters in the model. This work, to be published separately, is already in progress. Since vaccination may affect dengue and Zika transmission differently, we are also developing estimates of cost and disease burden to provide unified, fuller measures of the combined impact of both diseases. Such measures must acknowledge that transmission and cost parameters vary importantly by region and dengue serotype. Finally, we hope to extend this model to settings with more than one circulating dengue serotype.

Appendices

A Reproductive number calculations

A.1 Next-generation matrix for $\mathcal{R}_c$

Following the notation of van den Driessche and Watmough [27], to develop the next-generation matrix for the control reproductive number we first form a vector $\mathbf{x}(t)$ of the eighteen infected compartments of system (1). For convenience we group the seven dengue-monoinfected classes together (six human and one mosquito), then the seven Zika-monoinfected classes, and finally the four coinfected classes:

$$\mathbf{x}(t) = (I_d, J_d, I_{d0}, J_{d0}, I_{d\omega}, J_{d\omega}, I_{dm}, I_z, J_z, I_{z0}, J_{z1}, I_{z\omega}, J_{z2}, I_{zm}, I_c, I_{c0}, I_{c\omega}, I_{cm})^T.$$

To decompose the time-derivative vector of $\mathbf{x}$ as $d\mathbf{x}/dt = \mathcal{F} - \mathcal{V}$, we place all new infection terms (positive terms involving a β parameter) in $\mathcal{F}$ and all other terms in $-\mathcal{V}$. This gives

$$\mathcal{F} = \begin{bmatrix} \beta_{hd}\frac{S}{N_h}(I_{dm} + \nu_d I_{cm}) \\ \beta_{hd}\frac{R_z}{N_h}(I_{dm} + \nu_d I_{cm}) \\ \beta_{hd}\frac{V_0}{N_h}(I_{dm} + \nu_d I_{cm}) \\ \beta_{hd}\frac{R_{z0}}{N_h}(I_{dm} + \nu_d I_{cm}) \\ \beta_{hd}\frac{V_\omega}{N_h}(I_{dm} + \nu_d I_{cm}) \\ \beta_{hd}\frac{R_{z\omega}}{N_h}(I_{dm} + \nu_d I_{cm}) \\ \beta_{md}\frac{S_m}{N_h}T_d \\ \beta_{hz}\frac{S}{N_h}(I_{zm} + \nu_z I_{cm}) \\ \beta_{hz}\frac{R_d}{N_h}(I_{zm} + \nu_z I_{cm}) \\ \beta_{hz}\frac{V_0}{N_h}(I_{zm} + \nu_z I_{cm}) \\ \beta_{hz}\frac{V_1}{N_h}(I_{zm} + \nu_z I_{cm}) \\ \beta_{hz}\frac{V_\omega}{N_h}(I_{zm} + \nu_z I_{cm}) \\ \beta_{hz}\frac{V_2}{N_h}(I_{zm} + \nu_z I_{cm}) \\ \beta_{mz}\frac{S_m}{N_h}T_z \\ \beta_{hz}\frac{I_d}{N_h}T_{zm} + \beta_{hd}\frac{I_z}{N_h}T_{dm} \\ \beta_{hz}\frac{I_{d0}}{N_h}T_{zm} + \beta_{hd}\frac{I_{z0}}{N_h}T_{dm} \\ \beta_{hz}\frac{I_{d\omega}}{N_h}T_{zm} + \beta_{hd}\frac{I_{z\omega}}{N_h}T_{dm} \\ \beta_{mz}\frac{I_{dm}}{N_h}T_z + \beta_{md}\frac{I_{zm}}{N_h}T_d \end{bmatrix}, \quad \mathcal{V} = \begin{bmatrix} \beta_{hz}\frac{I_d}{N_h}(I_{zm} + \nu_z I_{cm}) + (\mu_h + \gamma_d)I_d \\ (\mu_h + \gamma_d)J_d - \gamma_z I_c \\ \beta_{hz}\frac{I_{d0}}{N_h}(I_{zm} + \nu_z I_{cm}) + (\mu_h + \gamma_d)I_{d0} \\ (\mu_h + \gamma_d)J_{d0} - \gamma_z I_{c0} \\ \beta_{hz}\frac{I_{d\omega}}{N_h}(I_{zm} + \nu_z I_{cm}) + (\mu_h + \gamma_d)I_{d\omega} \\ (\mu_h + \gamma_d)J_{d\omega} - \gamma_z I_{c\omega} \\ \beta_{mz}\frac{I_{dm}}{N_h}T_z + \mu_m I_{dm} \\ \beta_{hd}\frac{I_z}{N_h}T_{dm} + (\mu_h + \gamma_z + \phi(1-\chi))I_z \\ (\mu_h + \gamma_z + \phi\psi)J_z - \gamma_d I_c \\ \beta_{hd}\frac{I_{z0}}{N_h}T_{dm} + (\mu_h + \gamma_z)I_{z0} - \phi(1-\chi)a_0 I_z \\ (\mu_h + \gamma_z)J_{z1} - \gamma_d I_{c0} - \phi(1-\chi)a_1 I_z - \phi\psi b_1 J_z \\ \beta_{hd}\frac{I_{z\omega}}{N_h}T_{dm} + (\mu_h + \gamma_z)I_{z\omega} - \phi(1-\chi)a_\omega I_z \\ (\mu_h + \gamma_z)J_{z2} - \gamma_d I_{c\omega} - \phi(1-\chi)a_2 I_z - \phi\psi b_2 J_z \\ \beta_{md}\frac{I_{zm}}{N_h}T_d + \mu_m I_{zm} \\ (\mu_h + \gamma_d + \gamma_z)I_c \\ (\mu_h + \gamma_d + \gamma_z)I_{c0} \\ (\mu_h + \gamma_d + \gamma_z)I_{c\omega} \\ \mu_m I_{cm} \end{bmatrix},$$

with T_d and T_z as given in the main text, and $T_{dm} = I_{dm} + \nu_d I_{cm}$ and $T_{zm} = I_{zm} + \nu_z I_{cm}$ used as needed for space constraints.

Next we form the matrices $F = d\mathcal{F}/d\mathbf{x}|_{DFE}$ and $V = d\mathcal{V}/d\mathbf{x}|_{DFE}$. They can be given in block form as

$$F = \begin{bmatrix} F_d & 0_{7\times7} & F_{cd} \\ 0_{7\times7} & F_z & F_{cz} \\ 0_{4\times7} & 0_{4\times7} & 0_{4\times4} \end{bmatrix}, \quad V = \operatorname{diag}(\Gamma) + \begin{bmatrix} 0_{7\times7} & 0_{7\times7} & V_d \\ 0_{7\times7} & V_\phi \;\; 0_{7\times5} & V_z \\ 0_{4\times7} & 0_{4\times7} & 0_{4\times4} \end{bmatrix},$$

where

$$F_d = \begin{bmatrix} 0 & 0 & 0 & 0 & 0 & 0 & \beta_{hd}\frac{S^*}{N_h} \\ 0 & 0 & 0 & 0 & 0 & 0 & \beta_{hd}\frac{R_z^*}{N_h} \\ 0 & 0 & 0 & 0 & 0 & 0 & \beta_{hd}\frac{V_0^*}{N_h} \\ 0 & 0 & 0 & 0 & 0 & 0 & \beta_{hd}\frac{R_{z0}^*}{N_h} \\ 0 & 0 & 0 & 0 & 0 & 0 & \beta_{hd}\frac{V_\omega^*}{N_h} \\ 0 & 0 & 0 & 0 & 0 & 0 & \beta_{hd}\frac{R_{z\omega}^*}{N_h} \\ \beta_{md}\frac{N_m}{N_h} & k_d\beta_{md}\frac{N_m}{N_h} & \beta_{md}\frac{N_m}{N_h} & k_d\beta_{md}\frac{N_m}{N_h} & k_d\beta_{md}\frac{N_m}{N_h} & k_d\beta_{md}\frac{N_m}{N_h} & 0 \end{bmatrix},$$

$$F_z = \begin{bmatrix} 0 & 0 & 0 & 0 & 0 & 0 & \beta_{hz}\frac{S^*}{N_h} \\ 0 & 0 & 0 & 0 & 0 & 0 & \beta_{hz}\frac{R_d^*}{N_h} \\ 0 & 0 & 0 & 0 & 0 & 0 & \beta_{hz}\frac{V_0^*}{N_h} \\ 0 & 0 & 0 & 0 & 0 & 0 & \beta_{hz}\frac{V_1^*}{N_h} \\ 0 & 0 & 0 & 0 & 0 & 0 & \beta_{hz}\frac{V_\omega^*}{N_h} \\ 0 & 0 & 0 & 0 & 0 & 0 & \beta_{hz}\frac{V_2^*}{N_h} \\ \beta_{mz}\frac{N_m}{N_h} & k_z\beta_{mz}\frac{N_m}{N_h} & \beta_{mz}\frac{N_m}{N_h} & k_z\beta_{mz}\frac{N_m}{N_h} & k_z\beta_{mz}\frac{N_m}{N_h} & k_z\beta_{mz}\frac{N_m}{N_h} & 0 \end{bmatrix},$$

$$F_{cd} = \begin{bmatrix} 0 & 0 & 0 & \beta_{hd}\frac{S^*}{N_h}\nu_d \\ 0 & 0 & 0 & \beta_{hd}\frac{R_z^*}{N_h}\nu_d \\ 0 & 0 & 0 & \beta_{hd}\frac{V_0^*}{N_h}\nu_d \\ 0 & 0 & 0 & \beta_{hd}\frac{R_{z0}^*}{N_h}\nu_d \\ 0 & 0 & 0 & \beta_{hd}\frac{V_\omega^*}{N_h}\nu_d \\ 0 & 0 & 0 & \beta_{hd}\frac{R_{z\omega}^*}{N_h}\nu_d \\ \beta_{md}\frac{N_m}{N_h} & \beta_{md}\frac{N_m}{N_h} & k_d\beta_{md}\frac{N_m}{N_h} & 0 \end{bmatrix}, \quad F_{cz} = \begin{bmatrix} 0 & 0 & 0 & \beta_{hz}\frac{S^*}{N_h}\nu_z \\ 0 & 0 & 0 & \beta_{hz}\frac{R_d^*}{N_h}\nu_z \\ 0 & 0 & 0 & \beta_{hz}\frac{V_0^*}{N_h}\nu_z \\ 0 & 0 & 0 & \beta_{hz}\frac{V_1^*}{N_h}\nu_z \\ 0 & 0 & 0 & \beta_{hz}\frac{V_\omega^*}{N_h}\nu_z \\ 0 & 0 & 0 & \beta_{hz}\frac{V_2^*}{N_h}\nu_z \\ \beta_{mz}\frac{N_m}{N_h} & \beta_{mz}\frac{N_m}{N_h} & k_z\beta_{mz}\frac{N_m}{N_h} & 0 \end{bmatrix},$$

$$\Gamma = (\,\mu_h+\gamma_d, \mu_h+\gamma_d, \mu_h+\gamma_d, \mu_h+\gamma_d, \mu_h+\gamma_d, \mu_h+\gamma_d, \mu_m, \mu_h+\gamma_z, \mu_h+\gamma_z, \mu_h+\gamma_z,$$
$$\mu_h+\gamma_z, \mu_h+\gamma_z, \mu_h+\gamma_z, \mu_m, \mu_h+\gamma_d+\gamma_z, \mu_h+\gamma_d+\gamma_z, \mu_h+\gamma_d+\gamma_z, \mu_m)\,,$$

$$V_\phi = \begin{bmatrix} \phi(1-\chi) & 0 \\ 0 & \phi\psi \\ -\phi(1-\chi)a_0 & 0 \\ -\phi(1-\chi)a_1 & -\phi\psi b_1 \\ -\phi(1-\chi)a_\omega & 0 \\ -\phi(1-\chi)a_2 & -\phi\psi b_2 \\ 0 & 0 \end{bmatrix}, \quad V_d = \begin{bmatrix} 0 & 0 & 0 & 0 \\ -\gamma_z & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & -\gamma_z & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & -\gamma_z & 0 \\ 0 & 0 & 0 & 0 \end{bmatrix}, \quad V_z = \begin{bmatrix} 0 & 0 & 0 & 0 \\ -\gamma_d & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & -\gamma_d & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & -\gamma_d & 0 \\ 0 & 0 & 0 & 0 \end{bmatrix},$$

and $0_{m\times n}$ is the $m \times n$ zero matrix. Note that all the (nonlinear) terms denoting new coinfections in $d\mathbf{x}/dt$ zero out at the DFE in F and V because their partial derivatives remain linear in an infected class.

The next-generation matrix is then formed as FV^{-1} (note that V^{-1} has a sparseness structure similar to V); it has the same structure as F and can be given in block form as

$$FV^{-1} = \begin{bmatrix} M_d & 0_{7\times7} & M_{cd} \\ 0_{7\times7} & M_z & M_{cz} \\ 0_{4\times7} & 0_{4\times7} & 0_{4\times4} \end{bmatrix},$$

where

$$M_d = \begin{bmatrix} 0 & 0 & 0 & 0 & 0 & 0 & \frac{\beta_{hd}}{\mu_m}\frac{S^*}{N_h} \\ 0 & 0 & 0 & 0 & 0 & 0 & \frac{\beta_{hd}}{\mu_m}\frac{R_z^*}{N_h} \\ 0 & 0 & 0 & 0 & 0 & 0 & \frac{\beta_{hd}}{\mu_m}\frac{V_0^*}{N_h} \\ 0 & 0 & 0 & 0 & 0 & 0 & \frac{\beta_{hd}}{\mu_m}\frac{R_{z0}^*}{N_h} \\ 0 & 0 & 0 & 0 & 0 & 0 & \frac{\beta_{hd}}{\mu_m}\frac{V_\omega^*}{N_h} \\ 0 & 0 & 0 & 0 & 0 & 0 & \frac{\beta_{hd}}{\mu_m}\frac{R_{z\omega}^*}{N_h} \\ \frac{\beta_{md}}{\mu_h+\gamma_d}\frac{N_m}{N_h} & k_d\frac{\beta_{md}}{\mu_h+\gamma_d}\frac{N_m}{N_h} & \frac{\beta_{md}}{\mu_h+\gamma_d}\frac{N_m}{N_h} & k_d\frac{\beta_{md}}{\mu_h+\gamma_d}\frac{N_m}{N_h} & k_d\frac{\beta_{md}}{\mu_h+\gamma_d}\frac{N_m}{N_h} & k_d\frac{\beta_{md}}{\mu_h+\gamma_d}\frac{N_m}{N_h} & 0 \end{bmatrix},$$

$$M_z = \begin{bmatrix} 0 & 0 & 0 & 0 & 0 & 0 & \frac{\beta_{hz}}{\mu_m}\frac{S^*}{N_h} \\ 0 & 0 & 0 & 0 & 0 & 0 & \frac{\beta_{hz}}{\mu_m}\frac{R_d^*}{N_h} \\ 0 & 0 & 0 & 0 & 0 & 0 & \frac{\beta_{hz}}{\mu_m}\frac{V_0^*}{N_h} \\ 0 & 0 & 0 & 0 & 0 & 0 & \frac{\beta_{hz}}{\mu_m}\frac{V_1^*}{N_h} \\ 0 & 0 & 0 & 0 & 0 & 0 & \frac{\beta_{hz}}{\mu_m}\frac{V_\omega^*}{N_h} \\ 0 & 0 & 0 & 0 & 0 & 0 & \frac{\beta_{hz}}{\mu_m}\frac{V_2^*}{N_h} \\ q_0\frac{\beta_{mz}}{\mu_h+\gamma_z}\frac{N_m}{N_h} & k_z\frac{\beta_{mz}}{\mu_h+\gamma_z}\frac{N_m}{N_h} & \frac{\beta_{mz}}{\mu_h+\gamma_z}\frac{N_m}{N_h} & k_z\frac{\beta_{mz}}{\mu_h+\gamma_z}\frac{N_m}{N_h} & k_z\frac{\beta_{mz}}{\mu_h+\gamma_z}\frac{N_m}{N_h} & k_z\frac{\beta_{mz}}{\mu_h+\gamma_z}\frac{N_m}{N_h} & 0 \end{bmatrix},$$

$$M_{cd} = \begin{bmatrix} 0 & 0 & 0 & \frac{\beta_{hd}}{\mu_m}\frac{S^*}{N_h}\nu_d \\ 0 & 0 & 0 & \frac{\beta_{hd}}{\mu_m}\frac{R_z^*}{N_h}\nu_d \\ 0 & 0 & 0 & \frac{\beta_{hd}}{\mu_m}\frac{V_0^*}{N_h}\nu_d \\ 0 & 0 & 0 & \frac{\beta_{hd}}{\mu_m}\frac{R_{z0}^*}{N_h}\nu_d \\ 0 & 0 & 0 & \frac{\beta_{hd}}{\mu_m}\frac{V_\omega^*}{N_h}\nu_d \\ 0 & 0 & 0 & \frac{\beta_{hd}}{\mu_m}\frac{R_{z\omega}^*}{N_h}\nu_d \\ \frac{\beta_{md}}{\mu_h+\gamma_d}\frac{N_m}{N_h}\frac{\mu_h+\gamma_d+\gamma_z k_d}{\mu_h+\gamma_d+\gamma_z} & \frac{\beta_{md}}{\mu_h+\gamma_d}\frac{N_m}{N_h}\frac{\mu_h+\gamma_d+\gamma_z k_d}{\mu_h+\gamma_d+\gamma_z} & k_d\frac{\beta_{md}}{\mu_h+\gamma_d}\frac{N_m}{N_h} & 0 \end{bmatrix},$$

$$M_{cz} = \begin{bmatrix} 0 & 0 & 0 & \frac{\beta_{hz}}{\mu_m}\frac{S^*}{N_h}\nu_z \\ 0 & 0 & 0 & \frac{\beta_{hz}}{\mu_m}\frac{R_d^*}{N_h}\nu_z \\ 0 & 0 & 0 & \frac{\beta_{hz}}{\mu_m}\frac{V_0^*}{N_h}\nu_z \\ 0 & 0 & 0 & \frac{\beta_{hz}}{\mu_m}\frac{V_1^*}{N_h}\nu_z \\ 0 & 0 & 0 & \frac{\beta_{hz}}{\mu_m}\frac{V_\omega^*}{N_h}\nu_z \\ 0 & 0 & 0 & \frac{\beta_{hz}}{\mu_m}\frac{V_2^*}{N_h}\nu_z \\ \frac{\beta_{mz}}{\mu_h+\gamma_z}\frac{N_m}{N_h}\frac{\mu_h+\gamma_z+\gamma_d k_z}{\mu_h+\gamma_z+\gamma_d} & \frac{\beta_{mz}}{\mu_h+\gamma_z}\frac{N_m}{N_h}\frac{\mu_h+\gamma_z+\gamma_d k_z}{\mu_h+\gamma_z+\gamma_d} & k_z\frac{\beta_{mz}}{\mu_h+\gamma_z}\frac{N_m}{N_h} & 0 \end{bmatrix}.$$

The NGM is block triangular, so its eigenvalues are those of the diagonal blocks. The NGM has fourteen zero eigenvalues as well as $\pm\mathcal{R}_d$ and $\pm\mathcal{R}_z$, where the latter are as given in section 3.1. Thus the CRN of the system is $\max(\mathcal{R}_d, \mathcal{R}_z)$.

A.2 DEE calculations

To prove that there is no DEE (no positive solution to $Ax^2 + Bx + C = 0$) when $\mathcal{R}_d < 1$, we show first that $B^2 - 4AC > 0$, and then that $\mathcal{R}_d < 1 \Rightarrow B > 0$. Then, since $\mathcal{R}_d < 1 \Leftrightarrow C > 0$, we have $B^2 - 4AC < B^2$, implying that there are two roots of the same sign as the vertex $-B/2A$. Since then $A, B > 0$, the roots are negative and not biologically relevant.

To show $B^2 - 4AC > 0$, the only two negative terms in $B^2 - 4AC$ can be factored, along with four of the positive terms, into a perfect square:

$$
\begin{aligned}
&(\beta_{hd}\tfrac{N_m}{N_h})^2\beta_{md}^2c_1^2\left(\tfrac{\mu_h}{\mu_h+\gamma_d}\right)^2 - 2(\beta_{hd}\tfrac{N_m}{N_h})\beta_{md}c_1\left(\tfrac{\mu_h}{\mu_h+\gamma_d}\right)\mu_m\phi(1-\chi) + 2(\beta_{hd}\tfrac{N_m}{N_h})\beta_{md}^2c_1^2\left(\tfrac{\mu_h}{\mu_h+\gamma_d}\right)^2\mu_h \\
&+ \mu_m^2\phi^2(1-\chi)^2 + \mu_h^2\beta_{md}^2c_1^2\left(\tfrac{\mu_h}{\mu_h+\gamma_d}\right)^2 - 2\mu_h\beta_{md}c_1\left(\tfrac{\mu_h}{\mu_h+\gamma_d}\right)\mu_m\phi(1-\chi) \\
&= [\beta_{md}c_1\left(\tfrac{\mu_h}{\mu_h+\gamma_d}\right)((\beta_{hd}\tfrac{N_m}{N_h}) + \mu_h) - \mu_m\phi(1-\chi)]^2.
\end{aligned}
$$

As to the other point,

$$
\begin{aligned}
&C > 0 \Rightarrow B > \mu_h\mu_m + \beta_{md}\left(\tfrac{\mu_h}{\mu_h+\gamma_d}\right)\times \\
&\left[\left(\left(\beta_{hd}\tfrac{N_m}{N_h}\right) + \mu_h\right)\left(c_1\tfrac{\mu_h+\phi(1-\chi)(a_0+k_da_\omega)}{\mu_h} + (c_3+k_dc_5)\tfrac{\mu_h+\phi(1-\chi)}{\mu_h}\right) - (\beta_{hd}\tfrac{N_m}{N_h})(c_1+c_3+k_dc_5)\right] > 0.
\end{aligned}
$$

A.3 Next-generation matrix for $\tilde{\mathcal{R}}_z$

The NGM for the Zika IRN includes the nine human and two mosquito classes infected with Zika. We order them as follows:

$$\mathbf{x}(t) = (I_z, I_c, J_z, I_{z0}, I_{c0}, J_{z1}, I_{z\omega}, I_{c\omega}, J_{z2}, I_{zm}, I_{cm})^T.$$

Decomposing $d\mathbf{x}/dt = \mathcal{F} - \mathcal{V}$ and differentiating $F = d\mathcal{F}/d\mathbf{x}|_{DEE}$ and $V = d\mathcal{V}/d\mathbf{x}|_{DEE}$ yields a block off-diagonal F and triangular V:

$$F = \begin{bmatrix} 0_{9\times9} & F_{z1} \\ F_{z2} & 0_{2\times2} \end{bmatrix},$$

$$F_{z1} = \frac{\beta_{hz}}{N_h}\begin{bmatrix} S^* & I_d^* & R_d^* & V_0^* & I_{d0}^* & V_1^* & V_\omega^* & I_{d\omega}^* & V_2^* \\ \nu_z S^* & \nu_z I_d^* & \nu_z R_d^* & \nu_z V_0^* & \nu_z I_{d0}^* & \nu_z V_1^* & \nu_z V_\omega^* & \nu_z I_{d\omega}^* & \nu_z V_2^* \end{bmatrix}^T,$$

$$F_{z2} = \frac{\beta_{mz}}{N_h}\begin{bmatrix} S_{dm}^* & S_{dm}^* & k_zS_{dm}^* & S_{dm}^* & S_{dm}^* & k_zS_{dm}^* & k_zS_{dm}^* & k_zS_{dm}^* & k_zS_{dm}^* \\ I_{dm}^* & I_{dm}^* & k_zI_{dm}^* & I_{dm}^* & I_{dm}^* & k_zI_{dm}^* & k_zI_{dm}^* & k_zI_{dm}^* & k_zI_{dm}^* \end{bmatrix},$$

$$V = \begin{bmatrix}
\hat{\mu}+\phi_1+\Delta & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
-\Delta & \hat{\mu}+\gamma_d & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & -\gamma_d & \hat{\mu}+\phi_2 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
-\phi_1a_0 & 0 & 0 & \hat{\mu}+\Delta & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & -\Delta & \hat{\mu}+\gamma_d & 0 & 0 & 0 & 0 & 0 & 0 \\
-\phi_1a_1 & 0 & -\phi_2b_1 & 0 & -\gamma_d & \hat{\mu} & 0 & 0 & 0 & 0 & 0 \\
-\phi_1a_\omega & 0 & 0 & 0 & 0 & 0 & \hat{\mu}+\Delta & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & -\Delta & \hat{\mu}+\gamma_d & 0 & 0 & 0 \\
-\phi_1a_2 & 0 & -\phi_2b_2 & 0 & 0 & 0 & 0 & -\gamma_d & \hat{\mu} & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & \mu_m+\beta_{md}t_d^* & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & -\beta_{md}t_d^* & \mu_m
\end{bmatrix},$$

where (to conserve space) $\hat{\mu} = \mu_h + \gamma_z$, $\Delta = \beta_{hd} I^*_{dm}/N_h$, $\phi_1 = \phi(1-\chi)$, $\phi_2 = \phi\psi$. The NGM is then given by the product FV^{-1} which, like F, is block off-diagonal, of the form

$$\begin{bmatrix} 0_{9\times 9} & M_{z1} \\ M_{z2} & 0_{2\times 2} \end{bmatrix},$$

where

$$M_{z1} = \frac{\beta_{hz}}{\mu_m N_h} \begin{bmatrix} g_z S^* & g_z I^*_d & g_z R^*_d & g_z V^*_0 & g_z I^*_{d0} & g_z V^*_1 & g_z V^*_\omega & g_z I^*_{d\omega} & g_z V^*_2 \\ \nu_z S^* & \nu_z I^*_d & \nu_z R^*_d & \nu_z V^*_0 & \nu_z I^*_{d0} & \nu_z V^*_1 & \nu_z V^*_\omega & \nu_z I^*_{d\omega} & \nu_z V^*_2 \end{bmatrix}^T,$$

$$M_{z2} = \frac{\beta_{mz}}{(\mu_h+\gamma_z)N_h} \begin{bmatrix} q_d S^*_{dm} & d_i S^*_{dm} & k_z S^*_{dm} & d_v S^*_{dm} & d_i S^*_{dm} & k_z S^*_{dm} & k_z S^*_{dm} & k_z S^*_{dm} & k_z S^*_{dm} \\ q_d I^*_{dm} & d_i I^*_{dm} & k_z I^*_{dm} & d_v I^*_{dm} & d_i I^*_{dm} & k_z I^*_{dm} & k_z I^*_{dm} & k_z I^*_{dm} & k_z I^*_{dm} \end{bmatrix},$$

q_d, d_v, and d_i are as given in the main text, and (again to conserve space) $g_z = \frac{\mu_m + \beta_{md} t^*_d \nu_z}{\mu_m + \beta_{md} t^*_d}$. This matrix has eigenvalues zero (with multiplicity nine) and $\pm\tilde{\mathcal{R}}_z$, where $\tilde{\mathcal{R}}_z$ is as given in the main text.

A.4 Next-generation matrix for $\tilde{\mathcal{R}}_d$

The NGM for the dengue IRN includes the nine human and two mosquito classes infected with dengue. (The calculations are nearly identical to those for $\tilde{\mathcal{R}}_z$.) We order them as follows:

$$\mathbf{x}(t) = (I_d, I_c, J_d, I_{d0}, I_{c0}, J_{d0}, I_{d\omega}, I_{c\omega}, J_{d\omega}, I_{dm}, I_{cm})^T.$$

Decomposing $d\mathbf{x}/dt = \mathcal{F} - \mathcal{V}$ and differentiating $F = d\mathcal{F}/d\mathbf{x}|_{ZEE}$ and $V = d\mathcal{V}/d\mathbf{x}|_{ZEE}$ yields, as with the Zika IRN, a block off-diagonal F and triangular V:

$$F = \begin{bmatrix} 0_{9\times 9} & F_{d1} \\ F_{d2} & 0_{2\times 2} \end{bmatrix},$$

$$F_{d1} = \frac{\beta_{hd}}{N_h} \begin{bmatrix} S^* & I^*_z & R^*_z & V^*_0 & I^*_{z0} & R^*_{z0} & V^*_\omega & I^*_{z\omega} & R^*_{z\omega} \\ \nu_d S^* & \nu_d I^*_z & \nu_d R^*_z & \nu_d V^*_0 & \nu_d I^*_{z0} & \nu_d R^*_{z0} & \nu_d V^*_\omega & \nu_d I^*_{z\omega} & \nu_d R^*_{z\omega} \end{bmatrix}^T,$$

$$F_{d2} = \frac{\beta_{md}}{N_h} \begin{bmatrix} S^*_{zm} & S^*_{zm} & k_d S^*_{zm} & S^*_{zm} & S^*_{zm} & k_d S^*_{zm} & k_d S^*_{zm} & k_d S^*_{zm} & k_d S^*_{zm} \\ I^*_{zm} & I^*_{zm} & k_d I^*_{zm} & I^*_{zm} & I^*_{zm} & k_d I^*_{zm} & k_d I^*_{zm} & k_d I^*_{zm} & k_d I^*_{zm} \end{bmatrix},$$

$$V = \begin{bmatrix} \bar{\mu}+\bar{\Delta} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ -\bar{\Delta} & \bar{\mu}+\gamma_z & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & -\gamma_z & \bar{\mu} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & \bar{\mu}+\bar{\Delta} & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & -\bar{\Delta} & \bar{\mu}+\gamma_z & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & -\gamma_z & \bar{\mu} & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & \bar{\mu}+\bar{\Delta} & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & -\bar{\Delta} & \bar{\mu}+\gamma_z & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & -\gamma_z & \bar{\mu} & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & \mu_m+\beta_{mz}t^*_z & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & -\beta_{mz}t^*_z & \mu_m \end{bmatrix},$$

where (to conserve space) $\bar{\mu} = \mu_h + \gamma_d$, $\bar{\Delta} = \beta_{hz} I^*_{zm}/N_h$. The NGM is then given by the product FV^{-1} which, like F, is block off-diagonal, of the form

$$\begin{bmatrix} 0_{9\times 9} & M_{d1} \\ M_{d2} & 0_{2\times 2} \end{bmatrix},$$

where

$$M_{d1} = \frac{\beta_{hd}}{\mu_m N_h}\begin{bmatrix} g_dS^* & g_dI_z^* & g_dR_z^* & g_dV_0^* & g_dI_{z0}^* & g_dR_{z0}^* & g_dV_\omega^* & g_dI_{z\omega}^* & g_dR_{z\omega}^* \\ \nu_dS^* & \nu_dI_z^* & \nu_dR_z^* & \nu_dV_0^* & \nu_dI_{z0}^* & \nu_dR_{z0}^* & \nu_dV_\omega^* & \nu_dI_{z\omega}^* & \nu_dR_{z\omega}^* \end{bmatrix}^T,$$

$$M_{d2} = \frac{\beta_{md}}{(\mu_h+\gamma_d)N_h}\begin{bmatrix} q_zS_{zm}^* & z_iS_{zm}^* & k_dS_{zm}^* & q_zS_{zm}^* & z_iS_{zm}^* & k_dS_{zm}^* & k_dS_{zm}^* & k_dS_{zm}^* & k_dS_{zm}^* \\ q_zI_{zm}^* & z_iI_{zm}^* & k_dI_{zm}^* & q_zI_{zm}^* & z_iI_{zm}^* & k_dI_{zm}^* & k_dI_{zm}^* & k_dI_{zm}^* & k_dI_{zm}^* \end{bmatrix},$$

q_z and z_i are as given in the main text, and (again to conserve space) $g_d = \frac{\mu_m+\beta_{mz}t_z^*\nu_d}{\mu_m+\beta_{mz}t_z^*}$. This matrix has eigenvalues zero (with multiplicity nine) and $\pm\tilde{\mathcal{R}}_d$, where $\tilde{\mathcal{R}}_d$ is as given in the main text.

B The effect of dengue vaccination on the ZEE

From the equilibrium condition for I'_{zm} in system (1) we have that $t_z^* = \mu_m I_{zm}^*/\beta_{mz}(N_m - I_{zm}^*)$. By definition, we also have that $t_z^* = [I_z^* + I_{z0}^* + k_z(J_z^* + J_{z1}^* + I_{z\omega}^* + J_{z2}^*)]/N_h$. I_{zm}^* can therefore be determined from the equation obtained by setting these two expressions equal and dividing both sides by I_{zm}^*. This equation has the form $f_{zL}(I_{zm}^*) = f_{zR}(I_{zm}^*)$, where $f_{zL}(x) = \mu_m/\beta_{mz}(N_m - x)$ is increasing on $[0, N_m)$ and f_{zR} is obtained from $[I_z^* + I_{z0}^* + k_z(J_z^* + J_{z1}^* + I_{z\omega}^* + J_{z2}^*)]/(N_h I_{zm}^*)$ by substituting the equilibrium values at the ZEE and then the definitions of the c_i. After a significant amount of algebra, and denoting $u = a_0 + (1-a_0)k_z$ (note $u > 1$ since $k_z > 1$), we rewrite

$$\begin{aligned} f_{zR}(x) = &\frac{\beta_{hz}}{N_h}\frac{\mu_h}{\mu_h+\gamma_z}\left\{\frac{(1-\alpha)[1-p(1-\chi)]}{\mu_h+\beta_{hz}\frac{x}{N_h}+\phi(1-\chi)}\left[\frac{\mu_h+\gamma_z+\phi(1-\chi)u}{\mu_h+\gamma_z+\phi(1-\chi)}+\frac{\phi(1-\chi)u}{\mu_h+\beta_{hz}\frac{x}{N_h}}\right]\right. \\ &\left.+\frac{(1-\alpha)p(1-\chi)u}{\mu_h+\beta_{hz}\frac{x}{N_h}}+\frac{k_z\alpha}{\mu_h+\beta_{hz}\frac{x}{N_h}}\right\} \\ = &\frac{\beta_{hz}}{N_h}\frac{\mu_h}{\mu_h+\gamma_z}\left\{\frac{(1-\alpha)+k_z\alpha}{\mu_h+\beta_{hz}\frac{x}{N_h}}+(1-\alpha)(u-1)\times\right. \\ &\left.\left[\frac{[1-p(1-\chi)]\phi(1-\chi)}{\mu_h+\beta_{hz}\frac{x}{N_h}+\phi(1-\chi)}\left(\frac{1}{\mu_h+\gamma_z+\phi(1-\chi)}+\frac{1}{\mu_h+\beta_{hz}\frac{x}{N_h}}\right)+\frac{p(1-\chi)}{\mu_h+\beta_{hz}\frac{x}{N_h}}\right]\right\} \end{aligned}$$

to see that f_{zR} is decreasing on $[0, N_m)$. Since f_{zL} has a vertical asymptote at N_m, there is thus a unique intersection $I_{zm}^* \in (0, N_m)$ iff $f_{zL}(0) < f_{zR}(0)$. Further algebra shows that $f_{zR}(0)/f_{zL}(0) = \mathcal{R}_z^2$, so the condition is equivalent to $\mathcal{R}_z > 1$.

We now observe that if $\chi = 1$ or $p = \phi = 0$, f_{zR} simplifies to $\frac{\beta_{hz}}{N_h}\frac{\mu_h}{\mu_h+\gamma_z}\frac{(1-\alpha)+k_z\alpha}{\mu_h+\beta_{hz}\frac{x}{N_h}}$. Otherwise, by inspection $f_{zR}(x) > \frac{\beta_{hz}}{N_h}\frac{\mu_h}{\mu_h+\gamma_z}\frac{(1-\alpha)+k_z\alpha}{\mu_h+\beta_{hz}\frac{x}{N_h}}$ for each $x \in [0, N_m)$. Since $f_{zL}(x)$ is increasing, a higher value of $f_{zR}(x)$ moves the intersection point to the right; thus dengue vaccination (with $\chi < 1$) increases I_{zm}^*. Recalling that $t_z^* = \mu_m I_{zm}^*/\beta_{mz}(N_m - I_{zm}^*)$, we observe that increasing Zika prevalence in mosquitoes I_{zm}^*/N_m also increases the effective Zika prevalence t_z^* in humans t_z^*. We can also see that the true Zika prevalence in humans is increased: it is $I_{zm}^* f_{zR}(I_{zm}^*)$ with $u = 1$, which simplifies to $\frac{\mu_h}{\mu_h+\gamma_z}\frac{\beta_{hz}\frac{I_{zm}^*}{N_h}}{\mu_h+\beta_{hz}\frac{I_{zm}^*}{N_h}}$, which is clearly increasing in I_{zm}^*.

Declarations

Competing interests

CK received travel support from his home institution and is one of the guest editors for this Topical Collection. The authors received no other support from any organization for the submitted work.

Data availability

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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