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Impact of dengue vaccination choice on Zika risk: free riders and the tragedy of the commons

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Abstract

Dengue vaccination, long in development, has become controversial as it may cause antibody-dependent enhancement (ADE) in dengue-seronegatives. Under partial vaccine failure, ADE increases case severity and may also affect Zika infections since the two viruses are closely related. From an individual perspective, the vaccination of others appears beneficial, but becoming vaccinated oneself may increase the risk of ADE and thus serious illness, for both diseases. From a population-level perspective, vaccination is expected to reduce the spread of dengue but increase Zika incidence. Nevertheless, prior mathematical modeling research has shown that in some cases, a small number of dengue vaccinations may reduce the final size of a Zika outbreak despite increasing its ability to spread. This study reconciles these results and then evaluates individual risks to both the vaccinated and the unvaccinated in order to connect to broader themes in complex vaccination decisions, such as free riders and the tragedy of the commons. A substantial new finding is that a dual outbreak may change which vaccination decision minimizes risk, compared to single-outbreak scenarios.

Keywords: antibody-dependent enhancement, vector-borne disease, immune response, coinfection model, dengue seropositivity

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Impacto de la elección de la vacunación contra el dengue en el riesgo de Zika: oportunistas y la tragedia de los comunes

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Resumen

La vacunación contra el dengue, que lleva mucho tiempo en desarrollo, se ha vuelto controvertida ya que puede causar un aumento dependiente de anticuerpos (ADE) en los seronegativos para el dengue. En caso de falla parcial de la vacuna, ADE aumenta la gravedad de los casos y también puede afectar las infecciones por Zika, ya que los dos virus están estrechamente relacionados.

Desde una perspectiva individual, la vacunación de otros parece beneficiosa, pero vacunarse uno mismo puede aumentar el riesgo de ADE y, por lo tanto, de enfermedades graves, para ambas enfermedades. Desde una perspectiva a nivel de la población, se espera que la vacunación reduzca la propagación del dengue pero aumente la incidencia del Zika. Sin embargo, la investigación previa de modelos matemáticos ha demostrado que, en algunos casos, una pequeña cantidad de vacunas contra el dengue puede reducir el tamaño final de un brote de Zika a pesar de aumentar su capacidad de propagación. Este estudio reconcilia estos resultados y luego evalúa los riesgos individuales tanto para los vacunados como para los no vacunados para conectar con temas más amplios en decisiones de vacunación complejas, como los oportunistas y la tragedia de los comunes. Un nuevo hallazgo sustancial es que un brote dual puede cambiar la decisión de vacunación que minimiza el riesgo, en comparación con los escenarios de un solo brote.

Palabras clave: mejora dependiente de anticuerpos, enfermedad transmitida por vectores, respuesta inmune, modelo de coinfección, seropositividad al dengue

1. Introduction

The COVID-19 pandemic has brought to the forefront of public health policy the question of how best to control an infectious disease through mass vaccination when some of the population find it controversial. The only scientific concerns about COVID-19 vaccination have involved side effects that are relatively rare but are observed when millions of people are vaccinated. From a public health policy perspective, there is a need to judge the relative risks—of side effects if vaccinated, and of infection if unvaccinated—before making a recommendation as to which groups of people should be vaccinated, but each individual also makes his or her own decision, which may not always follow such recommendations. Regardless of the reasons, so-called "vaccine hesitancy" can affect the success of control programs, such as the notion of herd immunity.

Another recent example of a vaccine with controversial side effects involves the mosquito-borne dengue virus, endemic (with an estimated 100 million cases per year) to tropical areas, where the existence of four dengue serotypes and a phenomenon known as antibody-dependent enhancement (ADE) have complicated the use of a long-awaited dengue vaccine. ADE occurs when a person whose immune system has already developed antibodies to one virus serotype then develops increased, rather than decreased, vulnerability to infection by closely related pathogens. Those antibodies may falsely identify related pathogens as their intended target and flag them for removal by macrophages, but when the still-active related pathogen enters a macrophage, it uses the cell to replicate, raising the individual's viral load significantly. Subsequent, "secondary" dengue infections by a different serotype are thus often much more severe than primary dengue infections, leading to the sometimes fatal dengue hemorrhagic fever (DHF). Furthermore, the Zika virus is closely enough related to dengue that some evidence indicates that dengue-induced ADE may amplify later Zika infection in a patient and vice versa (see references in [7]). The tetravalent dengue vaccine Dengvaxia by Sanofi-Pasteur has been controversial since it was observed that in some cases vaccination induces ADE (like natural prior dengue exposure does) in subsequent dengue infections—and thus also potentially in Zika infections. Since vaccination against dengue provides no protection against Zika and may instead amplify Zika cases through ADE, widespread vaccination using Dengvaxia has been expected to increase the size of Zika outbreaks, regardless of whether its protective effects against dengue outweigh its exacerbation of dengue transmission through ADE. To address the latter issue, the World Health Organization (WHO) has recommended applying Dengvaxia only to individuals already screened as dengue-seropositive [12], since they already have ADE potential, so vaccination will not make things worse. This makes Dengvaxia more useful in areas with high dengue endemicity, where most people will pass screening.

The use of mathematical models to describe the transmission dynamics of infectious diseases and evaluate the potential impact of preventive measures has a long history, including notably the work of Ronald Ross, who showed at the turn of the twentieth century that malaria could be eradicated by reducing mosquito population density below a critical threshold level. Public health policy in the twenty-first century has drawn heavily on mathematical models to estimate the timing and size of epidemic peaks and the healthcare resources needed at any given time. The impact of potential dengue vaccination and associated ADE on the transmission of dengue and Zika in affected areas has been studied by several authors using mathematical models (e.g., [1, 4, 6, 9, 10, 11]). Of these studies, only [1] and [4] incorporated the WHO-recommended screening requirement for dengue vaccination, in order to study the likely impact of dengue vaccination using Dengvaxia on identified seropositives (individuals with dengue-specific antibodies). These studies were also the only ones to consider multiple dengue serotypes. However, [1] considered only the impact on dengue transmission, and did not study the interplay with Zika ([4] studied the impact of tetravalent vaccination following screening on the spread of both viruses).

A striking finding of [10], studying a single initial (at the start of the outbreak) round of vaccination without any screening or prior natural seropositivity, was that in settings with high dengue spread but limited Zika spread, a little dengue vaccination can reduce Zika incidence (final outbreak size), even though a lot of vaccination increases Zika incidence. (The authors sought a vaccination proportion to minimize Zika outbreak size.) The corresponding "dip" in the graph of final Zika outbreak size versus vaccination rate (Figures 2b and 3 in [10]) before turning around to rise monotonically afterward seems to run counter to the result, consistent across the studies mentioned above, that dengue vaccination should always increase Zika's reproductive number, and thus Zika incidence. The authors of [10] explain their result in terms of the (indirect) effect of dengue vaccination on the unvaccinated. This raises the issue of the tension which sometimes exists between the best interests of the population and the best interests of a single individual. This tension connects to concepts from economics such as *free riders*—individuals who benefit from a collective resource without paying for it—and *the tragedy of the commons*—a scenario where individuals' interests run counter to the interests of the community. In a classic tragedy of the commons scenario, individuals each take so much of a shared resource that it is unsustainably depleted and becomes unavailable—overfishing a species to extinction, for instance, instead of sustainable consumption. Here, the resources in question are drops in risks for dengue and Zika infections accessible through different vaccination choices. A mathematical model can quantify and explain these changes in risk from both the individual and collective perspectives.

This study uses the model developed in [4], which is essentially a generalization of the model used in [10], as a lens through which to examine these perspectives in the context of

tetravalent dengue vaccination and vaccine hesitancy, and their impact on Zika transmission. After reviewing the added resolution afforded by this model, we revisit the analysis of [10] in order to explain more precisely the factors underlying the "dip" in a Zika outbreak's final size as the initial dengue seropositivity rate increases from zero. We then conduct a formal analysis of relative risk for vaccinated and unvaccinated individuals in order to connect this result to a broader understanding of individual versus collective risk and reward.

2. Materials and Methods

Dengue and Zika infections are typically modeled using an SIR structure: individuals start out susceptible (S) to the pathogen, may become infected (I), and upon recovery (R) are considered to have developed lifelong immunity to that serotype. Since mosquito vectors carry the pathogen in their gut rather than hosting it, they have no "recovery" and may be classified as either susceptible or infectious. (Exposed periods are neglected as a simplifying assumption.) Assuming that an individual can be at any stage of either disease, this results in nine possible combinations of infection status for Zika and a single dengue serotype (and four for vectors). This basic structure, which allows one also to take ADE into account, has been used by [10] and other authors to study this co-circulation scenario, with vaccination or any other kind of prior exposure (seropositivity) confined to initial conditions.

Kribs and Greenhalgh [4] extend this model to incorporate the more complex dengue seropositivity status that arises in many areas, where either prior exposure involves a different dengue serotype than the one now circulating, or the use of a tetravalent vaccine such as Dengvaxia may generate an immune response against any combination of the four serotypes. This additional trajectory also has three stages: unvaccinated, vaccinated without immunity to a noncirculating serotype, and vaccinated with immunity to a noncirculating serotype. These stages are important to distinguish because (1) the unvaccinated (including those turned away by a negative screening test) may still seek vaccination in the future, when a so-called "catch-up" vaccination campaign is underway, and (2) immunity to a noncirculating dengue serotype can produce ADE in a secondary infection with the circulating serotype, while immunity to two or more dengue serotypes generally prevents further symptomatic dengue infections. The two vaccinated stages, along with the stage of dengue infection representing acquired immunity to the locally circulating serotype, account for all possible combinations of dengue serotype immunities because immunity to more than two serotypes is assumed to have the same effect as immunity to two.

Crossing these three trajectories (infection with the circulating dengue serotype, Zika infection, and dengue vaccination) then produces twenty-seven possible status combinations

for humans (alongside the four for mosquitoes). Human compartments can thus be labeled by a three-letter sequence indicating Zika infection status (Susceptible, Infected, or Recovered), dengue infection status (S, I, or R), and dengue vaccination status (Unvaccinated, Vaccinated but not protected, and Protected against one noncirculating serotype), respectively (so, for example, SSU and SSV are completely seronegative populations). Mosquito compartments are labeled with two letters indicating Zika and dengue infection status (S or I), respectively.

Figure 1 illustrates the flows and combinations for the basic two-infection model used by [10] and others, along with the additional dengue immunization trajectory of [4]. (A minor caveat is that [10] also considers simultaneous coinfection with both dengue and Zika. The model in [4] does not add this pathway.) Here, the increased viral load due to ADE is assumed to increase a person's infectivity by a given factor (which may also include behavior changes in the host and vector). Figure 2 illustrates the flows and combinations for the three-trajectory model from [4]. See [4] for a full discussion of the differential equations and parameters which make up the model.

An advantage of the model developed by [4] is that it distinguishes three ways that individuals may become dengue-seropositive: through prior exposure to the same or a different dengue serotype, through routine "age-in" vaccination upon reaching the age (currently nine years) of eligibility for vaccination, or through "catch-up" vaccination in which eligible individuals who were not vaccinated earlier (for instance, due to a negative screening test) may seek vaccination at any time. It also distinguishes seropositivity to different dengue serotypes, which is important because (as noted above) immunity to one noncirculating serotype can produce ADE in an infection with the circulating serotype, while immunity to two or more serotypes is assumed to preclude further clinical infections [3, 8]. Earlier models do not offer this level of detail (restricting any form of dengue seropositivity to a single parameter in the initial conditions, in several cases), which is necessary in order to disentangle the roles played in determining Zika outbreak size by these different causes of dengue seropositivity.

3. Results

3.1. When dengue vaccination reduces Zika incidence

Investigating the effects of dengue vaccination on Zika incidence at the population level with a model means simulating outbreaks, using known characteristics of dengue and Zika transmission and of vaccine and screening efficacy, and varying the characteristics of a hypothetical vaccination program, namely the coverage rates. In [4], the authors established a representative set of model parameter values based on primary literature reporting on

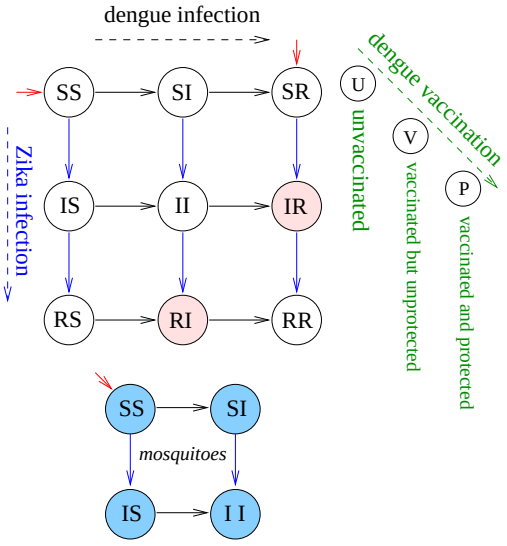

Figure 1: The two-infection model depicting the dengue and Zika transmission cycles, to which a dengue vaccination trajectory is added to form the model in [4]. "Protection" refers to seropositivity against a noncirculating dengue serotype. Classes with red shading in this figure and the next experience ADE.

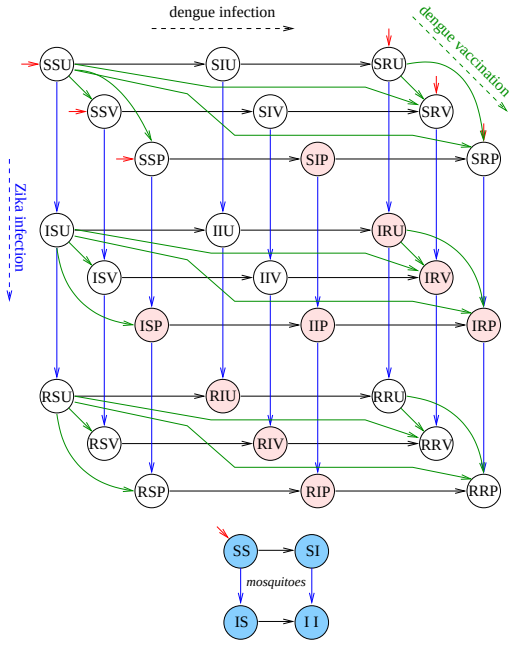

Figure 2: The three-trajectory flow of the model in [4], depicting dengue (horizontal, black arrows) and Zika (vertical, blue arrows) transmission as well as tetravalent dengue vaccination (diagonal, green arrows). Short, red arrows into Zika-susceptible classes show incoming dengue immune statuses. (Mortality omitted.)

studies from the countries where Dengvaxia's clinical trials occurred (population size was set to 10,000 for questions of scale). Using these values (which include baseline dengue seropositivity due to prior exposure) and varying the amount of vaccination, model simulations find the final size of a Zika outbreak to increase monotonically with vaccination rate (Figure 3), without the "dip" observed by [10] for low vaccination rates.

However, the authors of [10] only considered vaccination to take place prior to an outbreak, rather than ongoing age-in vaccination as new individuals age into eligibility for vaccination. Effectively, they were modeling dengue seropositivity developed before the simulation began. Since dengue seropositivity from prior infection tends to be significant in dengue-endemic areas, the representative parameters in [4] include that, meaning that even without any vaccination, the level of initial dengue seropositivity is too high to see

the drop observed when vaccination first increases from zero. To replicate their result, we therefore turned off vaccination and varied the prior exposure rate from zero. Under these conditions, the model observes a significant drop in the final Zika outbreak size before increasing (Figure 4).

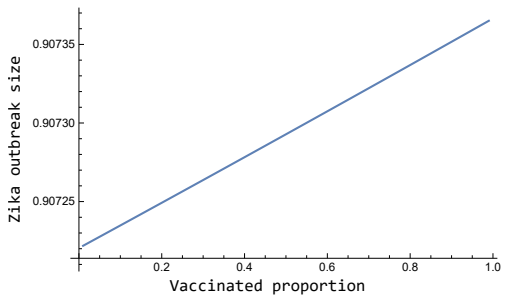

Figure 3: Vaccination always increases final Zika outbreak size using the default parameters in the model from [4].

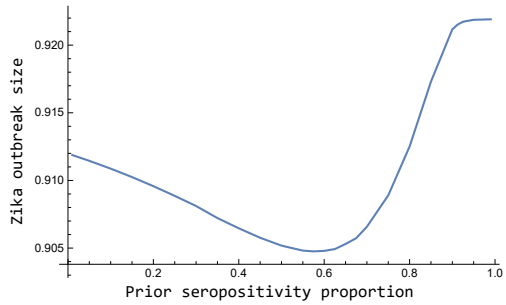

Figure 4: Using the model from [4] but varying prior dengue seropositivity instead of vaccination rate, the final Zika outbreak size drops as seropositivity rises, before increasing.

Further numerical analysis (details omitted) verifies that any of the three quantities prior seropositivity, age-in (routine) vaccination rate, and catch-up vaccination rate can generate the drop under different conditions. For instance, in a population with no prior exposure to dengue, age-in vaccination can provide the first dengue seropositivity in the population—but only if vaccine efficacy is significant *and* the screening test's specificity is poor enough. If the population starts out dengue-seronegative, accurate pre-vaccination screening will reject all of them, and no one will be vaccinated at first. Only false positives will lead to vaccinations, which lead to seropositivity only when the vaccine actually "takes" (vaccine efficacy). If the screening used produces no false positives, then in a population with no prior exposure to dengue, only catch-up vaccination will ever occur.

Making an individual dengue-seropositive (regardless of serotype) has two effects regarding later Zika infection. Most directly, the presence of dengue antibodies causes any subsequent Zika infection in that individual to exhibit ADE, and thus generate more Zika cases (than a non-ADE Zika case with the same contact rate). Indirectly, on the other hand, it prevents that individual from later spreading dengue to other, unvaccinated people. Those unvaccinated people who remain dengue-seronegative and are later infected with Zika will have non-ADE cases and thus generate fewer Zika cases. These two effects run counter to each other, so the net impact of dengue seropositivity on total Zika incidence depends on which effect is greater.

Why do the first few dengue-seropositives in a population reduce the final size of a Zika outbreak? When nearly the entire population is dengue-seronegative, nearly all the dengue cases averted by making one individual seropositive involve seronegatives, so the number of later Zika cases that have ADE drops by much more than 1. Thus, the negative effect on the Zika outbreak (preventing ADE in the unvaccinated) is stronger than the positive effect of making the one seropositive have ADE in any later Zika infection.

However, as the number of dengue-seropositives increases (by whatever means), more of those dengue cases averted by an additional dengue-seropositive involve individuals who are already dengue-seropositive themselves and will thus have ADE in any Zika infection anyway. Thus, the negative effect of dengue seropositivity on a Zika outbreak is diluted, while the positive effect (ADE in Zika infections among the dengue-seropositive) continues unabated. When there are enough dengue-seropositives already, adding one more (e.g., by vaccination) raises the final Zika count rather than lowering it, and the imbalance only widens as the dengue-seropositivity level increases.

The critical dengue seropositivity level at which the final Zika outbreak size reaches its minimum depends on both the vaccination rates and the reproductive abilities of the two pathogens. Regarding the latter, the authors of [10] observed that the drop in final Zika outbreak size for low vaccination rates only occurs in scenarios where dengue spreads well but Zika spreads relatively poorly (as measured by their reproductive numbers). The more dengue there is, the less restrictive the conditions (on vaccine efficacy and screening accuracy) are under which this drop occurs, but the more Zika there is, the more restrictive the conditions are. As dengue transmission increases and/or Zika transmission decreases, the critical dengue seropositivity level increases above zero to a point that may be achievable for small levels of prior exposure and vaccination, but in a more restrictive setting this critical level may be negative and the drop never observed.

However, since [10] incorporated vaccination exclusively through initial conditions, vaccination characteristics are not reflected in the corresponding reproductive numbers. But further analysis of the model in [4] shows how dengue seropositivity (prior exposure), screening, age-in vaccination, and catch-up vaccination all contribute differently to this phenomenon, which only manifests in a limited interval of vaccinations, after which further vaccination always increases the number of Zika cases. This analysis yields the following results.

When there is significant prior dengue exposure, then it matters whether the seropositivity is to the same serotype as the one currently circulating. If the serotypes are the same, then an increase in prior exposure without any vaccination produces the "dip" previously observed (Figure 4). If instead the serotypes differ, then prior seropositivity by itself only

increases the final Zika outbreak size, and vaccination is limited to containing the growth in dengue cases.

When there is high seropositivity to a different dengue serotype than the one in circulation, it changes how that prior exposure interplays with vaccination. Dengue-seropositives who get vaccinated and develop seropositivity to only one additional serotype are then considered immune to any further clinical dengue infection, whereas dengue-seronegatives with that same reaction to vaccination are then at risk of ADE to both dengue and Zika. Let us consider momentarily a situation where nearly everyone is eventually able to be vaccinated—and Kribs and Greenhalgh found that seeking screening 3–4 times a year, say once every 100 days, was enough to guarantee this when screening was imperfect. Among vaccinated seropositives, those in whom vaccination completely fails (i.e., causes no new antibodies to develop) are at risk of ADE of dengue, while the rest are immune to the circulating serotype (due to seropositivity to two or more serotypes). Among vaccinated seronegatives, those in whom vaccination completely fails are at normal risk of dengue, those in whom vaccination protects only against one noncirculating serotype are at risk of ADE of dengue, and the rest are immune to the circulating serotype. Some simple calculations using existing vaccine efficacy data (see Appendix A) show that in this case, vaccinated seropositives have a lower average dengue infectivity than vaccinated seronegatives. Therefore, prior dengue exposure to a different serotype, along with a significant vaccination rate, should lower the total number of dengue cases—but with so much dengue seropositivity, the overall effect on a Zika outbreak is to increase it.

Without significant prior dengue exposure, dengue's ability to spread (e.g., its reproductive number) and the screening sensitivity (probability of avoiding false negatives) and specificity (probability of avoiding false positives) determine whether age-in (routine) or catch-up vaccination will have a greater impact. When dengue spreads very well and sensitivity is high enough, or contrarily when dengue's spread is limited, but specificity is low enough (90%, for instance), age-in dengue vaccination has the first impact on Zika outbreak size and can generate the "dip." Otherwise, it results in too few vaccinations to have a significant impact, and catch-up vaccination becomes more important, since repeated (over time) screenings increase the proportion of people who receive the vaccine.

It is also worth noting that the drop in final Zika outbreak size for low (but nonzero) dengue seropositivity levels, when it occurs, does *not* contradict the fact (observed in [4]) that dengue seropositivity consistently increases Zika's control reproductive number. Any apparent discrepancy can be reconciled by recalling that the control reproductive number (like the basic reproductive number) measures a pathogen's ability to spread *at the beginning of an outbreak*, and not over the entire course of the outbreak, much less the cumulative total number of cases. The general trend is that both measures of outbreak

intensity are increased by any kind of dengue seropositivity (whether from vaccination or prior exposure), but low levels of it may slightly reduce the final outbreak size while also increasing the spread at the beginning of the outbreak.

3.2. Relative risks

Having examined the effects of dengue vaccination at the population level, in order to understand the decisions of individuals whether or not to seek vaccination, we must examine the effects at the individual level. To do this, we consider the relative risks for both dengue and Zika infection as a function of whether or not a person is vaccinated, assuming that a typical person does not know his/her dengue seropositivity status. Relative risk can be calculated using the (per capita) rate at which one unvaccinated or vaccinated person is infected and the proportion of such infections that exhibit ADE (the risk factor for severe cases). Comparing these quantities for an unvaccinated versus a vaccinated person shows how vaccination changes a person's risk of infection or severe infection. Vaccine hesitancy typically arises when a person believes (rightly or wrongly) that vaccination increases his or her overall risk.

The relative risk computations for both dengue and Zika are shown in Table 1 in Appendix B, in terms of the parameters of the model used by [4]. This analysis shows that while vaccinating oneself against dengue does not affect one's risk of Zika infection, it does increase the ADE risk for any later Zika infection. The amount of increase depends on the relative spreads of the two pathogens. When dengue spreads better than Zika, vaccination causes little change in ADE risk because most people will become dengue-seropositive from infection anyway before they become infected with Zika. When Zika spreads much better than dengue (or when both pathogens spread poorly), on the other hand, dengue-seronegative status is easier to keep until Zika infection, so vaccination increases ADE risk, by a factor inversely proportional to the prior dengue seropositivity rate. For instance, with 50% prior dengue exposure, ADE risk for Zika roughly doubles.

As regards dengue risk, dengue vaccination reduces one's overall risk of dengue infection (for seronegatives only, if prior seropositivity is to the circulating serotype) but may raise or lower the risk of ADE in those who do become infected with dengue. If any prior dengue exposure in the population is to the same serotype now circulating, then vaccination impacts only seronegatives (through screening failure: false positives), and increases the ADE risk of any dengue infection only if (according to parameter estimates, see Appendix B for details) dengue spreads more than 10 to 20 times as well as Zika—which is trivially true in the absence of a Zika outbreak, but unlikely when both pathogens are circulating. If instead prior dengue exposure is to a different serotype than the one now circulating, then in addition vaccination reduces both dengue infection and ADE risks for dengue-seropositives. In short, the presence of a Zika outbreak changes the individual calculus

regarding dengue risk and vaccination, because the possibility of Zika infection (prior to dengue infection) raises the risk of ADE of dengue even without vaccination.

The relative risks above all address the impact of vaccinating oneself against dengue. In examining motivations behind vaccination decisions, it is also important to consider the impact of others' vaccinations on one's own disease risks. In particular, the perspective behind the result discussed in the previous section, where unvaccinated benefit (enjoy reduced Zika ADE risk) from the vaccination of a small number of others, connects to the issue of so-called "free riders" who enjoy a collective benefit without contributing to it. Analysis of relative risks (see Appendix B again) indicates that, for the unvaccinated, other people getting vaccinated against dengue reduces one's risk of dengue infection but, in so doing, actually increases the risk of ADE of any dengue infection when Zika is circulating (since then any dengue infection is likely to occur later than a Zika infection, which will cause ADE in the later infection). Conversely, it generally increases one's risk of Zika infection (except in the special circumstance described in the previous section) while decreasing the risk of ADE of any Zika infection when dengue is circulating.

Since other people's vaccinations reduce an unvaccinated person's overall dengue risk as well as the risk of ADE of Zika in dengue-endemic areas, the "free rider" perspective may be attractive to some, and lead to vaccine hesitancy. The fact that this overall community benefit only arises when enough people become vaccinated makes it an example of a "tragedy of the commons" scenario. Here, the shared resource created by dengue vaccination is a reduction in community dengue infection risk, which could then lead to a reduction in ADE risk for Zika. This resource is created by those who vaccinate themselves but is automatically enjoyed by all members of the community, vaccinated and unvaccinated. The cost to create the resource is a concomitant increase in ADE risk for Zika. Unvaccinated individuals then act as free riders by enjoying the resource without paying the cost. This tragedy-of-the-commons scenario varies from the classic one in that, in the classic case, resource production is initially fixed and costless while consumption varies and has a collective cost; here, consumption (enjoying the benefits of others' vaccination) is fixed and costless while resource production (vaccinating oneself) varies and has an individual cost (see Figure 5 for an illustration). Thus, instead of resource production being free to consumers but individual resource consumption costing everyone, this vaccination scenario makes resource production cost individuals while resource consumption is free to all.

Public health practitioners who speak with individuals about vaccination may prefer to think about these risks in terms of impacts on the individual. Appendix C recasts these analyses in those terms.

As recently seen in the COVID-19 pandemic, vaccine hesitancy (regardless of motivation) can have a major impact on the course of an epidemic. Analysis of the kind of decision-

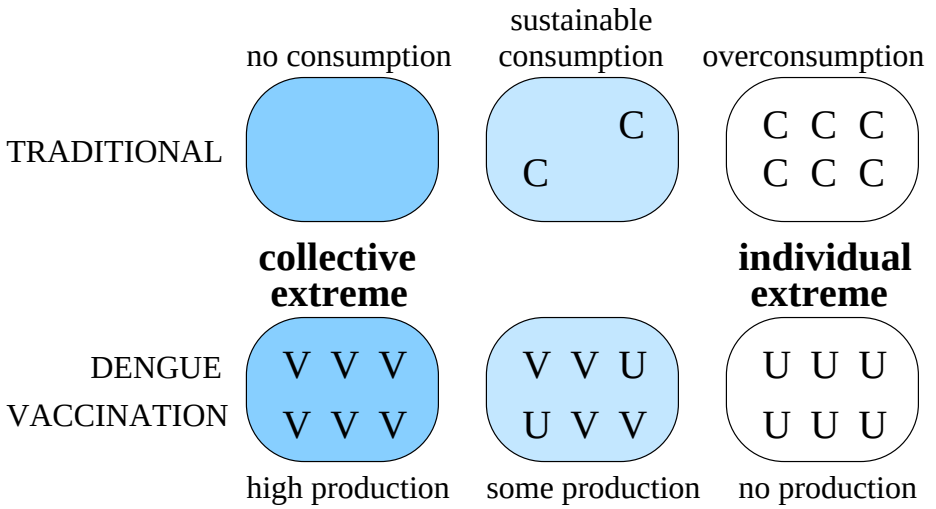

Figure 5: Illustrations of the classic tragedy of the commons scenario and the one discussed in this study. In both cases, shading indicates resource availability.

making that occurs when one considers the effects of others' actions can lead to more complex scenarios. It is important to note that there is a rich body of research literature applying ideas from the mathematical field of game theory to vaccination behaviors (e.g., [2, 5]); this study does not delve into these more complex mathematical analyses but limits itself to observations based on simple algebra and some numerical simulations of transmission dynamics. The main points established by the relative risk analysis in this section are the risk perspective of the free rider and the fact that, significantly, the cocirculation of both viruses actually changes the impact of dengue vaccination on individual risks for both dengue and Zika.

4. Discussion

The importance of individuals' decisions about vaccination and other disease-preventive behaviors has been highlighted by the COVID-19 pandemic. Regardless of government and public health directives, individuals make decisions based on their perceptions (right or wrong) of personal risk. The dengue vaccine Dengvaxia developed by Sanofi-Pasteur became controversial for its potential to activate ADE in dengue-seronegative vaccinees, causing severe, potentially fatal cases. The discovery that the dengue and Zika viruses are closely enough related for antibodies against one to cause ADE of the other has led to

theoretical studies using mathematical models to extend the study of vaccination's impact from dengue to include Zika transmission as well.

This study used one of these dynamical models which also incorporates the WHO-related screening prior to vaccination, in order to compare the impacts of vaccination at the population level and at the individual level. Investigating a previously observed result that low levels of dengue vaccination may reduce the final size of a Zika outbreak led to the determination that the first few instances of dengue seropositivity, whether from prior exposure or vaccination, offer a window in which the indirect effect of Zika ADE cases averted in the unvaccinated outweighs the direct effect of ensuring ADE in any Zika cases among the vaccinated, in scenarios where dengue spreads better than Zika (and thus the dengue cases averted would have occurred prior to Zika infections in those individuals). Otherwise, dengue vaccination increases the final size of a Zika outbreak.

In moving from the population to the individual level, we saw that while the vaccination of oneself or of others in the community may increase ADE risk for either dengue or Zika in a setting where only one of the viruses is circulating, the impact of vaccination on both infection and ADE risks can be reversed by the presence of both viruses in the community. For instance, vaccinating oneself is more likely to lower than to increase the risk of ADE of dengue (for seronegatives, the original concern over Dengvaxia) when Zika is circulating, because vaccine success is far more likely than the combination of vaccine failure *and* avoiding Zika infection (which would cause ADE anyway) until an eventual dengue infection. Meanwhile, remaining unvaccinated while others in the community get vaccinated increases one's risk that any dengue infection will have ADE (and be severe), for the same reason that the reduced overall dengue incidence means dengue infections take longer to happen, by which time one is more likely to have had a Zika infection. However, while any vaccinations raise the background risk of Zika infection by increasing overall incidence (except in the circumstances described in the previous paragraph), remaining unvaccinated does result in a lower risk of ADE of Zika than vaccinating oneself, for the dengue-seronegative.

This last fact reiterates the importance of screening for dengue seropositivity before vaccination. Successful screening protects the interests of the individual, over those of the community, at times. As observed in [4], a small amount (10%) of screening failure (false positives) or omission might reduce total cases in a dual outbreak by over 20% but increases the number of severe (ADE) cases significantly (by 2.4% in the simulation). Despite the tension that may arise between individual and collective interests, screening for dengue seropositivity, together with education regarding the impact of either decision (to vaccinate oneself or not) on infection-related risks, remains key to making an informed decision.

Previous studies have posed the question of dengue vaccination's impact on dengue and Zika incidence, but here we see an impact in the reverse direction: the presence of either pathogen affects dengue vaccination's impact on the other disease. Specifically, a dual outbreak with both pathogens spreading increases the baseline risk for ADE of both infections completely apart from vaccination. This means that even under limited vaccine efficacy, vaccination may lower risk of severe (ADE) dengue (since the cases it averts may then outweigh the fewer ADE cases than would occur without Zika), and may cause little or no increase in risk for ADE of Zika infections (since most of the previously dengue-seronegative vaccinated will be primed for ADE of Zika already due to dengue exposure before Zika infection). The fact that a dual outbreak may change which decision (to vaccinate oneself or not) minimizes risk to the individual is important enough to inform future recommendations for such vaccination programs.

It should be noted that there are currently other dengue vaccines in testing that do not appear to have the same effect on ADE risks as Dengvaxia. Any studies of the impact of vaccination on dengue and other infections should take into account the characteristics proper to the vaccine in question. Studies that aim to develop specific recommendations should likewise take into account the characteristics—epidemiological, economic, sociological—particular to a given setting; future work already in progress draws on data from each of the ten countries in which Dengvaxia's clinical trials were conducted to evaluate and compare the trade-offs discussed in this study.

Appendix. Mathematical details

A. Dengue vaccination effectiveness when prior exposure involves a noncirculating serotype

In terms of the model parameters [4], when prior (initial) dengue seropositivity involves a serotype different than the one in circulation, the average relative dengue infectivity (RDI) of a seropositive who gets vaccinated is $a_0 k_d$: the proportion a_0 in whom the vaccine produces no new immunity become (upon infection with the circulating dengue serotype) k_d times as infectious as a normal dengue case, due to ADE, while the remaining $(1 - a_0)$, in whom vaccination does produce some additional seropositivity, then become immune to further clinical infection, making their RDI 0.

Meanwhile, the average RDI of a seronegative who gets vaccinated is $a_0 + a_\omega * k_d$: those (a_0) in whom the vaccine fails are at risk of a normal dengue case (RDI of 1), those (a_ω)

in whom vaccination produces immunity against only one noncirculating serotype are at risk of an ADE dengue case (RDI of k_d), and those seronegatives $(1 - a_0 - a_\omega)$ in whom vaccination protects either only against the circulating serotype or else against two or more serotypes, will have no further dengue (RDI of 0).

In practice, vaccine efficacy against a given serotype is above 40%, so the probability of a fourfold fail is less than $(60\%)^4 \approx 13\%$, and less than $(60\%)^3 \approx 22\%$ for a threefold fail. Thus the probability a_0 of a fourfold (or even threefold) fail is much less than the probability a_ω of a single success against any of the three noncirculating serotypes (which involves a threefold fail times any of three mutually exclusive single successes, say $22\% \times 3 \times 40\% \approx 26\%$), so $a_0 k_d < a_0 + a_\omega * k_d$. (In fact, the more precise serotype-specific calculations produce an even greater difference: $a_0 \approx 1\%$ while a_ω is between 5% and 9%, depending on which serotype is circulating.) Thus in this scenario vaccinated seropositives are less dengue-infectious than vaccinated seronegatives.

B. Relative risk computations

Virus/	Unvaccinated		Vaccinated	
Scenario	Inf. risk	ADE risk	Inf. risk	ADE risk
Dengue, same	$(1-\alpha)t_d$	$(1-\alpha)\theta_z$	$(1-\alpha)(a_0+a_\omega)t_d$	$(1-\alpha)\,(a_0\theta_z + a_\omega)$
Dengue, diff.	t_d	$\alpha + (1-\alpha)\theta_z$	$(a_0+a_\omega)t_d$	$\alpha(a_0 + a_{1'}) + (1-\alpha)\,(a_0\theta_z + a_\omega)$
Zika	t_z	$\alpha + (1-\alpha)\theta_d$	t_z	$\alpha + (1-\alpha)\,(a_0\theta_d + (1-a_0))$

Table 1: Risks of infection and of ADE for unvaccinated and vaccinated individuals in the model from [4]. Dengue risk is differentiated by whether any initial seropositivity due to prior exposure is to the same or a different serotype than the one currently circulating.

Table 1 presents the risks of infection and (given that an infection occurs) ADE for unvaccinated and vaccinated individuals in each of three computations: the same dengue serotype as that of prior exposure, a different dengue serotype than that of prior exposure, and Zika. In each case, computations are made separately for the proportion α of the population that is dengue-seropositive and the seronegative remainder $(1 - \alpha)$ of the population. Infection rates are driven primarily by the current effective total prevalence t_d of dengue or t_z for Zika; in the case that existing dengue seropositivity involves the same serotype that is currently circulating, only seronegatives can be infected. Of dengue-vaccinated individuals, only the proportions a_0 in whom vaccination fails to "take" against any of the four serotypes and a_ω in whom vaccination takes in only one noncirculating serotype remain vulnerable to infection; thus dengue infection risk for this group is reduced by the proportion $(a_0 + a_\omega)$.

In computing the risk of ADE given that an infection occurs, the proportion α of dengue-seropositives is sure to have ADE in any infection with dengue or Zika that does occur

(in some cases the seropositivity prevents dengue infection). The proportion $(1-\alpha)$ of dengue-seronegatives risk ADE of a given pathogen only if they are first infected by the other pathogen. To this end, we define notation additional to that in [4], to denote the proportions of the population who are first infected with dengue, θ_d, or first infected with Zika, θ_z, in both cases driven directly by the current infection rate for each pathogen, $\beta_{hd}I_{dm}/N_h$ for dengue or $\beta_{hz}I_{zm}/N_h$ for Zika, relative to natural human mortality μ_h:

$$\theta_d = \frac{\beta_{hd}I_{dm}/N_h}{\beta_{hd}I_{dm}/N_h + \beta_{hz}I_{zm}/N_h + \mu_h}, \quad \theta_z = \frac{\beta_{hz}I_{zm}/N_h}{\beta_{hd}I_{dm}/N_h + \beta_{hz}I_{zm}/N_h + \mu_h}.$$

By inspection, we can observe that (in the bottom row of the table) baseline Zika infection risk is unaffected by dengue vaccination (of one person—vaccinating the entire population may impact current Zika prevalence t_z). However, the risk of ADE given a Zika infection is increased by vaccination, since $(a_0\theta_d + (1-a_0))$ is a weighted average of θ_d and 1, and thus falls between θ_d and 1 (in particular, it is greater than the corresponding term θ_d in the risk for the unvaccinated). The precise values fluctuate from moment to moment with the prevalences of each disease, but considering that $0 \le \theta_d < 1$, we may consider the extreme values. Substituting $\theta_d \approx 1$ there is no difference at all in ADE risk for vaccinated or unvaccinated. When $\theta_d = 0$, the ADE risks are α for unvaccinated and $\alpha + (1-\alpha)(1-a_0)$ for vaccinated; with $a_0 \lesssim 1\%$, the ADE risk for the vaccinated is nearly 100%, so the amplification factor caused by vaccination depends on how widespread prior dengue seropositivity is. For instance, one source quoted in [4] found prior seropositivity as high as 72%, making vaccination increase ADE risk of a Zika infection by $1/0.72 \approx 1.39$ or 39%.

To examine dengue vaccination's impact on the risk of dengue infection and ADE, we must specify whether prior exposure was to the circulating serotype or not. If they are the same (first row of the table), then vaccination affects only the seronegative, reducing infection risk by a factor $(a_0 + a_\omega)$ but altering any subsequent ADE risk in a more complex way, from θ_z to $(a_0\theta_z + a_\omega)$. Vaccination thus reduces ADE risk given an infection if $\frac{a_\omega}{1-a_0} < \theta_z$, that is, if the probability that any protection it provides is not against the circulating serotype is less than the probability of Zika infection before dengue infection or death. ($\frac{a_\omega}{1-a_0}$ can be interpreted as the probability that vaccination "takes" against only one noncirculating serotype, given that vaccination does not completely fail to "take" (a_0).) With estimated probabilities of $a_0 \lesssim 1\%$ and a_ω in the range 5–9%, the threshold value for θ_z lies in the range 5.05% to 9.1%. If θ_z exceeds this, vaccination reduces ADE risk; otherwise, it increases it. Since θ_z is a measure of Zika's spread relative to dengue's, at this threshold Zika only spreads about 5–10% as fast as dengue. Put the other way, at this threshold, dengue spreads 10–20 times as fast as Zika.

If instead prior dengue seropositivity involves a noncirculating serotype (second row of the table), then dengue vaccination reduces dengue infection risk for everyone, again by a factor (a_0+a_ω), and alters risk for ADE of dengue (given an infection) for prior seropositives from 100% to only those who develop no additional seropositivities from vaccination (a_0 complete vaccine failure, or $a_{1'}$ failure except against the serotype of prior exposure), and for prior seronegatives from θ_z to $(a_0\theta_z + a_\omega)$ as before. Thus, the difference is that prior seropositives have both risks reduced, which makes the overall ADE risk more likely to be reduced.

The impact on risks to the unvaccinated of *other* people getting vaccinated against dengue is determined by secondary effects, as vaccination affects overall dengue or Zika incidence, and therefore the prevalence-based quantities t_d, t_z, θ_d, and θ_z which appear in Table 1. In general, others being vaccinated reduces an unvaccinated person's risk of dengue infection, and in the absence of a Zika outbreak, it also reduces the risk of ADE of dengue. However, by making dengue infections rarer in general, in the presence of Zika it actually raises the risk that any dengue infection which does occur has ADE, since it is likely that a person will have been infected by Zika before being infected by dengue. Others becoming dengue-vaccinated generally increases the overall Zika incidence (except the first few when the population has no prior dengue exposure, see Section 3.1) and thus an unvaccinated person's risk of Zika infection. In the absence of a dengue outbreak, it leaves ADE of Zika risk unchanged, but in the presence of both pathogens it actually reduces risk for ADE of Zika, since on the whole vaccination lowers dengue spread and thus the chance that an unvaccinated person might develop a dengue infection before being infected with Zika.

C. Vaccination's impact on the individual

What will happen to me if I get vaccinated?

Your risk of getting Zika stays the same, but your risk of any Zika case you develop being severe increases—if you are dengue-seronegative and Zika spreads at least as well as dengue.

If you are dengue-seronegative before vaccination, vaccination reduces your risk of getting dengue by a factor of at least ten, and if vaccination fails to protect you against the circulating dengue serotype, the risk that any dengue infection you develop will be severe (from ADE) increases only if Zika spreads less than 5–10% as well as dengue (including if there is no Zika outbreak).

If you have prior exposure to the circulating dengue serotype before vaccination, then you are already immune to it and vaccination changes nothing in this regard. If you have prior exposure to a different dengue serotype before vaccination, then vaccination reduces your risks of dengue infection and ADE of dengue.

In short, dengue vaccination can only reduce your dengue infection risk and has no impact on your Zika infection risk. If you are dengue-seronegative before vaccination, then vaccination likely increases your risk of ADE in whichever of the two viruses is spreading more in your community and reduces your ADE risk for the other virus.

What will happen to me if other people get vaccinated (but I don't)?

Other people getting vaccinated against dengue will increase, probably slightly, the overall Zika incidence and thus your risk of Zika infection, and will decrease, probably slightly, the overall dengue incidence, which in turn reduces your risk of ADE if you do develop Zika infection.

If you are dengue-seronegative, other people getting vaccinated against dengue will decrease, potentially slightly, the overall dengue incidence and thus your risk of dengue infection, and will (by increasing Zika incidence) increase, probably slightly, your risk of ADE if you do develop dengue infection.

If you are dengue-seropositive to the circulating dengue serotype, then you are already immune to it and vaccination changes nothing in this regard. If you are dengue-seropositive to a different dengue serotype, then, as with seronegatives, other people getting vaccinated will decrease, potentially slightly, your risk of dengue infection; your risk of ADE if you do develop dengue infection is already 100% and other people getting vaccinated changes nothing in this regard.

In short, other people getting vaccinated against dengue increases your Zika infection risk but decreases your ADE risk for Zika, while it has the reverse effect for dengue-related risks, except when your own prior exposure to dengue has already fixed a risk at 0% or 100%.

D. Details of the mathematical model

The transmission dynamics model used for this study, taken from [4], consists of thirty-one differential equations: one for each population compartment for humans and mosquitoes, as described in the Materials and Methods section. All transitions indicated in Figure 2 are linear (i.e., the rate appearing in the respective differential equations is given by the population size of the source compartment, multiplied by a rate constant) except the infection rates, which use so-called standard incidence of the form $\beta S \cdot I_T/N_h$, where β is a rate constant, S is the size of the [susceptible] population becoming infected, N_h is the total human population, and I_T is the total infectious population of the species opposite S (that is, one of S and I_T counts humans and the other mosquitoes), modified as appropriate by altered infectivity. Human and mosquito populations are assumed to be at demographic

equilibrium, making birth/recruitment rates equal to the total death rates for each species. The system of differential equations, given in full in [4], can be reconstructed from Figure 2 by writing, for each compartment, a term corresponding to each flow arrow entering or leaving that compartment.

A list of rate constants and the values taken for them in [4] is given in Table 2. An asterisk in a compartment name represents each possible value, e.g., "*SU to *SV" includes transitions from SSU to SSV, from ISU to ISV, and from RSU to RSV. Vaccination rates and demographic recruitment rates for humans are calculated as functions of primitive parameters taken from [4]. In addition, the mosquito-to-human population density ratio is taken to be 1/2.

Rate	Value
demographics (entry: short, red arrows in Figure 2)	
rate of unvaccinated humans entering completely seronegative (SSU)	$0.0000101909/\text{day}\ N_h$
rate of vaccinated humans entering completely seronegative (SSV)	$2.99297 \times 10^{-10}/\text{day}\ N_h$
rate of humans entering seronegative to circulating viruses but protected against a noncirculating dengue serotype (SSP)	$2.58312 \times 10^{-9}/\text{day}\ N_h$
unvaccinated humans entering seropositive to only DENV-j (SRU)	$0.0000226963/\text{day}\ N_h$
vaccinated humans entering seropositive to only DENV-j (SRV)	$8.45974 \times 10^{-8}/\text{day}\ N_h$
humans entering seropositive to ≥ 2 dengue serotypes only (SRP)	$3.53096 \times 10^{-6}/\text{day}\ N_h$
human birth/death rate	$0.0000365/\text{day}$
mosquito birth/death rate	$(1/28)/\text{day}$
dengue infection cycle (black, horizontal arrows in Figure 2)	
rate at which mosquitoes infect humans with dengue (*S* to *I*)	$0.4489\ \frac{\text{people}}{\text{vector day}}$
recovery rate from DENV-j (*I* to *R*)	$(1/5.32)/\text{day}$
rate at which mosquitoes acquire dengue from hosts (*S to *I)	$0.6164/\text{day}$
relative host infectivity for DENV-j due to ADE	1.0,1.3,1.1,1.1
relative dengue infectivity factor for coinfected mosquitoes	12
Zika infection cycle (blue, vertical arrows in Figure 2)	
rate at which mosquitoes infect humans with Zika (S** to I**)	$0.1675\ \frac{\text{people}}{\text{vector day}}$
recovery rate from Zika (I** to R**)	$(1/7)/\text{day}$
rate at which mosquitoes acquire Zika from hosts (S* to I*)	$0.201/\text{day}$
relative host infectivity for Zika due to ADE	1.1
relative Zika infectivity factor for coinfected mosquitoes	0.11
vaccination stages (green, diagonal arrows in Figure 2)	
rate at which dengue-seronegatives receive a vaccine which...	
...completely fails to "take" (*SU to *SV)	$1.95206 \times 10^{-6}/\text{day}$
...takes only against the circulating serotype (*SU to *RV)	$2.74039 \times 10^{-6}/\text{day}$
...takes only against one noncirculating serotype (*SU to *SP)	$1.68474 \times 10^{-5}/\text{day}$
...takes against two or more serotypes (*SU to *RP)	$0.00017846/\text{day}$
rate at which dengue-seropositives receive a vaccine which...	
...fails to take against noncirculating serotypes (*RU to *RV)	$0.000213506/\text{day}$
...takes against one or more noncirculating serotypes (*RU to *RP)	$0.00888649/\text{day}$

Table 2: Rate constants and sample values, from [4], with source and destination compartments when applicable. DENV-j is the circulating serotype. Multiple values indicate variation by dengue serotype; numerical analysis in the present study uses serotype 1.

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