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Potential opportunities and perils of imperfect dengue vaccines☆

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ABSTRACT

Dengue vaccine development efforts have focused on the development of tetravalent vaccines. However, a recent Phase IIb trial of a tetravalent vaccine indicates a protective effect against only 3 of the 4 serotypes. While vaccines effective against a subset of serotypes may reduce morbidity and mortality, particular profiles could result in an increased number of cases due to immune enhancement and other peculiarities of dengue epidemiology. Here, we use a compartmental transmission model to assess the impact of partially effective vaccines in a hyperendemic Thai population. Crucially, we evaluate the effects that certain serotype heterogeneities may have in the presence of mass-vaccination campaigns.

In the majority of scenarios explored, partially effective vaccines lead to 50% or greater reductions in the number of cases. This is true even of vaccines that we would not expect to proceed to licensure due to poor or incomplete immune responses. Our results show that a partially effective vaccine can have significant impacts on serotype distribution and mean age of cases.

1. Introduction

Due to the possibility of severe disease arising from vaccine-induced immunity, the ideal dengue vaccine is one that has high and equal efficacy against all four serotypes. However, this ideal may be difficult to attain. The results of a recent Phase IIb trial indicate that the vaccine candidate furthest along in development protects against serotypes 1, 3 and 4 but not serotype 2 [1]. Though several statements of vaccine requirements have said that vaccines must protect against all four serotypes, partially effective vaccines may reduce morbidity and mortality [2,3]. Conversely, specific partially effective vaccines may result in increased clinical disease due to inducing immunity that pre-disposes individuals to more severe disease [4]. The potential population-level impacts of a partially effective vaccine have not been explored [5].

The dengue viruses exist as four antigenically distinct serotypes. Infection with one strain is thought to induce a life-long protective immune response to other viruses of the same serotype (homotypic immunity) and a short-term cross-protective response against other serotypes (heterotypic immunity), but waning heterotypic immunity has been associated with more severe illness upon secondary infection [6,7]. After secondary infection individuals generate a strong serological response that is broadly cross-reactive and, despite some evidence of tertiary and quaternary infections, it is generally assumed that most individuals can only undergo up to two infections [8].

While the target of dengue vaccine design has been to generate a balanced protective serological response to all four serotypes, vaccines targeting other antigenically diverse pathogens have shown a substantial public health impact even when inducing immunity to a subset of types of pathogen. Examples include pneumococcal conjugate vaccines [9], Human Papillomavirus (HPV) [10,11] and *Haemophilus influenza* B vaccines [12,13]. While dengue is unique due to the association that exists between secondary exposure and more severe forms of the disease, it is not clear that this difference needs to fundamentally change our approach to controlling dengue compared to other pathogens.

Evaluation of the potential impact of partially effective vaccines through simulation requires consideration of scenarios with heterogeneities between serotypes like those that are likely to exist in endemic/hyperendemic settings. Estimates of the force of infection derived from age-stratified seroprevalence studies conducted in Rayong, Thailand in 1980/1981 and 2010 suggest that the average transmission intensity (and R_0) of DENV-2 is higher than that of other serotypes [14,15]. Heterogeneity in the propensity to develop severe disease following infection with different serotypes has also been documented in multiple studies in Thailand and Nicaragua

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[16–19]. While the extent of immune enhancement of susceptibility/infectiousness by different infection sequences has been more difficult to estimate, there is some evidence to suggest that it might also vary between serotypes [14]. Furthermore, recent work suggests that such immune enhancement is important for serotype persistence in the presence of transmission heterogeneity [20].

The potential impact of vaccination on dengue transmission dynamics in Thailand and Vietnam has been explored in two recent publications by Chao et al. [21] and Coudeville et al. [22] using an agent-based model and an age-specific compartmental model, respectively. Both of these studies found that vaccines with efficacy of 70–90% against all serotypes have the potential to significantly reduce the frequency and magnitude of epidemics on a short to medium term. However, while both of these models do account for some sources of heterogeneity between serotypes, for example, differences between the serotypes in transmission intensity, they do not systematically examine the potential impact of these heterogeneities in the context of partially effective vaccines.

Here, we use an age-stratified dengue transmission model to assess the potential impact of vaccines with high efficacy against dengue serotypes 1, 3 and 4 and low efficacy against dengue serotype 2 in a hyperendemic Thai population. We explore multiple disease/transmission scenarios to identify those that might lead to increases in clinically apparent cases and to identify the potential reductions in disease. Crucially, we evaluate the effects that certain serotype heterogeneities may have in the presence of mass-vaccination campaigns. We also explore overall, direct and indirect effects of reducing (or in some cases increasing) infection and disease in vaccinated individuals vs. reductions in transmission population wide.

2. Materials and methods

2.1. Mathematical model

We formulated a deterministic, age-stratified compartmental dengue transmission model that includes explicit vector dynamics as well as cross-protection and infectiousness enhancement between dengue serotypes. Humans are assumed to be born susceptible and can undergo up to two infections by heterologous serotypes. Mosquito vectors are classified as susceptible or infected by each of the circulating serotypes.

We focus on the dengue vaccine being developed by *Sanofi-Pasteur* that requires three doses to achieve high protection. Vaccination reduces the susceptibility of vaccinated humans to dengue infection. We also allow for immune mediated vaccine induced enhancement in transmissibility.

Since the main objective of our study was to explore changes in the number of clinically apparent dengue cases, upon mass-vaccination, we made assumptions about the probability of developing clinically apparent disease following infection. These assumptions also allowed us to calibrate our model with data from surveillance systems. We assumed that: (i) in unvaccinated individuals, clinical cases arise mostly from secondary infections; (ii) in vaccinated individuals, clinical cases arise majorly from primary infection, but can arise from secondary infections depending on the vaccine's efficacy against heterologous serotypes. Although we conservatively assumed the probability of clinical infection to be independent of age, we performed sensitivity analyses to consider age dependence as has been previously considered.

We discuss our mathematical model and related assumptions in more detail in the supplementary material (Supplementary material S1).

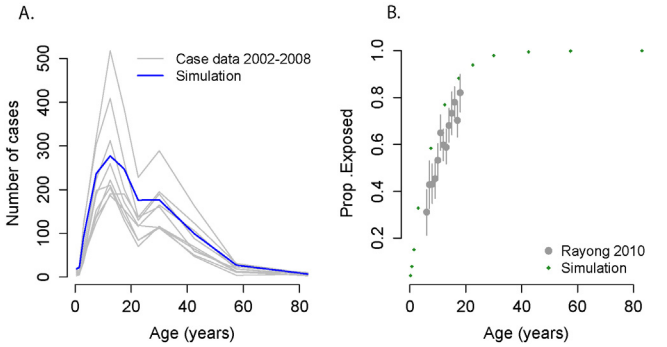

Fig. 1. Output from the model compared to (A) age-specific incidence from Rayong reported to the Ministry of Public Health, Thailand, 2002–2008. (B) Results from an age-stratified serological study conducted in Rayong district, 2010.

2.2. Vaccination campaign parameters

For all simulations, we assumed that that the vaccine was equally effective against serotypes DENV-1, DENV-3 and DENV-4 (vaccine efficacy = 0.8, after 3 doses) but only partially effective against DENV-2. We also assumed that vaccine-derived immunity does not wane. Rollout of the vaccine consisted of 3 years of catch-up targeting children 2–15 years of age, followed by regular vaccination of 2–5 year olds. The vaccine was administered in up to three doses that were given on average every six months apart. Vaccination rates in catch-up and routine programs were constant over time and set so that vaccination coverage would reach 89% among 2–5 year olds and 69% in 2–15 year olds after 5 years. These vaccination rates were chosen to roughly correspond with the rate of vaccination achieved in Thailand with the Japanese Encephalitis three-dose vaccination using a combination of catch-up and routine immunization campaigns.

2.3. Vaccine effects

To explore the effects of vaccination at the population level, we compared the cumulative number of clinically apparent dengue cases in the 10 years after vaccine introduction, to the cumulative number of cases over the same period in the *counterfactual population* (i.e. same population had the vaccine not been introduced).

We also isolated *overall*, *direct* and *indirect* vaccine effects as proposed by Halloran et al. [23]. In addition, we defined a *counterfactual vaccine effect*, comparing the cumulative incidence in vaccinated individuals of the vaccinated population to the cumulative incidence in "vaccinated" individuals of the counterfactual population (Supplementary material S1).

Since timing of vaccine introduction may impact the short and medium term effects of vaccination, we performed simulations introducing the vaccine at different points in the multiannual dengue cycle. We present vaccine effects that are averages over eight possible introduction years.

3. Results

3.1. Calibration and fit

We calibrated the model, at steady state, to the transmission dynamics of dengue in Rayong, Thailand, a traditionally hyperendemic setting (Fig. 1). To fit the model to the demography of Rayong, we used data from the 2010 Thai Census [24] (Supplementary Fig. S2.1). To estimate transmission parameters, we used age-specific incidence data from the Ministry of Public of Public Health (2002–2010) and age-stratified serological data from a