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Benefits and risks of the Sanofi-Pasteur dengue vaccine: Modeling optimal deployment

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Abstract

The first approved dengue vaccine has now been licensed in six countries. We propose that this live attenuated vaccine acts like a silent natural infection in priming or boosting host immunity. A transmission dynamic model incorporating this hypothesis fits recent clinical trial data well and predicts that vaccine effectiveness depends strongly on the age group vaccinated and local transmission intensity. Vaccination in low-transmission settings may increase the incidence of more severe "secondary-like" infection and, thus, the number of recipients hospitalized for dengue. In moderate transmission settings, we predict positive impacts overall but increased risks of hospitalization with dengue disease for individuals who are vaccinated when seronegative. However, in high-transmission settings, vaccination benefits both the whole population and seronegative recipients. Our analysis can help inform policy-makers evaluating this and other candidate dengue vaccines.

The first dengue vaccine, the product of a 20-year development process by Sanofi Pasteur Ltd., has now been approved for use in six countries. Its development was considerably more challenging than for other flavivirus infections because of the immunological interactions between the four dengue virus (DENV) serotypes and the risk of immune-mediated enhancement of disease (1–3). Individuals experiencing their second natural DENV infection have a higher risk, by more than sixfold, of severe disease compared with those experiencing primary infection (4, 5), which is hypothesized to be due to heterotypic

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antibody-dependent enhancement (4). If future trials are to avoid similar consequences, the ideal DENV vaccine should generate a balanced protective response against each of the four serotypes (1).

The Sanofi Pasteur vaccine, Dengvaxia, a recombinant chimeric live attenuated DENV vaccine based on a yellow fever 17D vaccine backbone, was evaluated in two large multicenter phase III trials. One trial was conducted in Southeast Asia (6), among ~10,000 children aged 2 to 14 years, and the other in Latin America (7), among ~21,000 children aged 9 to 16 years. Both trials reported efficacy of ~60% against virologically confirmed symptomatic dengue disease (the primary outcome), as well as higher efficacy against severe dengue and variation in efficacy by serotype (6–8). The trials also revealed high efficacy in recipients who were seropositive to DENV at the time of vaccination but much lower (and statistically insignificant) efficacy in those who were seronegative at the time of vaccination. Both trials also found lower vaccine efficacies in younger age groups—a pattern consistent with reduced efficacy in individuals who have not lived long enough to experience a natural infection.

Reduced efficacy in seronegative recipients initially indicates that it would be beneficial, but not essential, to optimize the target age group when developing vaccination programs. However, in July 2015, long-term follow-up results for the third year of the trial showed that vaccinees in the youngest age group (2 to 5 year olds) of the Asian trial had substantially and significantly higher risk of hospitalization for virologically confirmed dengue disease than controls had (9). In other age groups (in both trials), the vaccine was still protective against hospitalization, albeit efficacy was lower than that seen in the active phase of the trial [see supplementary materials (10)]. Immunogenicity data (11–18) have shown that seropositive vaccine recipients attain high and sustained antibody levels after the first dose of vaccine, whereas peak antibody levels in seronegative recipients are 10-fold lower on average and show rapid decay, apparent even between vaccine doses (18). Serological data were only collected from a subset of participants in each phase III trial, so it is not possible to determine whether the risk excess seen in the 2- to 5-year-old age group is driven by the effect of vaccine in the large proportion of seronegative recipients in this age group, but at present, this appears to be the most plausible explanation (19).

These trial results pose challenges in considering how best to use the vaccine. The heterogeneities in the efficacy profile—combined with the uncertainties regarding the vaccine's mechanism of action (20) and the underlying complexity of DENV epidemiology and transmission dynamics—make it far from simple to extrapolate from the trial results to predict the potential impact of wide-scale use of this vaccine.

We therefore developed mathematical models of DENV transmission (10) to explore hypotheses about vaccine action and to examine the potential consequences for the impact of routine use of this vaccine. Given the trial results (see table S1), any model needs to incorporate waning of efficacy over time. Hence, we fitted a "simple" model to the publicly available trial data (6–8), where efficacy was allowed to decay from an initial high value to some lower long-term value, with these efficacy values assumed to be different for seropositive and seronegative vaccine recipients. The resulting parameter estimates and poor

overall fit (table S5 and fig. S5) led us to propose a more biologically motivated model, in which the immunological effect of vaccination is comparable to a silent natural infection (fig. S1). Seronegative recipients gain transient protective cross-reactive immunity akin to that observed for natural infection (21–23). After this protection decays, lower concentrations of heterotypic antibodies increase the risk of severe disease upon a breakthrough primary infection to the same level seen for secondary infections in nonvaccinees (4, 5). Conversely, vaccination of recipients who have already had one DENV infection results in a boosting of immunity to levels comparable with someone who has had two natural infections, and their next infection will not have the higher severity associated with natural secondary infections, but rather, the much lower risk of severe disease associated with tertiary and quaternary (post-secondary) infections (24).

This model fitted well the patterns seen in both the active and long-term follow-up phases of the phase III clinical trial, including the variation in vaccine efficacy by age, serostatus at the time of vaccination, and time since vaccination (Fig. 1). The poorest aspect of model fit is to the sevenfold greater incidence of hospitalization with dengue seen in 2- to 5-year-old vaccine recipients compared with controls in the first year of the long-term follow-up in the Asian trial. However, model predictions lie within the confidence bounds of the data, and the model successfully reproduces a relative risk >1 for vaccine recipients compared with controls in that age group. Indeed, had the long-term follow-up data on the effects of vaccination in the 2- to 5-year-old age group not been included, our model would still have predicted a relative risk >1 in that age group, based on trends seen in the other age groups and the results of the active phase (table S4).

Consistent with prior knowledge (5), our parameter estimates indicated that secondary infections are about twice as likely to cause symptomatic infection as either primary or postsecondary infections (table S3). In addition, we estimated that the vaccine initially induces near-perfect heterologous protection in seronegative recipients but that this decays rapidly, with a mean duration of 7 months [95% confidence interval (CI) of 4 to 11 months]. Our analysis did not resolve the extent to which such transient heterologous protection is induced in seropositive recipients; the modal posterior estimate of the efficacy of such protection is 0 but the 95% credible interval spans 0 to 100%.

To predict the implications of our model of vaccine responses on the effectiveness of immunization policies, we simulated the effect of routine vaccination at 80% coverage, and explored the effect of varying the age at vaccination between 2 and 18 years of age. We deliberately examined ages below the 9-year minimum age approved by regulators to give greater insight into the interaction between, age, transmission intensity, seroprevalence, and the impact of vaccination on dengue disease. Owing to the dependence of efficacy on serostatus at the time of vaccination, the impact of the vaccine critically depends on the proportion of the target age group who have experienced 0, 1, or more natural DENV infections before vaccination. Therefore, we quantify transmission intensity as the long-term average of the proportion of 9 year olds who are seropositive. This metric maps monotonically onto the more commonly used metric of the basic reproduction number, R_0 (fig. S3) but has the advantages of being directly related to the key driver of vaccine efficacy

(i.e., serostatus), which is readily measureable and interpretable and not dependent on specific model assumptions (25).

The predicted mean population impact of routine vaccination on symptomatic dengue disease and case incidence of hospitalization with dengue over 10- and 30-year periods is shown in Fig. 2. In high-transmission settings, vaccination is associated with modest (20 to 30%) reductions in both symptomatic disease and hospitalization. For a specific level of transmission, there is an optimal age of vaccination that decreases as transmission intensity increases. Although short-term (10-year) impacts are generally positive, both positive and negative impacts of vaccination may occur for both symptomatic and hospitalized patients over longer periods of time (30 years). This is particularly true in low-transmission settings. Negative outcomes occur more frequently for hospitalized disease since secondary or secondary-like infections (i.e., primary infections in vaccine recipients) have an approximately eightfold higher risk of hospitalization than primary infections (10, 26) but only a twofold higher risk of uncomplicated symptomatic disease (10, 26).

The population-level impacts of vaccination hide enormous heterogeneity in benefits and risks at the level of the individual recipient (Fig. 3, A and B): Seropositive recipients always gain a substantial benefit from vaccination (>90% reduction in the risk of being hospitalized with dengue), whereas seronegative recipients experience an increased risk of being hospitalized with dengue. This is true both in the short-term (see supplementary material) and in the long-term and raises fundamental issues about individual versus population benefits of vaccination. The increase in risk is greatest for low-transmission settings, where a substantial fraction of seronegative recipients would not normally experience a natural secondary infection. Conversely, in the highest-transmission settings, the main effect of vaccination on seronegative individuals is to bring forward in time the more severe secondary-like infection that they would have eventually naturally experienced. This, combined with a small indirect effect of vaccination on reducing transmission, leads to a small overall positive benefit to all recipients in high-transmission settings. Restricting the minimum licensed age of use of the vaccine to 9 years mitigates, but does not remove, the risk of negative population-level impacts in low-transmission settings where the majority of 9 year olds are still seronegative. Conversely, in high-transmission settings, the optimal age to target for vaccination can be below 9 years.

The vaccination policies that risk producing adverse outcomes can therefore be defined. The minimum average prevaccination seroprevalence required to avoid negative impacts is shown in Fig. 3C from both the individual and population perspectives. An overall negative impact on the entire population can be avoided by choosing a target age for vaccination in which average seroprevalence exceeds ~35%. In contrast, it is harder to avoid increased risk of hospitalization for individuals who are seronegative when vaccinated. Doing so requires that the indirect effects of vaccination in reducing overall dengue transmission exceed the increased risk of disease which vaccination causes in seronegative individuals via immune priming. Over a period of 30 years, this is only possible in high–transmission intensity settings when $R_0 > 3$ or seroprevalence in 9 year olds exceeds ~70%. Only for the youngest age of vaccination considered (two years, below the licensed minimum age) do population and individual thresholds converge. In part based on the modeling presented here, the World

Health Organization's Strategic Group of Experts on Immunization has recently recommended population serological surveys be undertaken in populations where the vaccine is being considered for use and that vaccination is only recommended where seroprevalence in the targeted age group exceeds 50% (and preferably 70%) (27).

Serological testing of individuals offers an alternative solution to mitigate the potential risks and to maximize the benefits of dengue vaccination; rapid diagnostic tests could be used to screen potential vaccine recipients, with only seropositive individuals being vaccinated. Indeed, data from immunogenicity studies suggest that a single-dose vaccination schedule might be enough to achieve protective immunity in seropositive individuals. Such a policy could result in up to a 30% reduction in the incidence of hospitalization with the disease and a much-reduced risk of negative outcomes (Fig. 4A) after vaccinating only a fraction (those testing seropositive) of the target age group (Fig. 4B). Although such a policy would be logistically challenging in the context of mass vaccination campaigns, it should not be ruled out—if the cost of testing can be reduced to a level comparable with the cost of buying and delivering a single vaccine dose, such a strategy is likely to have substantially greater cost-effectiveness than the current three-dose strategy without testing. Using serological testing to inform vaccination decisions is not an entirely novel concept, as it has been recommended for pregnant women in relation to rubella and hepatitis B vaccination (28, 29).

Since vaccination only transiently reduces the risk of infection and the main effect of vaccination is to modify the risk of disease, our findings predict that the indirect effect of vaccination on DENV transmission will be limited. This explains why we found that the predicted impacts of routine vaccination (whether positive or negative) scale almost linearly with vaccine coverage. Our default assumption was that symptomatic infections are twice as infectious as asymptomatic infections, which leads to vaccination slightly reducing transmission in high–transmission intensity settings but slightly increasing transmission in low-transmission settings. Making the alternative assumption that all infections are equally infectious reduces the chance and magnitude of negative impacts of vaccine for low-transmission intensities but also reduces the positive impacts of vaccination when transmission intensity is high (figs. S9 and S10).

Our results also show that the effectiveness of vaccination would be expected to vary over time (figs. S6 to S8). In low-transmission settings, the introduction of vaccination could perturb transmission dynamics and lead to transient reductions in dengue disease incidence for 5 to 10 years. Only when the transmission dynamics reequilibrate are the long-term impacts seen. From the individual perspective, it is also important to consider the effect of vaccination on the cumulative life-time risk of dengue disease and hospitalization. Among seronegative recipients, reductions in risk resulting from short-term vaccine-induced protection might exceed later increases in risk resulting from vaccine-induced immunological priming. This is particularly true in high-transmission settings where, in the absence of vaccination, nearly everyone experiences secondary infection with dengue at some point in their lives. Special consideration should be given to the policy and ethical considerations of shifting infections and/or symptomatic episodes among individuals to different times in their life.

Our analysis has several limitations. We were not able to estimate serotype-specific efficacy parameters. Owing to cross-reactive immunity, in any one year, DENV incidence in single populations tends to be dominated by a single serotype, which is reproduced by our transmission model. However, the phase 3 trials showed substantial attack rates from all four serotypes, but underpinning this was much greater heterogeneity in serotype-specific attack rates between the countries contributing to the trial. To capture observed serotype-specific attack rates it is necessary to fit country- and serotype-specific trial data, which are not currently publically available (30). However, in the supplementary materials (10), we show how the apparent serotype-specific efficacies seen may reflect differences between serotypes in the propensity to cause disease in primary, secondary, and postsecondary infection rather than actual differences in (serostatus-specific) efficacy (fig. S12). Including such asymmetry does not qualitatively affect model predictions (figs. S13 and S14). We also do not consider persistent variation in exposure to DENV at the individual or neighborhood level; if substantial proportions of the population consistently experience lower and higher levels of exposure than the average throughout their lives, then both the risks (to the low-exposure group) and benefits (to the high-exposure group) of vaccination may be larger than we estimate here. Although characterizing real-world levels of exposure heterogeneity is difficult, this issue should be a priority for future work.

All efficacy outcomes measured in the trial were based on clinically apparent disease, so we are currently unable to resolve whether the vaccine protects against infection or just against disease (20, 31). Our baseline model assumes a combination of both—short-lived protection against infection, followed by a long-lived modification of future disease risk. We are also unable to assess the impact of breakthrough infections on vaccine-acquired immunity. If vaccination truly acts as a silent infection, then breakthrough infections in seronegative vaccinees should induce a broadly multitypic and protective immune response (akin to unvaccinated individuals who have experience two natural infections)—our current model assumption. Understanding any differences between naturally and vaccine-acquired immunity will be critical in assessing the overall impact of vaccination on this group. In addition, although not required to reproduce the main trends seen in the trial, variation of efficacy with age cannot be ruled out. If vaccine efficacy were lower in younger age groups, independent of serostatus, the predicted outcomes of vaccination programs targeting older children would increase, particularly in lower-transmission settings. Last, in the modeling presented here, we assumed that vaccine-induced protection in seropositive individuals is long-lasting—future data may allow this optimistic assumption to be tested.

Successful licensing of the first vaccine against a major global pathogen is a significant achievement. However, the dependence of vaccine efficacy on prior immunity presents challenges to planning large-scale use. Other recent modeling efforts have predicted impacts of vaccination that are more beneficial than those presented here but used models that were not fit to the data from the clinical trial (32) or the long-term follow-up (30). Our analysis indicates that to maximize the population impact of vaccination and to prevent negative impacts, it will be necessary to carefully tailor vaccination strategies to local epidemiological conditions. Our results indicate that the vaccine should only be used in moderate- to high-transmission settings, at least until more data are available to clarify the extent to which the vaccine primes seronegative recipients for a higher risk of hospitalized

disease. Careful selection of the age group to target for routine vaccination can maximize benefits, but our current estimates indicate that in all but the highest-transmission settings, use of this vaccine may lead to an increase in seronegative recipients hospitalized with dengue even if the overall impact of vaccination is positive. We predict routine vaccination will cause at most moderate (10 to 20%) reductions in disease incidence, so it is important to set realistic expectations of impact for the policy-makers and populations of countries likely to implement such policies. Population serosurveys can mitigate risks in planning routine vaccination, but individual serological testing, if feasible, might radically improve the benefit-risk trade-off.

The partial efficacy of this vaccine raises the question of how its use might be combined with more effective vector control measures [e.g., using new technologies, such as *Wolbachia* (33) to achieve greater overall public health impact]. Careful modelling of combined intervention strategies is a priority for future work, but a priori, the efficacy profile of this vaccine suggests the need for caution. If new vector control interventions substantially reduce (but do not eliminate) dengue transmission, population seroprevalence will decline over time. Unless vaccination strategies account for such effects, introduction of routine immunization against a background of recently substantially enhanced vector control may pose the same long-term risks of negative impacts of vaccination that we predict for vaccine use in other settings having low transmission intensity.

Efficacy data for the other DENV vaccine candidates under development are not yet available, but all candidates show differences in immunogenicity by prior serostatus comparable to the immunogenicity from the Sanofi vaccine (34, 35). Therefore, even though there are potentially relevant structural differences between the candidates, it is feasible that they may share similar efficacy profiles. Our analysis may have application beyond the Sanofi vaccine. More generally, our work and that undertaken for the RTS,S malaria vaccine (36) reinforce the value of modeling in interpreting trial results and planning how best to use partially effective vaccines with complex efficacy profiles.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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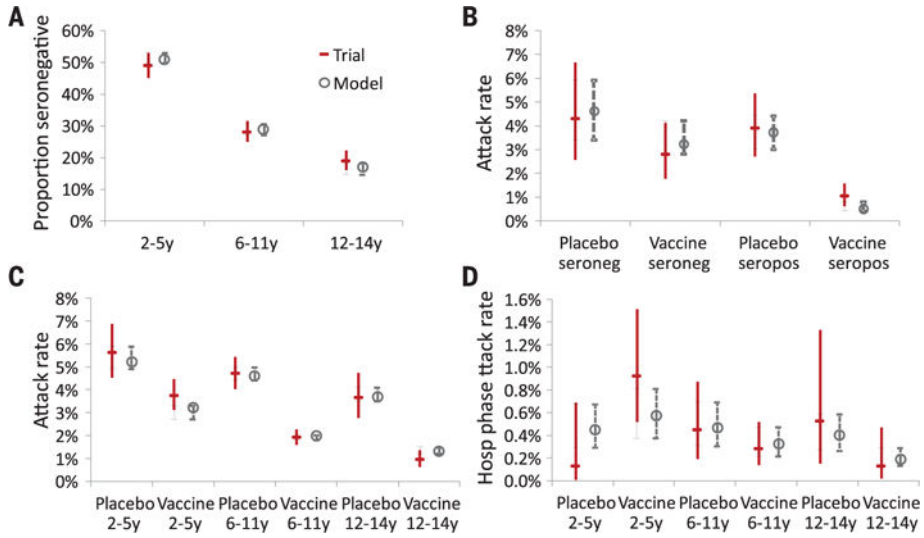
Fig. 1. Model fit to publicly available data from the Asian phase 3 clinical trial
See (6). Modal (best-fit) estimate and 95% credible intervals for four conditions. (**A**) proportion of participants of the immunological subset of the trial who were seronegative at the time of receiving their first dose, by age. (**B**) Attack rate of virologically confirmed symptomatic dengue in immunological subset in first two years after dose 1 by trial arm and baseline serostatus. (**C**) Attack rate of virologically confirmed symptomatic dengue in all trial participants in first two years after dose 1 by trial arm and age group. (**D**) Attack rate of virologically confirmed hospitalization with dengue disease in all trial participants in third year after dose 1 (first year of long-term follow-up) by trial arm and age group. Fit to Latin American trial shown in SM (10).
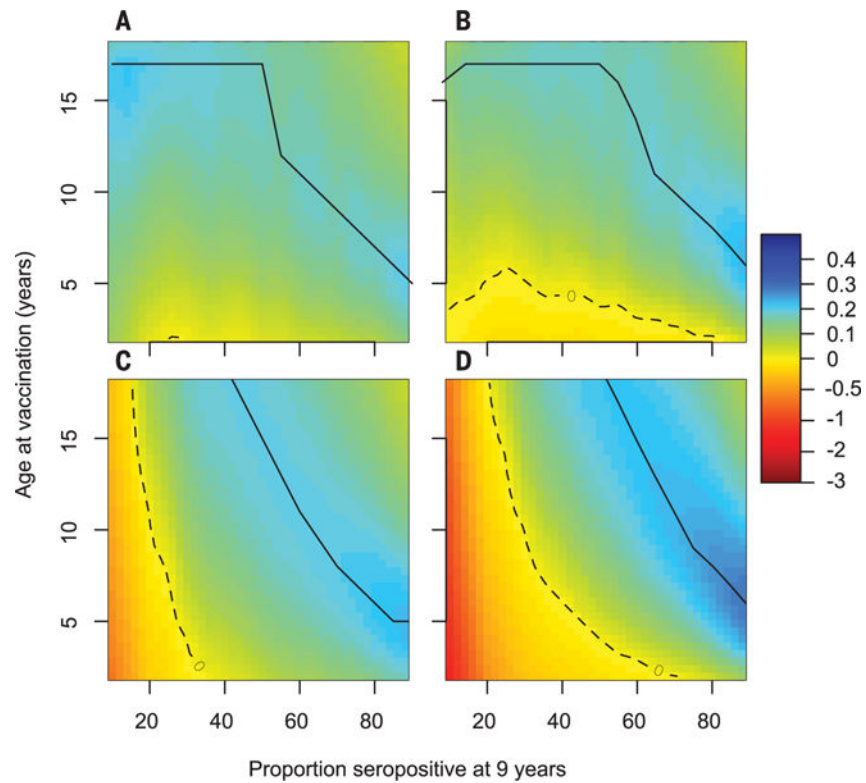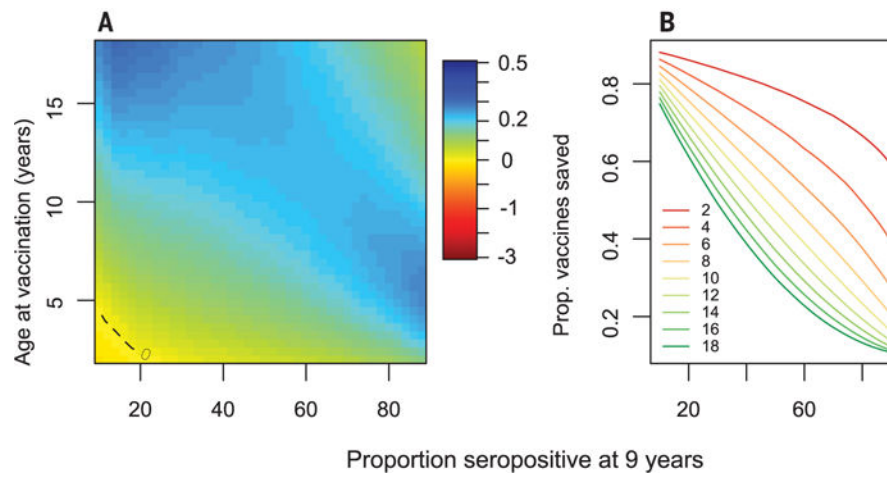
Fig. 2. Predicted population effects of vaccination on dengue disease for a range of transmission intensities (*x* axes) and ages of vaccination (*y* axes)

Color scale indicates proportion of cases averted in the whole population (**A**) over 10 years, for all symptomatic dengue; (**B**) over 10 years, for participants hospitalization with dengue; (**C**) over 30 years, for all symptomatic dengue; and (**D**) over 30 years, for hospitalization with dengue. Negative proportions of cases averted indicate vaccination increases risk. Solid contours indicate the optimal age of vaccination for each transmission intensity. Dashed contours indicate the youngest age group that may be targeted to avoid negative effects at the population level.
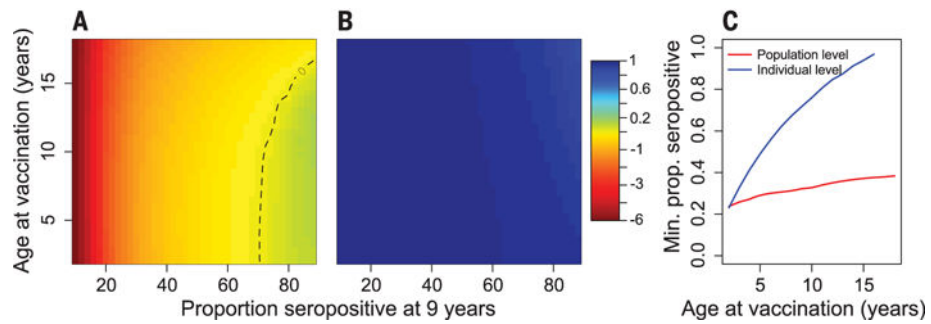
Fig. 3. Predicted individual effects of vaccination over 30 years

Proportion of hospitalized cases averted among individual vaccine recipients who are vaccinated: (**A**) when seronegative and (**B**) when seropositive. Dashed contour indicates the youngest age group that may be targeted to avoid negative effects at the individual level. (**C**) Minimum proportion of the age group (1-year age band) targeted for routine vaccination that should be seropositive before introduction of vaccination to avert negative impacts (over a 30-year time frame) at the population (red) and individual (blue) level.

Fig. 4. Expected population effects of vaccination if vaccination is preceded by serological testing (with a rapid test assumed to have 90% sensitivity and specificity) and only individuals who test seropositive for dengue are vaccinated

For the population, 80% coverage is assumed. (A) Proportion of hospitalizations averted over a 30-year period for different transmission intensities and target age at vaccination. (B) Proportion of vaccine doses saved (*y* axis) if only seropositive individuals are targeted, for different transmission intensities (*x* axis) and target ages (different curves).