Risks and benefits of the Sanofi-Pasteur dengue vaccine: modelling 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 incidence on hospitalized dengue. In moderate transmission settings, we predict positive impacts overall, but increased risks of hospitalized 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 policymakers evaluating this and other candidate dengue vaccines.

The first dengue vaccine, the product of a 20-year development process by Sanofi-Pasteur, 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 more than six-fold higher risk of severe disease compared with those experiencing primary infection(*4*, *5*), which is hypothesized to be due to heterotypic antibody-dependent enhancement (ADE) (*4*). Avoidance of similar consequences means the ideal DENV vaccine should generate a balanced protective responses 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 backbone, was evaluated in two large multi-center phase III trials. One trial was conducted in South-East Asia(*6*), among approximately 10,000 children aged 2 to 14 years, and the other in Latin America(*7*), among approximately 21,000 children aged 9 to 16 years . Both trials reported efficacy of approximately 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 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 2-5 year age group of the Asian trial had substantially and significantly higher risk of hospitalization for virologically confirmed dengue disease than controls (*9*). In other age groups (in both trials) the vaccine was still protective against hospitalisation, albeit efficacy was lower than seen in the active phase of the trial (see

Supplementary Material (SM), (*10*)) Immunogenicity data(*11-18*) has shown seropositive vaccine recipients attain high and sustained antibody levels after the first dose of vaccine, while 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 2-5 year age group is driven by the effect of vaccine in the large proportion of seronegative recipients in this age group, but this currently 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 makes 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 (see SM, (*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 being 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 non-vaccinees (*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 the patterns seen in both the active and long-term follow-up phases of the phase III clinical trial well, 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 7-fold greater incidence of hospitalised dengue seen in 2-5 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 2-5 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 approximately twice as likely to cause symptomatic infection than either primary or post-secondary 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% CI: 4-11 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 0-100%.

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), 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 hospitalised dengue case incidence over a 10 and 30-year periods are shown in Fig. 2. In high transmission settings, vaccination is associated with modest (20-30%) 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. While short-term (10-year) impacts are generally positive, both positive and negative impacts of vaccination may occur for both symptomatic and hospitalized disease 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 8-fold higher risk of hospitalization than primary infections (*10*, *26*) but only a 2-fold higher risk of uncomplicated symptomatic disease (*26*).

The population level impacts of vaccination hide enormous heterogeneity in benefits and risk at the level of the individual recipient (Fig. 3a and 3b): seropositive recipients always gain a substantial benefit from vaccination (>90% reduction in the risk of hospitalized dengue), while seronegative recipients experience an increased risk of hospitalized dengue. This is true both on a short-term (see supplementary material) and on a 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 pre-vaccination 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 approximately 35%. In contrast, it is harder to avoid increased risk of hospitalized disease in 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 approximately 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 modelling 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 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 suggests 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 hospitalized disease incidence 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). While 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, being 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 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 (Fig. S9 and S10).

Our results also show that the effectiveness of vaccination would be expected to vary over time (Fig. S6-S8). In low transmission settings, the introduction of vaccination could perturb transmission dynamics leading to transient reductions in dengue disease incidence for 5-10 years. Only when the transmission dynamics re-equilibrate 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 SM (*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 post-secondary infection rather than actual differences in (serostatus-specific) efficacy (Fig. S12). Including such asymmetry does not qualitatively affect model predictions (Fig. S13 and S14). We also do not consider persistent variation in exposure to DENV at the individual or neighbourhood 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. While

characterising 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 vacinees 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, while 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 programmes targeting older children would increase, particularly in lower transmission settings. Last, the modelling presented here 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 modelling 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 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 maximise benefits, but our current estimates indicate that in all but the highest transmission settings, use of this vaccine may lead to an increase in hospitalised dengue in seronegative recipients even if the overall impact of vaccination is positive. We predict routine vaccination will cause at most moderate (10-20%) 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 risk/benefit 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 we predict for vaccine use in other low transmission intensity settings.

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 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*) reinforces the value of modelling in interpreting trial results and planning how best to use partially effective vaccines with complex efficacy profiles.

References

1. J. R. Stephenson, Understanding dengue pathogenesis: implications for vaccine design. *Bull. World Health Organ.* **83**, 308–314 (2005).

2. R. Edelman, J. Hombach, "Guidelines for the clinical evaluation of dengue vaccines in endemic areas": summary of a World Health Organization Technical Consultation. *Vaccine*. **26** (2008), pp. 4113–4119.

3. B. R. Murphy, S. S. Whitehead, Immune Response to Dengue Virus and Prospects for a Vaccine*. *http://dx.doi.org/10.1146/annurev-immunol-031210-101315*. **29**, 587–619 (2011).

4. S. B. Halstead, Immune enhancement of viral infection. *Prog Allergy*. **31**, 301–364 (1982).

5. D. S. Burke, A. Nisalak, D. E. Johnson, R. M. Scott, A prospective study of dengue infections in Bangkok. *Am. J. Trop. Med. Hyg.* **38**, 172–180 (1988).

6. M. R. Capeding *et al.*, Clinical efficacy and safety of a novel tetravalent dengue vaccine in healthy children in Asia: a phase 3, randomised, observer-masked, placebo-controlled trial. *The Lancet* (2014), doi:10.1016/S0140-6736(14)61060-6.

7. L. Villar *et al.*, Efficacy of a tetravalent dengue vaccine in children in Latin America. *N Engl J Med*. **372**, 113–123 (2015).

8. A. Sabchareon *et al.*, Protective efficacy of the recombinant, live-attenuated, CYD tetravalent dengue vaccine in Thai schoolchildren: a randomised, controlled phase 2b trial. *The Lancet*. **380**, 1559–1567 (2012).

9. S. R. Hadinegoro *et al.*, Efficacy and Long-Term Safety of a Dengue Vaccine in Regions of Endemic Disease. *N Engl J Med*, 150727090428004 (2015).

10. Supplementary material is available in Science Online.

11. L. Á. Villar *et al.*, Safety and Immunogenicity of a Recombinant Tetravalent Dengue Vaccine in 9–16 Year Olds: A Randomized, Controlled, Phase II Trial in Latin America. *The Pediatric Infectious Disease Journal*. **32**, 1102–1109 (2013).

12. G. H. Dayan *et al.*, Immunogenicity and safety of a recombinant tetravalent dengue vaccine in children and adolescents ages 9-16 years in Brazil. *Am. J. Trop. Med. Hyg.* **89**, 1058–1065 (2013).

13. Y. S. Leo *et al.*, Immunogenicity and safety of recombinant tetravalent dengue vaccine (CYD-TDV) in individuals aged 2–45 years. *Human Vaccines & Immunotherapeutics*. **8**, 1259–1271 (2012).

14. C. F. Lanata *et al.*, Immunogenicity and safety of tetravalent dengue vaccine in 2–11 year-olds previously vaccinated against yellow fever: Randomized, controlled, phase II study in Piura, Peru. *Vaccine*. **30**, 5935–5941 (2012).

15. R. Z. Capeding *et al.*, Live-attenuated, tetravalent dengue vaccine in children, adolescents and adults in a dengue endemic country: Randomized controlled phase I trial in the Philippines. *Vaccine*. **29**, 3863–3872 (2011).

16. D. Morrison *et al.*, A novel tetravalent dengue vaccine is well tolerated and immunogenic against all 4 serotypes in flavivirus-naive adults. *J. Infect. Dis.* **201**, 370–377 (2010).

17. I. Dorigatti *et al.*, Modelling the immunological response to a tetravalent dengue vaccine from multiple phase-2 trials in Latin America and South East Asia. *Vaccine*. **33**, 3746–3751 (2015).

18. M. R. Capeding, T. M. Laot, M. Boaz, T. A. Wartel, D. Crevat, Immunogenicity and safety of a tetravalent dengue vaccine during a five-year follow-up period. *Trials in Vaccinology*. **4**, 19–23 (2015).

19. B. Guy, N. Jackson, Dengue vaccine: hypotheses to understand CYD-TDV-induced protection. *Nat. Rev. Microbiol.* **14**, 45–54 (2016).

20. I. Rodríguez-Barraquer, L. Mier-y-Teran-Romero, D. S. Burke, D. A. T. Cummings, Challenges in the Interpretation of Dengue Vaccine Trial Results. *PLoS Negl Trop Dis*. **7**, e2126 (2013).

21. T. J. Kochel *et al.*, Cross-serotype neutralization of dengue virus in Aotus nancymae monkeys. *J. Infect. Dis.* **191**, 1000–1004 (2005).

22. A. B. Sabin, Research on Dengue during World War II. *Am. J. Trop. Med. Hyg.* **1**, 30–50 (1952).

23. A. B. Sabin, The dengue group of viruses and its family relationships. *Bacteriol Rev*. **14**, 225–232 (1950).

24. S. Olkowski *et al.*, Reduced Risk of Disease During Postsecondary Dengue Virus Infections. *The Journal of Infectious Diseases*. **208**, 1026–1033 (2013).

25. P. S. Wikramaratna, C. P. Simmons, S. Gupta, M. Recker, The Effects of Tertiary and Quaternary Infections on the Epidemiology of Dengue. *PLoS ONE*. **5**, e12347 (2010).

26. A. Nisalak *et al.*, Serotype-specific dengue virus circulation and dengue disease in Bangkok, Thailand from 1973 to 1999. *Am. J. Trop. Med. Hyg.* **68**, 191–202 (2003).

27. SAGE, "Summary of the April 2016 meeting of the Strategic Advisory Group of Experts on immunization (SAGE)," (available at http://www.who.int/immunization/sage/meetings/2016/april/SAGE_April_2016_Meeting_Web_summary.pdf?ua=1).

28. H. Q. McLean, A. P. Fiebelkorn, J. L. Temte, G. S. Wallace, Centers for Disease Control and Prevention, Prevention of measles, rubella, congenital rubella syndrome, and mumps, 2013:

summary recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep*. **62**, 1–34 (2013).

29. Centers for Disease Control and Prevention, Recommendations of the Immunization Practices Advisory Committee Prevention of Perinatal Transmission of Hepatitis B Virus: prenatal screening of all pregnant women for hepatitis B surface Antigen. *MMWR*. **37** (1988), doi:10.1001/archpedi.1988.02150090019014.

30. L. Coudeville, N. Baurin, E. Vergu, Estimation of parameters related to vaccine efficacy and dengue transmission from two large phase III studies. *Vaccine* (2015), doi:10.1016/j.vaccine.2015.11.023.

31. I. Rodríguez-Barraquer, L. Mier-y-Teran-Romero, N. Ferguson, D. S. Burke, D. A. T. Cummings, Differential efficacy of dengue vaccine by immune status. *Lancet*. **385**, 1726 (2015).

32. T. J. Hladish *et al.*, Projected Impact of Dengue Vaccination in Yucatán, Mexico. *PLoS Negl Trop Dis*. **10**, e0004661 (2016).

33. N. M. Ferguson *et al.*, Modeling the impact on virus transmission of Wolbachia-mediated blocking of dengue virus infection of Aedes aegypti. *Science Translational Medicine*. **7**, 279ra37–279ra37 (2015).

34. C. Sirivichayakul *et al.*, Safety and Immunogenicity of a Tetravalent Dengue Vaccine Candidate in Healthy Children and Adults in Dengue-Endemic Regions: A Randomized, Placebo-Controlled Phase 2 Study. *J. Infect. Dis.*, jiv762 (2015).

35. B. D. Kirkpatrick *et al.*, Robust and Balanced Immune Responses to All 4 Dengue Virus Serotypes Following Administration of a Single Dose of a Live Attenuated Tetravalent Dengue Vaccine to Healthy, Flavivirus-Naive Adults. *J. Infect. Dis.* **212**, 702–710 (2015).

36. M. A. Penny *et al.*, Public health impact and cost-effectiveness of the RTS,S/AS01 malaria vaccine: a systematic comparison of predictions from four mathematical models. *The Lancet*. **387**, 367–375 (2016).

37. N. G. Reich *et al.*, Interactions between serotypes of dengue highlight epidemiological impact of cross-immunity. *J. R. Soc. Interface*. **10**, 20130414–20130414 (2013).

38. R. C. S. Seet, E. E. Ooi, H. B. Wong, N. I. Paton, An outbreak of primary dengue infection among migrant Chinese workers in Singapore characterized by prominent gastrointestinal symptoms and a high proportion of symptomatic cases. *Journal of Clinical Virology*. **33**, 336–340 (2005).

39. D. W. Vaughn *et al.*, Dengue viremia titer, antibody response pattern, and virus serotype correlate with disease severity. *J. Infect. Dis.* **181**, 2–9 (2000).

40. M. N. Nguyet *et al.*, Host and viral features of human dengue cases shape the population of infected and infectious Aedes aegypti mosquitoes. *PNAS*. **110**, 9072–9077 (2013).

41. M. Turelli, Cytoplasmic incompatibility in populations with overlapping generations. *Evolution*. **64**, 232–241 (2010).

42. D. M. Watts, D. S. Burke, B. A. Harrison, R. E. Whitmire, A. Nisalak, Effect of temperature on the vector efficiency of Aedes aegypti for Dengue 2 Virus (1986).

43. J. R. Anderson, R. Rico-Hesse, Aedes Aegypti Vectorial Capacity Is Determined By The Infecting Genotype Of Dengue Virus. *Am. J. Trop. Med. Hyg.* **75**, 886–892 (2006).

44. M. I. Salazar, J. H. Richardson, I. Sánchez-Vargas, K. E. Olson, B. J. Beaty, Dengue virus type 2: replication and tropisms in orally infected Aedes aegypti mosquitoes. *BMC Microbiology 2007 7:1*. **7**, 1 (2007).

45. M. Otero, H. G. Solari, N. Schweigmann, A stochastic population dynamics model for Aedes Aegypti: Formulation and application to a city with temperate climate. *Bull. Math. Biol.* **68**, 1945–1974 (2006).

46. Sheppard, P. M., et al. The dynamics of an adult population of Aedes aegypti in relation to dengue haemorrhagic fever in Bangkok. *The journal of animal. ecology*. 661-702. 13 (1969).

47. T. W. Scott *et al.*, Longitudinal Studies of Aedes aegypti (Diptera: Culicidae) in Thailand and Puerto Rico: Blood Feeding Frequency. *J. Med. Entomol.* **37**, 89–101 (2000).

48. M. Chan, M. A. Johansson, The Incubation Periods of Dengue Viruses. *PLoS ONE*. **7**, e50972 (2012).

49. V. Duong *et al.*, Asymptomatic humans transmit dengue virus to mosquitoes. *PNAS*. **112**, 14688–14693 (2015).

50. B. Murgue, C. Roche, E. Chungue, Prospective study of the duration and magnitude of viraemia in children hospitalised during the 1996-1997 dengue-2 outbreak in French Polynesia. *Journal of medical Virology* (2000).

51. D. J. Gubler, W. Suharyono, R. Tan, M. Abidin, A. Sie, Viraemia in patients with naturally acquired dengue infection. *Bull. World Health Organ.* **59**, 623–630 (1981).

52. L. M. Bartley, C. A. Donnelly, G. P. Garnett, The seasonal pattern of dengue in endemic areas: mathematical models of mechanisms. *Trans R Soc Trop Med Hyg*. **96**, 387–397 (2002).

53. H. Nishiura, Mathematical and statistical analyses of the spread of dengue. *Dengue Bulletin*. **30** (2006), doi:10.1111/j.1365-3156.2006.01560.x/full.

54. I. Rodríguez-Barraquer *et al.*, Revisiting Rayong: shifting seroprofiles of dengue in Thailand and their implications for transmission and control. *Am. J. Epidemiol.* **179**, 353–360 (2014).

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Supplementary materials

Materials and Methods

Supplementary Text

Figs. S1 to S14

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Figure legends

Figure 1:

Model fit to publicly available data from the Asian phase 3 clinical trial (*6*). Panels show modal (best fit) estimate and 95% credible intervals for (A) proportion of participants of the immunological subset of 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 2 years after dose 1 by trial arm and baseline serostatus; (C) attack rate of virologically confirmed symptomatic dengue in all trial participants in first 2 years after dose 1 by trial arm and age group; (D) attack rate of virologically confirmed hospitalized 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*).

Figure 2:

Predicted population effects of vaccination on dengue disease for a range of transmission intensities (horizontal axes) and ages of vaccination (vertical axes). Colour scale indicates proportion of cases averted in the whole population (A) over 10 years, for all symptomatic dengue; (B) over 10 years, for hospitalized dengue; (C) over 30 years, for all symptomatic dengue; (D) over 30 years, for hospitalized 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.

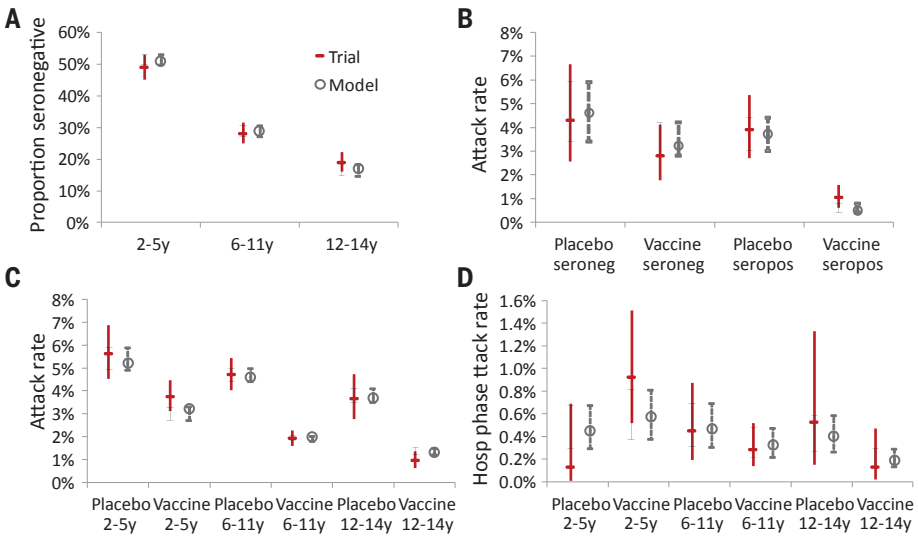
Figure 3.

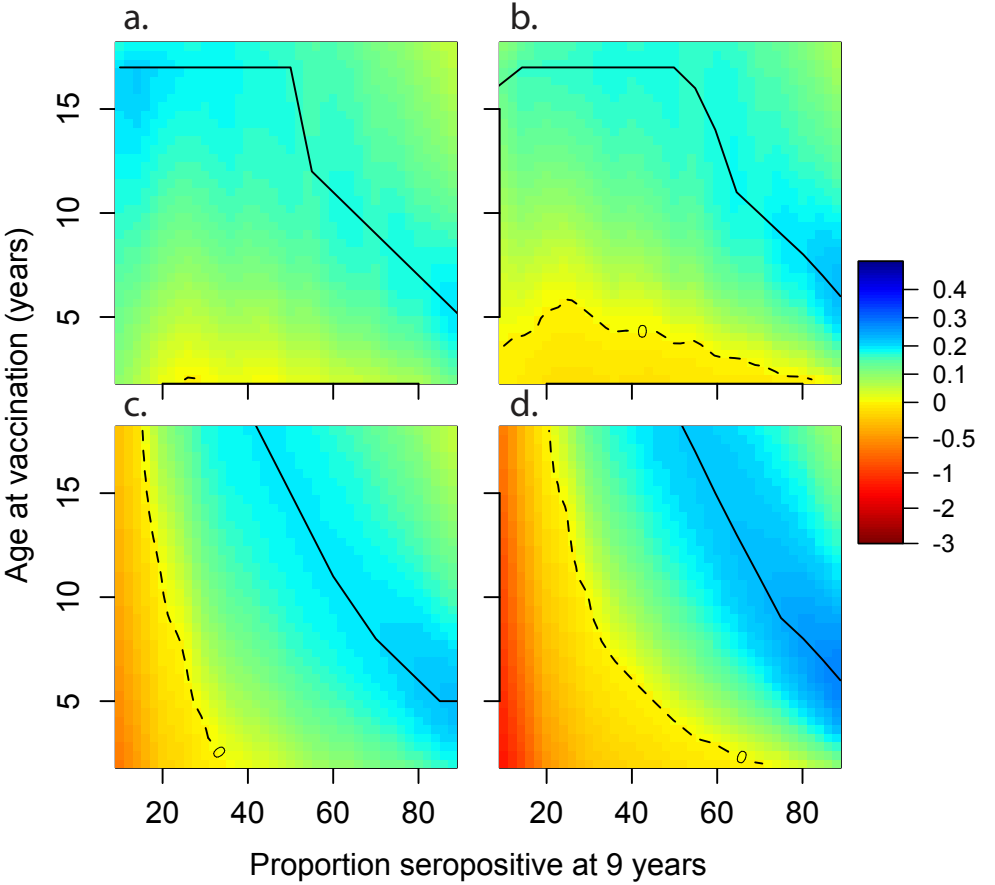
Predicted individual effects of vaccination over 30 years. Proportion of hospitalized cases averted among individual vaccine recipients who are vaccinated (A) when seronegative, and (B) when seropositive. Dashed contour indicates the youngest age-group that may be targeted to avoid negative effects at the individual level. (C) Minimum proportion of the age-group (one-year age band) targeted for routine

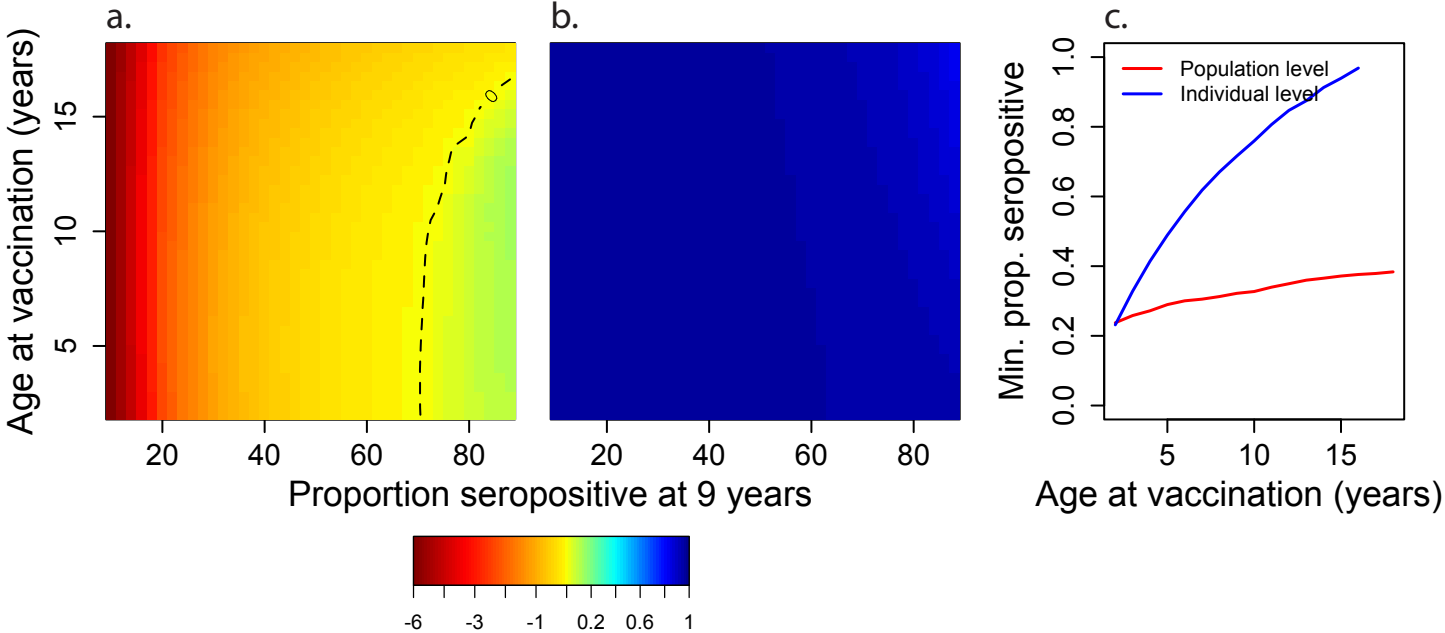
vaccination that should be seropositive prior to introduction of vaccination to avert negative impacts (over a 30-year time frame) at the population (red) and individual (blue) level.

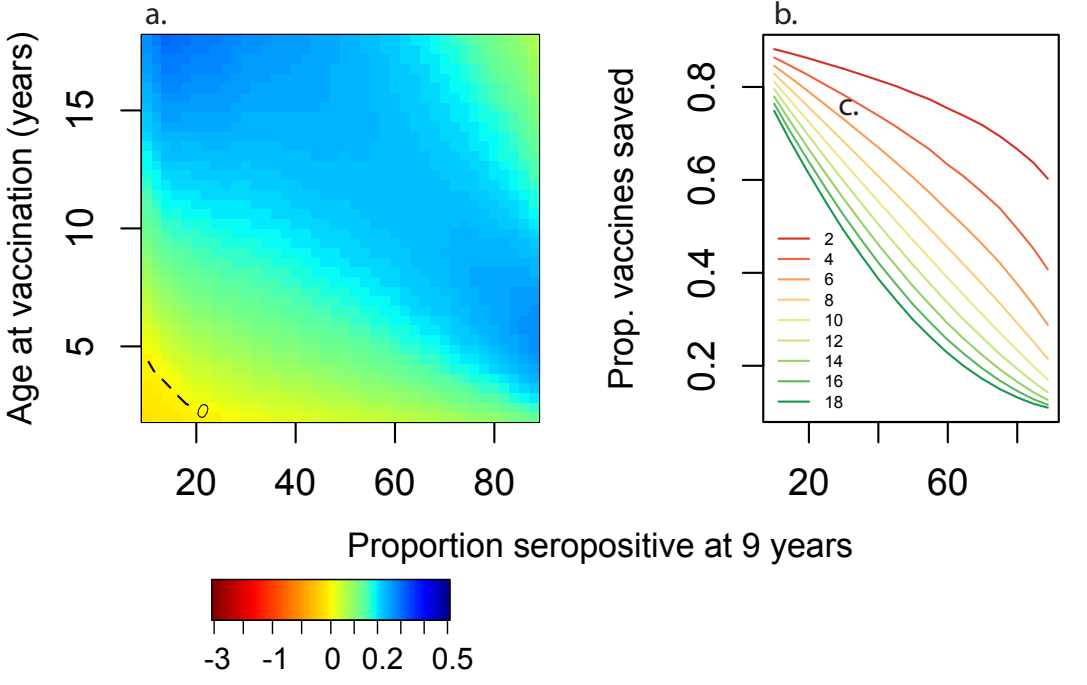
Figure 4:

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. 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 (vertical axis) if only seropositive individuals are targeted, for different transmission intensities (horizontal axis) and target ages (different curves).


A
Proportion seronegative
60%
50%
40%
30%
20%
10%
0%
Trial
Model
2-5y
6-11y
12-14y
B
Attack rate
8%
7%
6%
5%
4%
3%
2%
1%
0%
Placebo seroneg
Vaccine seroneg
Placebo seropos
Vaccine seropos
C
Attack rate
8%
7%
6%
5%
4%
3%
2%
1%
0%
Placebo 2-5y
Vaccine 2-5y
Placebo 6-11y
Vaccine 6-11y
Placebo 12-14y
Vaccine 12-14y
D
Hosp phase ttack rate
1.6%
1.4%
1.2%
1.0%
0.8%
0.6%
0.4%
0.2%
0.0%
Placebo 2-5y
Vaccine 2-5y
Placebo 6-11y
Vaccine 6-11y
Placebo 12-14y
Vaccine 12-14y


a.
b.
c.
d.
Age at vaccination (years)
5
10
15
20
40
60
80
Proportion seropositive at 9 years
0
0.4
0.3
0.2
0.1
0
-0.5
-1
-2
-3


a.
b.
c.
Age at vaccination (years)
Proportion seropositive at 9 years
Min. prop. seropositive
Age at vaccination (years)
Population level
Individual level
0
-6
-3
-1
0.2
0.6
1


a.
Age at vaccination (years)
5
10
15
0
20
40
60
80
Proportion seropositive at 9 years
-3
-1
0
0.2
0.5
b.
Prop. vaccines saved
0.2
0.4
0.6
0.8
c.
2
4
6
8
10
12
14
16
18
20
60

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Supplementary Materials for

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

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1. Materials and Methods

1.1 Model of vaccine action

Figure S1 illustrates the default model of vaccine action described in detail in section 2 below. As discussed in the main text, the model assumes that the immunological effect of vaccination is akin to a (silent) natural infection.

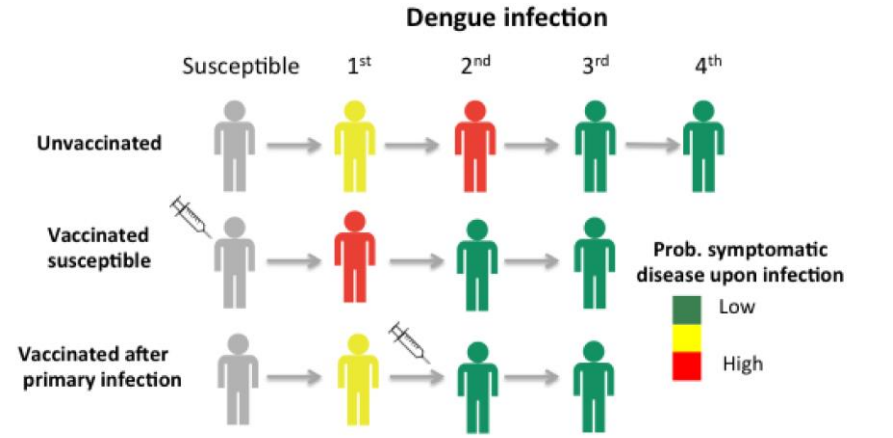

Figure S1: Mechanism of action of the vaccine assumed in the default model.

Unvaccinated individuals (top row of Figure S1) experience a moderate severity primary infection, a more severe secondary infection, then mild tertiary and quaternary infections. Seronegative individuals who are vaccinated while still fully susceptible to dengue (middle row) are transiently protected against the four dengue serotypes as is generally observed after the first natural infection(*22*, *37*). As antibody titers decay, they stop being protective and become enhancing, thus increasing the probability of symptomatic and severe disease upon a primary breakthrough infection(*4*, *5*). Thus, the model assumes that in individuals who are vaccinated while still seronegative, a first breakthrough infection will cause symptomatic or hospitalized disease with the same (high) probability as a secondary natural infection in unvaccinated individuals.

Conversely, vaccination of individuals who have experienced one or more dengue infections (bottom row of Figure S1) boosts their immunity to levels comparable to those of individuals who have experienced two or more infections. Thus, a secondary infection in an individual vaccinated after their primary infection will cause symptomatic or severe disease with the same (low) probability as a tertiary infection in unvaccinated individuals.

Table S1 shows the key temporal trends in vaccine efficacy seen in the phase 3 trials, shown as the relative risk of hospitalized dengue comparing the vaccine group with the control group. The relative risks vary by age (but not significantly by trial within the same age group) and over time, in both studies and in both the under 9 and over 9 age groups. However, all relative risks increased approximately 3 fold between the active phase and the first year of long term follow-up.

Table S1. Relative risks of virologically confirmed hospitalized dengue disease in the phase 3 trials of the Sanofi vaccine. Results for years 1 and 2 post dose 1 (active phase) and Y3 (first year of passive long term follow-up phase) are given, together with the ratio of the relative risks between the two phases. 95% confidence intervals given in parentheses. Efficacy = 1-Relative Risk. Data derived from reference (*9*).

Trial and age group	Y1&2: Active phase Relative Risk	Y3: Long term follow-up phase Relative Risk	Fold increase (ratio of relative risks)
Latin America: 9-16 years	0.19 (0.11-0.35)	0.53 (0.26-1.07)	2.8 (1.1-7.0)
Southeast Asia: 9-14 years	0.19 (0.09-0.38)	0.57 (0.20-1.58)	3.0 (0.9-10.6)
Southeast Asia: 2-8 years	0.44 (0.27-0.72)	1.58 (0.63-3.94)	3.6 (1.3-10.2)

The model of vaccine action described above is able to reproduce these data because secondary infections have a much higher relative risk for hospitalization than primary or post-secondary infections(*26*). Thus our model predicts that nearly all hospitalized cases in the vaccine arm will be in seronegative vaccinees, who benefit from transient immunity in the active phase but lose this protection by the long term follow-up phase and are then primed to have 'secondary-like' natural infections. Conversely, the large majority of hospitalized cases in the control group are expected to be secondary infections.

The relative risks by age group therefore vary according to the proportion of the age group who were seropositive when vaccinated, but increase by the same factor over time because decay of transient heterologous protection in seronegative vaccinees is assumed to occur at the same rate independent of age. In the absence of decay of efficacy in seropositive recipients, we would expect the relative risks to stabilize after year 3 of the trial.

1.2 Transmission model definition

Our dengue transmission model captures the history of infections with any combination of the four dengue serotypes in an age-structured host population. In addition, the vaccination status of the host population is tracked, stratified by the serostatus of vaccinees at the time of vaccination. Table S2 lists the state variables of the system, while table S3 lists model parameter and assumed values (plus sources for those values). We denote incidence rates with the suffix by '*c*'.

Table S2. State variables of transmission model. Subscript notation '*i*|Θ' refers to a current infection with serotype *i* (1..4) and past infection with the set of serotypes Θ where Θ = {*j*}, Θ = {*j*,*k*} or Θ = {*j*,*k*,*l*} for 1, 2 and 3 past infections respectively. Note that the ordering of past infections is not tracked, so *j*<*k*<*l*. Superscript *v* refers to vaccine group (0=not vaccinated, 1= vaccinated when seronegative, 2= vaccinated when seropositive) and *t* and *a* refer to time and age, respectively.

Symbol	Description
$S^v_\Theta(t,a)$	Number of people of age *a* at time *t* with vaccine status *v* who were previously infected and are now immune to serotypes in the set Θ, but remain susceptible to infection from all other serotypes $i \notin \Theta$
$R^v_\Theta(t,a)$	Number of people of age *a* at time *t* with vaccine status *v* who were previously infected and are now immune to serotypes in the set Θ and are currently temporarily protected against heterologous infection
$cI^v_{i\|\Theta}(t,a)$	Incidence at time *t* of infection with serotype *i* in people with past exposure to serotype set Θ, age *a* and vaccine status *v*
$cD^v_{i\|\Theta}(t,a)$	Incidence of symptomatic disease at time *t* due to infection with serotype *i* in people with past exposure to serotype set Θ, age *a* and vaccine status *v*
$cH^v_{i\|\Theta}(t,a)$	Incidence of hospitalized disease at time *t* due to infection with serotype *i* in people with past exposure to serotype set Θ, age *a* and vaccine status *v*
$L(t)$	Number of larval stage female mosquitoes
$A(t)$	Number of uninfected adult female mosquitoes
$H^j_i(t)$	Number of adult female mosquitoes infected with serotype *i* and in incubation state *j* (1..4)
$Y_i(t)$	Number of adult female mosquitoes infected and infectious with serotype *i*

The time evolution of the human-related state variables is governed by the following set of partial differential equations:

$$\frac{\partial S_{\emptyset}^{v}}{\partial t}+\frac{\partial S_{\emptyset}^{v}}{\partial a}=p_V(t)\delta(a-A_V)\left[\delta_{v,1}S_{\emptyset}^{0}-\delta_{v,0}S_{\emptyset}^{v}\right]$$
$$-\sum_{i}\Lambda_i(t)f_v(a-A_V)S_{\emptyset}^{v}-\mu(a)S_{\emptyset}^{v}$$
$$\frac{\partial S_{\Theta}^{v}}{\partial t}+\frac{\partial S_{\Theta}^{v}}{\partial a}=\sigma R_{\Theta}^{v}+p_V(t)\delta(a-A_V)\left[\delta_{v,2}S_{\Theta}^{0}-\delta_{v,0}S_{\Theta}^{v}\right] \quad (1)$$
$$-\sum_{i\notin\Theta}\Lambda_i(t)f_v(a-A_V)S_{\Theta}^{v}-\mu(a)S_{\Theta}^{v}$$
$$\frac{\partial R_{\Theta}^{v}}{\partial t}+\frac{\partial R_{\Theta}^{v}}{\partial a}=p_V(t)\delta(a-A_V)\left[\delta_{v,2}R_{\Theta}^{0}-\delta_{v,0}R_{\Theta}^{v}\right]$$
$$+\sum_{i\in\Theta}\Lambda_i(t)f_v(a-A_V)S_{\Theta/i}^{v}-[\sigma+\mu(a)]R_{\Theta}^{v}$$

Here $\emptyset$ represents the empty set, $|\Theta|$ represents the cardinality of set Θ (*i.e.* the number of serotypes an individual has been exposed to), Θ/i is the subset of Θ which excludes element i, $\delta(x)$ is the Dirac delta function and $\delta_{i,j}$ is the Kronecker delta (or identity matrix). Summation is over serotypes or all (unordered) sets of between zero and four unique serotypes, with $\Theta \not\ni i$ representing all sets which do not include i as a member.

Note that the equation for $S_{\emptyset}^{v}$ is only defined for v=1, 2; by definition, $S_{\emptyset}^{2} \equiv 0$. Similarly, when $\Theta \neq \emptyset$, the equations for S_{Θ}^{v} and R_{Θ}^{v} are only defined for v=0, 2 and $S_{\Theta}^{1} = R_{\Theta}^{1} \equiv 0$.

Incidence-related state variables are defined thus:

$$cI_{i|\Theta}^{v}(t,a)=\Lambda_i(t)f_v(a-A_V)S_{\Theta}^{v}$$
$$cD_{i|\Theta}^{v}(t,a)=\mathcal{P}_{|\Theta|+(1-\delta_{0,v})}\,\Lambda_i(t)f_v(a-A_V)S_{\Theta}^{v} \quad (2)$$
$$cH_{i|\Theta}^{v}(t,a)=\mathcal{Q}_{|\Theta|+(1-\delta_{0,v})}\,cD_{i|\Theta}^{v}(t,a)$$

Parameterization of host demography is detailed in Section 2 below; in the equations above, $\mu(a)$ represents the mortality hazard experienced by an individual of age a.

Vaccination occurs at age A_V, with a proportion $p_V(t)$ of eligible individuals receiving 3 doses of vaccine. Everyone who receives vaccine is assumed to complete all courses. The function $p_V(t)$ is modelled as a step function (T_V being the time the vaccination program starts):

$$p_V(t)=0 \quad \text{if } t<T_V$$
$$=p_{V0} \quad \text{if } t\geq T_V$$

The force of infection on humans due to serotype i is Λ_i, defined below. Host immunity to natural infection has two components: (a) a period of heterologous cross-protection following infection with any serotype (represented by the

compartments R_Θ^v) of mean duration $1/\sigma$, and (b) permanent and complete protection from reinfection with previously encountered serotypes. Heterologous vaccine-induced protection against infection decays over time and is described by the relative risk function $f_v(\tau)$, τ being the time since vaccination, defined thus:

Unvaccinated individuals: $f_0(\tau) = 1$

Individuals vaccinated when seronegative: $f_1(\tau) = 1 - VE_- h(\tau)$

Individuals vaccinated when seropositive: $f_2(\tau) = 1 - VE_+ h(\tau)$

The decay function $h(\tau)$ assumes exponential decay of protection after each vaccine dose with mean duration T_D:

$$h(\tau) = \exp(-\tau/T_D) \quad \text{if } \tau < 0.5 \text{ years}$$
$$= \exp(-(\tau - 0.5)/T_D) \quad \text{if } 0.5 < \tau < 1 \text{ years}$$
$$= \exp(-(\tau - 1)/T_D) \quad \text{if } \tau > 1 \text{ years}$$

However, the major impact of vaccination is long-lived modification of future disease risk (as discussed in the main text). $\mathcal{P}_n$ represents the probability that an unvaccinated individual who has had *n* previous dengue infections will be symptomatic if they experience their (n+1)$^{\text{th}}$ infection. $\mathcal{Q}_n$ is then the proportion of those symptomatic cases that are sufficiently severe to require hospitalization.

Vector population dynamics followed a simple Ross-Macdonald type model:

$$\frac{dL}{dt} = bM - \alpha L - \omega L[1 + L/K(t)]$$
$$\frac{dA}{dt} = \alpha L - \sum_i \Psi_i A - \epsilon A$$
$$\frac{dH_i^j}{dt} = \delta_{1,j}\Psi_i A + 4\eta\left(1 - \delta_{1,j}\right)H_i^{j-1} - (4\eta + \epsilon)\, H_i^j \quad \text{for } 1 \le j \le 4$$
$$\frac{dY_i}{dt} = 4\eta H_i^4 - \epsilon\, Y_i$$

Here *M* is the total adult female mosquito population size:

$$M = A + \sum_{i,j} H_i^j + \sum_i Y_i$$

The rate at which adult females produce female larvae is b, the mean development time of larvae is $1/\alpha$, the mean extrinsic incubation period is $1/\eta$, the larval mortality rate is ω and the adult mortality rate is ϵ. Larval carrying capacity varies seasonally (t in years) and is assumed to scale linearly with human population size, N:

$$K(t) = K_0 N[1 + \Delta_K \sin(2\pi t)]$$

Here K_0 is the average carrying capacity across the year and Δ_K is the magnitude ($0 \leq \Delta_K \leq 1$) of seasonal variation in carrying capacity.

We assign b by fixing the required value of R_m, the mosquito reproduction number, which can be shown to be given by:

$$R_m = \frac{\alpha}{\epsilon(\alpha + \omega)} b$$

The force of infection on mosquitoes due to serotype i, Ψ_i, is defined by:

$$\Psi_i = \frac{\kappa \beta_{hm}}{N} \int_0^\infty \int_{T_{\text{IP}}}^{T_{\text{IP}}+T_{\text{Inf}}} \sum_{\Theta \not\ni i} \left[cI^v_{i|\Theta}(t-\tau, a) + (\theta - 1) cD^v_{i|\Theta}(t-\tau, a) \right] d\tau da$$

Here T_{IP} is the intrinsic incubation period, T_{Inf} is the infectious period in humans, θ represents the factor by which infectiousness of symptomatic infection exceeds that of asymptomatic infections, κ is the biting rate per adult female mosquito, β_{hm} is the per bite transmission probability from humans to mosquitoes and N is the total human population size. Given that infectivity to mosquitoes increases with plasma viremia and that viremia is usually higher among individuals with symptomatic diseases (*38-40*), we assume that θ=2; *i.e.* infectiousness of symptomatic infections is twice than that of asymptomatic infections, but vary this in sensitivity analyses. Note that mosquitoes can only be infected with a single dengue serotype and that infection is assumed to be life-long.

The force of infection on humans due to serotype i, Λ_i, is defined by:

$$\Lambda_i = \frac{\kappa \beta_{mh}}{M} Y_i$$

where, β_{mh} is the per bite transmission probability from mosquitoes to humans and M is the total adult female mosquito size.

The basic reproduction number of serotype i, R_{0i}, is then given by

$$R_{0i} = \frac{\kappa^2 \beta_{mh} \beta_{hm} T_{\text{Inf}}}{\epsilon(1 + \epsilon/\eta)} m$$

Here m=M/N, the number of adult female mosquitoes per person. In the absence of seasonal forcing of carrying capacity, the equilibrium value of m is given by:

$$m_{eq} = \frac{\alpha}{\epsilon} \left[\frac{\alpha(b - \epsilon)}{\epsilon \omega} - 1 \right] K_0$$

K_0 is assigned by fixing the required value of m_{eq} and inverting this equation.

We vary transmission intensity by fixing the ratios of all pairs of serotype reproduction numbers and then vary the value of R_{02}(reproduction number of DENV2) by adjusted the value of β_{hm}. R_{02} could equally well have been varied by adjusting β_{hm}, κ or m_{eq} (or a combination of all four); all give exactly identical results when modelling the impact of vaccination alone.

1.3 List of parameter assignments

Table S3 lists all model parameters, assigned values and sources for these. It also highlights which parameters are estimated from the CYD vaccine trial data or are varied in sensitivity analysis; these are the parameters which principally affect mode results. We note that for a given transmission intensity (R_0), model results presented in this paper are nearly completely insensitive to the values of entomological parameters – indeed almost identical results can be obtained without including vectors in the model (*i.e.* treating dengue as a directly transmitted disease). Vectors were included to allow the same model to explore the combined impact of vaccination and vector control.

Table S3. Parameters of transmission model. Estimated parameters are indicated or assigned values are listed.

Symbol	Description	Estimated or value if assigned	Source references
$\boldsymbol{\mu(a)}$	Human hazard of death at age a	Fitted to approximate Philippines demography	See text below
$\boldsymbol{B}$	Human birth rate	Assigned to give fixed equilibrium population size of 1 million	See text below
$\boldsymbol{p_{V0}}$	Vaccine coverage	0.8	N/A
$\boldsymbol{A_V}$	Age at vaccination	Varied between 2 & 18 years	N/A
$\boldsymbol{T_V}$	Time vaccination starts	Between 150 and 200 years after simulation start	N/A
$\boldsymbol{VE_-}$	Maximum vaccine efficacy against infection in seronegative recipients	Fitted – see Table S4	N/A
$\boldsymbol{VE_+}$	Maximum vaccine efficacy against infection in seropositive recipients	Fitted – see Table S4	N/A
$\boldsymbol{T_D}$	Mean duration of vaccine-induced protection against infection	Fitted – see Table S4	N/A
$\boldsymbol{1/\sigma}$	Duration of heterologous protection following natural infection	1 year	(*22*, *23*, *37*)

$\mathcal{P}_0$	Proportion of primary infections which are symptomatic	Fitted – see Table S4	N/A
$\mathcal{P}_1$	Proportion of secondary infections which are symptomatic	Fitted – see Table S4	N/A
$\mathcal{P}_2 = \mathcal{P}_3$	Proportion of tertiary and quaternary infections which are symptomatic	Fitted (assumed to be the same for tertiary and quaternary) – see Table S4	N/A
Q_0	Proportion of symptomatic primary infections which require hospitalization	Fixed such that Q_0/Q_1=0.25 (i.e. primary symptomatic infections are 75% less likely to be severe enough to be hospitalized than secondary)	Ratio Q_0/Q_1 derived from reference (*26*)
Q_1	Proportion of symptomatic secondary infections which require hospitalization	Fitted – see Table S4	N/A
$Q_2 = Q_3$	Proportion of symptomatic tertiary and quaternary infections which require hospitalization	Assumed to be the same for tertiary and quaternary. In the absence of reliable data, we fixed these parameters such that Q_2/Q_1=0.25 (i.e. symptomatic tertiary and quaternary infections are 75% less likely to be severe enough to be hospitalized than secondary)	Ratio Q_2/Q_1 assumed
R_m	Mosquito reproduction number	2.69 based on estimate of female fecundity of 0.269/day and adult mortality rate of 0.1/day	(*41*)
b	Rate at which adult females produce female larvae	Assigned to match required value of R_m	N/A
$1/\alpha$	Mean development time of mosquito larvae	19 days	

$\mathbf{1/\eta}$	Mean extrinsic incubation period	10 days	(*42-44*)
$\boldsymbol{\omega}$	Larval mosquito mortality rate	0.025/day	(*45*)
$\boldsymbol{\epsilon}$	Adult mosquito mortality rate	0.1/day	(*46*)
$\boldsymbol{m_{eq}}$	Equilibrium number of adult female mosquitoes per person in the absence of seasonal variation in carrying capacity	1.5 (typical of endemic settings)	(*47*)
$\boldsymbol{K_0}$	Mean larval mosquito carrying capacity	Assigned to match required value of *m*	N/A
$\Delta_{\boldsymbol{K}}$	Amplitude of seasonal variation in carrying capacity	Assigned value of 0.3 to match observed periodicity and amplitude of dengue epidemics	
$\boldsymbol{T}_{\mathrm{IP}}$	Intrinsic incubation period	6 days	(*48*)
$\boldsymbol{T}_{\mathrm{Inf}}$	infectious period in humans	4 days	(*49-51*)
$\boldsymbol{\theta}$	factor by which infectiousness of symptomatic infection exceeds that of asymptomatic infections	2 for baseline results, varied to 1 in sensitivity analysis in SM section 5.1.	(*39*, *40*, *49*)
$\boldsymbol{\beta_{hm}}$	Per bite transmission probability from humans to mosquitoes	Arbitrarily set to 1 (for fixed R_{0i}, varying this parameter does not affect predictions of vaccine impact)	N/A
$\boldsymbol{\beta_{mh}}$	Per bite transmission probability from mosquitoes to humans	Assigned to match required value of R_0	N/A
$\boldsymbol{\kappa}$	Biting rate per mosquito	0.6/day (for fixed R_{0i}, varying this parameter does not affect predictions of vaccine impact)	(*52*) (*53*)

$\boldsymbol{R_{01}/R_{02}}$	R_0 of DENV1 relative to that of DENV2	0.85	(*54*)
$\boldsymbol{R_{03}/R_{02}}$	R_0 of DENV3 relative to that of DENV2	0.81	(*54*)
$\boldsymbol{R_{04}/R_{02}}$	R_0 of DENV4 relative to that of DENV2	0.82	(*54*)
$\boldsymbol{R_{02}}$	R_0 of DENV2	Varied from between approximately 1.1 and 5 to match required equilibrium pre-vaccination seropositivity in 9 year olds	

Demographic parameters were calibrated to approximate the age distribution of the Brazilian population, under the simplifying assumption that population size is constant over time. Figure S2 shows the age-specific mortality rates assumed and the match of the modelled population age distribution to the age distributions of the populations of Brazil and the Philippines.

To reduce the computational requirements of solving the transmission model numerically, we approximated the continuous representation of age given in the model specification detailed above with discrete age classes. Annual age classes were used for the first 20 years of life, followed by 8 10-year age classes. Age was updated once per year in solving the model to ensure accurate tracking of age for ages under 20 (i.e. including all subjects in the phase 3 trials).

Initial conditions were set to approximate the multistrain equilibrium for the model without seasonal variation in transmission, but the model still needed to be run for 150 years of modelled time to equilibriate.

In the main text, we use the long-term average proportion of 9 year olds who are dengue seropositive prior to the start of vaccination as a measure of transmission intensity. Figure S3 shows the relationship between this measure and the basic reproduction number of DENV2 in our transmission model for the assigned parameter values given in Tables S3 and the median values given in Table S4.

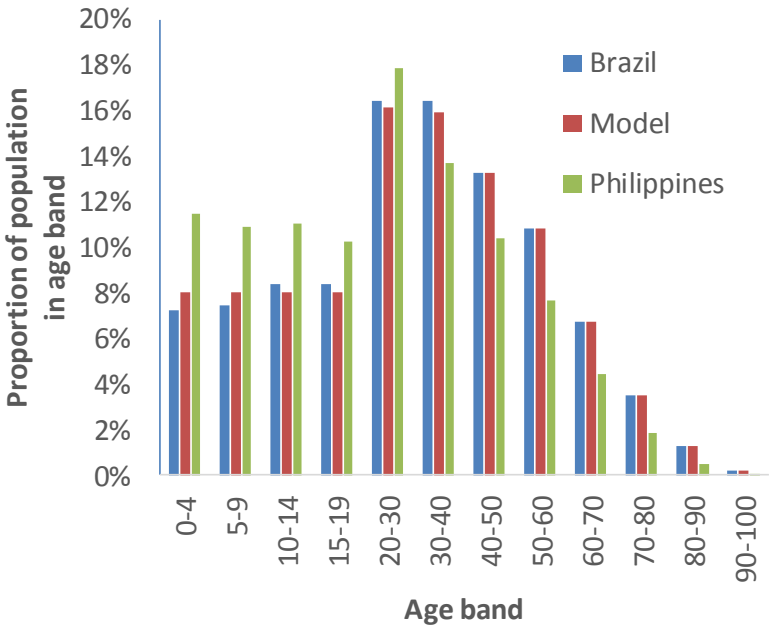

Figure S2. Comparison of modelled age distribution and age distributions of Brazil and the Philippines in 2015 (UN World Population Prospects 2015 - http://esa.un.org/unpd/wpp/).

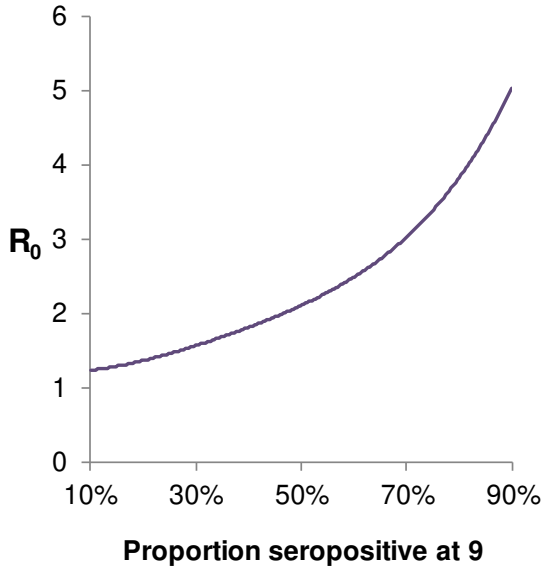

Figure S3. Relationship between R_0 of DENV2 and the equilibrium proportion of 9 year olds who are seropositive to any dengue serotype for the transmission model presented above.

1.4 Estimation of vaccine parameters and model fit

Models were fitted to both phase 3 trials simultaneously. The likelihood used incorporated 4 components:

a) clinical attack rates of virologically confirmed dengue disease by age group in the active phase of the trials (cumulative case numbers for the two years following dose 1). We define $n_{\mathrm{a,i}}^{v}$ to be the number of subjects in age group a, arm v (0=control, 1=vaccine) and trial i (0=SE Asian, 1=Latin American). Similarly, $c_{\mathrm{a,i}}^{v}$ is the number of virologically confirmed cases reported in age group a, arm v and trial i in the active phase of the trial. A binomial likelihood was assumed for every age group, arm and trial; *i.e.* $c_{\mathrm{a,i}}^{v} \sim \mathrm{Binomial}\left(p_{\mathrm{a,i}}^{v}, n_{\mathrm{a,i}}^{v}\right)$ where $p_{\mathrm{a,i}}^{v}$ is the predicted attack rate from the model (calculated from $cD_{i|\Theta}^{v}(t,a)$ in equation 2 in section 1 by integrating over the relevant time interval).

b) proportion of participants in the immunogenicity subset of each trial who were seronegative at baseline by age group. We define $ns_{\mathrm{a,i}}^{s,v}$ to be the number of immunogenicity subset subjects in age group a, arm v (0=control, 1=vaccine) and trial i (0=SE Asian, 1=Latin American) with baseline serostatus s (0=seronegative, 1=seropositive). A binomial likelihood was then assumed: *i.e.* $ns_{\mathrm{a,i}}^{0,0} + ns_{\mathrm{a,i}}^{0,1} \sim \mathrm{Binomial}\left(ps_{a,i}, ns_{\mathrm{a,i}}^{0,0} + ns_{\mathrm{a,i}}^{0,1} + ns_{\mathrm{a,i}}^{1,0} + ns_{\mathrm{a,i}}^{1,1}\right)$, where $ps_{a,i}$ is the proportion of age group a in the immunogenicity subset of trial i predicted to be seronegative by the model (calculated from $S_{\emptyset}^{v}(t,a)$ from equation 1 above evaluated at the simulated start of the trial).

c) active phase clinical attack rates by baseline serostatus for the immunogencity subset of the trials. We define $cs_{\mathrm{i}}^{s,v}$ as the number of virologically confirmed cases reported in the immunogenicity subset arm v and trial i with baseline serostatus s (case numbers were too low in the immunogencity subsets to permit stratification by age, and the relevant data are in any case not publically available). A binomial likelihood was assumed; *i.e.* $cs_{\mathrm{i}}^{s,v} \sim \mathrm{Binomial}\left(ps_{\mathrm{i}}^{s,v}, \sum_{a} ns_{\mathrm{a,i}}^{s,v}\right)$ where $ps_{\mathrm{i}}^{s,v}$ is the serostatus-specific attack rate predicted by the model (calculated from $cD_{i|\Theta}^{v}(t,a)$ in equation 2 in section 1 by integrating over the relevant time interval).

d) hospitalization rates for virologically confirmed dengue disease by age group in the first year of the long-term follow-up (LTFU) phase of the trials. We define $hc_{\mathrm{a,i}}^{v}$ as the number of (hospitalized) virologically confirmed cases reported in age group a, arm v and trial i in the first year of the passive phase of the trial (year 3 overall). A binomial likelihood was assumed for every age group, arm and trial; *i.e.* $ch_{\mathrm{a,i}}^{v} \sim \mathrm{Binomial}\left(ph_{\mathrm{a,i}}^{v}, n_{\mathrm{a,i}}^{v}\right)$ where $ph_{\mathrm{a,i}}^{v}$ is the relevant predicted attack rate from the model (calculated from $cH_{i|\Theta}^{v}(t,a)$ in equation 2 in section 1 by integrating over the relevant time interval).

We used our transmission model to simulate the phase 3 trials. Since the trials enrolled only a small proportion of the populations of the countries in which trial

sites were located, indirect effects (on transmission) of vaccination in the trial can be neglected. We therefore recorded simulated dengue infection attack rates over the first 3 years of the trial in cohorts with age distributions matching those of the actual trials (given by $n^{v}_{\mathrm{a,i}}$ and $ns^{s,v}_{\mathrm{a,i}}$). These outputs were used to calculate clinical attack rates in both the vaccine and control arms of the trials (using equations 2 in Section 1 above) under across the full range of possible values for efficacy parameters.

Parameter estimation was undertaken by discretizing parameter space and evaluating the model likelihood over a multidimensional grid of parameter combinations. This allowed massive parallelization of what otherwise would have been a computationally infeasible inferential problem (given the model required 60-90s of CPU time on a single v2 Xeon E5 2.9Ghz core to solve). We estimated 9 parameters. Six parameters were fitted as common to both trials:

a) The proportion of primary, secondary and post-secondary infections that are symptomatic ($\mathcal{P}_0, \mathcal{P}_1, \mathcal{P}_2$). Values of $\mathcal{P}_0$ and $\mathcal{P}_1$ between 0 and 1 in steps of 0.05 were evaluated. After initial exploration indicated estimates of $\mathcal{P}_2$ were considerably lower than those of $\mathcal{P}_0$ or $\mathcal{P}_1$ so values of $\mathcal{P}_2$ between 0 and 0.3 in steps of 0.02 were evaluated in the final analysis.
b) The initial degree of heterologous protection against infection afforded by the vaccine in seronegative and seropositive recipients (VE_{-} and VE_{+}). Values of both parameters between 0 and 1 in steps of 0.02 were evaluated.
c) The mean duration of that heterologous protection (T_D). After initial exploration, values between 3 months and 14 months in steps of 1 month were evaluated.

In addition, three parameters were fitted as trial-specific:

a) The starting time of the trial relative to the start of the simulation. Similar to observed trends in dengue incidence, our transmission model generates semi-chaotic epidemic dynamics over time, with considerable variation in the attack rates seen in any 3-year period (the timescale of the trial). However, it was not appropriate to fit the initial conditions of the model directly to the trial data, as it would be highly likely that the resulting estimates would be far from the pseudo-equilibrium of the model. We therefore allowed the transmission model to equilibrate for at least 200 years of modelled time, and then treated the start time of the trial after that time point as a fitted parameter. Start times between 0 and 150 years (after year 200) in steps of 28 days were evaluated.
b) The basic reproduction number of DENV in the trial population (R_{02}). After initial exploration of a wider range, values between 2 and 3.5 in steps of 0.1 were evaluated.
c) The probability that a symptomatic secondary case is hospitalized (Q_1). The maximum likelihood value of this parameter was analytically calculated for every combination of all other parameters.

In total, the model was run for approximately 10^5 transmission and disease propensity parameter combinations, and the (log) likelihood was evaluated for a total of approximately 10^8 combinations of the other parameters for each model run, giving a total of approximately 10^{13} total likelihood evaluations. The calculated likelihood values are equivalent (up to a constant multiple) to exact evaluations of the posterior density under the assumption of uniform priors (given the parameter discretization detailed above). The posterior distribution thus calculated was used to evaluate median and 95% credible intervals on all parameters. In addition, parameter sets were randomly drawn from the joint posterior distribution of all parameters and for use in evaluating the predicted impact of large-scale use of vaccination.

Table S4 below lists the median values and 95% credible intervals of all estimated parameters for the model, which assumes the immunological effect of vaccination is comparable to a silent natural infection. Three sets of estimates are shown:

(a) one where the efficacy of transient heterologous protection is estimated (parameters VE_- and VE_+);
(b) one where such protection is assumed to be initially entirely protective in seronegative recipients and is assumed to be absent in seropositive recipients. The motivation for the latter simpler model variant is that the main effect of vaccination for a recipient who has had one prior natural dengue infection is to reduce the risk of disease in the next dengue infection to the much lower level experienced by individuals who have had two natural dengue infections; adding short-lived protection to this dominant effect did not improve model fit: the maximum posterior likelihood is unchanged, the mean posterior likelihood decreases by 1.4 and the Bayesian Information Criterion increases by 3.5 with the addition of one additional estimated parameter. In addition, when VE_+ is estimated, estimates are highly correlated with those of $\mathcal{P}_2$ (the proportion of post-secondary infections which are symptomatic). This is the model variant used to generate projections of vaccine impact in the main text;
(c) as (a) but estimated from a dataset which excluded the 2-5y age group results from the first year of long-term follow-up. The nearly identical estimates obtained demonstrate that the parameter estimation used is not sensitive to a single potential outlier data point (namely the one data point showing a relative risk of dengue disease in the vaccine group compared with the control group which was greater than one).

Model fit to the SE Asian phase 3 trial(*6*) is shown in Figure 1 of the main text; Figure S4 shows the fit to the Latin American trial(*7*, *9*).

Table S4. Parameter estimates for the model assuming the immunological effect of vaccination is comparable to a silent natural infection. Median posterior values with 95% credible intervals are shown. Three sets of estimates are shown, as described above. Estimates of the start time of the trials are not listed, as these are entirely specific to the model code and initial conditions used.

Parameter	Description	Estimate when all parameters estimated	Estimate for model with VE_-=1 and VE_+=0	Estimate when fitted to data excluding 2-5y LTFU Y1 result
$\mathcal{P}_0$	Proportion of primary infections which are symptomatic	0.45 (0.25-0.70)	0.45 (0.25-0.70)	0.45 (0.25-0.70)
$\mathcal{P}_1$	Proportion of secondary infections which are symptomatic	0.8 (0.5-1)	0.8 (0.55-1)	0.8 (0.5-1)
$\mathcal{P}_2 = \mathcal{P}_3$	Proportion of tertiary and quaternary infections which are symptomatic	0.14 (0.07-0.24)	0.1 (0.06-0.16)	0.14 (0.07-0.24)
VE_-	Maximum vaccine efficacy against infection in seronegative recipients	0.88 (0.64-1) Modal value of 1	Fixed at 1	0.86 (0.62-1) Modal value of 1
VE_+	Maximum vaccine efficacy against infection in seropositive recipients	0.4 (0-0.94) Modal value of 0	Fixed at 0	0.4 (0-0.94) Modal value of 0
T_D	Mean duration of vaccine-induced protection against infection	9 (5-15) months	7 (4-11) months	9 (5-15) months
R_{02}	R_0 of DENV2 (R_0 for other serotypes kept	2.7 (2.5-3.0) for SE Asian trial	2.7 (2.5-3.0) for SE Asian trial	2.7 (2.5-3.0) for SE Asian trial

	at constant ratio to DENV2 R_0)	2.6 (2.4-2.8) for Latin American trial	2.6 (2.4-2.8) for Latin American trial	2.6 (2.4-2.8) for Latin American trial
Q_1	Proportion of symptomatic secondary infections which require hospitalization	0.16 (0.06-0.42) for SE Asian trial 0.045 (0.03-0.18) for Latin American trial	0.16 (0.07-0.37) for SE Asian trial 0.045 (0.03-0.16) for Latin American trial	0.14 (0.06-0.37) for SE Asian trial 0.045 (0.03-0.19) for Latin American trial

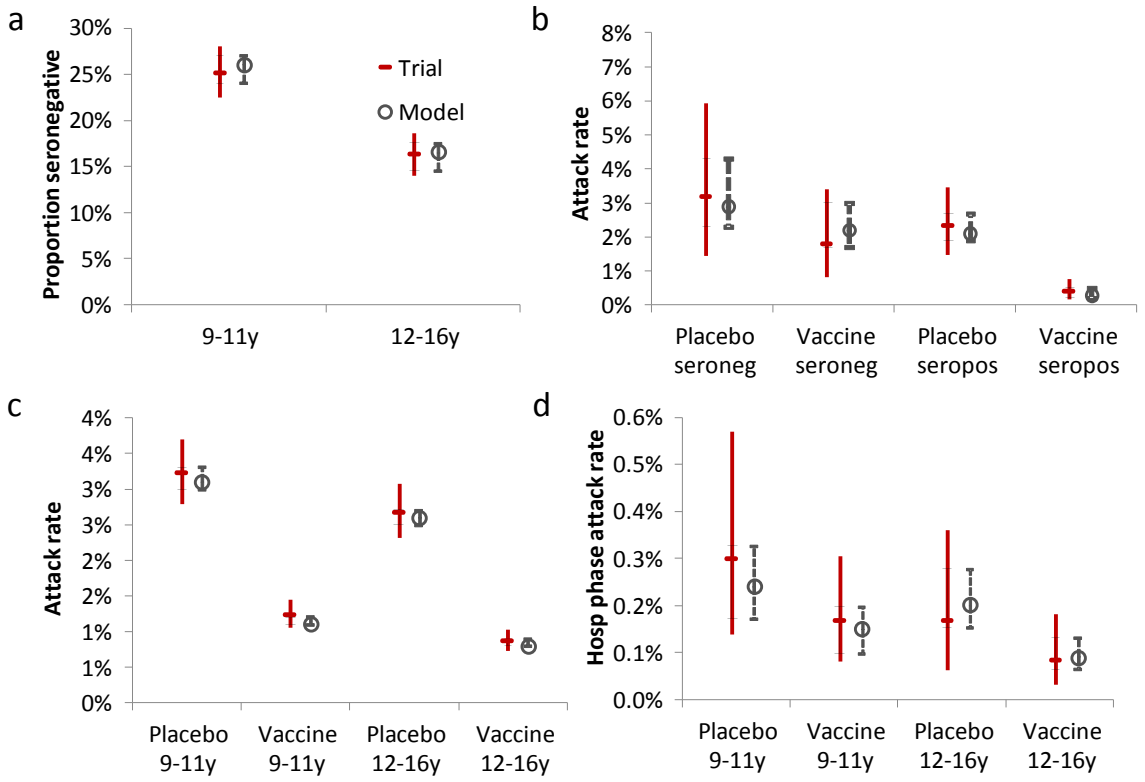

Figure S4. Model fit to publicly available data from the Latin American phase 3 clinical trial (*7*, *9*). Panels show modal (best fit) estimate and 95% credible intervals for (a) proportion of immunological subset of trial who were seropositive at the time of their first dose, by age group; (b) attack rate of virologically confirmed symptomatic dengue in immunological subset in first 2 years after dose 1 by trial arm and baseline serostatus; (c) attack rate of virologically confirmed symptomatic dengue in all trial participants in first 2 years after dose 1 by trial arm and age group; (d) attack rate of virologically confirmed hospitalized dengue disease in all trial participants in third year after dose 1 (first year of LTFU) by trial arm and age group.

1.5 Forward simulations

For each combination of transmission intensity and age at vaccination (see main text), we generated 70 model realizations, each realization using a randomly selected start time for vaccination (between 150 and 250 years after the start of the simulation, to allow the dynamics to equilibrate) and a random sample from the joint posterior density of the non trial-specific parameters listed above (Table S4). Given the difference in the estimates of the proportion of secondary infections requiring hospitalization between the SE Asian and Latin American trials (see Table S4), we assumed that 10% of secondary cases are hospitalized for the forward simulations (*i.e.* Q_1=0.1).

Each realization was run with and without vaccination, and the proportion of symptomatic dengue disease and hospitalized dengue case incidence averted by vaccination were recorded each month over a 50-year time window.

When modelling rapid diagnostic testing of serostatus prior to vaccination, we assumed that 80% coverage of the testing plus vaccination policy and that testing would be 90% sensitive and 90% specific, leading to 72% coverage in seropositive individuals and 8% coverage in seronegative individuals in the target age group.

2. Supplementary Text

2.1 Fit of a simple model of vaccine action

Development of the default model of vaccine action detailed above was motivated by extensive discussions with colleagues in Sanofi-Pasteur (*19*) and in the wider dengue research community, but also by the results of fitting a simpler model of vaccine action to the reported phase 3 trial data. This 'simple' model assumed that vaccination does not modify the risk of symptomatic disease for primary, secondary or post-secondary infection, meaning equations 2 above for disease incidence are changed to:

$$cI^{v}_{i|\Theta}(t,a) = \Lambda_i(t) f_v(a - A_V) S^{v}_{\Theta}$$

$$cD^{v}_{i|\Theta}(t,a) = \mathcal{P}_{|\Theta|} \Lambda_i(t) f_v(a - A_V) S^{v}_{\Theta}$$

$$cH^{v}_{i|\Theta}(t,a) = \mathcal{Q}_{|\Theta|} cD^{v}_{i|\Theta}(t,a)$$

In addition, the simple model assumed vaccine gave constant partial protection against infection in seropositive recipients and protection in seronegative recipients which starts at level VE_{-}^{initial} but decays exponentially over time to level VE_{-}^{final}. The relative risk function representing the effect of vaccination $f_v(\tau)$ is modified thus:

Unvaccinated individuals: $f_0(\tau) = 1$

Individuals vaccinated when seronegative:

$$f_1(\tau) = \left(1 - VE_{-}^{\text{final}}\right)\left[1 - \left(1 - \frac{1 - VE_{-}^{\text{initial}}}{1 - VE_{-}^{\text{final}}}\right) h(\tau)\right]$$

Individuals vaccinated when seropositive: $f_2(\tau) = 1 - VE_{+}$

Note that we impose the constraint that $\left(1 - VE_{-}^{\text{final}}\right)\mathcal{P}_0 \leq 1$ since vaccination is assumed not to be able to increase the risk of infection (as compared with disease) above that experienced by controls.

Fitting this simple model to the trial data results in a poorer fit than our default model of vaccine action ('vaccination as silent infection'). In particular, the model is unable to reproduce a relative risk in 2-5 year-old vaccines >1 in the first LTFU year of the trial, but does predict a worse outcome for 2-5 year old vaccinees than controls in the active phase (Figure S5). The active phase trial results are well reproduced, however. Table S5 list the parameter estimates obtained.

Most parameter estimates for the simpler model are similar to those obtained for the default model used in the rest of this paper, the notable exceptions being efficacy and hospitalization parameters. Efficacy in seropositive vaccinees (assumed not to decay), VE_{+}, is estimated to be high, while in the default model the same level of impact on dengue disease was achieved by the difference in the proportions of secondary and post-secondary infections that result in disease. Conversely, long-term efficacy in seronegative recipients (after the initial decay of heterologous protection), VE_{-}^{final}, is estimated to be highly negative, driven by the results of first year of long term follow-up (LTFU) of the trial. However, it should be noted that the

effect of such negative efficacy only lasts until the first post-vaccination natural infection, at which point a vaccine is assumed to gain the level of vaccine induced protection enjoyed by seropositive recipients (i.e. the order of vaccination and natural infection does not affect the final immune state reached).

Estimated rates of hospitalization are more than double those obtained from our default model. This reflects the underlying reason for the simple model's poor fit: most 2-5 year olds hospitalized for dengue in the first year of the LTFU of the trials are predicted to be experiencing their primary infection, yet the risk of hospitalization for a primary case is substantially less than for a secondary case (here we assume, based on available data (*26*), a four-fold reduced risk, see Table S3). Hence the estimate of the risk of hospitalization needs to be high for the simple model to reproduce the high rates of hospitalization seen in year 1 of the LTFU.

The differential risk of hospitalization for primary and secondary symptomatic cases also explains why the simple model predicts negative effects of vaccination for 2-5 year olds in the active phase of the trial (which monitored all dengue disease), but positive effects in the LTFU phase (which monitored hospitalized disease) (Figure S5). Primary infections represent a much larger proportion of all dengue disease in the 2-5 year age group than they do of hospitalized disease. Hence the predicted negative long term vaccine efficacy in seronegative recipients influences predictions of incidence of all disease much more than incidence of hospitalized disease, which is dominated by secondary infections (for which the vaccine group experiences high vaccine efficacy).

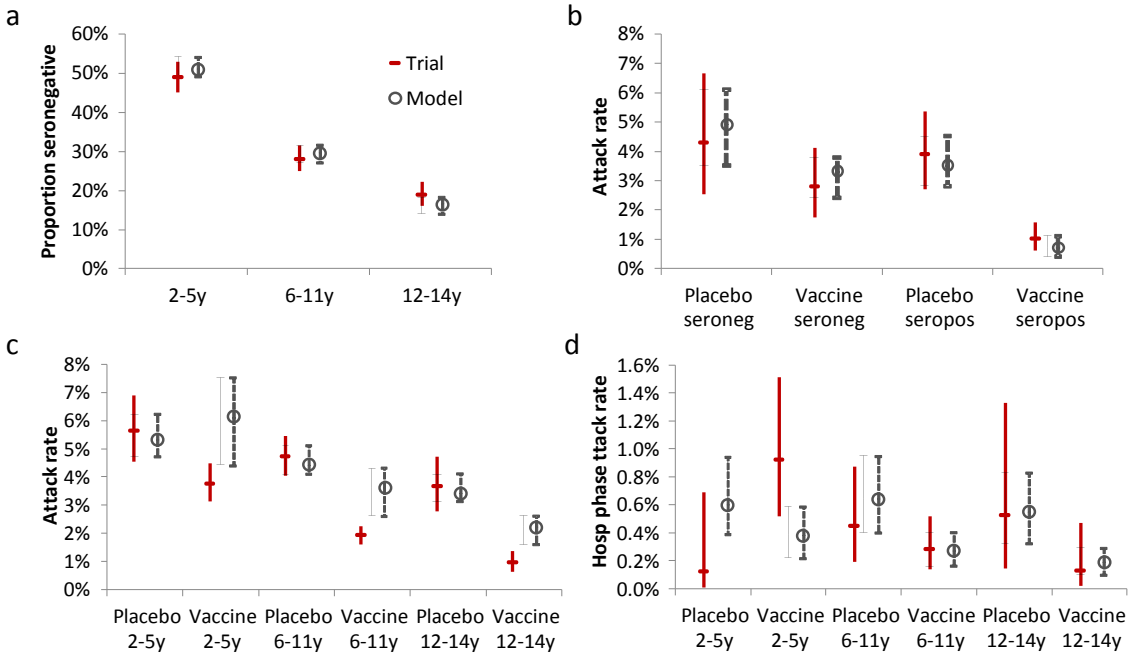

Figure S5. As Figure 1 in the main text and Figure S4 above, but showing fit of the simple model to publicly available data from the Asian phase 3 clinical trial.

It would be possible to achieve a much better model fit by introducing different parameters for efficacy against mild and hospitalized disease and by allowing different rates of hospitalization between primary and secondary infections. However, the cost in terms of model complexity (4 or more additional parameters) provides strong motivation for exploring simpler and more biologically plausible models of vaccine action (*i.e.*; the default model).

Table S5. Parameter estimates for the simple model of vaccine action. Median posterior values with 95% credible intervals are shown. The parameter VE_{-}^{initial} was fixed at 1, as it was unable to be estimated independently of other parameters.

Parameter	Description	Estimate
$\mathcal{P}_0$	Proportion of primary infections which are symptomatic	0.35 (0.25-0.55)
$\mathcal{P}_1$	Proportion of secondary infections which are symptomatic	0.6 (0.35-0.95)
$\mathcal{P}_2 = \mathcal{P}_3$	Proportion of tertiary and quaternary infections which are symptomatic	0.11 (0.01-0.25)
VE_{-}^{final}	Vaccine efficacy against infection in seronegative recipients after initial efficacy has waned	-1.4 (-3 – -0.4)
VE_{+}	Maximum vaccine efficacy against infection in seropositive recipients	0.78 (0.7-0.84)
T_D	Mean duration of vaccine-induced protection against infection	11 (5-19) months
R_{02}	R_0 of DENV2 (R_0 for other serotypes kept at constant ratio to DENV2 R_0)	2.8 (2.6-3.1) for SE Asian trial 2.6 (2.4-2.9) for Latin American trial
Q_1	Proportion of symptomatic secondary infections which require hospitalization. Hospitalization rates of primary and post-secondary infections are assumed to be ¼ of this value.	0.39 (0.14-0.71) for SE Asian trial 0.095 (0.045-0.36) for Latin American trial

2.2 Variability in predictions

Our model has been parameterized to reproduce the variability of dengue over time (Figure S7). High temporal variability in incidence and thus the immune state of the population at the introduction of the vaccine means that vaccination impact is highly variable and more predictable when evaluated over longer rather than shorter timescales (e.g. 30 years versus 10 years). It also means that it is essential to average over many model realizations when calculating the predicted average impact.

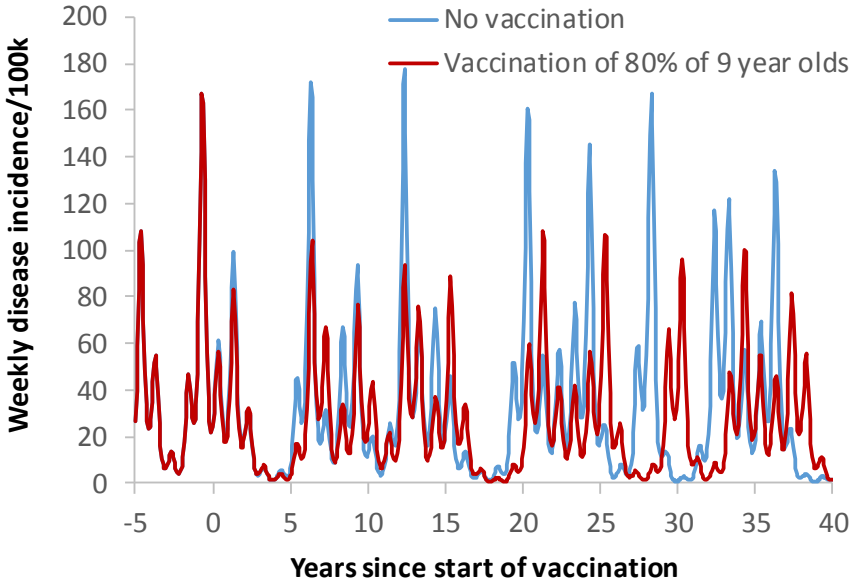

Figure S6. Example of simulated dengue epidemic dynamics with and without vaccination (introduced at year 0). Simulated weekly incidence of symptomatic dengue disease per 100,000 population is shown. Simulations were conducted at an average pre-vaccination seroprevalence in 9 year olds of 70% (corresponding to a DENV2 R_0 of approximately 3). Impacts stabilize after approximately 10 years.

The average (across multiple model realizations) impact of vaccination shows distinct temporal trends (Figure 2, 3 and S7). The 30 year impact of vaccination is typically negative in lower transmission settings and for lower ages of vaccination, especially when considering hospitalized dengue (Figure 2c,d in the main text). Over 10 years, negative outcomes on overall dengue case incidence are not yet apparent (Figure 2a), and the region of scenarios for which a negative impact on hospitalizations is seen remains small (Figure 2b). When vaccination commences, it slightly perturbs transmission dynamics in low transmission settings, which causes a temporary dip in incidence until the system equilibrates again, a process that can take 5-10 years.

Conversely, individual seronegative vaccinees see a worse outcome over the 10 year horizon than the 30 year one (Figure S7). This is because the vaccine-induced priming of such individuals means their first (breakthrough) natural infection is secondary-like (and thus more severe); however, had they not been vaccinated, then

in moderate to high transmission settings most would have eventually experienced a true secondary dengue infection. Hence vaccination can be seen as bringing forward an infection that would have happened anyway to most vaccinees – leading to a substantial increase in risk over the short term (e.g. 10 years) but a smaller increase (or even decrease, in very high transmission settings – see Figure 2, main text) when evaluated over longer time windows. Thus evaluating impact over a relatively short (e.g. 20 year) time frame can over-estimate the negative impact of vaccine at an individual level. Potential negative impacts of vaccination are also reduced as population life-expectancy increases (our model assumes a mean lifespan of 65 years).

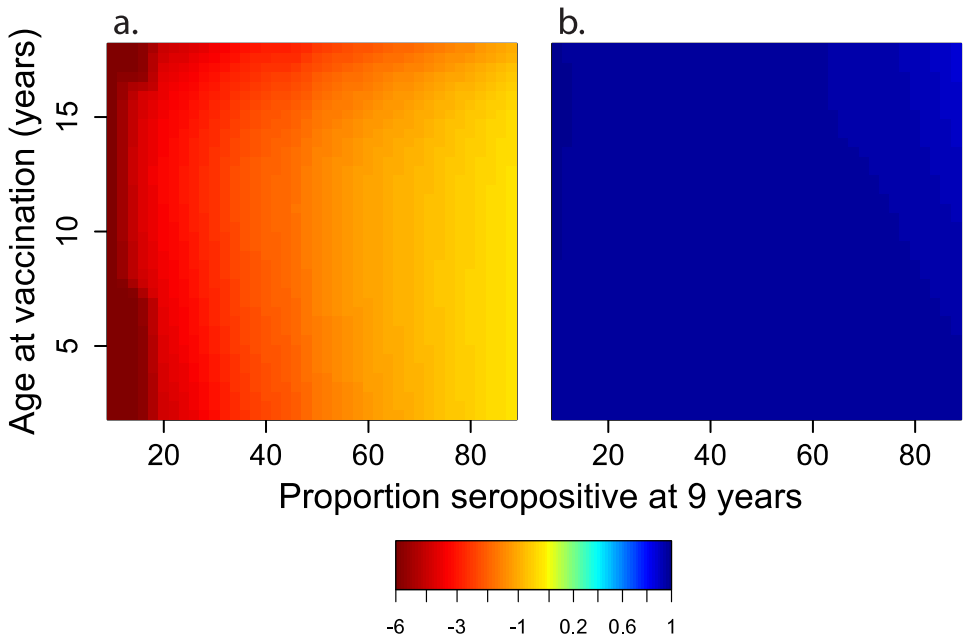

Figure S7. Predicted individual effects of vaccination over 10 years. Proportion of hospitalized cases averted among individual vaccine recipients who are vaccinated when (a) seronegative and when (b) seropositive. Over this time frame, individual impact on seronegative recipients is predicted to be always negative.

Countering these effects is that our model assumes homogeneity of exposure to dengue across the population; in reality the life-time hazard of exposure often varies substantially, even between people living in the same city. Seronegative recipients are likely to be those with lower exposure on average, and may continue to experience lower exposure to dengue throughout their lives (e.g. due to socioeconomic status). Thus in settings where exposure heterogeneity is large, our model may underestimate the potential negative impacts of vaccination on seronegative recipients.

Predictions based on the average impact of vaccination, across multiple model realizations, also hides the large variability of specific model runs (Figure S8). The specific impact of introducing the vaccine in a population will be largely driven by the immune status of the population at the time of vaccine introduction. While, on average, the impact of vaccination on symptomatic disease over 10 years (Figure S8a) is positive across transmission settings, there are some instances in which introducing the vaccine may lead to increases in symptomatic disease. Similarly, while introducing the vaccine in low transmission settings would on average lead to increases in hospitalizations over 10 years (Figure S8c), there are cases in which it could lead to modest reductions. In contrast, introducing the vaccine in lower transmission settings is likely to lead to increases in hospitalizations over a 30-year period, irrespective of the timing of vaccine introduction (Figure S8d).

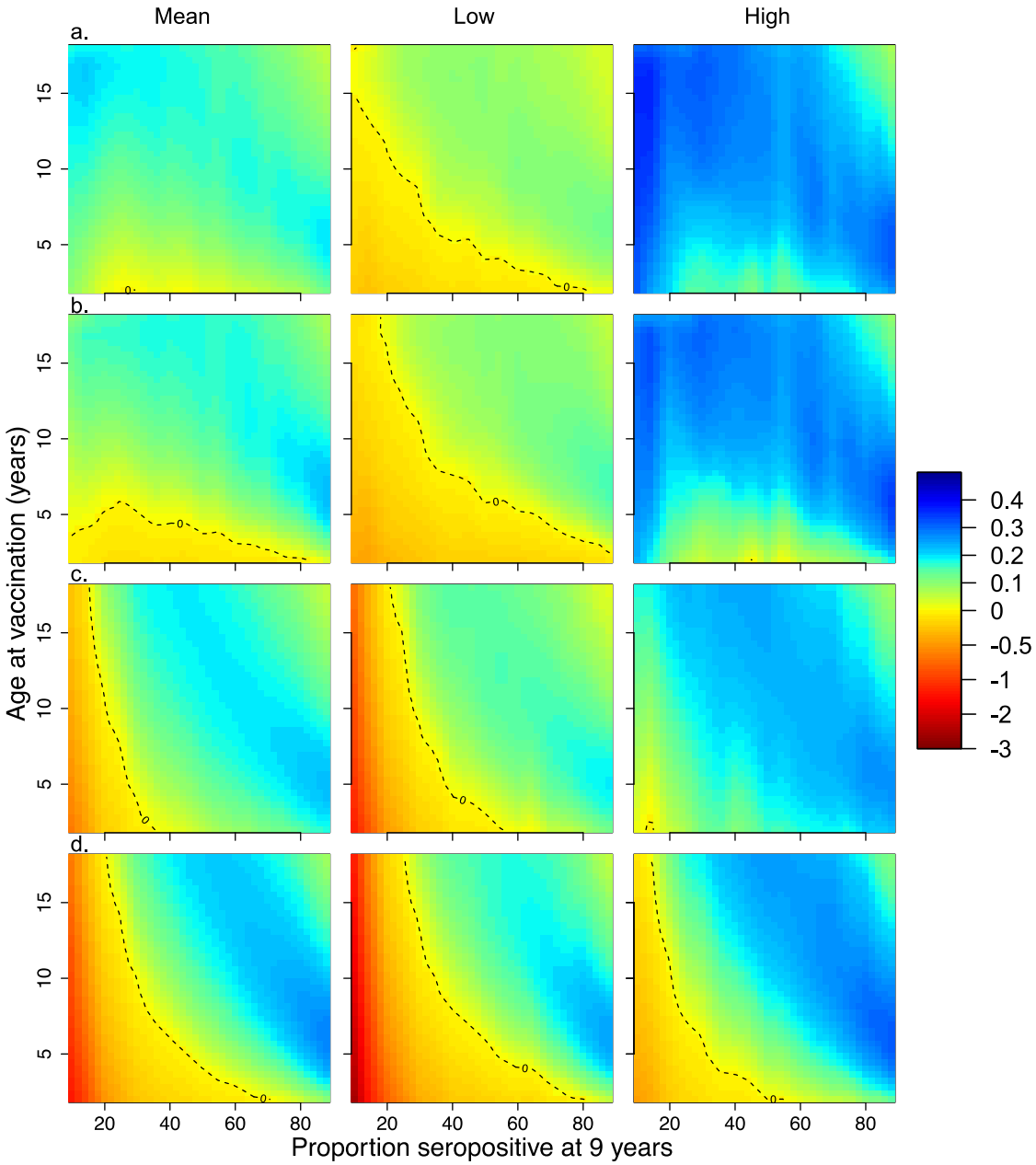

Figure S8. Extension to Figure 2 in the main text, showing 95% confidence bounds of the predicted population effects of vaccination. Color scale indicates proportion of cases averted in the whole population (a) over 10 years, for all symptomatic dengue; (b) over 10 years, for hospitalized dengue; (c) over 30 years, for all symptomatic dengue; (d) over 30 years, for hospitalized dengue. Columns represent mean value (also shown in Figure 2), lower and upper bounds of the 95% confidence intervals. Negative proportions of cases averted indicate vaccination increases risk. Dashed contours indicate the youngest age-group that may be targeted to avoid negative effects at the population level.

2.3 Sensitivity analyses

Infectiousness of symptomatic vs asymptomatic dengue infections

By default, we assume that both symptomatic and asymptomatic human dengue infections can transmit dengue to mosquitoes, but that symptomatic dengue infections are twice as infectious as asymptomatic infections (*39*, *40*, *49*) – as represented by the parameter θ=2 (Table S3). However, limited data exists to estimate this parameter accurately. Since we estimate that vaccination substantially affects the chance that an infection is symptomatic, we therefore also examined the scenario where all dengue infections have the same infectiousness to mosquitoes (*i.e.* θ=1).

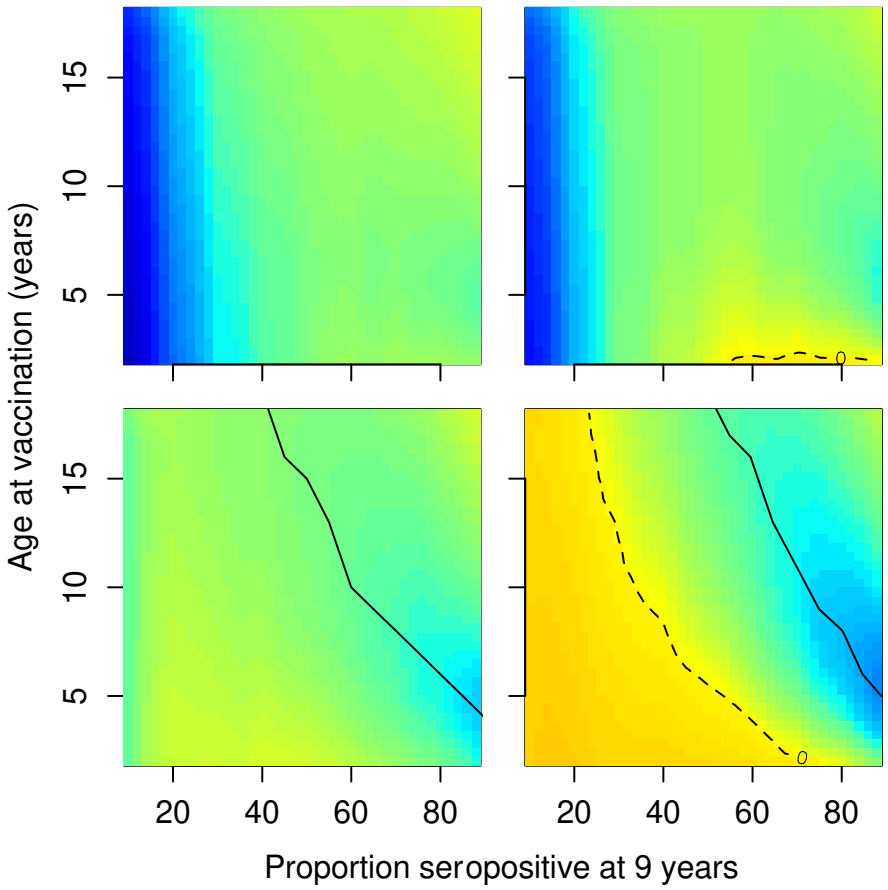

Figure S9. As Figure 2 in the main text, but for the model where asymptomatic and symptomatic cases are equally infectious: Predicted population effects of vaccination on dengue disease for a range of transmission intensities (horizontal axes) and ages of vaccination (vertical axes). Colour scale indicates proportion of cases averted in the whole population (a) over 10 years, for all symptomatic dengue; (b) over 10 years, for hospitalized dengue; (c) over 30 years, for all symptomatic dengue; (d) over 30 years, for hospitalized 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.

Figure S9 and S10 presents the projected impact of vaccination for the θ=1 scenario; Figures 2 and 3 in the main text show the comparable results for the default θ=2 scenario. The results are qualitatively similar for both, but the extent of potential negative impacts is reduced if asymptomatic and symptomatic infectiousness is the same. We no longer see any combination of transmission intensity and age of vaccination which gives negative impacts on total symptomatic dengue cases in the 30 years following start of vaccination. Negative impacts on hospitalized dengue cases still occur for the same range of transmission intensities and vaccination ages as before, but the magnitude of the negative impact is reduced. Impacts on seronegative and seropositive recipients are very similar to those projected for the default scenario.

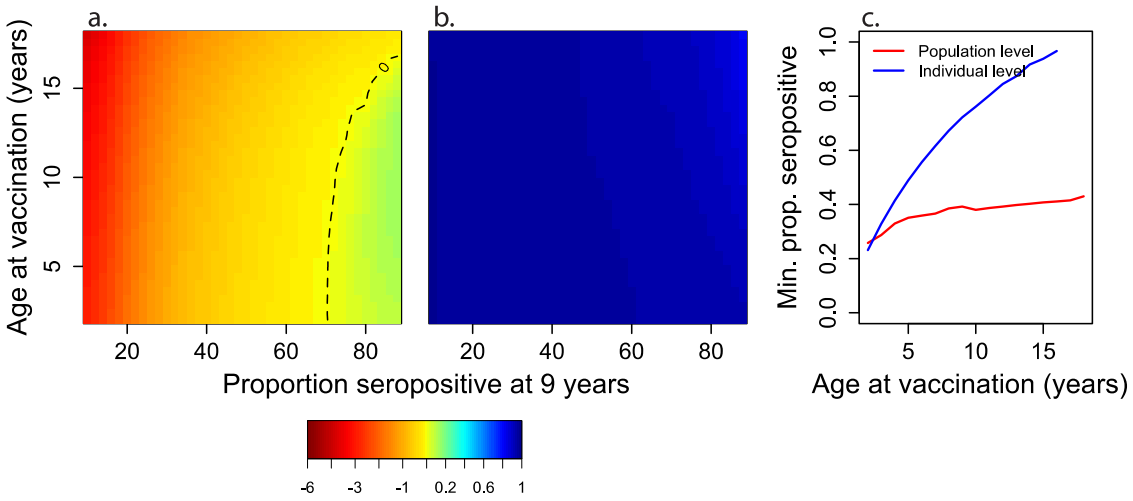

Figure S10. As Figure 3 in the main text, but for the model where asymptomatic and symptomatic cases are equally infectious. Colour scale indicates proportion of hospitalized cases averted over 30 years among individual vaccine recipients who are vaccinated (a) when seronegative, and (b) when seropositive. 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 (one-year age band) targeted for routine vaccination that should be seropositive prior to introduction of vaccination to avert negative impacts (over a 30 year time frame) at the population (red) and individual (blue) level.

Serotype-specific variation in efficacy

A limitation of our analysis is that we were not able to estimate (or model) serotype specific vaccine efficacy parameters due to the very limited nature of the data that is publicly available. Even if more finely stratified data were available, there are substantial technical challenges to fitting to trial outcomes in multiple countries simultaneously (needed to reproduce the distribution of serotype-specific attack rates seen in the trial – see main text).

Results of the phase 2 and 3 trials suggest that the vaccine may be more protective against clinical disease caused by DENV3 and DENV4 and least protective against DENV-2 (*9*). However, under our model of vaccine action, this observation does not necessarily imply that the immunity conferred by the vaccine is heterogeneous. In fact, much of the observed heterogeneity may simply reflect differences in the relative propensity of each serotype to cause disease upon primary, secondary or post-secondary infection. Vaccine will seem less protective against a serotype that has a higher probability of symptomatic disease upon secondary infection than the average across serotypes and a lower than average risk of disease in primary/tertiary infection.

While for our default model we assumed that the probabilities of primary, secondary, tertiary and quaternary disease did not vary between serotypes, we performed sensitivity analyses where we relaxed this assumption. Figure S11 shows the fit of a model where we assumed:

DENV1:	estimated $\mathcal{P}_{10}, \mathcal{P}_{11}, \mathcal{P}_{12}, \mathcal{P}_{13}$	
DENV2:	$\mathcal{P}_{20} = 0.5\,\mathcal{P}_{10}$	$\mathcal{P}_{21} = 2\,\mathcal{P}_{10}$
	$\mathcal{P}_{32} = \mathcal{P}_{12}$	$\mathcal{P}_{33} = \mathcal{P}_{13}$
DENV3/4	$\mathcal{P}_{30} = \mathcal{P}_{40} = 1.5\,\mathcal{P}_{10}$	$\mathcal{P}_{31} = \mathcal{P}_{41} = 1$
	$\mathcal{P}_{32} = \mathcal{P}_{42} = 0.66\,\mathcal{P}_{12}$	$\mathcal{P}_{33} = \mathcal{P}_{43} = 0.66\,\mathcal{P}_{13}$

Here $\mathcal{P}_{ij}$ represents the probability that an infection with serotype *i* will cause symptomatic disease in an individual who has previously experienced *j* infections. The choice of ratios between serotypes were selected to approximate the serotype-specific efficacies seen in the trial (see below).

The best estimates of $\mathcal{P}_{ij}$ were $\mathcal{P}_{10} = 0.48,\ \mathcal{P}_{11} = 1, \mathcal{P}_{12} = 0.28$ and $\mathcal{P}_{13} = 0$, giving $\mathcal{P}_{20} = 0.24,\ \mathcal{P}_{21} = 0.96,\ \mathcal{P}_{12} = 0.28,\ \mathcal{P}_{23} = 0$, and $\mathcal{P}_{30} = \mathcal{P}_{40} = 0.72,\ \mathcal{P}_{31} = \mathcal{P}_{41} = 1,\ \mathcal{P}_{32} = \mathcal{P}_{42} = 0.28,\ \mathcal{P}_{33} = \mathcal{P}_{43} = 0$. The fit of this model to the trial data was slightly worse than for our default (symmetric serotype) model, but other parameter estimates obtained were very similar.

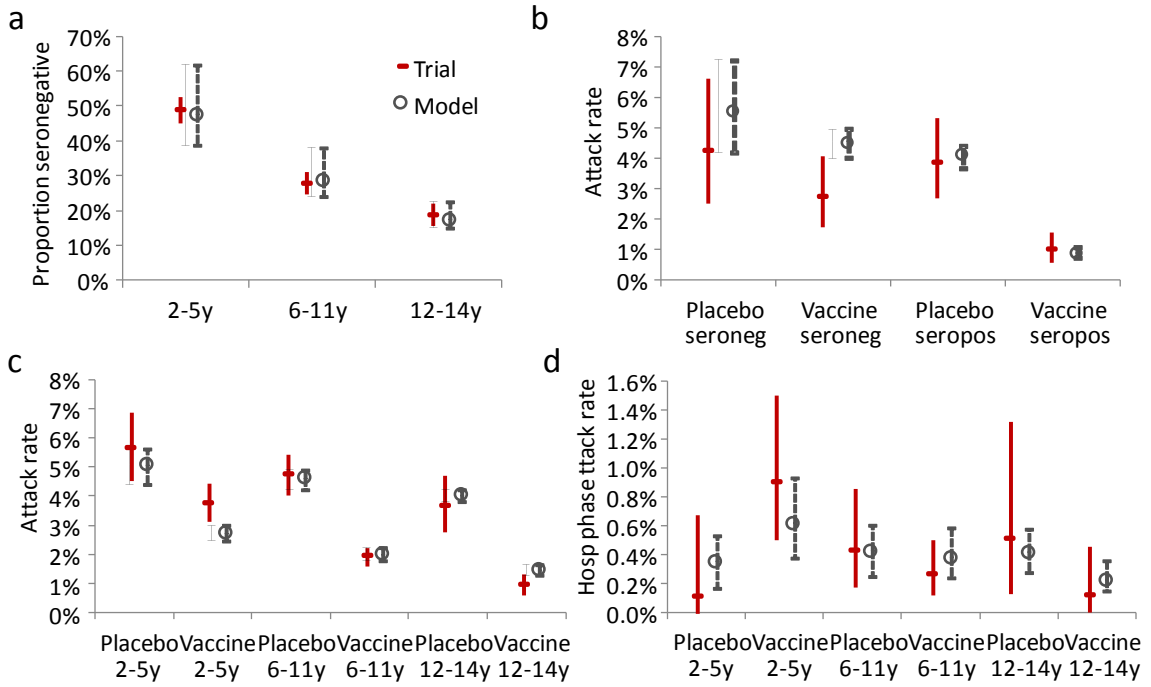

Figure S11. As Figure 2 in the main text and Figure S4 above, but showing fit to publicly available data from the Asian Phase 3 clinical trial of model where the probabilities of clinical disease upon primary, secondary, tertiary and quaternary infections varied between serotypes as described above.

When used to simulate the phase 3 trials, the choice of probabilities of symptomatic disease by serotype listed immediately above generates predicted serotype specific efficacies (against symptomatic disease) which are broadly consistent with what was observed during the phase 3 trials (Figure S12).

In addition, this model predicts very similar long-term impacts of routine vaccination to our default model (Figures S13 and S14), indicating that introducing serotype-specific heterogeneity in the propensity of infections to cause disease does not substantially alter the key conclusions from our overall analysis.

Thus, while there may be some true underlying heterogeneity in the magnitude and/or duration of vaccine-induce protection to the different serotypes, our results suggest that such heterogeneity is not necessary to explain the trial results observed.

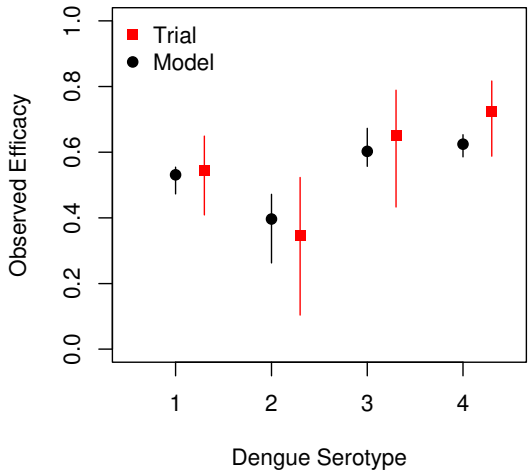

Figure S12: Serotype specific vaccine efficacies against symptomatic disease measured in the active phase (first two years after receiving the first dose of vaccine), compared to those predicted by a model where the probabilities of clinical disease upon primary, secondary, tertiary and quaternary infections varied between serotypes as described above.

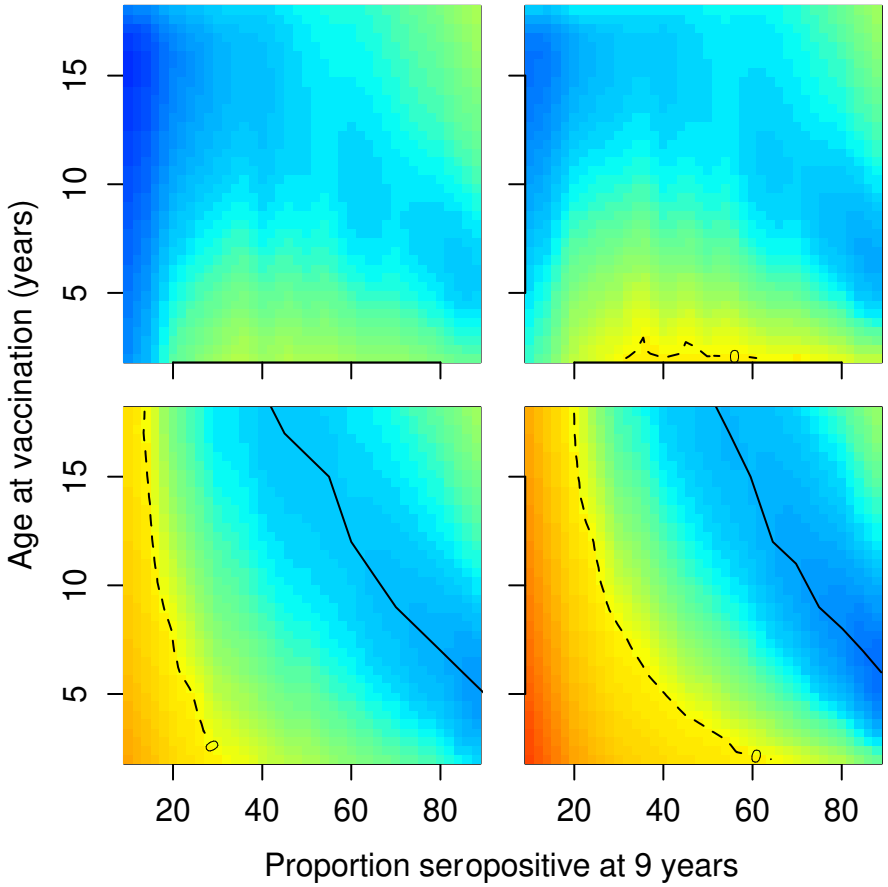

Figure S13. As Figure 2 in the main text, but for the model where the probabilities of clinical disease upon primary, secondary, tertiary and quaternary infections varied between serotypes (see text immediately above). (a)-(d) as described in legend for Figure S9.

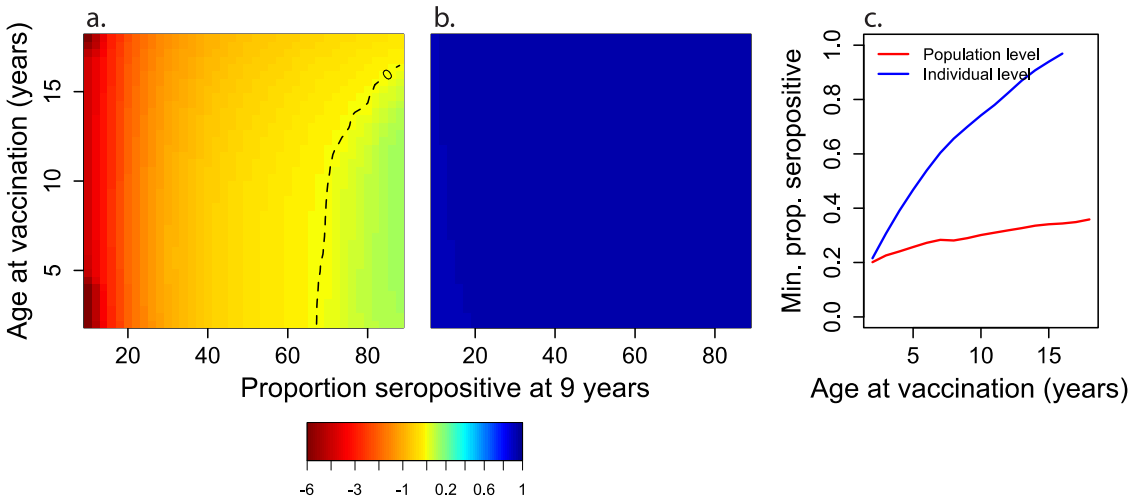

Figure S14. As Figure 3 in the main text, but for the model where the probabilities of clinical disease upon primary, secondary, tertiary and quaternary infections varied between serotypes (see text immediately above). (a)-(c) as described in legend for Figure S10.

References and Notes

1. J. R. Stephenson, Understanding dengue pathogenesis: Implications for vaccine design. *Bull. World Health Organ.* **83**, 308–314 (2005). Medline

2. R. Edelman, J. Hombach, "Guidelines for the clinical evaluation of dengue vaccines in endemic areas": Summary of a World Health Organization Technical Consultation. *Vaccine* **26**, 4113–4119 (2008). Medline doi:10.1016/j.vaccine.2008.05.058

3. B. R. Murphy, S. S. Whitehead, Immune response to dengue virus and prospects for a vaccine. *Annu. Rev. Immunol.* **29**, 587–619 (2011). 10.1146/annurev-immunol-031210-101315 Medline doi:10.1146/annurev-immunol-031210-101315

4. S. B. Halstead, Immune enhancement of viral infection. *Prog. Allergy* **31**, 301–364 (1982). Medline

5. D. S. Burke, A. Nisalak, D. E. Johnson, R. M. Scott, A prospective study of dengue infections in Bangkok. *Am. J. Trop. Med. Hyg.* **38**, 172–180 (1988). Medline

6. M. R. Capeding, N. H. Tran, S. R. Hadinegoro, H. I. Ismail, T. Chotpitayasunondh, M. N. Chua, C. Q. Luong, K. Rusmil, D. N. Wirawan, R. Nallusamy, P. Pitisuttithum, U. Thisyakorn, I. K. Yoon, D. van der Vliet, E. Langevin, T. Laot, Y. Hutagalung, C. Frago, M. Boaz, T. A. Wartel, N. G. Tornieporth, M. Saville, A. Bouckenooghe; CYD14 Study Group, Clinical efficacy and safety of a novel tetravalent dengue vaccine in healthy children in Asia: A phase 3, randomised, observer-masked, placebo-controlled trial. *Lancet* **384**, 1358–1365 (2014). 10.1016/S0140-6736(14)61060-6 Medline doi:10.1016/S0140-6736(14)61060-6

7. L. Villar, G. H. Dayan, J. L. Arredondo-García, D. M. Rivera, R. Cunha, C. Deseda, H. Reynales, M. S. Costa, J. O. Morales-Ramírez, G. Carrasquilla, L. C. Rey, R. Dietze, K. Luz, E. Rivas, M. C. Miranda Montoya, M. Cortés Supelano, B. Zambrano, E. Langevin, M. Boaz, N. Tornieporth, M. Saville, F. Noriega; CYD15 Study Group, Efficacy of a tetravalent dengue vaccine in children in Latin America. *N. Engl. J. Med.* **372**, 113–123 (2015). Medline doi:10.1056/NEJMoa1411037

8. A. Sabchareon, D. Wallace, C. Sirivichayakul, K. Limkittikul, P. Chanthavanich, S. Suvannadabba, V. Jiwariyavej, W. Dulyachai, K. Pengsaa, T. A. Wartel, A. Moureau, M. Saville, A. Bouckenooghe, S. Viviani, N. G. Tornieporth, J. Lang, Protective efficacy of the recombinant, live-attenuated, CYD tetravalent dengue vaccine in Thai schoolchildren: A randomised, controlled phase 2b trial. *Lancet* **380**, 1559–1567 (2012). Medline doi:10.1016/S0140-6736(12)61428-7

9. S. R. Hadinegoro, J. L. Arredondo-García, M. R. Capeding, C. Deseda, T. Chotpitayasunondh, R. Dietze, H. I. Muhammad Ismail, H. Reynales, K. Limkittikul, D. M. Rivera-Medina, H. N. Tran, A. Bouckenooghe, D. Chansinghakul, M. Cortés, K. Fanouillere, R. Forrat, C. Frago, S. Gailhardou, N. Jackson, F. Noriega, E. Plennevaux, T. A. Wartel, B. Zambrano, M. Saville; CYD-TDV Dengue Vaccine Working Group, Efficacy and long-term safety of a dengue vaccine in regions of endemic disease. *N. Engl. J. Med.* **373**, 1195–1206 (2015). Medline

doi:10.1056/NEJMoa1506223

10. Supplementary materials are available on *Science* Online.

11. L. Á. Villar, D. M. Rivera-Medina, J. L. Arredondo-García, M. Boaz, L. Starr-Spires, M. Thakur, B. Zambrano, M. C. Miranda, E. Rivas, G. H. Dayan, Safety and immunogenicity of a recombinant tetravalent dengue vaccine in 9-16 year olds: A randomized, controlled, phase II trial in Latin America. *Pediatr. Infect. Dis. J.* **32**, 1102–1109 (2013). Medline doi:10.1097/INF.0b013e31829b8022

12. G. H. Dayan, P. Garbes, F. Noriega, A. D. Izoton de Sadovsky, P. M. Rodrigues, C. Giuberti, R. Dietze, Immunogenicity and safety of a recombinant tetravalent dengue vaccine in children and adolescents ages 9-16 years in Brazil. *Am. J. Trop. Med. Hyg.* **89**, 1058–1065 (2013). Medline doi:10.4269/ajtmh.13-0304

13. Y. Sin Leo, A. Wilder-Smith, S. Archuleta, L. P. Shek, C. Y. Chong, H. Nam Leong, C. Yong Low, M.-L. H. Oh, A. Bouckenooghe, T. A. Wartel, D. Crevat, Immunogenicity and safety of recombinant tetravalent dengue vaccine (CYD-TDV) in individuals aged 2–45 years: Phase II randomized controlled trial in Singapore . *Hum. Vaccin. Immunother.* **8**, 1259–1271 (2012). Medline doi:10.4161/hv.21224

14. C. F. Lanata, T. Andrade, A. I. Gil, C. Terrones, O. Valladolid, B. Zambrano, M. Saville, D. Crevat, Immunogenicity and safety of tetravalent dengue vaccine in 2-11 year-olds previously vaccinated against yellow fever: Randomized, controlled, phase II study in Piura, Peru. *Vaccine* **30**, 5935–5941 (2012). Medline doi:10.1016/j.vaccine.2012.07.043

15. R. Z. Capeding, I. A. Luna, E. Bomasang, S. Lupisan, J. Lang, R. Forrat, A. Wartel, D. Crevat, Live-attenuated, tetravalent dengue vaccine in children, adolescents and adults in a dengue endemic country: Randomized controlled phase I trial in the Philippines. *Vaccine* **29**, 3863–3872 (2011). Medline doi:10.1016/j.vaccine.2011.03.057

16. D. Morrison, T. J. Legg, C. W. Billings, R. Forrat, S. Yoksan, J. Lang, A novel tetravalent dengue vaccine is well tolerated and immunogenic against all 4 serotypes in flavivirus-naive adults. *J. Infect. Dis.* **201**, 370–377 (2010). Medline doi:10.1086/649916

17. I. Dorigatti, R. Aguas, C. A. Donnelly, B. Guy, L. Coudeville, N. Jackson, M. Saville, N. M. Ferguson, Modelling the immunological response to a tetravalent dengue vaccine from multiple phase-2 trials in Latin America and South East Asia. *Vaccine* **33**, 3746–3751 (2015). Medline doi:10.1016/j.vaccine.2015.05.059

18. M. R. Capeding, T. M. Laot, M. Boaz, T. A. Wartel, D. Crevat, Immunogenicity and safety of a tetravalent dengue vaccine during a five-year follow-up period. *Trials Vaccinol.* **4**, 19–23 (2015). doi:10.1016/j.trivac.2015.03.002

19. B. Guy, N. Jackson, Dengue vaccine: Hypotheses to understand CYD-TDV-induced protection. *Nat. Rev. Microbiol.* **14**, 45–54 (2016). Medline doi:10.1038/nrmicro.2015.2

20. I. Rodríguez-Barraquer, L. Mier-y-Teran-Romero, D. S. Burke, D. A. T. Cummings, Challenges in the interpretation of dengue vaccine trial results. *PLOS Negl. Trop. Dis.* **7**, e2126 (2013). Medline doi:10.1371/journal.pntd.0002126

21. T. J. Kochel, D. M. Watts, A. S. Gozalo, D. F. Ewing, K. R. Porter, K. L. Russell, Cross-serotype neutralization of dengue virus in *Aotus nancymae* monkeys. *J. Infect. Dis.* **191**, 1000–1004 (2005). Medline doi:10.1086/427511

22. A. B. Sabin, Research on dengue during World War II. *Am. J. Trop. Med. Hyg.* **1**, 30–50 (1952). Medline

23. A. B. Sabin, The dengue group of viruses and its family relationships. *Bacteriol. Rev.* **14**, 225–232 (1950). Medline

24. S. Olkowski, B. M. Forshey, A. C. Morrison, C. Rocha, S. Vilcarromero, E. S. Halsey, T. J. Kochel, T. W. Scott, S. T. Stoddard, Reduced risk of disease during postsecondary dengue virus infections. *J. Infect. Dis.* **208**, 1026–1033 (2013). Medline doi:10.1093/infdis/jit273

25. P. S. Wikramaratna, C. P. Simmons, S. Gupta, M. Recker, The effects of tertiary and quaternary infections on the epidemiology of dengue. *PLOS ONE* **5**, e12347 (2010). Medline doi:10.1371/journal.pone.0012347

26. A. Nisalak, T. P. Endy, S. Nimmannitya, S. Kalayanarooj, U. Thisayakorn, R. M. Scott, D. S. Burke, C. H. Hoke, B. L. Innis, D. W. Vaughn, Serotype-specific dengue virus circulation and dengue disease in Bangkok, Thailand from 1973 to 1999. *Am. J. Trop. Med. Hyg.* **68**, 191–202 (2003). Medline

27. Strategic Advisory Group of Experts on Immunization, "Summary of the April 2016 meeting of the Strategic Advisory Group of Experts on Immunization (SAGE)," Geneva, Switzerland, 12 to 14 April 2016 (SAGE, WHO, Geneva, 2016); http://www.who.int/immunization/sage/meetings/2016/april/SAGE_April_2016_Meeting_Web_summary.pdf?ua=1.

28. H. Q. McLean, A. P. Fiebelkorn, J. L. Temte, G. S. Wallace; Prevention of measles, rubella, congenital rubella syndrome, and mumps, 2013: Summary recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm. Rep.* **62** (RR-04), 1–34 (2013). Medline

29. Centers for Disease Control and Prevention, Recommendations of the immunization practices advisory committee prevention of perinatal transmission of hepatitis B virus: Prenatal screening of all pregnant women for hepatitis B surface antigen. *Morb. Mortal. Wkly. Rep.* **37**, 341–346 (1988)

30. L. Coudeville, N. Baurin, E. Vergu, Estimation of parameters related to vaccine efficacy and dengue transmission from two large phase III studies. *Vaccine* (2015). 10.1016/j.vaccine.2015.11.023 Medline doi:10.1016/j.vaccine.2015.11.023

31. I. Rodríguez-Barraquer, L. Mier-y-Teran-Romero, N. Ferguson, D. S. Burke, D. A. T. Cummings, Differential efficacy of dengue vaccine by immune status. *Lancet* **385**, 1726 (2015). Medline doi:10.1016/S0140-6736(15)60889-3

32. T. J. Hladish, C. A. Pearson, D. L. Chao, D. P. Rojas, G. L. Recchia, H. Gómez-Dantés, M. E. Halloran, J. R. Pulliam, I. M. Longini, Projected impact of dengue vaccination in Yucatán, Mexico. *PLOS Negl. Trop. Dis.* **10**, e0004661 (2016). Medline doi:10.1371/journal.pntd.0004661

33. N. M. Ferguson, D. T. Kien, H. Clapham, R. Aguas, V. T. Trung, T. N. Bich Chau, J. Popovici, P. A. Ryan, S. L. O'Neill, E. A. McGraw, V. T. Long, T. Dui, H. L. Nguyen, N. V. Vinh Chau, B. Wills, C. P. Simmons, Modeling the impact on virus transmission of *Wolbachia*-mediated blocking of dengue virus infection of *Aedes aegypti*. *Sci. Transl. Med.* **7**, 279ra37 (2015). Medline doi:10.1126/scitranslmed.3010370

34. C. Sirivichayakul, E. A. Barranco-Santana, I. Esquilin-Rivera, H. M. Oh, M. Raanan, C. A. Sariol, L. P. Shek, S. Simasathien, M. K. Smith, I. D. Velez, D. Wallace, G. S. Gordon, D. T. Stinchcomb, Safety and immunogenicity of a tetravalent dengue vaccine candidate in healthy children and adults in dengue-endemic regions: A randomized, placebo-controlled phase 2 study. *J. Infect. Dis.* **213**, 1562–1572 (2016). Medline doi:10.1093/infdis/jiv762

35. B. D. Kirkpatrick, A. P. Durbin, K. K. Pierce, M. P. Carmolli, C. M. Tibery, P. L. Grier, N. Hynes, S. A. Diehl, D. Elwood, A. P. Jarvis, B. P. Sabundayo, C. E. Lyon, C. J. Larsson, M. Jo, J. M. Lovchik, C. J. Luke, M. C. Walsh, E. A. Fraser, K. Subbarao, S. S. Whitehead, Robust and balanced immune responses to all 4 dengue virus serotypes following administration of a single dose of a live attenuated tetravalent dengue vaccine to healthy, flavivirus-naive adults. *J. Infect. Dis.* **212**, 702–710 (2015). Medline doi:10.1093/infdis/jiv082

36. M. A. Penny, R. Verity, C. A. Bever, C. Sauboin, K. Galactionova, S. Flasche, M. T. White, E. A. Wenger, N. Van de Velde, P. Pemberton-Ross, J. T. Griffin, T. A. Smith, P. A. Eckhoff, F. Muhib, M. Jit, A. C. Ghani, Public health impact and cost-effectiveness of the RTS,S/AS01 malaria vaccine: A systematic comparison of predictions from four mathematical models. *Lancet* **387**, 367–375 (2016). Medline doi:10.1016/S0140-6736(15)00725-4

37. N. G. Reich, S. Shrestha, A. A. King, P. Rohani, J. Lessler, S. Kalayanarooj, I. K. Yoon, R. V. Gibbons, D. S. Burke, D. A. Cummings, Interactions between serotypes of dengue highlight epidemiological impact of cross-immunity. *J. R. Soc. Interface* **10**, 20130414–20130414 (2013). Medline doi:10.1098/rsif.2013.0414

38. R. C. S. Seet, E. E. Ooi, H. B. Wong, N. I. Paton, An outbreak of primary dengue infection among migrant Chinese workers in Singapore characterized by prominent gastrointestinal symptoms and a high proportion of symptomatic cases. *J. Clin. Virol.* **33**, 336–340 (2005). Medline doi:10.1016/j.jcv.2005.03.002

39. D. W. Vaughn, S. Green, S. Kalayanarooj, B. L. Innis, S. Nimmannitya, S. Suntayakorn, T. P. Endy, B. Raengsakulrach, A. L. Rothman, F. A. Ennis, A. Nisalak, Dengue viremia titer, antibody response pattern, and virus serotype correlate with disease severity. *J. Infect. Dis.* **181**, 2–9 (2000). Medline doi:10.1086/315215

40. N. M. Nguyen, D. Thi Hue Kien, T. V. Tuan, N. T. H. Quyen, C. N. B. Tran, L. Vo Thi, D.

L. Thi, H. L. Nguyen, J. J. Farrar, E. C. Holmes, M. A. Rabaa, J. E. Bryant, T. T. Nguyen, H. T. C. Nguyen, L. T. H. Nguyen, M. P. Pham, H. T. Nguyen, T. T. H. Luong, B. Wills, C. V. V. Nguyen, M. Wolbers, C. P. Simmons, Host and viral features of human dengue cases shape the population of infected and infectious *Aedes aegypti* mosquitoes. *Proc. Natl. Acad. Sci. U.S.A.* **110**, 9072–9077 (2013). Medline doi:10.1073/pnas.1303395110

41. M. Turelli, Cytoplasmic incompatibility in populations with overlapping generations. *Evolution* **64**, 232–241 (2010). Medline doi:10.1111/j.1558-5646.2009.00822.x

42. D. M. Watts, D. S. Burke, B. A. Harrison, R. E. Whitmire, A. Nisalak, Effect of temperature on the vector efficiency of *Aedes aegypti* for dengue 2 virus. *Am. J. Trop. Med. Hyg.* **36**, 143–152 (1987). Medline

43. J. R. Anderson, R. Rico-Hesse, *Aedes aegypti* vectorial capacity is determined by the infecting genotype of dengue virus. *Am. J. Trop. Med. Hyg.* **75**, 886–892 (2006). Medline

44. M. I. Salazar, J. H. Richardson, I. Sánchez-Vargas, K. E. Olson, B. J. Beaty, Dengue virus type 2: Replication and tropisms in orally infected *Aedes aegypti* mosquitoes. *BMC Microbiol.* **7**, 9 (2007). Medline doi:10.1186/1471-2180-7-9

45. M. Otero, H. G. Solari, N. Schweigmann, A stochastic population dynamics model for *Aedes aegypti*: Formulation and application to a city with temperate climate. *Bull. Math. Biol.* **68**, 1945–1974 (2006). Medline doi:10.1007/s11538-006-9067-y

46. P. M. Sheppard, W. W. Macdonald, R. J. Tonn, B. Grab, The dynamics of an adult population of *Aedes aegypti* in relation to dengue haemorrhagic fever in Bangkok. *J. Anim. Ecol.* **38**, 661–702 (1969). doi:10.2307/3042

47. T. W. Scott, P. H. Amerasinghe, A. C. Morrison, L. H. Lorenz, G. G. Clark, D. Strickman, P. Kittayapong, J. D. Edman, Longitudinal studies of *Aedes aegypti* (Diptera: Culicidae) in Thailand and Puerto Rico: Blood feeding frequency. *J. Med. Entomol.* **37**, 89–101 (2000). Medline doi:10.1603/0022-2585-37.1.89

48. M. Chan, M. A. Johansson, The incubation periods of Dengue viruses. *PLOS ONE* **7**, e50972 (2012). Medline doi:10.1371/journal.pone.0050972

49. V. Duong, L. Lambrechts, R. E. Paul, S. Ly, R. S. Lay, K. C. Long, R. Huy, A. Tarantola, T. W. Scott, A. Sakuntabhai, P. Buchy, Asymptomatic humans transmit dengue virus to mosquitoes. *Proc. Natl. Acad. Sci. U.S.A.* **112**, 14688–14693 (2015). Medline doi:10.1073/pnas.1508114112

50. B. Murgue, C. Roche, E. Chungue, X. Deparis, Prospective study of the duration and magnitude of viraemia in children hospitalised during the 1996-1997 dengue-2 outbreak in French Polynesia. *J. Med. Virol.* **60**, 432–438 (2000). Medline doi:10.1002/(SICI)1096-9071(200004)60:4<432::AID-JMV11>3.0.CO;2-7

51. D. J. Gubler, W. Suharyono, R. Tan, M. Abidin, A. Sie, Viraemia in patients with naturally acquired dengue infection. *Bull. World Health Organ.* **59**, 623–630 (1981). Medline

52. L. M. Bartley, C. A. Donnelly, G. P. Garnett, The seasonal pattern of dengue in endemic areas: Mathematical models of mechanisms. *Trans. R. Soc. Trop. Med. Hyg.* **96**, 387–397 (2002). Medline doi:10.1016/S0035-9203(02)90371-8

53. H. Nishiura, Mathematical and statistical analyses of the spread of dengue. *Dengue Bull.* **30**, (2006). 10.1111/j.1365-3156.2006.01560.x/full

54. I. Rodríguez-Barraquer, R. Buathong, S. Iamsirithaworn, A. Nisalak, J. Lessler, R. G. Jarman, R. V. Gibbons, D. A. Cummings, Revisiting Rayong: Shifting seroprofiles of dengue in Thailand and their implications for transmission and control. *Am. J. Epidemiol.* **179**, 353–360 (2014). Medline doi:10.1093/aje/kwt256