Pre-analysis plan
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Efficacy and safety of the Dengvaxia vaccine for dengue fever: a simulation-based reanalysis of clinical trial data

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Objective:

To perform a modeling re-analysis of the Dengvaxia vaccine clinical trial (CYD14) in Asia to identify the causative mechanism for the key clinical trial finding that seronegative vaccine recipients (often younger children) were observed to have higher risk of hospitalization than their unvaccinated counterparts in later years of the study.

Model design:

A microsimulation model was developed to describe the natural history and transmission of dengue fever to simulate the Dengvaxia vaccine clinical trial from study year 1 to 5. The model structure included human transitions among susceptible, exposed, infectious, recovered (lifelong immunity and cross-protected) and vaccinated states. We accounted for age-structure and modeled four serotypes and their immunologic interaction. The model was calibrated to include study country-specific case counts and seasonality (Indonesia, Malaysia, Philippines, Thailand, and Vietnam).

Model parameters and calibration:

The microsimulation model will be calibrated using published data from the Dengvaxia vaccine clinical trial (CYD14 Asia)[1-3] and related papers[4,5] using Bayesian Markov chain Monte Carlo (MCMC) methods. We will use study data reported in incidence density, and calibrate the fitted model parameters using the following data:

1) Virologically confirmed dengue disease as country-specific monthly case counts during active surveillance period (Y1-Y2)
2) Virologically confirmed dengue disease as total case counts by age group and baseline serological status from study during active surveillance period (Y1-Y2)
3) Hospitalized dengue disease as total case counts by age group from study during active and passive surveillance period (Y1-Y5)
4) Virologically confirmed dengue disease as total case counts by serotype from study during active surveillance period (Y1-Y2)

The model parameters that will be estimated are shown in Table 1. The formulation of dengue clinical presentation is shown in Table 2.

Table 1: Fitted model parameters

Parameter	Symbol
Transmission coefficient, country-specific (5 terms)	λ_c
Seasonality of transmission, two terms per country (10 terms)	φ_c, δ_c
Mean duration of cross-protection following natural infection	$1/\omega_{cross}$
Vaccine efficacy, serotype-specific (4 terms)	ε_i
Mean duration of vaccine protection, serotype-specific (4 terms)	$1/\omega_{vacc,i}$
Probability of dengue disease, primary infection	θ_d
Probability of severe dengue disease (hospitalized case), primary infection	θ_s
Relative risk of severe dengue, secondary compared to primary infection	π_{ADE}
Relative risk of severe dengue disease, vaccinated compared to unvaccinated primary infection	$\pi_{ADE\,vacc}$
Reporting coverage of passive surveillance compared to active	$\theta_{passive}$

Table 2: Dengue clinical presentation and reporting

	First natural infection[a]	Secondary infection	Seronegative vaccinated, first natural infection	Seropositive vaccinated, natural infection
Probability, asymptomatic dengue infection	$1-\theta_{sum}$	$1-\theta_{sum}$	$1-\theta_{sum}$	$1-\theta_{sum}$
Probability, dengue disease	θ_d	$2\theta_d$	θ_d	$2\theta_d$
Probability, severe dengue disease (hospitalized)	θ_s	$\theta_s\pi_{ADE}$	$\theta_s\pi_{ADE\,vacc}$	$\theta_s\pi_{ADE}$

[a]Category also includes tertiary and quaternary infections.

In the case of problems with model parameter identifiability for vaccine response, we will re-formulate the model for vaccine response to further incorporate person-level serological data from the clinical trial that may be linked with epidemiologic data for clinical outcomes. If problems with model parameter identifiability persist, we will re-formulate the dengue clinical presentation.

Hypotheses:

We tested two hypotheses to explain the key clinical trial finding that seronegative vaccine recipients (often younger children) were observed to have higher risk of hospitalization than the control group in year 3 of study, but not year 4-5.

(1) Immunologic and transmission dynamics theory: The vaccinated group had rapid waning of the immunity generated by vaccination (especially in seronegative and/or younger age groups) that caused a build up of susceptibles by year 3 of the study, which resulted in a sharp increase in number of dengue cases in the vaccinated group (possibly related to seasonal peak or particular serotype). In comparison, the control group had maximal immunity at year 3 of study from natural infections and cross-protection generated during year 1-2 of the study.

a. Primary testing strategy: Estimate relative risk of seronegative vaccinated persons to have severe dengue disease (hospitalized case) following first natural infection relative to seronegative unvaccinated persons.
b. Secondary testing strategy: Estimate relative risk of seronegative vaccinated persons to have higher risk of severe dengue disease (hospitalized case) following pseudo-primary natural infection while also incorporating an age-specific or serostatus-specific vaccine efficacy term to account for lower immunogenicity in younger age groups or seronegative study participants.

(2) Vaccine-related antibody-dependent enhancement or temporal clustering theory: Vaccine acted as a pseudo-primary infection, so secondary (more severe) infections happened earlier during study period in a temporally focused manner. In comparison, the control group may experience more severe infections overall, but they will be in future and temporally diffuse.
   a. Primary testing strategy: Estimate relative risk of seronegative vaccinated persons to have severe dengue disease (hospitalized case) following first natural infection relative to seronegative unvaccinated persons.
   b. Secondary testing strategy: Estimate cumulate risk of seronegative vaccinated persons to have severe dengue disease (hospitalized case) over lifetime relative to seronegative unvaccinated persons.

Primary and secondary outcomes:

We formulated the model to include a relative risk of severe dengue disease from primary infection for seronegative vaccine recipients compared to their unvaccinated counterparts ($\pi_{ADE_{vacc}}$). The primary outcome of the study is the posterior estimate of this key fitted model parameter. If the 95% credible interval of the posterior distribution for $\pi_{ADE_{vacc}}$ is greater than one, we consider this to be consistent with hypothesis #2 (vaccine causes more severe disease in seronegative study participants). If the 95% credible interval of the posterior distribution for $\pi_{ADE_{vacc}}$ crosses one, then we consider this to be less consistent with hypothesis #2 and more plausibly explained by hypothesis #1. The secondary outcome of the study uses the alternative formulation of the model that accounts for age- and serotype-specific differences in vaccine immunogenicity and efficacy (see "Hypotheses" section), and otherwise follows the same stated definition for interpretation.

References

1. Arredondo-Garcia JL, Hadinegoro SR, Reynales H, et al. Four-year safety follow-up of the tetravalent dengue vaccine efficacy randomized controlled trials in Asia and Latin America. *Clin Microbiol Infect* 2018.
2. Capeding MR, Tran NH, Hadinegoro SR, 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. *Lancet* 2014; **384**(9951): 1358-65.
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