Estimation of parameters related to vaccine efficacy and dengue transmission from two large phase III studies

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\textbf{A B S T R A C T}

\textbf{Background:} A tetravalent dengue vaccine was shown to be efficacious against symptomatic dengue in two phase III efficacy studies performed in five Asian and five Latin American countries. The objective here was to estimate key parameters of a dengue transmission model using the data collected during these studies.

\textbf{Methods:} Parameter estimation was based on a Sequential Monte Carlo approach and used a cohort version of the transmission model. Serotype-specific basic reproduction numbers were derived for each country. Parameters related to serotype interactions included duration of cross-protection and level of cross-enhancement characterized by differences in symptomaticity for primary, secondary and post-secondary infections. We tested several vaccine efficacy profiles and simulated the evolution of vaccine efficacy over time for the scenarios providing the best fit to the data.

\textbf{Results:} Two reference scenarios were identified. The first included temporary cross-protection and the second combined cross-protection and cross-enhancement upon wild-type infection and following vaccination. Both scenarios were associated with differences in efficacy by serotype, higher efficacy for pre-exposed subjects and against severe dengue, increase in efficacy with doses for naive subjects and by a more important waning of vaccine protection for subjects when naive than when pre-exposed. Over 20 years, the median reduction of dengue risk induced by the direct protection conferred by the vaccine ranged from 24% to 47% according to country for the first scenario and from 34% to 54% for the second.

\textbf{Conclusion:} Our study is an important first step in deriving a general framework that combines disease dynamics and mechanisms of vaccine protection that could be used to assess the impact of vaccination at a population level.

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1. Introduction

Dengue, an arthropod-borne viral disease caused by four distinct virus serotypes, has become an increasing public health problem. An estimated 3.9 billion people in 128 countries live in tropical and subtropical regions where they are at risk of the disease [1]. Globally, there are an estimated 390 million dengue infections annually, of which 96 million result in manifest disease [2]. Symptoms range from mild to moderate undifferentiated febrile illness to more complex severe clinical manifestations which can lead to death. Despite life-long immunity to the infecting serotype and limited duration of cross-protection against other serotypes [3,4], severe dengue disease is more often associated with second or subsequent infection with heterologous dengue serotype, hypothesized to be due to antibody-dependent enhancement of infection by preexisting “cross-enhancing” antibodies [5].

There is no specific treatment for dengue other than supportive therapy, and no currently licensed vaccine. A recombinant yellow fever-17D–dengue virus, live, attenuated, tetravalent dengue vaccine (CYD-TDV) has undergone extensive safety and immunogenicity assessment [6–12], and is currently in late phase development. Two, recently completed, landmark, phase III studies undertaken in five countries in South East Asia (NCT01373281) and five countries in Latin America (NCT01374516) have shown the vaccine to be effective in reducing symptomatic, virologically-confirmed dengue. The observed efficacy 28 days after the third injection (i.e. from month 13 through to month 25 of follow-up) was 56.5% (95% confidence interval; 43.8–66.4) in the Asian trial and 60.8% (95% confidence interval; 52.0 to 68.0) in the Latin American trial. In addition, CYD-TDV reduced the rates of severe disease

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and associated hospitalizations in both studies, suggesting [13] that the vaccine has the potential to provide a significant public health benefit [14,15].

Following the successful completion of these phase III studies with CYD-TDV, policymakers need evidence on the public health impact of vaccination to inform decisions regarding implementation of country-specific vaccination strategies/programs. Models of dengue transmission dynamics, use of which has been recommended by WHO [16], can provide insights on these important questions.

In this paper, we built on a previously developed dengue transmission model [17]. The main objective of the study presented here was to estimate the key parameters of this model using the large amount of information collected during the two phase III efficacy studies [14,15]. The first motivation for these estimations comes from the efficacy profiles observed during the studies. Differences were observed according to serotype, level of dengue severity and prior exposure to dengue infection. Interpreting these differences requires a combination of parameters accounting for the underlying mechanisms of vaccine protection which can be adequately represented with a disease transmission model.

The second important motivation was related to the role of interactions between serotypes in dengue dynamics. In a vaccine trial, vaccine efficacy informs on the risk reduction of developing the disease upon exposure through a comparison between the incidence observed in the vaccine and control groups. An important assumption rests on the independence between disease exposure over time (hazard rates) and protection conferred by vaccination upon exposure. However, this independence does not hold in the presence of interacting serotypes, where at each point in time, both the risk of developing infection upon exposure (through cross-protection) and the potential risk that this infection leads to a symptomatic case (through possible cross-enhancement) is a function of past exposure to other serotypes. In this case, protection conferred by vaccination against one serotype influences future infection by other serotypes. This can therefore interfere with the correct interpretation of vaccine efficacy in terms of risk reduction upon exposure required for understanding of the differences in efficacy observed across settings or when assessing vaccination impact at a population level.

A correct assessment of vaccine efficacy in the presence of interacting serotypes can in fact be obtained through a separate evaluation of hazard rates in the vaccine and control groups accounting for these interactions. This was done, in the analysis presented here, through a transmission model. Such an approach requires an assessment of dengue exposure since birth. Therefore, two types of estimation were performed. The first focused on dengue exposure from birth to inclusion in the trial, and the second, the main one, focused on dengue exposure during the trial period.

As such, the parameters estimated relate to efficacy, interaction between serotypes and transmission intensity in the ten countries included in the phase III studies. Using the parameter estimates, we also assessed through simulations the long-term direct protection conferred by the vaccine. This analysis, which is completed by the results presented in a companion paper [18], is the first step in a global approach aimed at informing on the population-level impact of dengue vaccination in endemic countries.

2. Methods

2.1. The mechanistic transmission model

The analysis presented here builds on a previously developed deterministic age-structured compartmental model [17] representing the transmission dynamics of the four dengue serotypes in human and mosquito populations. More precisely, we used here a cohort version of this model focused on the infection process among hosts and modified several assumptions. Notably, we modified the representation of vaccine protection by allowing a complete loss of vaccine protection over time, a decrease in disease severity for breakthrough cases (i.e. dengue cases among vaccinated subjects) and a level of vaccine protection dependent on the number of previous dengue infections. Following Rodriguez-Barraquer et al. [19], we also simplified the representation of cross-enhancement. As in the previous version, we considered a “leaky-type” vaccine [20], i.e. each vaccinated subject benefits from a partial protection in case of exposure. The set of equations defining the infection process among hosts as well the corresponding flow diagram are presented in detail in supplementary information S1. The other equations of the model, which are not directly used in the analysis presented here, can be found in a companion paper [18].

2.2. Clinical and immunological data

Results of the efficacy and safety of CYD-TDV from the two pivotal phase III efficacy studies have been published previously [14,15]. In brief, the two studies involved 31,144 children between the ages of 2 and 16 years of whom 20,771 were assigned CYD-TDV and 10,373 to control (2:1 ratio). Participants received three doses of CYD-TDV or placebo at months 0, 6, and 12, and were actively followed up for any febrile illnesses and assessed for dengue until month 25 after the first study injection. During this time, there were 1282 vireologically-confirmed dengue episodes (574 and 708 episodes in the CYD-TDV and control groups, respectively) and of these, 161 episodes resulted in hospitalization (57 and 104 episodes in the two groups, respectively). The information on the serological status at baseline was available for a total of 3927 participants included in the immunogenicity subsets embedded in the two efficacy studies [14,15].

Two types of estimation were performed from these data. The first focused on dengue transmission prior to the trial and was based on the immunological subset embedded in each trial. The immunogenicity subsets provided information on the age-stratified serological profile at baseline based on the concentration of dengue neutralizing antibody measured with the plaque reduction neutralization test (PRNT50) (see S2.1.1 in Supplementary information S2). Subjects included in these immunological subsets were divided into 105 cohorts according to country of origin (Indonesia, Malaysia, Philippines, Thailand, and Vietnam in the Asian study, and Brazil, Colombia, Honduras, Mexico and Puerto Rico in the Latin American study) and age at inclusion (2 to 14 years in the Asian study, and 9 to 16 years in the Latin American study).

For the second estimation, which focused on dengue transmission during the study period, subjects were also divided by country of origin and age at inclusion, as well as by vaccine group and month of enrolment (June to December 2011 in the Asian study, June 2011 to March 2012 in the Latin American study). A total of 1710 cohorts were considered with 24 months of dengue cases observed, corresponding to 41,040 cohort months’ observation. Given its importance from a public health perspective, we used hospitalization as a proxy for dengue severity.

2.3. Estimation method

All estimations performed were based on a sequential Monte Carlo (SMC) algorithm using the method proposed by Toni et al. [21], which extends from the one of Sisson et al. [22]. Starting from prior distributions, parameter values were iteratively proposed through sampling based on SMC. Final values of parameters (forming the posterior distribution) were those for which model predictions were close to the observed clinical data. This method provides flexibility in the definition of the distance function that
measures the proximity between predictions and observations. In our case, this distance was a negative multinomial likelihood. This enabled us to use the Deviance Information Criterion (DIC) to assess the quality of the fit associated to each of the candidate models [23]. Alternatively, we considered the distribution of $-2 \log$-likelihood for this assessment. The posterior median value and the 95% credible interval (95% CI) were used to present the results obtained for estimated parameters.

The first estimation considered the level of dengue exposure among subjects from birth to study enrolment and provided an estimation of the country- and serotype-specific annual force of infection from 1995 to 2010 for Latin American, and from 1997 to 2010 for Asia. As with Ferguson et al. and Imai et al. [24,25], we used PRNT50 data, distinguished between naïve, monotypic and multitypic immunological profiles and considered a multinomial likelihood. This estimation also enabled us to assess the serotype-specific basic reproduction numbers ($R_0$) for each of the 10 countries.

Six scenarios of vaccine efficacy were tested in the second estimation, by fitting to data observed during the trials (Table 1). Depending on the scenario, 4 to 22 parameters related to vaccine efficacy were estimated. Parameters included the relative risk of developing disease upon exposure depending on the serotype and the serological profile of the subject ($r_{s,m}^k$, where $s$ is the serotype, and $k$, $l$ and $m$ symbolize the dengue immune status for the other serotypes); the reduction of severity after infection by serotype $s$ in case of disease among vaccinated ($s_{v}$), and the waning of vaccine protection over time ($w_{s,m}^k$).

Two main scenarios for the interactions between the four dengue serotypes were considered. In the first scenario, interactions between serotypes were limited to temporary cross-protection against any heterotypic infection for a limited period of time after a dengue infection (Scenario CP—"cross-protection only"). In this scenario, the only estimated parameter related to serotype interactions was the average duration of cross-protection ($s_{HI}$). The second scenario included, in addition to cross-protection, a differential risk of developing symptomatic dengue between primary, secondary, tertiary and quaternary infections (Scenario CPE—"cross-protection and cross-enhancement"). This allowed, besides the average duration of cross-protection, the estimation of three additional parameters: the relative risk, compared to primary infection, of developing a hospitalized and ambulatory case upon secondary infection ($zs(2)$, $zm(2)$) and of developing a dengue case upon tertiary or quaternary infection (assumed to be $zs(3) = zm(3) = zs(4) = zm(4)$). For each of the 10 countries considered, we also estimated the force of infection, seasonality in transmission and proportion of dengue cases leading to hospitalization.

2.4. Comparison with routine surveillance data

We performed a qualitative assessment of the estimation by comparing observed and estimated attack rates in the control group of the vaccine trials with available information from national routine surveillance systems. For these comparisons, we used surveillance data on suspected dengue cases corresponding to the age groups and areas in the countries in which study sites were located and to the study period (June 2011 to December 2013 for the Asian countries and June 2011 to March 2014 for the Latin American countries). To account for under-reporting in surveillance systems [26], we rescaled reported incidence rates to match the observed attack rates during the trials.

2.5. Evolution of vaccine efficacy over time

Finally, using the posterior distribution of estimated parameters, we ran Monte Carlo simulations to assess the evolution of vaccine efficacy over 20 years for different scenarios of vaccine efficacy at different ages and serological status at the time of vaccination. We compared simulated attack rates for vaccinated and non-vaccinated subjects to obtain a measure corresponding to observed efficacy.

3. Results

3.1. Country-specific basic reproduction numbers ($R_0$)

The observed and estimated age-stratified seroprevalence data at baseline per country are presented in supplementary information S2 (Figures 4, 6, 8, 10, 12, 14, 16, 18, 20, 22). In general, we observed a good fit across all countries with only a few points outside the estimated 95% CI. The estimated country-specific serotype-specific force of infection prior to the study period is also summarized in supplementary information S2 (Figs. 3, 5, 7, 9, 11, 13, 15, 17, 19, and 21). Combined with the estimated force of infection during the trial based on the model exhibiting the best fit we were able to calculate the serotype-specific reproduction numbers ($R_0$)

<table>
<thead>
<tr>
<th>Table 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Six vaccine efficacy profiles assessed for the two scenarios of serotypes interaction, CP (cross protection only) and CPE (cross-protection and cross-enhancement) and corresponding DIC.</td>
</tr>
<tr>
<td>Efficacy by serotype</td>
</tr>
<tr>
<td>Efficacy for naïve subjects</td>
</tr>
<tr>
<td>Efficacy against hospitalizations</td>
</tr>
<tr>
<td>Increase in efficacy with doses</td>
</tr>
<tr>
<td>Waning of vaccine efficacy</td>
</tr>
<tr>
<td>Accelerated exposure to secondary infection(\d)</td>
</tr>
<tr>
<td>Deviance information criterion (DIC)(\d)</td>
</tr>
<tr>
<td>Scenario CP</td>
</tr>
</tbody>
</table>

\(\d\) Each cell contains the DIC value for each of the 12 scenarios tested (e.g. the top left cell corresponds to scenario CP1, the first bottom left to scenario CPE1, etc.).

\(\d\) Vaccination plays a role similar to natural infection and exposes those who were seronegative to the same level of risk associated with secondary infection and those who were pre-exposed to natural infection to the same level of risk associated with post-secondary infections.
across all ten countries (see Table 2 and Table 26 in Supplementary information S2 for results with another vaccine efficacy scenario). $R_0$ was greater than 1 for all serotypes (range 1.2 to 5.2) suggesting that all dengue serotypes contribute to dengue transmission in these countries. Overall, higher $R_0$ were observed for Dengue 2 followed by Dengue 1 whereas the lowest $R_0$ was observed for Dengue 4 in seven countries including the five Latin American countries. Thailand was the country with the highest reproduction numbers whereas in three countries (Mexico, Puerto Rico and Malaysia) the median $R_0$ was below 3 for all serotypes.

### 3.2. Evolution of monthly dengue incidence in the control group

The monthly dengue incidence for the observed cases, estimated cases and those notified to the national surveillance systems are summarized in supplementary information S2 for all countries (Section S2.2.3.6 and S2.2.4.7 for scenario CP and CPE, respectively). In the control group, we compared observed and estimated incidence rates with rescaled surveillance data. In general, the estimated seasonality and year-to-year variation were broadly aligned with national surveillance reports indicating that data collected during the trial were representative of dengue dynamics in the region and that the estimation performed was able to reproduce underlying seasonality.

### 3.3. Interaction between serotypes

Estimated parameters for the two scenarios of interaction with serotypes (CP and CPE) are summarized in Table 3. The two scenarios differed with respect to the duration of cross-protection with a lower value for scenario CP (7 months [95% CI, 6–9] versus 15 months [95% CI, 11–18] for scenario CPE). In scenario CPE, we identified a moderate increased relative risk of symptomatic illness in case of secondary infection and no major difference between hospitalized (1.88) and ambulatory cases (1.72).

Both scenarios were relatively similar in their ability to fit to observed data as indicated by very similar log-likelihoods. However, the DIC was lower for scenario CP. This can be related to the use of fewer parameters in scenario CP (1 versus 4 for serotype interactions) since the DIC accounts for the effective number of parameters.

### 3.4. Vaccine efficacy

The detailed results of the estimations performed can be found in supplementary information S2 (S2.2.3 for interaction scenario CP, S2.2.4 for interaction scenario CPE) and corresponding DIC are presented Table 1. The hierarchy of vaccine profiles in terms of DIC was similar for scenario CP and CPE. The fit to observed data was significantly improved when considering differences in efficacy between subjects previously exposed or not exposed to dengue infection prior to vaccination (pre-exposed or naïve). The difference in DIC values between scenario CP1 and CP2 was ~32 and between scenario CPE1 and CPE2 ~50. Further improvement in data fit was obtained when accounting for differences in severity (scenario 3) and increase in efficacy with doses for naïve subjects (scenario 4). There was no scenario with an increase in efficacy with doses for all subjects that improved data fit compared to scenario 4.

The estimation performed allowed us to go a step further by including waning of vaccine protection in the estimation. Both scenarios CP and CPE led to marked differences in the waning of vaccine protection for naïve and pre-exposed subjects. The estimated annual waning rate was 55% [95% CI, 15–93] for naïve and 5% [95% CI, 0–15]) for pre-exposed subjects in scenario CP5. The

### Table 2

Serotype-specific basic reproduction number ($R_0$) estimates and seasonal variation of dengue transmission in the 10 countries participating in the phase III efficacy trials (Posterior median value and 95% CI calculated from estimated annual force of infection prior and during the trial—scenario CP).

<table>
<thead>
<tr>
<th>Country</th>
<th>Dengue 1</th>
<th>Dengue 2</th>
<th>Dengue 3</th>
<th>Dengue 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brazil</td>
<td>2.7 [2.3;3]</td>
<td>3.3 [2.3;5]</td>
<td>3.3 [2.3;4]</td>
<td>2 [1;2.2]</td>
</tr>
<tr>
<td>Colombia</td>
<td>4.2 [3.8;4.7]</td>
<td>3.3 [2.9;3.7]</td>
<td>3.2 [2.9;3.4]</td>
<td>1.9 [1;2.1]</td>
</tr>
<tr>
<td>Honduras</td>
<td>2.4 [2.1;2.6]</td>
<td>3.3 [2.9;3.7]</td>
<td>3.2 [2.9;3.4]</td>
<td>1.9 [1;2.1]</td>
</tr>
<tr>
<td>Mexico</td>
<td>2.3 [2.1;2.5]</td>
<td>2.4 [2.3;2.6]</td>
<td>1.9 [1;2.2]</td>
<td>1.3 [1;2.1]</td>
</tr>
<tr>
<td>Puerto Rico</td>
<td>2.5 [2.3;2.7]</td>
<td>2.7 [2.3;3]</td>
<td>2.2 [2;2.5]</td>
<td>1.2 [1;2.1]</td>
</tr>
<tr>
<td>Indonesia</td>
<td>3.4 [2.7;3.5]</td>
<td>3.6 [3.2;4.1]</td>
<td>2.7 [2.4;3]</td>
<td>2.2 [1;2.4]</td>
</tr>
<tr>
<td>Malaysia</td>
<td>2.2 [1.9;2.6]</td>
<td>2.5 [2.1;2.8]</td>
<td>1.8 [1;2.1]</td>
<td>1.9 [1;2.2]</td>
</tr>
<tr>
<td>Philippines</td>
<td>3.9 [3.5;4.3]</td>
<td>3.2 [2.8;3.5]</td>
<td>2.1 [2.2]</td>
<td>2.4 [2;2.6]</td>
</tr>
<tr>
<td>Thailand</td>
<td>3.9 [3.4;4.5]</td>
<td>5.2 [4.6;5.9]</td>
<td>3.4 [2.9;3.8]</td>
<td>2.2 [1.9;2.6]</td>
</tr>
<tr>
<td>Vietnam</td>
<td>2.8 [2.5;3.3]</td>
<td>3 [2.6;3.4]</td>
<td>2.1 [1.7;2.3]</td>
<td>3 [2;3.7]</td>
</tr>
<tr>
<td>Average</td>
<td>3.0</td>
<td>3.2</td>
<td>2.6</td>
<td>2.0</td>
</tr>
<tr>
<td>Minimum</td>
<td>2.2</td>
<td>2.4</td>
<td>1.8</td>
<td>1.2</td>
</tr>
<tr>
<td>Maximum</td>
<td>4.2</td>
<td>5.2</td>
<td>3.4</td>
<td>3.0</td>
</tr>
</tbody>
</table>

### Table 3

Parameter estimates and goodness-of-fit measures in the two scenarios of serotypes interaction assessed.

<table>
<thead>
<tr>
<th>Scenarios of interaction between serotypes</th>
<th>Cross protection only (scenario CP)</th>
<th>Cross-protection and cross-enhancement (scenario CPE)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Posterior median [95% CI]</td>
<td>Posterior median [95% CI]</td>
</tr>
<tr>
<td>Average duration of cross-protection (months)</td>
<td>6.99 [6.1;9.1]</td>
<td>15.30 [11.5;17.8]</td>
</tr>
<tr>
<td>Increased risk of severe case (2nd infection)</td>
<td>1</td>
<td>1.88 [1;4.2]</td>
</tr>
<tr>
<td>Increased risk of mild case (2nd infection)</td>
<td>1</td>
<td>1.72 [1;5.2]</td>
</tr>
<tr>
<td>Increased risk of case (3rd–4th infection)</td>
<td>1</td>
<td>0.47 [0.12;0.8]</td>
</tr>
<tr>
<td>Deviance Information Criterion</td>
<td>21,080.3</td>
<td>22,085.1</td>
</tr>
<tr>
<td>-2@Log-likelihood</td>
<td>21,059 [21,053;21,067]</td>
<td>21,059 [21,053;21,063]</td>
</tr>
</tbody>
</table>

1 Results presented derived from models corresponding to reference scenarios for vaccination (respectively scenario CP5 and scenario CPE5).

2 Compared to the risk associated with primary infection.
inclusion of waning of vaccine protection significantly improved
the fit for scenario CP (the DIC was lower (-5) for scenario CP5
compared to scenario CP4).

Finally, we considered a scenario where vaccination was likely
to generate cross-enhancement. More specifically, in this scenario,
we considered that vaccination played a role similar to natural
infection by exposing naïve subjects directly to the same level of
risk associated with secondary infection. Similarly, we considered
that pre-exposed subjects when vaccinated faced the same level of
risk associated with post-secondary infection (tertiary instead of
secondary). As in natural infection, this was expected to occur once
protection (here vaccine-induced) had waned. This scenario led to
a decrease in the DIC for scenario CPE 21,085 for scenario CPE6
versus 21,092 for scenario CP4) although the DIC remained higher
for scenario CPE6 compared to scenario CP5 (Table 1).

The overall quality of data fit remained similar for scenario CP5
and CPE6 as indicated by the results of observed and estimated effi-
cacy in Fig. 1. The difference in DIC was probably due to the fewer
number of estimated parameters in scenario CP5. In terms of the
level of primary efficacy for each profile (Table 4), scenario CPE6 led
overall to a slightly higher efficacy notably for naïve subjects com-
pared to scenario CP5. This can be seen as a direct consequence
of the consideration of vaccine-induced cross-enhancement in sce-
nario CPE6.

Both scenarios CP5 and CPE6 led to a good fit to observed efficacy
considering serotype-specific efficacy or efficacy against hospital-
ized cases (Fig. 1). With respect to country-specific results, both
scenarios also performed similarly well for all except 3 countries
(Malaysia, Mexico and Vietnam). Although the fit was not fully
accurate for efficacy with doses, scenario CPE6 captured slightly
better than scenario CP5 the differences between doses. The two
scenarios captured increase in efficacy with age but none of the
scenarios fully reproduced the lower efficacy observed in the 2–5
year age group. Since the underlying transmission model was not
stochastic, estimation results did not fully capture the random
variation in the observed efficacy induced by a limited number of
observations in some of the subgroups considered (Fig. 1).

3.5. Evolution of vaccine efficacy over time

The two reference scenarios CP5 and CPE6 differ with respect
to the evolution of vaccine efficacy over time. The results for
Malaysia presented in Fig. 2a and d highlight that the main dif-
fERENCE pertains to the evolution of vaccine efficacy over time for
young children between 2 and 5 years after vaccination. Whereas
a steady decrease is expected for scenario CP5, vaccine-induced
cross-enhancement considered in scenario CPE6 was likely to gen-
erate a sharp decrease in efficacy once the initial protection had
waned, leading in some scenarios to a negative efficacy for a period
of time. This result is mainly driven by the consequence of vac-
cination for naïve subjects that face an accelerated exposure to
secondary infection with this scenario. This can be seen with the
results presented in Fig. 2 specifically for this category (Fig. 2c and
f). This drop is not visible in case of vaccination of children aged 9
years (Fig. 2b and e), an age at which the proportion of seronegative
children is lower. Results reported in Supplementary information
S2 showed similar evolution whatever the country considered (Sec-
tion S2.2.4.7).

Over 20 years, the median reduction of dengue risk induced by the
direct protection conferred by the vaccine ranged from 24% to
47% according to country for scenario CP5 and from 34% to 54%
for scenario CPE6 (Fig. 3). Scenario CPE6 mainly generates more
uncertainty in the following 2 to 5 years after vaccination for young
children. Overall, especially given the higher estimated efficacy for
subjects when seropositive (Table 4), scenario CPE6 leads to similar,
if not larger, cumulated vaccination benefits than scenario CP5.

4. Discussion

We estimated in this paper the key parameters of a previously
developed mathematical model [17] related to vaccine efficacy,
interaction between serotypes and transmission intensity using
data collected from two recently completed phase III studies with
CYD-TDV [14,15]. The estimation performed first enabled us to
characterize dengue transmission intensity in the 10 countries
involved in these two trials. This confirmed that the four dengue
serotypes contribute to dengue transmission in these countries
with the following hierarchy (dengue serotype 2, 1, 3 and 4), but
with some differences across countries (see Table 2). Interestingly,
although not fully aligned, the results for the countries assessed in
our study are consistent with those reported recently by Imai et al.
[25] (Thailand and Indonesia) and Rodriguez-Barraquer et al. [27]
(Thailand). Of note, our estimation was based on data collected at
study sites selected to participate in the efficacy trials because of
Table 4

Scenario CP5 and CPE6 according to serotype, dose schedule, status at baseline (pre-exposed or naive), severity (ambulatory or hospitalized cases) and waning. Data shown as median values with upper/lower bounds (95% CI).

### Scenario CP5

<table>
<thead>
<tr>
<th>Dengue 1</th>
<th>Ambulatory cases</th>
<th>Hospitalized cases</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre-exposed</td>
<td>Naive</td>
</tr>
<tr>
<td>1 dose</td>
<td>67 [59,76]</td>
<td>19 [2,40]</td>
</tr>
<tr>
<td>2 doses</td>
<td>67 [59,76]</td>
<td>31 [3,63]</td>
</tr>
<tr>
<td>3 doses</td>
<td>67 [59,76]</td>
<td>39 [4,71]</td>
</tr>
<tr>
<td>Dengue 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 dose</td>
<td>59 [49,69]</td>
<td>8 [0,25]</td>
</tr>
<tr>
<td>Dengue 3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 dose</td>
<td>81 [75,87]</td>
<td>26 [2,56]</td>
</tr>
<tr>
<td>2 doses</td>
<td>81 [75,87]</td>
<td>50 [6,84]</td>
</tr>
<tr>
<td>3 doses</td>
<td>81 [75,87]</td>
<td>73 [30,87]</td>
</tr>
<tr>
<td>Dengue 4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 dose</td>
<td>91 [84,97]</td>
<td>19 [1,52]</td>
</tr>
<tr>
<td>2 doses</td>
<td>91 [84,97]</td>
<td>26 [2,67]</td>
</tr>
<tr>
<td>3 doses</td>
<td>91 [84,97]</td>
<td>41 [3,85]</td>
</tr>
</tbody>
</table>

**Annual waning rate—Naive**

55.1 [15,93]

**Annual waning rate—Pre-exposed**

5.0 [0,15]

**−2° Log-likelihood**

21,058.8 [21053,21067]

**Deviance Information criterion**

21,080.3

### Scenario CPE6

<table>
<thead>
<tr>
<th>Dengue 1</th>
<th>Ambulatory cases</th>
<th>Hospitalized cases</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre-exposed</td>
<td>Naive</td>
</tr>
<tr>
<td>1 dose</td>
<td>71 [63,79]</td>
<td>13 [1,45]</td>
</tr>
<tr>
<td>2 doses</td>
<td>71 [63,79]</td>
<td>36 [2,73]</td>
</tr>
<tr>
<td>3 doses</td>
<td>71 [63,79]</td>
<td>55 [7,79]</td>
</tr>
<tr>
<td>Dengue 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 dose</td>
<td>67 [56,76]</td>
<td>7 [0,27]</td>
</tr>
<tr>
<td>2 doses</td>
<td>67 [56,76]</td>
<td>14 [1,45]</td>
</tr>
<tr>
<td>3 doses</td>
<td>67 [56,76]</td>
<td>22 [1,57]</td>
</tr>
<tr>
<td>Dengue 3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 dose</td>
<td>84 [77,89]</td>
<td>18 [1,53]</td>
</tr>
<tr>
<td>2 doses</td>
<td>84 [77,89]</td>
<td>33 [2,78]</td>
</tr>
<tr>
<td>3 doses</td>
<td>84 [77,89]</td>
<td>68 [1,89]</td>
</tr>
<tr>
<td>Dengue 4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 dose</td>
<td>89 [83,95]</td>
<td>34 [3,69]</td>
</tr>
<tr>
<td>2 doses</td>
<td>89 [83,95]</td>
<td>45 [4,81]</td>
</tr>
<tr>
<td>3 doses</td>
<td>89 [83,95]</td>
<td>58 [6,89]</td>
</tr>
</tbody>
</table>

**Annual waning rate—Naive**

60.5 [15,97]

**Annual waning rate—Pre-exposed**

3.5 [0,11]

**−2° Log-likelihood**

21,058.6 [21053,21063]

**Deviance Information criterion**

21,085.1

dengue endemicity in their region. The results obtained are therefore more directly representative of these regions than the entire country.

With respect to interaction between serotypes, we obtained relatively similar fit to the observed data with a scenario considering only short-term cross-protection after a dengue infection (scenario CP5) and a scenario combining cross-protection with increased risk in case of secondary infection (scenario CPE6). Interactions between serotypes have been the subject of a number of publications in the dengue field with contrasting results [16]. Although comprehensive, the datasets used in our analysis were not ideally suited to end this debate. We, in fact, confirm the finding of our previous publication that different representations of interaction between serotypes are likely to represent observed data [17]. With respect to the duration of cross-protection, the two scenarios differ with a lower value for scenario CP than CPE (7 months versus 15 months). The link between duration of cross-protection and level of increased symptomatic illness in case of secondary infection has already been noted by Mizumoto et al. [28]. These durations, notably for scenario CP, are shorter than the results published recently (1 to 3 years [29,30]) but higher than the seminal publication from Sabin (6 months [31]). In scenario CPE, we identified a moderate increased risk of symptomatic infection in case of secondary infection and no major difference in the relative risk for hospitalized (1.9) and ambulatory cases (1.7). This result is at the low end of data reviewed by Mizumoto et al. [28] (from 1.9 to 14.3 for relative risk of symptomatic illness in case of secondary infection). A number of factors, may, in part, explain this difference, starting with the active surveillance performed during the phase III trials and the differing methods for case detection used in the...
studies reviewed by Mizumoto et al. [28]. The age groups considered in the trials (2–14 years and 9–16 years) can also play a role since dengue symptomaticity has been shown to vary with age [32,33]. To fully interpret these results, it can also be useful to determine how the relative risks we estimated translate into the proportion of symptomatic cases due to secondary infections at the population level. This was done in a subsequent companion paper [18].

The estimation performed led to a vaccine efficacy profile characterized by differences in efficacy per serotype, increased efficacy for seropositive subjects, increased efficacy against severe forms, and increased efficacy with doses for naïve individuals. These results are consistent with the findings reported both in the Asian and Latin American studies [14,15] and were observed for the two scenarios of serotype interactions considered. We were also able to account for waning of vaccine protection. The data used are arguably limited to the 25 months of the active surveillance implemented in the two phase III studies, but were nonetheless sufficient for us to detect a marked difference in vaccine protection waning between naïve (55% [95% CI, 13–93]) and pre-exposed subjects (5% [95% CI, 0–15]). This waning, however, does not entirely dictate the overall duration of protection since the status of vaccinated subjects' changes as they experience a dengue infection. We finally considered a scenario (scenario CPE6) with vaccine-induced cross-enhancement along the lines of the scenarios explored by Rodríguez-Barraquer et al. [34]. This scenario was not associated with the best fit, based on the DIC criterion, but led to an overall similar quality of fit compared to the other reference scenario. The results obtained cannot, therefore, rule it out as a possible scenario for explaining mechanisms of vaccine protection.

Although the two scenarios are similar in their ability to reproduce data observed during the phase III studies, they differ regarding the evolution of vaccine efficacy over time. More specifically, scenario CPE6 generated wide uncertainty in vaccine efficacy following 2 to 5 years after vaccination for naïve subjects or young children, where a significant proportion of subjects were naïve when vaccinated. Nevertheless, in the long term (20 years), this scenario produces a similar if not larger reduction in dengue cases than scenario CP5, including for naïve subjects. Vaccine-induced cross-enhancement considered here essentially accelerates exposure to secondary infection for naïve subjects, and as such, its main impact would be on modifying the time at which a subject develops dengue, with a lower impact on the overall risk. It is noteworthy that age-specific differences in the risk of developing dengue disease are likely to influence this result. Current evidence [32,33], however, indicates an increase in symptomaticity with age may

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**Fig. 2.** Monthly reduction of dengue cases over 20 years for subjects vaccinated at age 2 years (a and d) and 9 years (b and e), and for 9-year-old subjects never exposed to dengue before vaccination (c and f)—Results for Malaysia, as an example.

**Fig. 3.** Cumulative reduction of dengue cases over 20 years for subjects vaccinated at age 9 years for scenario CP5 (a) and scenario CPE6 (b).
possibly limit the negative consequences of accelerated exposure to secondary infection.

Dengue dynamics influence the way vaccine-induced cross-enhancement impacts the evolution of vaccine efficacy over time. Its impact is more visible when the level of dengue incidence changes between the time vaccine recipients get vaccinated and lose their protection (e.g., switch from low to high force of infection). The influence of dengue circulation in the previous years on the interpretation of epidemiological observations is well known. Previous dengue seasons have, for instance, been identified as an epidemiological risk factor for explaining the observed rate of inapparent infections [35]. Our results for vaccine-induced cross-enhancement cannot be compared directly with those obtained by Rodriguez-Barraquer et al. [34] since we did not consider the exact same mechanisms, their focus was on dengue serotype 2 and they did not explicitly considered the results of the two phase III studies with CYD-TDV as they were not available at the time of their analysis. However, we share the same conclusion that vaccine-induced cross-enhancement does not necessarily imply that vaccination is detrimental. Moreover, our analysis of vaccine efficacy over time was limited to direct effects and did not include the potential positive effects associated to indirect protection [36]. The contribution of indirect protection will be addressed more directly in a follow-up paper focused on the impact of dengue vaccination at the population level [18].

Our study has a number of limitations linked first to the data used. To keep the estimation tractable, we used a cohort-based approach and not an individual-based approach that could have helped to better characterize dengue status notably for subjects known to have experienced dengue during the trial. We also assumed a similar exposure to dengue for all subjects within each country, whereas some differences were observed between different sites in the same country. In addition, we used hospitalizations as a proxy for severe outcomes related to dengue mainly because of its importance from a public health perspective. However, although hospitalization rates reflect dengue severity, they may also be influenced by differences in clinical practice patterns.

A wide range of additional scenarios of serotype interactions could also have been tested. For instance, we assumed that the duration of cross-protective immunity following natural infection would be the same, irrespective of dengue serotype or severity. Anderson et al. [30] reported differences in the duration of cross-protection for clinical and subclinical infections. In addition, we did not specifically differentiate between tertiary and quaternary infections when considering the probability of symptomatic infection. The nature of available information was a limiting factor. Although comprehensive, the datasets used in our analysis do not provide detailed serological information for all subjects and longitudinal information over a long period of time. Thus, we had limited ability to differentiate between very detailed representations of serotype interactions. We, therefore, preferred to concentrate the analysis on a limited number of scenarios capturing the state of knowledge on the topic (i.e. the consideration of both cross-protection and cross-enhancement). Besides, the two main scenarios selected led overall to a similar quality of fit to observed data.

Regarding vaccine efficacy, the scenarios considered enabled us to assess the main factors related to vaccine protection including vaccine-induced cross-enhancement. We, however, limited our analysis to a leaky-type vaccine (partial immunity for all subjects) and did not consider all-or-nothing protection (full protection of a subset of vaccinated subjects) [20]. This can nevertheless be seen as conservative with respect to vaccination benefits over time since, contrary to all-or-nothing protection, it accounts for possible vaccine failure following repeated exposure. Similarly, since our analysis was only based on the 25 months of active follow-up, the estimated waning in vaccine efficacy needs to be revisited as more information becomes available.

Our estimation of vaccine efficacy was able to partially but not fully reproduce the differences in efficacy between age groups. This could be improved by the consideration of an age effect independent from the serological status. We also did not fully capture the observed evolution of efficacy with doses. At this level, analyses that can be performed on the additional benefit provided by the second and third dose are nevertheless limited since almost all participants in the vaccine studies ultimately received three doses.

We used the SMC algorithm developed by Toni et al. [21]. Recently, a number of Bayesian methods have been proposed to estimate parameters of transmission models [37], including Monte Carlo Markov Chains methods with data augmentation, different SMC techniques or a combination of these methods like particle MCMC [38]. Each method comes with strengths and weaknesses regarding its efficiency, suitability to the problem at hand and also with respect to computational aspects. One important advantage of the SMC approach used here is that it can be easily parallelized. That proved to be critical considering the large number of observations included in our analysis that required intensive computer processing time (>100,000 h). Another example of the use of the method developed by Toni et al. [21] for estimating the parameters of a transmission model can be found in Brooks-Pollock et al. [39] who also dealt with a large dataset in their analysis.

Our ability with this approach to use the detailed information collected during the two large phase III studies to estimate key parameters in our transmission model for ten countries is the main strength of the work presented here. It allowed us to reconcile the complex dynamics of dengue with a detailed analysis of factors impacting vaccine efficacy. It also provided insights beyond efficacy on the transmission intensity of dengue in the ten participating countries. To our knowledge, examples of estimation of the parameters of a transmission model directly from the results of large-scale multi-country trials are scarce. Our analysis, however, did not address all uncertainties regarding the efficacy of CYD-TDV. The ongoing longitudinal surveillance for an additional 4 years in both these phase III studies will help better establish the long-term benefits of vaccination. Besides, the recent publication by Hadinegoro et al. [40] of the first year results of this longitudinal surveillance (year 3 from start of vaccination) has led to a number of important observations. The results for this specific year indicated a lower incidence of hospitalization for dengue for children aged ≥9 years at the time of vaccination (relative risk 0.5 [95% CI, 0.29–0.86] but also a higher incidence of hospitalization for children aged <9 years when vaccinated (relative risk 1.58 [95% CI 0.83–3.02]). Although additional analyses are required to further validate this point, these results showed some consistency with the results evidenced here for scenario CPE6 i.e. uncertainty in efficacy 2 to 5 years after vaccination for young and naïve children despite positive long term benefits of vaccination.

In conclusion, our study forms an important first step in deriving a general framework that combines disease dynamics and mechanisms of vaccine protection that can be used to assess the public health impact of dengue vaccination. It has provided us with a better understanding of the heterogeneity in the efficacy data observed which can have important implications for epidemiological projections. This is addressed in the follow-up paper focused on the public health impact expected from the implementation of vaccination programs in endemic countries.

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Funding for this study was provided by Sanofi Pasteur. The sponsor participated in all operational aspects of this modelling study,
including data collection, statistical analyses, and writing of the report.

Contributors

LC conceived the analysis and designed the estimation method with EV. LC and NB performed the analyses. All authors discussed data analyses and interpretation, helped to draft and critically revise the manuscript, and approved the final version submitted.

Conflict of interest statement

Laurent Coudeville and Nicolas Baurin are employees of Sanofi Pasteur.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.vaccine.2015.11.023.

References