Vaccine 34 (2016) 6426–6435

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Potential impact of dengue vaccination: Insights from two large-scale phase III trials with a tetravalent dengue vaccine

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ARTICLE INFO

Article history:
Received 13 August 2015
Received in revised form 11 August 2016
Accepted 16 August 2016
Available online 3 September 2016

Keywords:
Dengue
Epidemiology
Prevention & control
Dengue vaccines

ABSTRACT

Background: A tetravalent dengue vaccine demonstrated its protective efficacy in two phase III efficacy studies. Results from these studies were used to derive vaccination impact in the five Asian (Indonesia, Malaysia, Philippines, Thailand, Vietnam) and the five Latin American countries (Brazil, Colombia, Honduras, Mexico and Puerto Rico) participating in these trials.
Methods: Vaccination impact was investigated with an age-structured, host-vector, serotype-specific compartmental model. Parameters related to vaccine efficacy and levels of dengue transmission were estimated using data collected during the phase III efficacy studies. Several vaccination programs, including routine vaccination at different ages with and without large catch-up campaigns, were investigated.
Results: All vaccination programs explored translated into significant reductions in dengue cases at the population level over the first 10 years following vaccine introduction and beyond. The most efficient age for vaccination varied according to transmission intensity and 9 years was close to the most efficient age across all settings. The combination of routine vaccination and large catch-up campaigns was found to enable a rapid reduction of dengue burden after vaccine introduction.
Conclusion: Our analysis suggests that dengue vaccination can significantly reduce the public health impact of dengue in countries where the disease is endemic.

1. Introduction

Dengue is a mosquito-borne viral disease that has become an increasing public health problem in tropical and subtropical regions of the world [1–4]. Four viral serotypes of the *Flavivirus* genus cause dengue disease in proportions that change unpredictably over time, and from place to place, even within the same country [5,6]. There is no specific treatment for dengue and current vector control measures have in general failed to reduce the occurrence of dengue epidemics [7].

A recombinant yellow fever-17D–dengue virus, live, attenuated, tetravalent dengue vaccine (CYD-TDV) has recently demonstrated its efficacy against symptomatic, virologically-confirmed dengue during the active surveillance phase (up to 25 months after the first injection) of two phase III studies in 10 countries in Asia and Latin America (Indonesia, Malaysia, Philippines, Thailand, Vietnam, and Brazil, Colombia, Honduras, Mexico, and Puerto Rico) [8,9]. During this period, vaccine efficacy rates against symptomatic dengue were 60.3% (95% confidence interval [CI], 55.7–64.5) for all participants, 65.6% (95% CI, 60.7–69.9) for those aged 9 years or older and 44.6% (95% CI, 31.6–55.0) for those younger than age 9 years [10]. A long-term safety follow-up based on hospital surveillance was undertaken beyond the active surveillance phase of these two efficacy studies. The first results, corresponding to year 3 after the first injection, indicated a 50% (95% CI, 0.29 to 0.86) reduction in hospitalization for dengue among vaccinated participants aged 9 years or older. In contrast, an increase of 58% (95% CI, –0.17 to 2.02) was observed for those aged under 9 years. Based on this information, five countries (Mexico, Brazil, Philippines, El Salvador, Costa Rica) recently approved the use of CYD-TDV for individuals aged 9–45 years living in endemic areas.

Following the completion of the active surveillance phase of the two phase III studies, and the first registration of CYD-TDV, policy-makers need evidence of the public health impact of vaccination to inform decisions on vaccine introduction. In line with the World Health Organization (WHO) recommendations, models of dengue transmission can be used to address these important questions

DOI of original article: http://dx.doi.org/10.1016/j.vaccine.2015.11.023
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http://dx.doi.org/10.1016/j.vaccine.2016.08.050
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by assessing the benefits expected from various vaccination strategies [11]. Several mathematical models, including the one used here [12], have been used to assess the population impact of dengue vaccination before the final results of the CYD-TDV phase III efficacy studies were available [13–19]. Nonetheless, these modeling studies generally concluded that vaccination has the potential to significantly reduce the burden of dengue.

We estimated in a companion paper [20] the key parameters of our transmission model using the information collected during the active surveillance of the two CYD-TDV phase III efficacy studies. Here, our main objective was to assess the population impact of dengue vaccination in the 10 countries participating in the phase III efficacy studies. Since the publication of the companion paper, data collected during the first year of the long-term safety follow-up became available. We therefore revisited the estimation of model parameters in the light of this additional data. We also focused on vaccination programs targeting individuals aged 9 years or older for whom the vaccine is indicated.

2. Methods

2.1. Model design

The mathematical model used in this analysis is an age-structured, host-vector, serotype-specific compartmental model that includes seasonality and accounts for the transmission dynamics of the four dengue serotypes in human and mosquitoes at the population level [12]. It can consider different types of serotype interactions: temporary cross-protection (i.e. no risk of developing a heterotypic infection for a limited time after an infection), cross-enhancement (i.e. differential risk of developing symptomatic cases upon primary, secondary, tertiary and quaternary infection), or a combination of cross-protection and cross-enhancement.

Some modifications have been incorporated into the model since it was first published. Following on from the work of Rodriguez-Barraquer et al. [21], we simplified the representation of cross-enhancement. We also modified the representation of vaccine protection by allowing a complete loss of vaccine protection over time, a decrease in severity for breakthrough cases, and a level of vaccine protection dependent on the number of previous dengue infections. We also accounted for possible differences between the efficacy against symptomatic and asymptomatic infections and did not account for natural boosting of vaccine-derived immunity. In line with the previous version of the model, we considered a "leaky type" vaccine [22], i.e. each vaccinee retains a residual risk of infection in case of exposure. This assumption can be seen as conservative since, contrary to the alternative assumption ("all-or-nothing", i.e. where a subset of individuals are fully protected against the disease), it accounts for possible vaccine failure following repeated exposure. The set of equations defining the model is detailed in Supplementary information S1 (section S1.1).

Another difference from the previous model is the relative contributions of symptomatic and asymptomatic infections to disease transmission. Using available literature on the level of viremia generated by symptomatic and asymptomatic infections, and the level required for virus transmission [23–27], we considered that both contribute to disease transmission but with a higher risk for symptomatic infection to generate a subsequent mosquito infection (relative risk set to four).

As with any transmission model, our model allows consideration of both direct protection to vaccinees and indirect protection for the entire population related to reduced disease transmission due to vaccination. More complete information on the mechanisms of indirect protection and the evidence used for its assessment can be found in supplementary information S1 (section S1.3).

2.2. Model calibration

The main source of information for the calibration was derived from the estimation performed with data collected during the two CYD-TDV phase III studies [8,9]. We presented in the companion paper [20] the results of the estimation performed on data collected during the active surveillance phase (up to 25 months after the first injection). Here, we revisited this estimation to account for data collected during the first year of the long term safety follow-up. This new estimation is presented in supplementary information S1 (section S1.5) and was used for the assessment of the serotype-specific basic reproduction numbers (Table 1).

To move from data collected among children and adolescents (aged 2–14 years for Asian countries and 9–16 years for Latin American countries) to a population-based analysis, we complemented the phase III data with demographic information and routine surveillance data for the 10 countries included in the analysis. To account for differences between the dengue incidence observed during the trials, based on very active surveillance, and the incidence of suspected dengue reported through passive surveillance systems [28], we calculated country-specific expansion factors. These expansion factors (Table 1) were based on the ratio between the two incidences for the same age group, same area and same period of time and were used to correct routine surveillance data in all age groups.

Table 1
Expansion factors (ratio between incidence of virologically-confirmed dengue and suspected dengue cases during phase III trials and reported incidence[a]) and estimated basic reproduction numbers[b] for the ten countries participating in the phase III efficacy trials.

	Expansion factors[c]	Basic reproduction numbers (R_0)				
	Median [95% CI]	Dengue 1 Median [95% CI]	Dengue 2 Median [95% CI]	Dengue 3 Median [95% CI]	Dengue 4 Median [95% CI]	Rank[d]
Thailand	6.2 [4.6;8]	3.4 [3;3.9]	4.9 [4.3;5.6]	2.8 [2.5;3.1]	2.4 [2.1;2.7]	0
Colombia	10.3 [9.3;11.9]	4.3 [3.8;4.7]	2.9 [2.6;3.3]	3.4 [3.1;3.8]	2 [1.7;2.2]	1
Philippines	13.8 [11.5;16.5]	3.8 [3.5;4.1]	3.1 [2.8;3.4]	2.2 [2;2.4]	2.4 [2.1;2.6]	2
Brazil	1.8 [1.5;2.2]	2.7 [2.3;3.1]	3 [2.6;3.5]	3.3 [2.8;3.8]	2.1 [2.1;2.2]	3
Honduras	265.2 [207.6;322.6]	2.4 [2.1;2.6]	3.4 [3;3.8]	3.2 [3;3.4]	1.9 [1.7;2.1]	4
Indonesia	12.3 [9.6;15.5]	2.9 [2.5;3.3]	3.4 [3;3.9]	2.5 [2.2;2.7]	2.1 [1.8;2.4]	5
Vietnam	10.1 [8.1;13]	2.7 [2.4;3.1]	3 [2.6;3.4]	2 [1.8;2.3]	2.7 [2.5;3]	6
Puerto Rico	10.7 [4.9;16.2]	2.4 [2.3;2.6]	2.7 [2.3;3]	2.2 [2;2.5]	1.2 [1.2;1.3]	7
Mexico	10.9 [8.1;13.9]	2.4 [2.2;2.6]	2.5 [2.4;2.7]	1.9 [1.7;2]	1.3 [1.2;1.3]	8
Malaysia	14.3 [7.2;22.6]	2.1 [1.8;2.5]	2.3 [2;2.7]	1.8 [1.6;2]	1.8 [1.6;2.1]	9

[a] For periods, areas and age groups corresponding to the population of phase III studies.
[b] Derived from the estimation performed on CYD-TDV phase III efficacy studies.
[c] Based on Scenario CPA.
[d] Derived from the average R_0 over the 4 serotypes.

We also investigated the differences between simulated and reported age distribution of dengue cases. This comparison highlighted similar trends across countries; the reported incidence was lower than that predicted in younger children but higher than that predicted in older children. This result is consistent with publications reporting age-specific differences in the clinical features of dengue [29–31] and the probability of developing symptomatic infection [32,33], which reflects age-specific differences not directly captured by the estimation performed on the data from the specific age groups. Since age distribution of cases is an important dimension in the burden of dengue, we accounted for these differences by considering age-specific differences in expansion factors. All impact result presented therefore account for the age distribution of cases provided by country-specific surveillance systems while being corrected for under-reporting. More complete information on the calibration procedure can be found in section S1–6 of Supplementary information S1.

2.3. Scenarios of vaccine efficacy

The estimation performed on data collected during the active surveillance phase of the two CYD-TDV phase III efficacy studies presented in a companion paper [20] led to the identification of vaccine efficacy scenarios accounting for differences in efficacy by serotype, by severity, according to the number of previous infections, and an increase in efficacy for vaccinated subjects never exposed to dengue infections (seronegative or naïve subjects). We also considered differences in the annual waning rate (exponential decay) for subjects vaccinated when seronegative or seropositive.

Since the publication of this companion paper, data collected during the first year of the long-term safety follow-up indicated contrasting evolution of cases according to age [10]. Guy and Jackson [34] identified three interconnected hypotheses likely to explain these results. Two of these hypotheses are included in one of the scenarios identified in [20] (Scenario CPE): differences in waning according to serological status at baseline and accelerated exposure to a second dengue infection. The underlying assumption behind accelerated exposure to a secondary dengue infection is that vaccination acts as a primary natural infection and exposes seronegative subjects directly to the same level of risk of the infection becoming symptomatic corresponding to a second dengue infection. Similarly, individuals exposed to at least one dengue infection prior to vaccination (seropositive or pre-exposed subjects) become exposed to the same level of risk of infection becoming symptomatic associated with post-second infection (i.e. second to third, and third to fourth). A similar assumption was explored by Rodriquez-Barraquer et al. [14]. A more detailed presentation of this mechanism can be found in section S1–4 of Supplementary information S1.

Guy and Jackson [34] also identified a third hypothesis interconnected to the two former ones, and likely to explain observations made during the first year of long-term safety surveillance: an age-specific mechanism independent from seropositivity. Here, we revisited the estimation of model parameters to account for data collected during the first year of the long-term safety surveillance. We used scenario CPE but also explored additional scenarios including age-specific mechanisms independent from seropositivity. The best fit was obtained for scenario CPA that accounts for the three hypotheses considered by Guy and Jackson [34]. The characteristics of scenario CPA, used to assess the impact of vaccination presented here, are summarized in Table 2. Detailed results of the estimation combining data collected during the active phase and the first year of long-term safety surveillance can be found in section S1–5 of supplementary information S1.

The estimation performed did not provide direct information on the efficacy against asymptomatic infections. For this part, we used the results of an analysis performed on immunological data collected during the two CYD-TDV phase III efficacy studies showing a positive but lower efficacy than the one observed against symptomatic cases [35]. This led us to consider, in the base case, an efficacy against asymptomatic infection equal to 50% of the one observed against symptomatic cases.

Table 2
Characteristics of the scenario considered for vaccine efficacy and interactions between serotypes.

	Scenario CPA
Interaction between serotypes[a]	Temporary cross-protection & cross-enhancement
Efficacy against symptomatic cases[a]	
Efficacy per serotype	Serotype-specific
Efficacy according to dengue status	Lower for dengue naïve subjects
Efficacy against hospitalizations	Higher efficacy against hospitalized cases
Increase in efficacy with doses	Increase in efficacy with doses for naïve subjects
Annual waning rate for subjects aged 9 years or older	Naïve subjects: 129.2% [90–311] Pre-exposed subjects: 5.5% [2–10]
Vaccine-induced cross-enhancement	Accelerated exposure to secondary infection[b]
Efficacy against asymptomatic infection	50% [0–100] of the efficacy estimated for symptomatic cases

[a] Estimated from data collected during the phase III efficacy trials.
[b] Vaccination plays a role similar to natural infection and exposes naïve subjects to the same level of risk associated with a second dengue infection and pre-exposed to the same level of risk associated to post-second dengue infections.

2.4. Vaccination strategies

The impact of vaccination was simulated at the population level through a comparison of the number of total dengue cases and hospitalized dengue cases expected to occur with and without vaccination over a given period of time (from 5 to 50 years). In accordance with phase III trials [8,9], we considered the tetravalent vaccine administered in a three dose, 0–6–12 month regimen.

Strategies explored included routine vaccination at different ages with a catch-up program corresponding to a mass vaccination campaign at the beginning of the vaccination program targeting people not eligible for routine vaccination. Once initiated, routine vaccination occurs on a daily basis throughout the entire period considered in the analysis. All individuals eligible for a catch-up campaign receive the first dose during the first year of the vaccination program. These campaigns target individuals just too old for routine vaccination, e.g., a catch-up campaign including four age cohorts complementing routine vaccination at age 9 years will target children aged between 9 and 12 years on the day before the initiation of the vaccination program. Except where specifically stated, we used for all vaccination programs, a coverage rate set at 90%, i.e. vaccination each year of 90% of children reaching the age targeted for routine vaccination and, in case of catch-up campaign, vaccination of 90% of individuals who, at the time of vaccine introduction, belonged to the targeted age group for this campaign. For all strategies considered, we assumed no changes in vector control activities once the vaccine is introduced.

2.5. Sensitivity analyses

All impact results presented in this paper are based on multiple simulations. We used 100 Monte Carlo simulations and presented the median values as well as 95% confidence intervals. For each of these simulations we used the posterior distribution of the estimated vaccine efficacy parameters. We also varied the level of transmission intensity in the range observed in each country for

serotype-specific basic reproduction numbers and considered different starting points for the introduction of the vaccine (with a 10 year reference period). Finally, we used a uniform distribution for the relative efficacy against asymptomatic infections (0–100% of the efficacy against ambulatory cases). The impact of vaccination was measured using, for each simulation, the same set of parameters with and without vaccination. Sensitivity analyses also included specific analyses focused on the impact of efficacy against asymptomatic infections, coverage rates, duration of protection and the contribution of indirect protection to vaccination impact. The method used for identifying the specific contribution of indirect protection is detailed in sections S1–3 of supplementary information S1.

3. Results

The main results of the analysis performed on the potential impact of dengue vaccination at the population level are summarized in Figs. 1–5. They are supported by a more extensive set of results presented successively for each of the 10 countries in Supplementary information S2.

3.1. Simulated evolution of dengue incidence in the absence of vaccination

The simulated evolution of dengue incidence is characterized by important year-to-year variations in rates and changes in dominant serotype over time. The results for the Philippines are presented in Fig. 1a and in Supplementary information S2 for all 10 countries. No clear cyclic patterns were visible for the 40-year period considered in the simulations. The simulated incidences were characterized either by frequent changes in annual dengue incidence (e.g. Thailand, Honduras, Philippines) or periods of stable incidence followed or preceded by a period of higher incidence (e.g. Malaysia, Mexico). Whatever the country considered, second and subsequent dengue infections accounted for the majority of infections in those aged 9 years or older (from 75% in Mexico to 95% in Thailand).

3.2. Routine vaccination impact at different ages

We considered the potential impact of routine vaccination programs targeting children or adults aged 5–29 years. The median cumulative reductions obtained for these vaccination programs over a 20-year period in all countries are presented in Fig. 2. All strategies tested resulted in a reduction of the dengue burden. According to country, the largest reductions ranged from 21% (Indonesia) to 29% (Mexico) for all dengue cases, and from 24% (Indonesia) to 31% (Honduras) for dengue hospitalizations. In most countries, the largest reduction in dengue burden was observed at age 9 years, the only exceptions were Honduras, Malaysia (13 years) and Mexico (17 years) for dengue hospitalizations.

3.3. Combination of routine and catch-up vaccination

We compared the potential impact over 10 years of catch-up vaccination campaigns of different magnitudes complementing

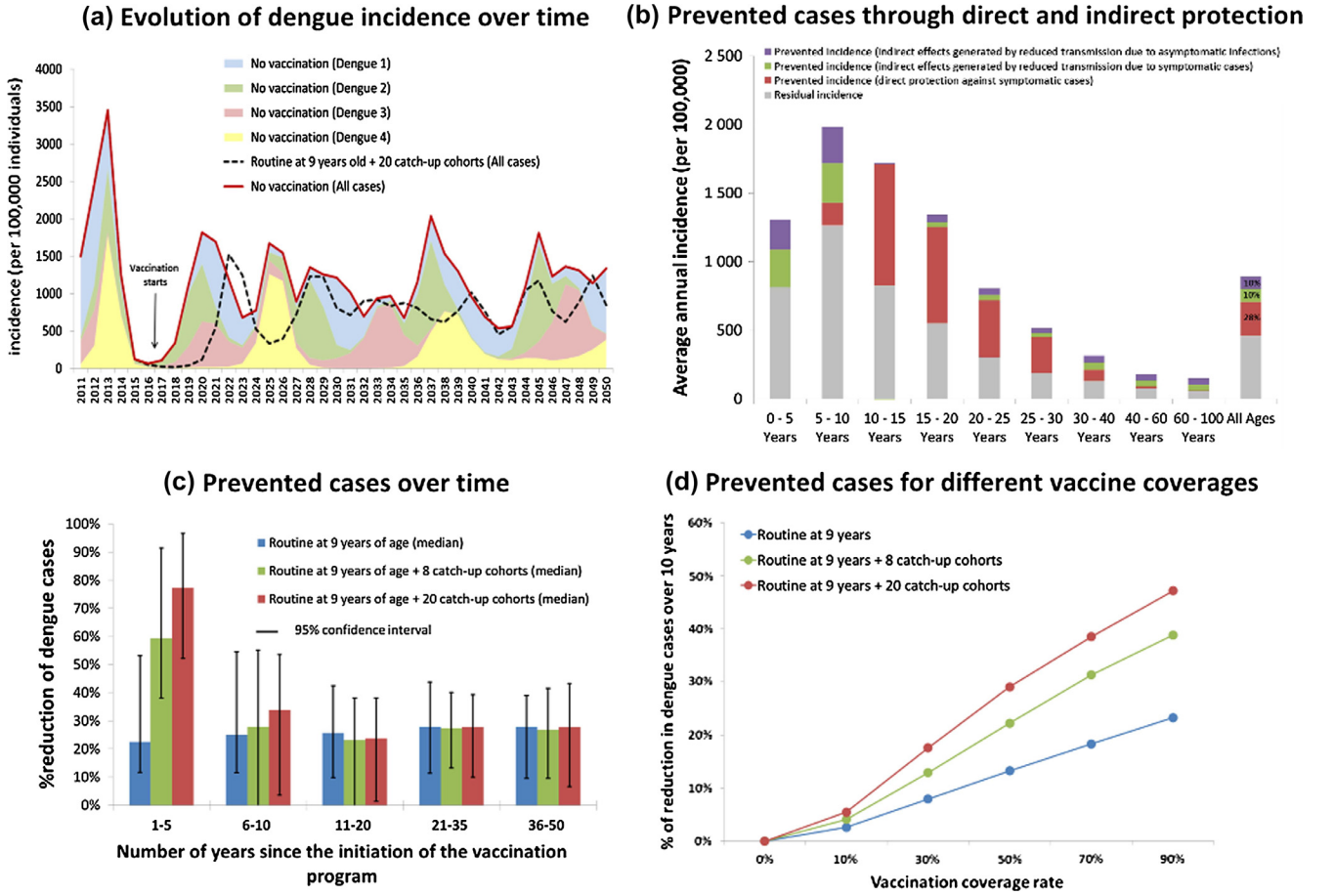

Fig. 1. Selected results for the Philippines. (a) Simulated evolution of dengue incidence in the absence of vaccination and after the implementation of a vaccination program in 2016. (b) Prevented cases through direct and indirect protection over 10 years. (c) Prevented cases at different periods after the implementation of a vaccination program. (d) Prevented cases over 10 years for different vaccinations programs over 10 years. Vaccination program considered in (a) and (b) includes routine vaccination at age 9 years and 20 catch-up cohorts (Vaccination coverage: 90%).

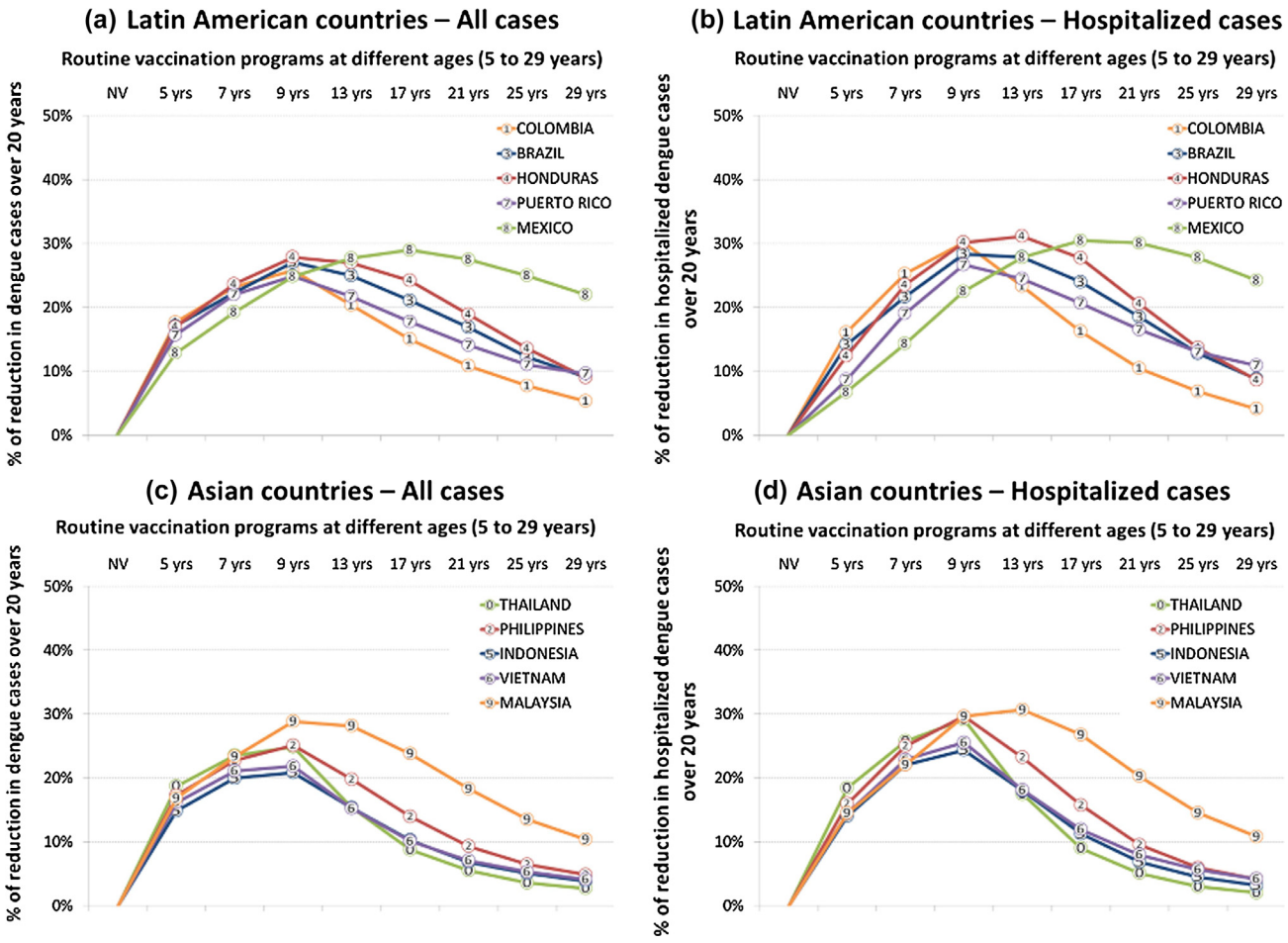

Fig. 2. Cumulative reduction of dengue cases and dengue hospitalizations over 20 years in the population for routine vaccination programs only implemented at different ages (R2: routine at age 2 years, NV: no vaccination) for Latin American countries (a and b), and Asian countries (c and d). Vaccination coverage: 90%, median reduction derived from the results of the probabilistic sensitivity analysis. Number associated with each country corresponds to their endemicity rank (see Table 1).

routine vaccination at age 9 years (Fig. 3). For all countries considered, broader catch-up campaigns were always associated with larger reductions in dengue cases and hospitalizations. For a program including 20 catch-up cohorts, the reductions in hospitalizations ranged from 45% (Thailand) to 68% (Honduras).

The number of dengue cases prevented by vaccine dose administered indicates that catch-up campaigns of adequate size are likely to improve the efficiency of the program. In most cases, this indicator peaks for programs including four to eight catch-up cohorts (Fig. 3). The more complete analysis that can be found in Supplementary information S2, nevertheless, indicates moderate changes in the number of cases prevented per vaccine dose across strategies (the range of variation of this indicator never exceeded 20%).

Contrary to routine vaccination, the largest reductions in dengue cases and hospitalizations with catch-up vaccination were observed for countries with the lowest transmission intensity (e.g. Malaysia in Asia; Mexico and Puerto Rico in Latin America). Moving from 16 to 20 cohorts was still associated with significant reductions in Malaysia (e.g. from 62% to 68% for hospitalizations) whereas the additional gain was more limited in Thailand (43–45%).

3.4. Vaccination impact on hospitalization

Results reported in Fig. 3b highlight that whatever the country and scenario considered, the reduction of hospitalized cases was always slightly larger than the reduction against all dengue cases (median percentage of reduction 1–4 points higher over a 10 year timescale).

3.5. Impact of routine and catch-up vaccination over time

The implementation of a vaccination program does not stop the year-to-year variations in dengue incidence but rather limits the frequency and intensity of these variations. In the example shown in Fig. 1a, once the vaccination is introduced the annual incidence goes above 1.5% for only 3 years between 2016 and 2050 versus 9 years in the absence of vaccination. Similarly, the highest annual dengue incidence after the implementation of the vaccination program was lower than that with no vaccination (1.5% versus 2.0%, respectively).

The impact of routine vaccination increased initially but plateaued thereafter. For example, in the Philippines (Fig. 1c), the reduction in dengue cases with routine vaccination reached 22%, 25% and 26%, respectively, during the first 5 years, 6–10 years and 11–20 years after vaccine introduction. Compared to routine vaccination only, the additional benefits generated by the catch-up campaigns occur mainly during the first 10 years and more specifically the first 5 years (77% reduction of dengue cases during the first 5 years for the largest program considered in Fig. 1c). The results presented in Supplementary information S2 show similar trends whatever the country. The median levels of reduction over 5 years for a program including routine and 20 catch-up cohorts range from 51% in Indonesia to 81% in Mexico.

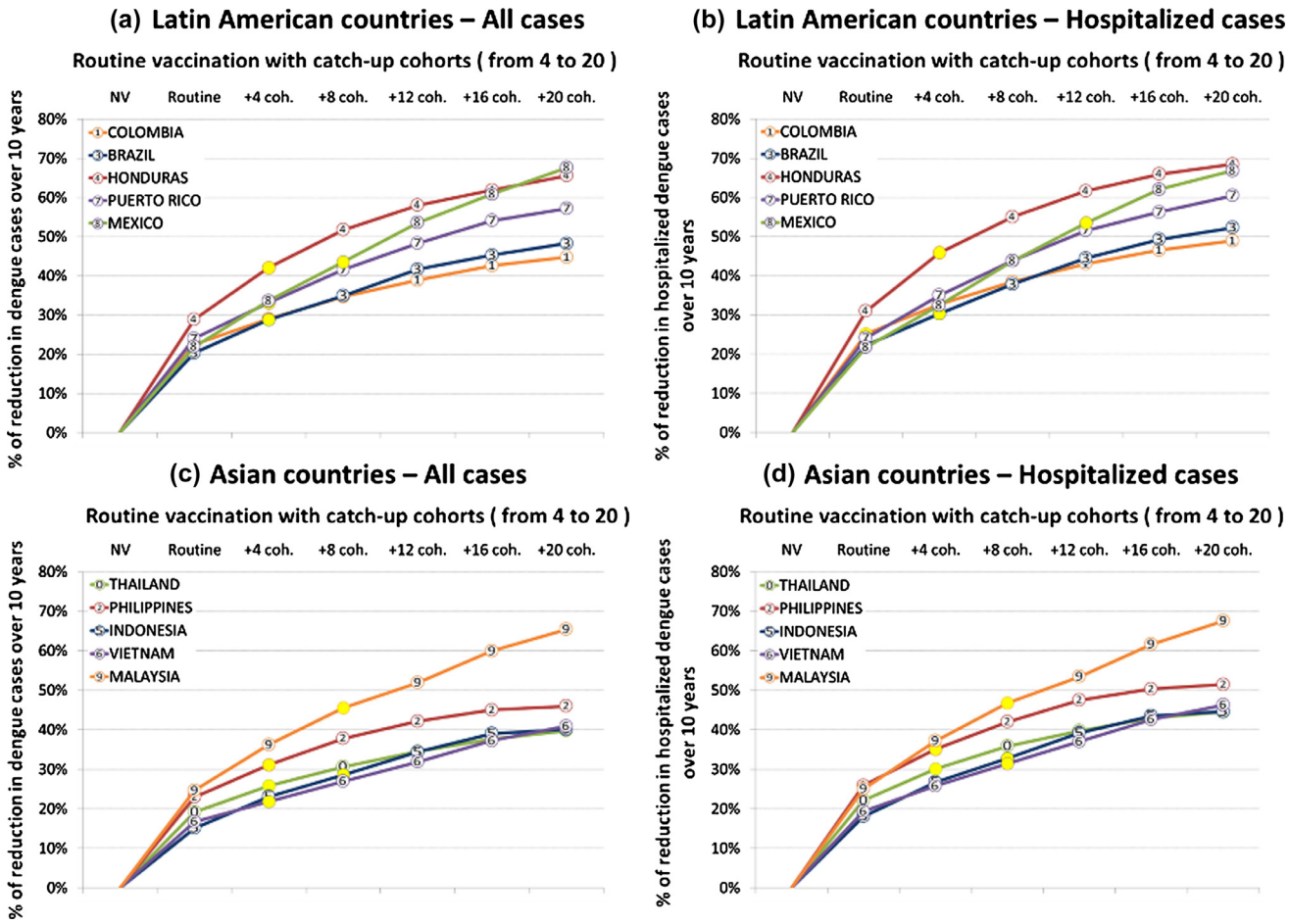

Fig. 3. Cumulative reduction of dengue cases and dengue hospitalizations over 10 years in the population according to the routine vaccination program with catch-up cohorts implemented (R9: routine at age 9 years, +4C: routine at age 9 years with 4 catch-up cohorts [9–12 years old], NV: no vaccination) for Latin American countries (a and b), and for Asian countries (c and d). Vaccination coverage: 90%, median reduction derived from the results of the probabilistic sensitivity analysis. Number associated with each country corresponds to their endemicity rank (see Table 1) and yellow circle to the strategy associated with the largest number of cases prevented per vaccine dose administered.

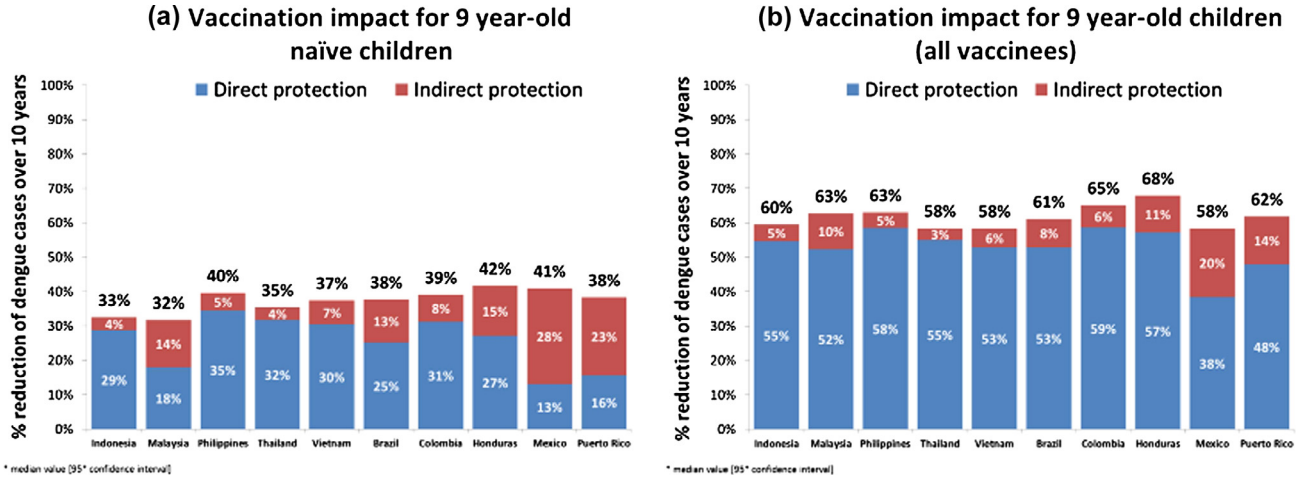

Fig. 4. Vaccination impact over 10 years for the first cohort of 9-year-old children receiving vaccination. (a) Children vaccinated when seronegative. (b) All vaccinated children. The vaccination program considered is a routine vaccination program at age 9 years combined with a catch-up campaign for those aged 10–17 years (8 catch-up cohorts). Vaccination coverage: 90%.

3.6. Coverage rates

The impact of broader vaccination coverage is illustrated for the Philippines in Fig. 1d. Higher coverage leads systematically to better impact, irrespective of the vaccination strategy (routine vaccination alone or in combination with a catch-up program including eight or 20 age cohorts). Conversely, Fig. 1d highlights that the additional benefit of a catch-up campaign can only be observed with sufficient coverage rates. The reduction in dengue cases associated with a program including routine and 20 catch-

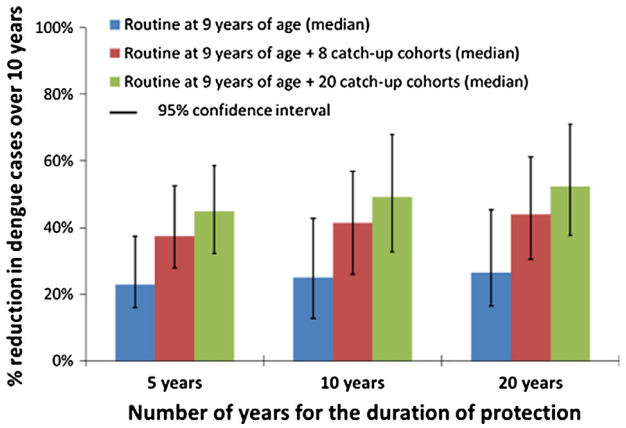

Fig. 5. Cumulative reduction of dengue cases over 10 years in the Philippines population for a routine vaccination program alone or in combination with 8 or 20 catch-up cohorts according to the duration of protection (same duration for all vaccinated subjects). Vaccination coverage: 90%.

up cohorts, and a coverage rate of 30%, was for instance lower than routine only with a 90% coverage rate (18% and 23%, respectively).

3.7. Indirect protection

The roles of direct and indirect protection can be shown by simulating the evolution of dengue taking into account or not the reduced transmission generated by a vaccination program. The results for the Philippines over 10 years for a program including routine vaccination at age 9 years and 20 catch-up cohorts are presented in Fig. 1b. For this scenario, the majority of the reduction was driven by direct protection (28% for direct protection versus 20% for indirect protection). However, the relative contributions of direct and indirect protection were variable. Results reported in Supplementary information S2 for all 10 countries indicate that, for the same vaccination program as in Fig. 1b, 37–68% of the overall reduction of dengue cases with vaccination was related to indirect protection. The importance of indirect protection is that it benefits the entire population (for instance in Fig. 1b, the 38% reduction of dengue cases for children younger than age 5 years was entirely driven by indirect protection). The benefits of direct protection are substantial but limited to the population targeted for vaccination (55% for 10–20-year-old vaccinated adolescents in Fig. 1b).

3.8. Vaccination benefits for naïve subjects

The vaccination benefits over 10 years for 9-year-old children vaccinated before any dengue infection is presented Fig. 4a. In all countries for these children, vaccination translated into a reduction of dengue cases despite the lower protection conferred by vaccination and the potential of accelerated exposure to a second dengue infection. This reduction, which results from a combination of direct and indirect protection, ranges from 32% for Malaysia to 42% in Honduras. As expected the reduction was larger for all children vaccinated at age 9 years, i.e. seronegative and seropositive children. The results presented in Fig. 4b indicate reductions in dengue cases ranging from 58% to 68%.

3.9. Duration of vaccine protection

To assess the specific impact of different durations of vaccine protection, we explored vaccination impact over 10 years for specific values of the average duration of vaccine protection, ranging 5–20 years (Fig. 5). For this analysis, we did not make any distinction between the duration of protection for naïve and pre-exposed subjects.

Overall, vaccination impact increases with the duration of protection, but remains significant even for a short duration of protection. For instance, the median cumulative reduction in dengue cases over 10 years for a routine vaccination program at age 9 years is 27% if the average duration of protection was 20 years compared to 23% if the duration was 5 years. For programs including catch-up campaigns, the duration of protection has a slightly more important effect on the level of vaccination impact achieved over 10 years. For instance, for a program including routine and 8 catch-up cohorts, the median reduction was 44% for a 20-year duration of protection and 37% for a 5-year duration (7 point difference between the two scenarios versus 4 points for routine only programs).

4. Discussion

In this paper, we explored the potential impact of various dengue vaccination strategies in 10 endemic countries. All strategies considered translated into significant reductions in dengue cases at the population level. Routine vaccination at age 9 years was shown to generate reductions in dengue cases ranging from 21% to 29% over 20 years. Complementing routine vaccination with a catch-up campaign was also found to significantly improve vaccination impact during the first 10 years following vaccine introduction. For instance, a program including routine vaccination at age 9 years and 8 catch-up cohorts could prevent, on average over the 10 countries considered in our analysis, 46% of the total number of dengue cases in the population over 5 years. Such vaccination program would require the vaccination of about 20% of the population within 5 years. The vaccination impact was also larger when considering specifically the benefits for vaccinated individuals (58–68% over 10 years for 9-year-old children).

The implementation of a vaccination program was not found to stop variation of dengue incidence over time but rather limited the frequency and intensity of these variations. However, the combination of routine vaccination and large catch-up campaigns significantly limited the risk of a high dengue incidence during the first few years following vaccine introduction.

Our analysis also provides insights into the potential value of vaccination at different ages. The most efficient age for vaccination varies with the intensity of transmission. This age increases as the transmission intensity decreases. This finding is a direct consequence of the efficacy profile of the vaccine characterized by a better protection for subjects already exposed to a first dengue infection before their vaccination. Given this profile, it is optimal to vaccinate between the first and the second infection. This “ideal” period for vaccination occurs on average at older ages as the transmission intensity decreases. However, in the 10 countries considered, age 9 years was generally close to the most efficient age at the population level, i.e. it maximizes, in most settings, the number of vaccinations performed between the first and second dengue infection among vaccine recipients. This result fits well with the age range for which the vaccine is intended for use and is in line with the indication recently approved by the authorities of five Asian and Latin American countries (individuals aged 9–45 years living in endemic areas [36]).

Interestingly, no significant drop in vaccination impact over time was observed for routine vaccination even though vaccination tends to reduce the proportion of individuals exposed to dengue at a given age. The 25–30% reduction of dengue cases generated by vaccination in the mid- and long-term was not found to sufficiently alter the disease dynamics for a drop in vaccination impact to occur.

Vaccination was also found to provide a positive impact for 9-year-old children vaccinated before their first dengue infection, i.e. seronegative at baseline and considered dengue-naive. According to country, the reduction of dengue risk ranged from 32% to 42% over 10 years. This reduction is clearly lower than the one observed for the entire vaccinated group (from 60% to 68%) but remains positive. The lower impact for naïve subjects is a consequence of the lower vaccine protection and the mechanism of accelerated exposure considered in scenario CPA. However, this reduces the direct protection but not the potential indirect protection that naïve subjects benefit from as well as anyone else in the population. The consideration of a stronger waning of vaccine protection or a large enhancement in case of a second dengue infection would result in a more negative impact for subjects vaccinated when seronegative for the 10-year period considered here. In addition, the increase in risk, under a scenario of accelerated exposure to secondary infection, is only temporary and disappears for individuals facing at least two infections. In the setting considered here the lifetime probability to face at least two dengue infections is very high (>99%). Therefore, the long-term benefit of vaccination in naïve individuals is expected in any case to remain positive.

Catch-up campaigns are of clear value in all countries to obtain a rapid and significant reduction in dengue cases, but their impact also depends on transmission intensity. The largest reductions were observed in the countries with the lowest transmission intensity such as Mexico or Malaysia. This result is related to the ability of the vaccine to reduce transmission through indirect protection in case of lower transmission intensity. It is also a consequence of the vaccine efficacy profile i.e. increase in the optimal age for vaccination as the transmission intensity decreases. In lower transmission intensity settings, the catch-up campaigns considered (from age 10 years) are more efficient in targeting directly age groups in which the vaccination benefits are the largest.

Additional benefits generated by catch-up campaigns are also visible during the first 5 years following their implementation but not after 10 years. Interestingly, this absence of difference after 10 years compared to routine vaccination only indicates that the additional benefits generated by catch-up campaigns are limited in time but definitely acquired. However, we limited our analysis to routine vaccination programs complemented by catch-up campaigns implemented at the time of vaccine introduction. Additional vaccination programs (e.g. booster vaccination, mass vaccination programs implemented several years after vaccine introduction) are likely to modify the evolution of vaccination impact over time.

It should be noted that, to ease comparisons, we considered the same vaccination programs whatever the country and did not account for all programmatic constraints (e.g. the ability to reach the same vaccination coverage rate for different programs). The differences in the impact of catch-up campaigns according to country, however, highlights the value of adapting catch-up programs to the endemic setting considered. At this level, two additional findings are of interest when performing more comprehensive setting-specific analyses than the one presented here. First, we found that the efficiency of a vaccination program, measured through the number of dengue cases prevented per dose administered, improves for a catch-up program of adequate size. The difference in efficiency remains, however, limited for vaccination programs of different magnitude. Second, the analysis on vaccination coverage rates showed the value of high coverage rates over extensive programs associated with low coverages.

We observed that the percentage reduction generated by a vaccination program is slightly larger for hospitalized dengue than all symptomatic dengue cases. This better impact is a consequence of the higher efficacy of the vaccine against hospitalized dengue. However, the difference in impact remains lower than differences in efficacy observed during phase III trials [8,9]. This stems from a combination of direct protection (higher for hospitalized cases) and indirect protection (similar for hospitalized and non-hospitalized cases).

The contribution of indirect protection in the reduction of dengue burden generated by vaccination varies according to the epidemiologic setting, the vaccination program and the period of time considered, but is always significant. However, when assessing indirect protection, in contrast to other modeling analyses [13–19], we did not assume similar but considered reduced efficacy against asymptomatic compared to symptomatic infections [35]. One interesting aspect of indirect protection is that it provides a way for the entire population to benefit from a vaccination program and not just those eligible for vaccination.

The consideration of indirect protection is critical for an adequate evaluation of population impact of a vaccination program. Its contribution is, however, a subject of particular attention since, contrary to direct protection, its direct assessment is generally performed in post-licensure studies through specific study designs [37]. Such studies are available for a number of vaccine-preventable diseases [38–45] and all conclude on the importance of indirect protection. Even if planned, such studies are not yet available for dengue and we attempted here to make the best use of available evidence.

We presented in the companion paper [20] the results and methods used for estimating model parameters from data collected during the active surveillance phase of CYD-TDV efficacy studies. Here, we revisited the estimation performed to account for data collected during the first year of the long-term safety follow-up. The scenario that best simulated the observed data identified allowed us to better reproduce differences observed among age groups both during the active phase and the long-term follow-up and notably the imbalance observed during the first year of long-term safety surveillance in the 2–5-year-old population. Compared to the scenarios identified in [20], the main difference related to the consideration of an age-specific difference in efficacy not related to the serological status of individuals before vaccination. Such difference have been reported previously [10], with a marked difference in efficacy between seronegative subjects aged 9 years and above (52.5%; CI: 5.9–76.1) and those aged under 9 years (14.4%; CI: −111 to 63.5). The scenario used for the impact results presented here account for three hypothesis proposed by Guy and Jackson [34] to explain the results observed during the first year of the long-term follow-up i.e. stronger waning of vaccine protection for naïve subjects, accelerated exposure to a second dengue infection in case of vaccination and age-specific mechanisms independent of seropositivity.

Even if the model used was able to reproduce data observed during the two efficacy studies, caution should be exercised when extrapolating the conclusions we derived to settings different from those considered here, notably to settings characterized by very low transmission intensity and seropositivity rates in adolescent and adult populations. Such settings are characterized by a lower probability of acquiring two dengue infections which, according to the scenario identified here, impacts the long-term benefits of vaccination for seronegative subjects.

From a broader perspective, the uncertainties inherent to modeling analyses like ours, based on a broad range of information of varying robustness, should not be underestimated [46]. Although we accounted for the two main aspects of interactions between serotypes (cross-protection and cross-enhancement) identified in the literature, we did not consider the whole range of possible representations of dengue dynamics [11]. The vaccine mode of action considered, even if it provides a plausible explanation of observations made during the trial, is also partly based on assumptions not directly supported by observed data. In any case, it will there-

fore be important to revisit the analysis presented here as more information from the long-term safety surveillance or post-licensure studies become available.

Our conclusion that vaccination has the potential to significantly impact dengue burden is, however, consistent with previous analyses on the topic [13–19]. Moreover, some of these conclusions were obtained using representations of dengue dynamics different from those considered in our analysis (e.g. no third and fourth dengue infections [14], agent-based approach [13]).

An additional finding in our analysis was related to age-specific differences in the probability of symptomatic disease upon infection not directly related to the higher symptomaticity of second dengue infections. Such differences were already noted in previous publications [32,33] and proved to be critical for reconciling data collected during the trials with the various age distributions of dengue cases obtained from routine surveillance. We also confirmed a level of under-reporting in routine surveillance systems [28]. However, the objective here was not to precisely assess the level of under-reporting in each country. This has been analyzed in more detail in another publication through the consideration of differences in the level of reporting of ambulatory and hospitalized cases [28].

5. Conclusion

The World Health Organization recommends the use of mathematical models to inform decisions on vaccine introduction [11]. Our analysis contributes to this effort. Routine vaccination from age 9 years was found to have a significant impact on dengue cases across all settings explored. The combination of routine vaccination and catch-up campaigns provide an opportunity for a more rapid reduction in the dengue burden compared with routine vaccination alone. The reduction in the burden of dengue at the population level was obtained for scenarios of vaccine efficacy including the possibility of vaccine-induced cross-enhancement.

Financial disclosure

Funding for this study was provided by Sanofi Pasteur.

Contributors

LC conceived the analysis and performed the analyses with NB. BG contributed to the interpretation of the protection conferred by the vaccine and ML provided data and expertise for the epidemiological data used in the analysis. All authors discussed data analyses and interpretation, helped to draft and critically revise the manuscript, and approved the final version submitted.

Competing interests

The four authors are employees of Sanofi Pasteur.

Acknowledgements

Editorial assistance with the preparation of this manuscript was provided by Simon Lancaster, inScience Communications, Springer Healthcare. Funding for this assistance was provided by Sanofi Pasteur. Many thanks also to our Sanofi Pasteur colleagues Christophe Boissière, Bruno Vanpee-Gautier and Pierre Volta for the development of the dengue modeling (DENMOD) and epidemiological (EPIVIEW) platforms used for generating the results presented in this paper and to the dedicated technical support of Hanna El Fezzazi for the generation of impact results with this platform. We are also very grateful to Jo-Ann West for her management of the preparation of this manuscript. Finally, we would also like to acknowledge the surveillance system managers for kindly providing access to their data.

Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.vaccine.2016.08.050.

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