BACKGROUND PAPER ON DENGUE VACCINES

REVISION TO THE BACKGROUND PAPER
FROM 17 MARCH 2016

PREPARED BY THE SAGE WORKING GROUP ON DENGUE VACCINES AND WHO SECRETARIAT

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1. EXECUTIVE SUMMARY

Dengue is the most frequent mosquito-borne virus diseases, with 30-fold increase in annual reported cases over the past 50 years and continued geographic expansion. Infection with any of the four dengue viruses (serotypes 1-4) may result in clinical manifestations ranging from relatively mild febrile illness to severe dengue manifested by plasma leakage, haemorrhagic tendencies, organ failure, shock, and possibly death. Dengue occurs in epidemics of unpredictable timing and often requires hospitalization, thereby challenging fragile health care systems. Fatality rates are around 0.1% to 1% in hospitalized cases. Patients with a second dengue infection with a different dengue serotype to the first are at increased risk for severe dengue. Thus, dengue vaccines must be tetravalent, protecting against all 4 virus serotypes. This document only refers to the first licensed dengue vaccine CYD-TDV.

CYD-TDV (Dengvaxia®) was licensed in December 2015 and as of writing has now been approved by regulatory authorities in 20 countries in Asia, Latin America, and in Australia. WHO issued its position on the use of CYD-TDV in July 2016, based on recommendations provided by SAGE in April 2016. These recommendations by SAGE were based on a review of the following key observations from two large clinical trials in 10 dengue endemic countries involving over 30,000 participants aged 2 to 16 years:

- Efficacy varied by age, dengue serotype, disease severity, and whether or not individuals had a previous natural dengue infection at vaccination.
- Vaccine efficacy against virologically confirmed dengue, over 25 month period from the first dose of a three dose immunization regimen among 9-16 year-olds was 65.6% and in this age-group severe dengue was reduced by 93% and hospitalizations with dengue by 82%.
- Two or more years after the first dose, an increased risk of hospitalized dengue was seen in the 2-5 year age group, with the largest excess in Year 3 (12-24 months after the last vaccine dose). During the 4+ years of trial follow up after the first dose, there was a non-statistical significant overall excess risk of hospitalized dengue in 2-5 year-olds (Relative risk 1.26, 95%CI: 0.76 to 2.13).
- This increased risk was not observed in those aged 9 years and above.

Because of the higher efficacy of the vaccine against dengue and the absence of an increased risk of hospitalized dengue observed in older compared to younger children, licensure of the vaccine was sought with an indication of 9 years and above. A working hypothesis for the increase in severe dengue during the longer term follow up among the 2-5 year olds was that the vaccine acted like a silent primary infection, priming individuals who had not been exposed to dengue previously (seronegatives) to more serious infections. It was unclear at the time whether the poorer performance of the vaccine in younger age groups compared to those over 9 years of age was attributable to a higher proportion of seroegative individuals, or a specific age effect, or to some combination of age and serostatus. Because blood samples before vaccination were collected from only about 2,000 children in the trials, there were limited data available to evaluate these possible vaccine effects by preceding serostatus. SAGE recognized that an increased risk of severe and hospitalized dengue also in older age groups was a theoretical possibility, but this was not substantiated by the available empiric data at the time.

Mathematical modelling suggested that the public health benefits of vaccination could be maximized if seroprevalence in the age group targeted for vaccination was high. In April 2016, SAGE recommended that countries interested in introducing the vaccine consider the use of the vaccine only in areas with a seroprevalence of ≥70%, but not in those below 50%. Although serosurveys to determine seroprevalence were recognized to be challenging due to cost, logistics, and spatial heterogeneity of dengue transmission, vaccination was proposed as a path forward for countries to reduce the burden of dengue in areas that met the seroprevalence criteria.

SAGE further noted that the evidence of the absence of a safety issue in seronegatives aged 9 and above was based on the limited data set of 10%-20% of the trial population from whom pre-vaccination blood samples were taken, further compounded by the fact that severe dengue is a relative rare event. This important evidence gap was highlighted, as was the need to better describe the benefit-risk ratio of CYD-TDV in seronegative individuals 9 years of age and older.

On 29 November 2017, Sanofi Pasteur announced the results of additional studies they had conducted to better describe the benefit-risk in seronegative individuals. A newly developed NS1 based antibody assay, which was designed to distinguish prior infection from prior vaccination, was applied to serum samples taken 13 months after vaccination (which had been stored for all participants). The assay results, combined with statistical imputation methods, enabled the serostatus of trial participants prior to vaccination to be inferred retrospectively. Though this new method has limitations with respect to sensitivity and specificity, the assays enabled the company to estimate the efficacy and long-term safety of the vaccine by serostatus prior to vaccination.

The new analyses from the long-term safety follow up indicate the following:

CYD-TDV has a differential performance based on serostatus at the time of vaccination

- Overall population level benefit is favourable
- Vaccine efficacy (VE) was high among inferred baseline seropositive participants 9 years of age or older: 76% (95%CI: 63.9, to 84.0), but much lower among baseline seronegative participants: 38.8% (95%CI: –0.9 to 62.9%) in the first 25 months after the first dose of vaccine
- In the approximate 5 year follow-up period after the first dose of vaccine, an overall higher risk of severe dengue and hospitalizations from dengue was observed in vaccinated seronegative trial participants of all ages compared to unvaccinated seronegative trial participants
- For the entire trial population aged 2-16 years, these results were statistically significant: Hazard Ratio (HR) in seronegative subjects aged 2-16 over an observation period of 60-72 months for severe dengue was 2.87 (95%CI: 1.09-7.61; p=0.034)
- The excess risk in those aged 9 to 16 was apparent from year 3 and persisted through the 5 years of follow up time point but, over the whole follow-up period, was not statistically significant
- Clinical manifestations and relative risk of severe dengue were similar in vaccinated seronegative persons compared to unvaccinated seropositive persons, consistent with the working hypothesis that CYD-TDV mimics a primary-like infection

Following the release of the new findings, Sanofi Pasteur has stated its intention to change the label so that individuals who have not been previously infected by dengue virus (those who are seronegative) should not be vaccinated. WHO`s Global Advisory Committee on Vaccine Safety (GACVS) and the WHO Secretariat published interim statements on December 7, 2007 (1), and December 22, 2017 (2), respectively. WHO`s interim recommendation posted on 22 December 2017 was to vaccinate seropositive individuals only.

It is important to understand the extent of risk at a population level. Based on the incidence in the epidemiological settings of the trials, for those aged 9 years and above, the new analysis indicates that the risk of severe dengue over 5 years stratified by serostatus was as follows:

- In those seropositive prior to vaccination, the incidence of severe dengue was 1.0 per 1,000 in those vaccinated and 4.8 per 1,000 in those not vaccinated (benefit).
- In those seronegative prior to vaccination, the incidence of severe dengue was 4.0 per 1,000 in those vaccinated and 1.7 per 1,000 in those not vaccinated (harm)

Overall, in the trial populations, the number of severe cases prevented in those who were seropositive was substantially greater than the excess number induced in seronegatives. The extent of the population benefit depends on the dengue seroprevalence and the annual dengue incidence in any given setting:

- In areas of 70% dengue seroprevalence, over a 5 year follow up, based on the epidemiological settings of the trials, every 1 excess case of hospitalized dengue in vaccinated seronegatives would be offset by 7 hospitalized cases prevented in vaccinated seropositives, and 1 excess severe dengue in vaccinated seronegatives by 4 severe cases prevented in vaccinated seropositives.

- In areas of 85% dengue seroprevalence, the overall benefit would be predicted to be higher. Every 1 excess case within a 5- year period of hospitalized dengue in vaccinated seronegatives would be offset by 18 cases prevented in vaccinated seropositive persons, and 1 excess severe dengue in vaccinated seronegatives by 10 prevented severe cases in vaccinated seropositives.

Taking into consideration the now demonstrated evidence of increased risk in vaccinated seronegatives in the licensed age group of 9 years and above, the SAGE Working Group on Dengue Vaccines (WG) was re-established to consider the new evidence and propose revised recommendations for SAGE consideration.

Deliberations of the SAGE Working group on Dengue Vaccines, December 2017-March 2018

The WG came to the overall conclusion that CYD-TDV has a potential public health role, in the absence of currently available alternative solutions to combat the expanding problem of the global dengue burden. The challenge is how best to use CYD-TDV to maximize the public health impact, and minimize harm, and restore public confidence in dengue vaccines. In these deliberations, two main approaches were considered if the vaccine were to be further used in public programs:

(1) Subnational or national mass vaccination strategy based on population seroprevalence criteria, and
(2) Pre-vaccination screening and vaccinating only those testing seropositive.

Population Seroprevalence Criteria:

The rationale for this strategy is that vaccination based on a high seroprevalence criterion would result in a substantially larger number of severe and hospitalized dengue cases prevented in seropositive individuals than the number of excess cases resulting from priming seronegatives through vaccination. In this strategy, first a population survey would be undertaken to identify areas where seroprevalence thresholds are high enough to maximize public impact and minimize harm, followed by implementation of mass vaccination in the eligible area. With currently available data, harm to seronegatives would be minimized by not vaccinating them, but mathematical modelling, based on plausible assumptions on the immunity induced by the vaccine, predicts that the excess cases in seronegative individuals following vaccination will eventually be offset by a reduction in cases among these seronegatives at later time periods, compared to unvaccinated, when they experience their second natural dengue infection (in areas of high transmission where nearly all individuals will be infected with dengue at least twice). The seroprevalence threshold at which this overall benefit to seronegatives accrues depends on the timescale over which cumulative risk and benefit in seronegatives is evaluated. The shorter the time frame, the higher the threshold to accrue overall vaccine benefit. Furthermore, age at which vaccination would be introduced is an important factor. At age 9 years, the seroprevalence required for predicted benefit in seronegative recipients within 10 years is 80%. At age 16 years, the seroprevalence required is 86%. However, it is important to note that, although eventual reductions in the excess risk of severe and hospitalized disease in seronegative vaccinees are predicted by modelling, there are no available data on the risk in seronegative individuals beyond 5-6 years after vaccination against which this prediction can be tested.

Several major challenges of a seroprevalence-based strategy warrant consideration:

(1) To minimize harm in seronegatives, high seroprevalence thresholds of 80% and above in 9-year olds would be required.

(2) Very few locations have seroprevalence > 80% in 9 year olds, and even fewer have locations with seroprevalence >90% in 9 year olds.
(3) The spatiotemporal heterogeneity of dengue transmission combined with the need for high seroprevalence thresholds would necessitate large scale serosurveys to identify suitable areas at micro scale, thus adding complexity and cost to any public vaccination programme.
(4) Given the limited areas with such high seroprevalence rates, national coverage rates would be low and hence the overall public health impact limited.
(5) A technically identifiable subpopulation of seronegative persons would be put at increased risk of severe dengue, at least for a period of time.
(6) Communication around a strategy where a subset of individuals are put risk for the sake of overall population level benefit would be challenging, and may undermine vaccine confidence in general.

Recognizing the hurdles of individual testing, combined with the documented overall population benefit of CYD-TDV in very high transmission settings, the use of CYD-TDV without individual pre-vaccination testing could be considered by countries with subnational areas with very high transmission intensity, as defined by seroprevalence in 9-year olds of 80% and above. It is expected that only a very small proportion of (if any) subnational areas in most endemic countries will meet this criterion. Local, recent, age-stratified seroprevalence studies would have to be used to guide decision-making and introduction at subnational levels. Such programmes would need to take into account the feasibility and cost of seroprevalence studies, public confidence in national vaccination programmes, and perceptions of ethical considerations with regard to population level benefit versus individual level risk. Communication would have to ensure due regard for appropriate and full disclosure of risks of vaccination with regards to unknown serostatus.

Pre-vaccination Screening

With this strategy, only persons with evidence of a past dengue infection would be vaccinated (based on a screening test, or in some cases based on a documented laboratory confirmed dengue infection in the past). This approach would maximize the benefit from the vaccine by targeting seropositives, and minimize the risk associated with vaccinating seronegatives. The pre-test probability of an individual being seropositive will be higher in settings with high endemic transmission and thus a “pre-vaccination screening” strategy would likely be more cost effective in such settings than in areas of lower endemicity. The advantage of the “pre-vaccination screening strategy” over “population seroprevalence criteria” is that this strategy may also be considered in low to moderate transmission settings. Preliminary mathematical modelling shows that the population level coverage rates achieved by the “screen and vaccinate” strategy would be higher than the seroprevalence based strategy. Individuals who only had one past dengue infection (monotypic past infection) will benefit most from CYD-TDV. The likelihood of having had two or more dengue infections increases with age and with the transmission intensity in any given country. Therefore, the optimal age to target for vaccination varies significantly with transmission intensity. With high transmission intensity optimal ages are lower, while with low transmission intensity optimal ages are higher. The age group in which the highest dengue hospitalizations occur in a given area, based on surveillance, would be the modelled optimum age target for vaccination.

Despite the advantages of the “pre-vaccination screening” strategy, major challenges remain:

(1) Screening tests would need to be highly specific to minimize harm in seronegative persons and would need to have high sensitivity to ensure that a high proportion of seropositive persons would benefit
(2) Such tests would preferentially need to be deliverable at point-of-care as rapid diagnostic tests (RDT).

(3) To date, no RDTs have been validated and licensed for the indication of screening for past dengue infection (seropositivity)
(4) Pre-vaccination screening may pose significant hurdles in large-scale vaccination programmes

Therefore, both "Population Seroprevalence Criteria" and "Pre-vaccination screening" are imperfect approaches for achieving high population protection from dengue because they are each programmatically difficult, for different reasons and with different consequences.

Proposed Recommendations

For countries considering vaccination as part of their dengue control program, a "pre-vaccination screening strategy" would be the preferred option, in which only dengue-seropositive persons are vaccinated.

Conventional serological testing for dengue virus IgG (e.g. dengue IgG ELISA) could be used to identify persons who have had previous dengue infections. Sensitivity and specificity of dengue IgG ELISA should be assessed in a local context, and will depend on the prevalence of other flaviviruses, and past use of flavivirus vaccines (such as Japanese encephalitis and yellow fever vaccines).

Currently available rapid diagnostic tests - despite their lower sensitivity and specificity to detect past dengue infection compared with conventional dengue IgG ELISA - could be considered in high transmission settings until better tests are available. In settings with high dengue transmission (high numbers of seropositives), a test with lower specificity might be acceptable.

The pre-test probability of an individual being seropositive will be higher in settings with high transmission. However, a pre-vaccination screening strategy may also be considered in low to moderate transmission settings. In settings with low transmission (high numbers of seronegatives) a test with high specificity is needed.

Given that no assay will be 100% specific, some truly seronegative individuals may be vaccinated due to a false positive test result. Furthermore, although the efficacy against dengue infections in seropositive individuals is high, it is still not complete. Hence, the limitations of CYD-TDV will need to be clearly communicated to populations offered vaccination.

There is a continued need to adhere to other disease preventive measures and to seek prompt medical care in the event of dengue-like symptoms, regardless of whether vaccinated or not. Vaccination should be considered as part of an integrated dengue prevention and control strategy together with well-executed and sustained vector control and the best evidence-based clinical care for all patients with dengue.

Decisions about implementing a "pre-vaccination screening" strategy with the currently available tests will require careful assessment at the country level, including consideration of the sensitivity and specificity of available tests and of local priorities, dengue epidemiology, country-specific dengue hospitalization rates, and affordability of both CYD-TDV and screening tests.

Age

Whether there are age-specific effects, independent of serostatus, is the subject of ongoing research. Currently, the vaccine should be used within the indicated age range, which is typically 9 to 45 years of age. The age to target for vaccination depends on the dengue transmission intensity in a given country, and will be lower in countries with high transmission, and higher in countries with low transmission. The optimal age group to be targeted is the age at which severe dengue disease incidence is highest, and this can be ascertained from national and subnational routine hospital surveillance data.

Schedule

In the absence of data on vaccine efficacy and safety with fewer than three doses, CYD-TDV is recommended as a three dose series given 6 months apart. Should a vaccine dose be delayed for any reason, it is not necessary to restart the course and the next dose in the series should be administered.

Booster

There are currently no data on the use of booster doses. Additional studies to determine the utility of a booster dose and its best timing are under way. Accordingly, there is no current recommendation for a booster dose.

Research priorities

Development of a highly sensitive and specific rapid diagnostic test to determine serostatus, and assessment of simplified immunization schedules and booster needs should be prioritized.

2. INTRODUCTION AND RATIONALE FOR THE SAGE RECOMMENDATIONS IN APRIL 2016

There are several dengue vaccine candidates in development. This document only refers to the first licensed dengue vaccine, CYD-TDV (Dengvaxia®), developed by Sanofi Pasteur.

Dengue is the most extensively spread mosquito-borne virus. In the last 50 years the incidence of dengue reported to WHO has increased 30-fold, with outbreaks of increasing frequency and magnitude, and continuing geographic expansion. Vector control is an important component of a comprehensive dengue control strategy; however, as a single strategy, it has been difficult to demonstrate its effectiveness in reducing the human dengue burden. As such, a vaccine is critical and must protect against the four different dengue viruses (i.e. be tetravalent).

Dengue is caused by any one of four viruses (serotypes 1-4). Infection by one serotype is thought to provide lifelong immunity against that particular serotype, but susceptibility remains to the other 3 and hence a person can be infected by up to four serotypes during his or her lifetime. After infection with one serotype, cross-immunity provides temporary partial protection against the other serotypes. There is a small risk of severe disease after any dengue infection, but the second infection by a different serotype to the first is associated with the highest risk of severe dengue, while the third and fourth infections are usually associated with a milder clinical course. Fatality rates are around 0.1% to 1% in hospitalized cases. Dengue often requires hospitalization, thereby challenging already fragile health care systems.

The first dengue vaccine, CYD-TDV (Dengvaxia®) has now been licensed by 20 dengue-endemic countries in Asia, Latin America and Australia, typically for use in persons aged 9-45 years, (exceptions are: Singapore (12-45 year-olds), Indonesia (9-16 year-olds) and Paraguay (9-60 year-olds). The first public program was launched in the Philippines in April 2016 with the aim to vaccinate almost 750,000 students from 6,000 public schools, in three highly dengue-endemic regions in the Philippines. A community-based dengue vaccination program began in June 2017, in a fourth region in the Philippines, Cebu, with the aim to vaccinate almost 450,000 children and adolescents. The Paraná State in Brazil has also launched the first public dengue immunization program in the Americas, targeting vaccination of 500,000 of the state's residents in 2016. In addition, people living in Brazil, Mexico, El Salvador, the Philippines, Costa Rica, Indonesia, Peru, Paraguay, Guatemala, Thailand and Singapore can also access CYD-TDV through the private market. Various countries have licensed the vaccine, but not launched it (Argentina, Australia, Bolivia, Cambodia, Honduras, Malaysia, Myanmar, Venezuela).

Licensure of CYD-TDV was based on two parallel Phase 3 clinical trials, known as CYD14 and CYD15 (3, 4). CYD14 was conducted in 5 countries in Asia (Indonesia, Malaysia, Philippines, Thailand, and Vietnam), with 10,275 participants aged 2-14 years at first vaccination. CYD15 was conducted in 5 countries in Latin America (Brazil, Colombia, Honduras, Mexico, and Puerto Rico (US)), with 20,869 participants aged 9-16 years at first vaccination. Furthermore, thePhase 2b study in Thailand (CYD23/57) provided some longer term follow data(5). In these trials the vaccine was evaluated with a 3-dose schedule with doses given 6 months apart. For more details, refer to the WHO background paper on dengue vaccines published in April 2016:

http://www.who.int/immunization/sage/meetings/2016/april/1_Background_Paper_Dengue_Vaccines_2016_03_17.pdf

Because of lower efficacy among children first vaccinated aged 2-5-year-old age group and the safety signal in this age group (see below), licensing for the vaccine was sought for those aged 9 years or older. Pooled data from CYD14 and CYD15 (post-hoc analysis) showed that in the 25 months following the first dose, among 9-16 year-olds, the vaccine efficacy was 65.6% (95%CI 60.7-69.9) against virologically confirmed dengue illness (VCD) due to any serotype(6). Protection was evident in the six months following the first dose and showed little variation up to one year following the third dose. Vaccine efficacy varied by infecting serotype (higher protection against DENV 3 and 4), age (higher protection in the 9-16 year age group than in the 2-8 year group), and severity (higher protection against hospitalized and severe dengue). In the subset of 10-20% of the trial population who were serotested before the first dose, vaccine efficacy was higher among participants 9 years of age or older who were seropositive at baseline (i.e., had previous exposure to dengue) (81.9%, 95%CI 67.2-90.0), than among participants who were seronegative at baseline (52.5%, 95%CI 5.9-76.1). Serostatus and age were highly correlated in the population studied. The seroprevalence among participants 9 years of age or older was approximately 70-80% in both Phase 3 trials, although there was large variation between countries.

After the first 25 months of follow up, participants were monitored by surveillance that only captured hospitalised cases of dengue. In those aged 5 years or above, substantial protection against hospitalised disease was seen through to the 5th year of follow up (which is ongoing). In those first vaccinated at ages 2-5 years (only included in Asia), an increased risk of hospitalized dengue was seen in vaccine recipients in the third year after the first dose. The increased risk diminished in the 4th and 5th years and, overall, in the whole follow-up period from the first dose, although the risk was elevated compared to controls, the increase was not statistically significant. No other safety signals were identified in any age group. Aggregated across both trials, with over 4 years of follow up, there was evidence that CYD-TDV was substantially protective against hospitalized dengue in those aged older than 5 years at first vaccination. These findings led to the current licensed indication, starting at 9 years of age.

In 2015, WHO convened eight independent modelling groups to model the long-term safety, public health impact, and cost-effectiveness of routine vaccination with CYD-TDV in a range of transmission settings, as characterised by seroprevalence levels among 9-year-olds. The models used assumed that the CYD-TDV vaccine acted akin to a silent natural infection, in priming or boosting immunity, since this hypothesis fitted the trial data well (including the potential safety signal in 2-5 year-olds). Thus, models included the potential risk of seronegative individuals being primed by vaccination, leaving them at higher risk of severe disease when infected with the first wild type dengue virus than they would have been had they not been vaccinated. The mathematical modelling indicated that in high[1] transmission settings, the introduction of CYD-TDV in early adolescence through routine immunization could reduce dengue hospitalizations by 10-30% over the period of 30 years, representing a substantial public health benefit(7). However, the modelling predicted that the vaccine would be less beneficial in low transmission settings and might even increase incidence of hospitalised dengue in very low transmission settings.

[1] For the purposes of this document, transmission settings are defined by average seroprevalence at age 9 years: very low ~10%, low ~30%, moderate ~50%, high ~70%, very high ~80-90%.

In all settings, the vaccine was predicted to have high sustained efficacy in seropositive recipients, but to prime seronegative recipients to be at higher risk of hospitalised dengue disease upon their first breakthrough infection. The population impact of vaccination therefore depended upon the proportion of the age group targeted for vaccination who might be expected to be seropositive – which would be high in high transmission settings, but low in low transmission settings. In addition, long-term outcomes of vaccination in seronegative vaccine recipients were predicted to differ by transmission setting. In high transmission settings[1], nearly everyone experiences at least 2 natural infections at some time, so, in the modelling, the priming effect of vaccination in seronegative recipients can be seen as bringing forward the response to the natural second infection they would have eventually experienced. In low transmission settings, not everyone would be expected to experience a natural second infection, so vaccination of seronegative recipients can lead to an absolute increase in the lifetime risk of hospitalised dengue disease. It is important to note that underpinning these conclusions was the assumption that seronegative vaccine recipients who have experienced one breakthrough natural infection gain the high level of immunity associated with two consecutive natural infections in unvaccinated individuals. This assumption is consistent with the "silent natural infection" hypothesis of CYD-TDV action but cannot currently be conclusively tested with the trial data available. Since, in the modelling, vaccination only transiently reduces the risk of infection and the main effect of vaccination is to modify the risk of disease, the modelling findings predicted that the indirect (herd) effect of vaccination on DENV transmission would be limited(8).

Overall, vaccination was predicted to be potentially cost-effective at a threshold of US $2,000 per DALY saved across all models in moderate- to high-transmission settings, if the costs of vaccinating an individual could be kept well below approximately US$50 (from a provider perspective) or US$100 (from a societal perspective). At a threshold cost per DALY averted of US$2,000, most of the benefit of vaccination in all the models came from averting health care costs rather than DALYs.

The increased risk that vaccination may be ineffective or may even increase the risk for severe dengue in those who are seronegative at the time of first vaccination was considered during the SAGE discussions. However, the available evidence at the time did not show such an increased risk for the licensed age group of 9 years and above, based on the table provided by Sanofi Pasteur, as presented to SAGE on April 14, 2016, available at: http://www.who.int/immunization/sage/meetings/2016/april/2_Smith_Clinical_Trial_Results_SAGE.pdf

Table 1: Number of hospitalized and/or severe virologically confirmed dengue cases by age group and dengue serostatus at baseline. Pooled data from CYD14, CYD15, and CYD57, as presented to SAGE in April 2016.

		Active phase cases/N (%)		Hospital phase- SEP+ cases/N (%)		Cumulative cases/N (%)	
Age group	**Serostatus at baseline**	**CYD group**	**Control group**	**CYD group**	**Control group**	**CYD group**	**Control group**
2-8 years	Seropositive	2/493 (0.4)	8/240 (3.3)	7/476 (1.5)	3/234 (1.3)	9/481 (1.9)	11/236 (4.7)
	Seronegative	2/337 (0.6)	2/178 (1.1)	15/326 (4.6)	3/170 (1.8)	17/330 (5.2)	5/173 (2.9)
9-16 years	Seropositive	0/1605 (0.0)	6/777 (0.8)	7/1508 (0.5)	9/736 (1.2)	7/1546 (0.5)	15/752 (2.0)
	Seronegative	0/398 (0.0)	2/214 (0.9)	7/372 (1.9)	3/197 (1.5)	7/382 (1.8)	4/204 (2.0)

SAGE noted that the evidence on the absence of a safety signal in those aged 9 years and above who were seronegative at vaccination was based on the small immunogenicity data set (about 10% of the trial population for which baseline samples were available to enable stratification by dengue serostatus prior to vaccination). Based on the review of the quality of the body of evidence, using GRADE, a final score of 2 was given (meaning that the evidence supports a limited level of confidence that the true effect lies close to that of the estimate of the effect on the health outcome). It was concluded that while the absence of a safety signal was reassuring, there were insufficient data to determine conclusively an absence of a safety issue in seronegative subjects(9).

Informed by the results shown in Table 1 and by the modelling work, the efficacy results showing higher benefit in seropositives than in seronegatives, the WHO SAGE committee in April 2016 recommended countries consider introduction of CYD-TDV only in national or subnational settings with high endemicity, as defined by seroprevalence of approximately 70% or more in the targeted age group, and recommended against its use in age groups with seroprevalence <50%. In high transmission settings, as defined by seroprevalence above 70%, the population health benefit was estimated to be substantial, and, in the longer term, beyond the follow-up period in the trial, even seronegative vaccine recipients were expected to gain benefit, based on the modelling, for the reasons discussed above.

The possibility that vaccination might be ineffective or might even increase the risk of severe dengue in those who are seronegative (at the time of first vaccination) led to the recommendation that further studies would be needed to address this concern, otherwise it would remain a controversial issue and could compromise public confidence in the vaccine programme. SAGE considered further research into the efficacy and safety of the vaccine in seronegative persons a high priority. Hence, WHO requested that Sanofi Pasteur provide more data on efficacy and safety in seronegative vaccine recipients.

3. STUDY DESIGN TO RETROSPECTIVELY IDENTIFY SEROSTATUS AT BASELINE

Serostatus refers to whether a person has experienced a dengue infection in the past, which is determined by a serological assay. A seronegative individual has not had a previous dengue infection. A seropositive individual has had a previous dengue infection with at least one serotype. A person may not know whether he or she was infected in the past, because many dengue infections are clinically inapparent.

Since only a small subset of participants in the Phase 3 trials had blood samples collected before vaccination, the serostatus of most trial participants was not known (i.e., whether they were seropositive or seronegative at the time of receiving the first vaccine dose). Therefore, there was hitherto very limited statistical power to analyse the efficacy and long-term safety data of CYD-TDV according to serostatus.

3.1 Additional analyses

Sanofi Pasteur utilized a new assay to perform additional serological testing to infer pre-vaccination serostatus based on samples that had been collected from all trial participants at month 13 (M13), one month after the 3rd dose was administered. The assay was based on an NS1 antibody ELISA, developed by the University of Pittsburgh. Participant samples were re-tested using this yet unpublished assay that identifies antibodies against the dengue non-structural protein 1 (NS1). The CYD-TDV encodes yellow fever vaccine non-structural proteins including NS1, rather than those for dengue, and thus the new test was able to distinguish immune responses due to past dengue infection from those due to vaccination.

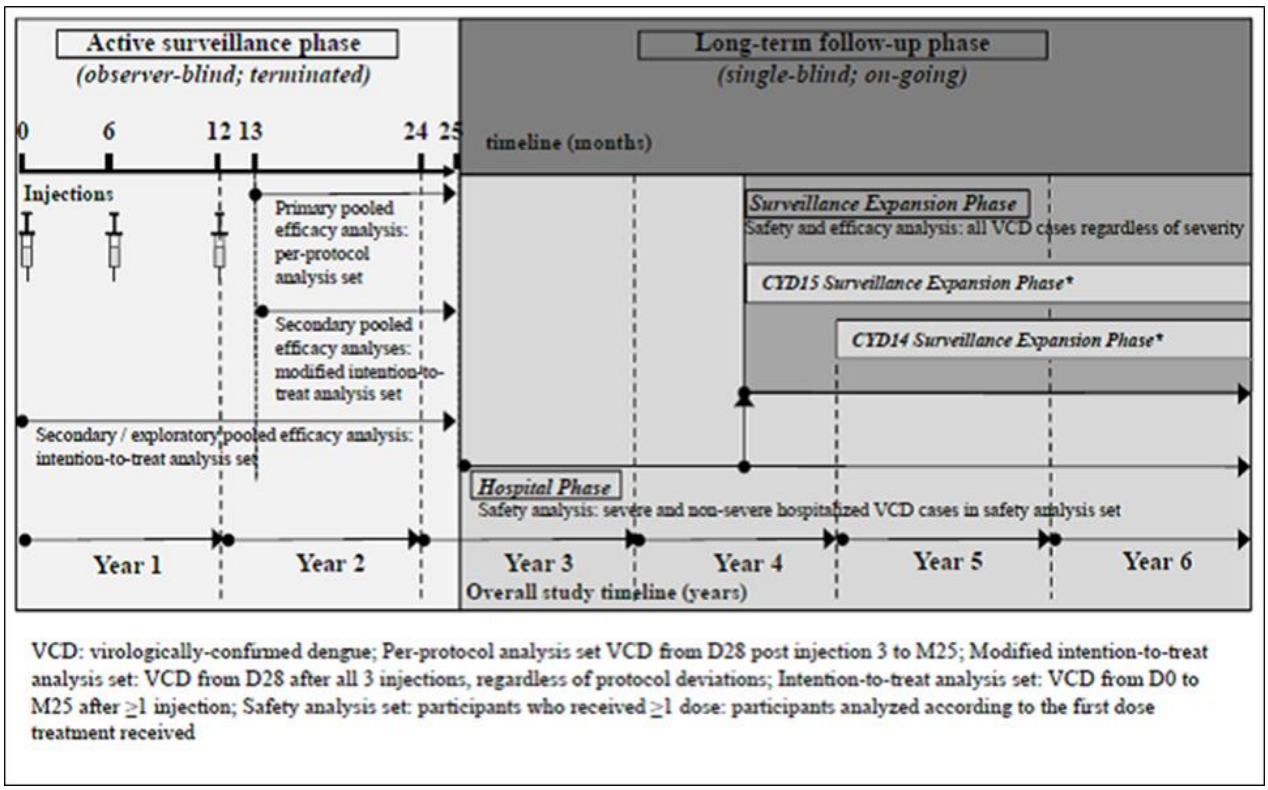


Figure 1. Summary of Phase 3 trial design, including blood sampling at Month 13, and the long-term follow up.

The sensitivity of the NS1 assay (ability to correctly detect "dengue exposed" individuals as seropositive) was estimated to be 95.3%, which means that the false negative rate ("dengue exposed" samples misclassified as seronegative) was 4.7%. The specificity of the assay (ability to correctly identify dengue unexposed individuals as seronegative) subjects was estimated to be 68.6% which means that the false seropositive rate (misclassify "dengue unexposed" samples as seropositive by the assay) was 31.4%. Therefore, among subjects classified as

seropositive by the anti-NS1 assay (Threshold 9), a proportion would be actually seronegative. Thus, it is likely that the efficacy/relative risk estimates obtained for subjects classified as seropositive by the anti-NS1 assay would underestimate benefit to some extent (i.e. disfavour the vaccine), due to the influence of the misclassified seronegative individuals on the estimates. Similarly, those classified as seronegative, would include a small proportion who were truly seropositive.

In addition to the misclassification due to the assay performance, an excess misclassification of about 8% of seronegative subjects as seropositive (anti-NS1 assay threshold of 9 EU/ml) was observed in vaccine recipients compared to placebo recipients due to the impact of CYD vaccination on anti-NS1 titres. To eliminate concerns of biases introduced by the vaccine effect on the dengue anti-NS1 titres and to be consistent with historical assessments based on serostatus, Sanofi Pasteur used PRNT50 to classify serostatus for subjects with pre-vaccination serum samples and used imputation methods to impute baseline PRNT50 titres from M13 anti-NS1 titres and other variables for trial participants for whom baseline PRNT50 measurements had not been made, who constituted the majority of participants. The multiple imputation method is a commonly-used statistical approach to deal with missing data. In addition, a non-parametric statistical method(Targeted Minimal Loss-based Estimator, TMLE) was employed as an alternative to multiple imputation. This approach used machine learning (called "SuperLearner2") to select among a library of candidate algorithms for estimating the probability that a subject has a given baseline serostatus conditional on M13 anti-NS1 titres, M13 PRNT50 titres (if observed), vaccination status, age, and country.The two key advantages of the multiple imputation and TMLE are: first, it overcomes the limitation of potential bias due to vaccine-effect misclassification of serostatus using a threshold of anti-NS1 titres at M13; second, it enables the estimation of vaccine risk and efficacy from the time of vaccination (M0) onwards.

The primary objective of the analyses was to assess the risk of hospitalization for dengue and of severe dengue (based on the classification of cases of dengue by the Independent Data Monitoring Committee) in vaccinated seronegative participants aged ≥9 years at enrolment. Secondary objectives included assessment of the risk of dengue hospitalization and severe dengue for subjects of any age and for those aged <9 years at enrolment, and evaluation of efficacy against symptomatic VCD up to 25 months in subjects ≥9 years, <9 years of age, and any age.Objectives also included the assessment of vaccine efficacy among vaccinated seropositive subjects. Clinical outcome definitions and assessments methods were the same as previously reported (3-5).

A case-cohort study was undertaken to re-analyse all cases of symptomatic virologically-confirmed dengue (VCD) (n=1258), hospitalized VCD (n=644) and severe VCD (n=142) by serostatus from the three efficacy trials (CYD14, CYD15 and CYD23/57). To represent the population in which cases occurred, a sub-cohort of 10% of all participants from each trial was randomly selected after stratifying by age and trial site. All cases of hospitalized VCD and severe VCD over the follow-up period (60-72 months), and all cases of symptomatic VCD in the first 25 months were included in the analyses.

For more detailed explanations on the three methods employed to infer baseline serostatus retrospectively, refer to Appendix 2 (on WHO website).

4. EFFICACY AGAINST VIROLOGICALLY-CONFIRMED DENGUE STRATIFIED BY SEROSTATUS

4.1 CYD-TDV vaccine efficacy in the active follow-up stratified by serostatus and age group

It was originally planned to evaluate vaccine efficacy (VE) against virologically-confirmed dengue (VCD) of any severity only during the first 25 months after the first dose, and active surveillance was put in in place to

detect such cases. In this period there was a total of 1258 cases detected. The per protocol analysis of vaccine efficacy was based on cases arising from one month after the last dose until 12 months later (M13 to M25).

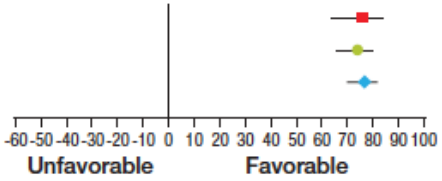
Figure 2 shows vaccine efficacy estimates, measured during the 25 months after the first vaccine dose, against dengue of any severity, using the three different methods of taking account of baseline serostatus. The first row in each age grouping show the estimates based on multiple imputation (MI), the second based on the TMLE method and the third using the NS1 results directly but with efficacy only from month 13 (when blood samples were collected from all participants). The first 2 methods broadly gave very similar finding and results are discussed primarily in relation to the MI method. Using this method, VEs among seropositive participants, were 76% (95%CI: 64;84, p<0.001), 60% (95%CI: 31;76, p=0.002) and 73% (95%CI: 59;82, p<0.001), and for participants aged 9-16 years, 2-8 years, and of any age, respectively.

Figure 3 shows similar estimates for seronegative participants. VEs against symptomatic VCD (up to M25) were 39% (95%CI: −1;63, p=0.05), 19% (95%CI: −47;55, p=0.48), and 32% (95%CI: −9;58, p=0.10) in 9–16-year-olds, 2–8-year-olds and at for all ages, respectively.

a)

Age 9-16 years

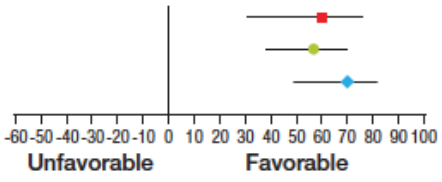
Dengue serostatus	Vaccine group (n/M)	Control group (n/M)	Vaccine efficacy (%)	95% CI	p–value
Seropositive					
Symptomatic VCD MI-M0	192.7/1441.4	372.1/697.3	76	(64, 84)	<0.001
Symptomatic VCD TMLE-M0	175.1/1384.4	317.9/663.7	74	(66, 80)	<0.001
Symptomatic VCD NS1-Th9-M13	111/1389	222/656	77	(70, 82)	<0.001



b)

Age 2-8 years

Dengue serostatus	Vaccine group (n/M)	Control group (n/M)	Vaccine efficacy (%)	95% CI	p–value
Seropositive					
Symptomatic VCD MI-M0	88.5/217.3	104.3/109.5	60	(31, 76)	0.002
Symptomatic VCD TMLE-M0	71.8/211.7	80.8/103.3	57	(38, 70)	<0.001
Symptomatic VCD NS1-Th9-M13	30/209	42/91	70	(49, 82)	<0.001



c)

Age 2-16 years

Dengue serostatus	Vaccine group (n/M)	Control group (n/M)	Vaccine efficacy (%)	95% CI	p–value
Seropositive					
Symptomatic VCD MI-M0	281.2/1658.7	476.4/806.8	73	(59, 82)	<0.001
Symptomatic VCD TMLE-M0	246.9/1596	398.6/767	71	(64, 76)	<0.001
Symptomatic VCD NS1-Th9-M13	141/1598	264/747	75	(69, 80)	<0.001

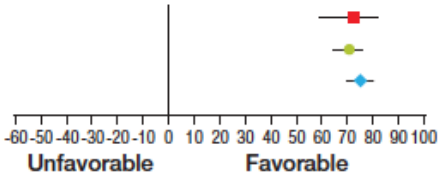
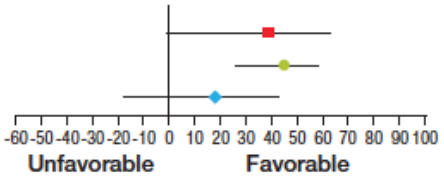


Figure 2. Efficacy against symptomatic VCD up to 25 months after first vaccination in seropositive subjects.

a)

Age 9-16 years

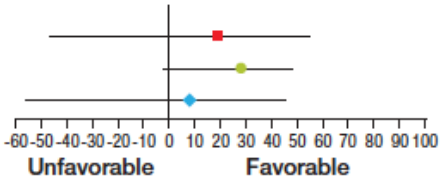
Dengue serostatus	Vaccine group (n/M)	Control group (n/M)	Vaccine efficacy (%)	95% CI	p–value
Seronegative					
Symptomatic VCD MI-M0	174.3/353.6	148.9/193.7	39	(–1, 63)	0.054
Symptomatic VCD TMLE-M0	187.9/338.7	194.1/196	45	(26, 58)	<0.001
Symptomatic VCD NS1-Th9-M13	104/309	62/157	18	(–18, 43)	0.284



b)

Age 2-8 years

Dengue serostatus	Vaccine group (n/M)	Control group (n/M)	Vaccine efficacy (%)	95% CI	p–value
Seronegative					
Symptomatic VCD MI-M0	107.5/141.7	69.7/74.5	19	(–47, 55)	0.484
Symptomatic VCD TMLE-M0	103.2/141.6	76.2/73.4	28	(–2, 48)	0.064
Symptomatic VCD NS1-Th9-M13	49/128	29/73	8	(–56, 46)	0.750



c)

Age 2-16 years

Dengue serostatus	Vaccine group (n/M)	Control group (n/M)	Vaccine efficacy (%)	95% CI	p–value
Seronegative					
Symptomatic VCD MI-M0	261.8/495.3	218.6/268.2	32	(–9, 58)	0.101
Symptomatic VCD TMLE-M0	291.1/480.3	270.4/269.3	40	(25, 52)	<0.001
Symptomatic VCD NS1-Th9-M13	153/437	91/230	15	(–15, 37)	0.292

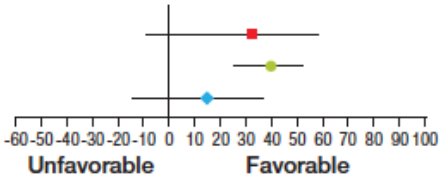


Figure 3. Efficacy against symptomatic VCD up to 25 months after first vaccination in seronegative subjects.

Figures 4 and 5 show efficacy estimates based on the MI method, in finer age strata. In both seropositives and seronegatives efficacy appears to increase with age. Among seronegatives, in no age stratum is the VE estimate formally statistically significant, though it is close to significance in the oldest age group.

Age Strata	CYD		Control		Vaccine Efficacy (95% CI)	P-value
	n	N	n	N		
2-5 years	49.2	119.4	48.1	58.2	0.084 0.53 0.759	0.027
6-8 years	39.3	97.9	56.2	51.3	0.32 0.648 0.818	0.002
9-11 years	107.7	638.5	191.1	311.2	0.585 0.739 0.835	<0.001
12-16 years	85	802.9	181	386.1	0.657 0.783 0.862	<0.001

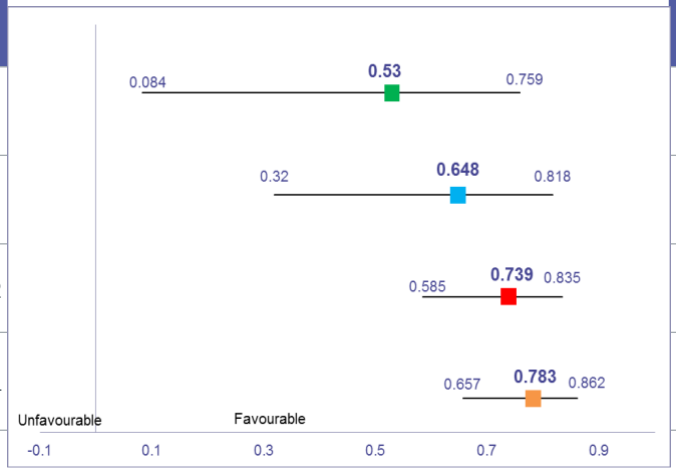


Figure 4. Efficacy against symptomatic VCD in the 25 months after first vaccination in seropositive participants, stratified by age (Multiple Imputation method).

Age Strata	CYD		Control		Vaccine efficacy (95% CI)	P-value
	n	N	n	N		
2-5 years	70.8	96.6	40.9	47.8	-0.688 0.127 0.548	0.682
6-8 years	36.7	45.1	28.8	26.7	-0.782 0.264 0.696	0.49
9-11 years	103.3	181.5	81.9	96.8	-0.208 0.356 0.658	0.161
12-16 years	71	172.1	67	96.9	-0.003 0.432 0.678	0.051

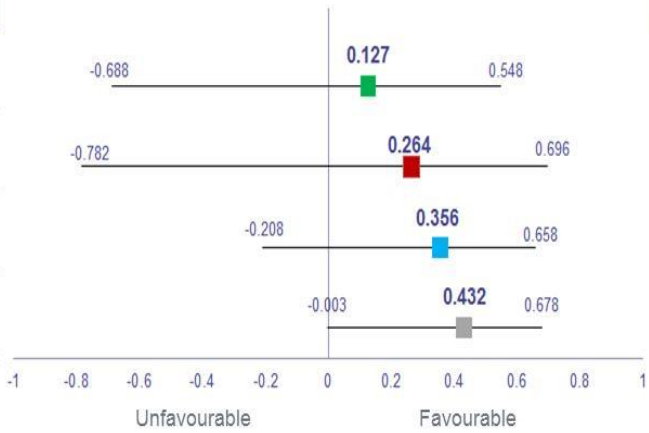


Figure 5. Efficacy against symptomatic VCD in the 25 months after first vaccination in seronegative participants, stratified by age (Multiple Imputation method).

4.2 Duration of efficacy against symptomatic VCD beyond 2 years

Vaccine efficacy against symptomatic VCD of any severity was evaluated in Years 1-2 (active phase). Active surveillance for cases of virologically-confirmed dengue of any severity was reinstituted in year 4 after first vaccination (called the Surveillance Expansion Phase (SEP)) and will continue until the end of 6 years after first vaccination. Thus, there was a gap in active surveillance after the first 2 years and the ability to make inferences about duration of protection against dengue of any severity are therefore limited. Data for cases arising during the SEP period will be available later, likely in Q4 2018. Knowledge on duration protection against VCD beyond 25 months constitutes an important data gap.

5. LONG-TERM SAFETY RESULTS STRATIFIED BY SEROSTATUS

The case-cohort included 644 hospitalized VCD cases, and 142 severe VCD cases, arising during the follow-up time up to 66 months after first vaccination.

5.1 Risk of hospitalized and severe dengue by serostatus

Participants aged 9-16 years

In seropositive participants aged 9-16 years, Hazard Ratios (HRs) were calculated, that is, the ratio of incidence rates in vaccinated and control participants (HRs for hospitalized VCD and severe VCD were 0.21 (95%CI: 0.14;0.31, p<0.001) and 0.16 (95%CI: 0.07;0.37, p<0.001), respectively (Figure 6, MI method). Cumulative incidences of hospitalized VCD and severe VCD through to M60 in vaccine recipients were 0.38% (95%CI: 0.26;0.54) and 0.08% (95%CI: 0.03;0.17), respectively, and 1.88% (95%CI: 1.54;2.31) and 0.48% (95%CI: 0.34;0.69) in controls.

The HRs for hospitalized VCD and severe VCD in seronegative participants were 1.41 (95%CI: 0.74;2.68, p=0.29) and 2.44 (95%CI: 0.47;12.56, p=0.28), respectively. Cumulative incidences of hospitalized VCD and severe VCD through to M60 in vaccine recipients were 1.57% (95%CI: 1.13;2.19) and 0.40% (95%CI:0.22; 0.75) in vaccine recipients, respectively, and 1.09% (95%CI: 0.53;2.27) and 0.17% (95%CI: 0.04;0.83) in controls.

Participants aged 2-8 years

In seropositive participants aged 2-8 years, the HRs for hospitalized VCD and severe VCD were 0.50 (95%CI: 0.33;0.77, p=0.002) and 0.58 (95%CI: 0.26;1.30, p=0.183), respectively.

The HRs for hospitalized VCD and severe VCD in seronegative participants aged 2-8 were 1.95 (95%CI: 1.19;3.19, p=0.008) and 3.31 (95%CI: 0.87;12.54, p=0.077), respectively.

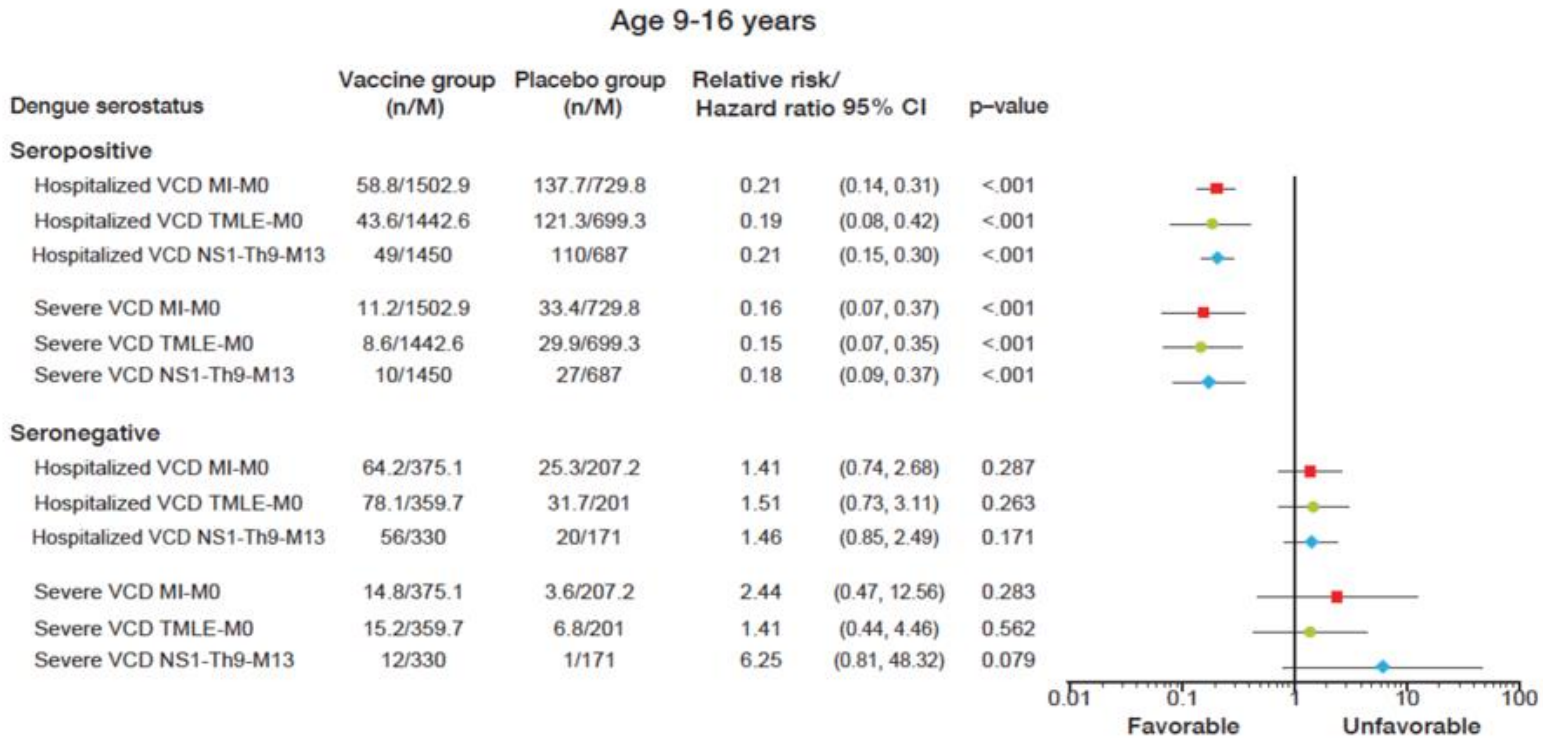


Figure 6. Risk of hospitalized and severe VCD by serostatus in trial participants aged 9–16 years, M0-M66.

a)

Age 2-8 years

Dengue serostatus	Vaccine group (n/M)	Control group (n/M)	Relative risk/ Hazard ratio	95% CI	p–value
Seropositive					
Hospitalized VCD MI-M0	93.6/313.2	89.8/156.4	0.50	(0.33, 0.77)	0.002
Hospitalized VCD TMLE-M0	55.6/299.7	78.2/147.4	0.35	(0.10, 1.22)	0.098
Hospitalized VCD NS1-Th9-M13	75/300	65/135	0.53	(0.36, 0.77)	0.001
Severe VCD MI-M0	23.9/313.2	20/156.4	0.58	(0.26, 1.30)	0.183
Severe VCD TMLE-M0	19.6/299.7	20.0/147.4	0.45	(0.19, 1.04)	0.062
Severe VCD NS1-Th9-M13	21/300	17/135	0.56	(0.29, 1.08)	0.083
Seronegative					
Hospitalized VCD MI-M0	137.4/192.8	37.2/100.6	1.95	(1.19, 3.19)	0.008
Hospitalized VCD TMLE-M0	165.9/187.4	33.8/95.9	2.48	(0.64, 9.54)	0.188
Hospitalized VCD NS1-Th9-M13	131/182	33/101	2.24	(1.43, 3.50)	<0.001
Severe VCD MI-M0	30.1/192.8	5/100.6	3.31	(0.87, 12.54)	0.077
Severe VCD TMLE-M0	29.4/187.4	3.2/95.9	4.31	(0.80, 23.15)	0.089
Severe VCD NS1-Th9-M13	25/182	4/101	3.43	(1.17, 10.09)	0.025

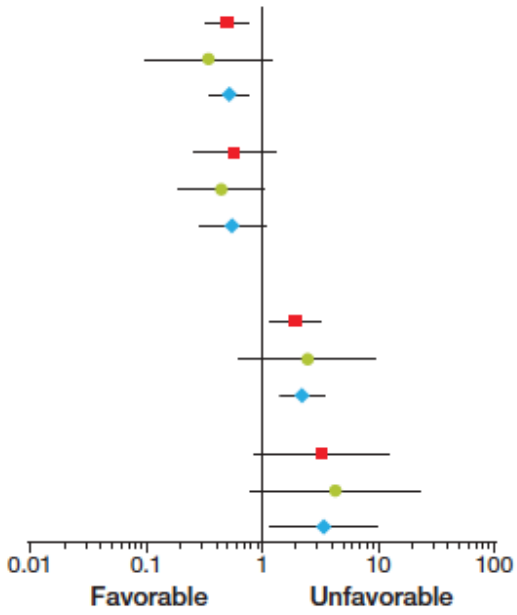


Figure 7. Risk of hospitalized and severe VCD by serostatus in trial participants aged 2-8 years, M0-M66.

Figure 8 shows the estimates for hospitalised dengue among seronegative participants in finer age strata.

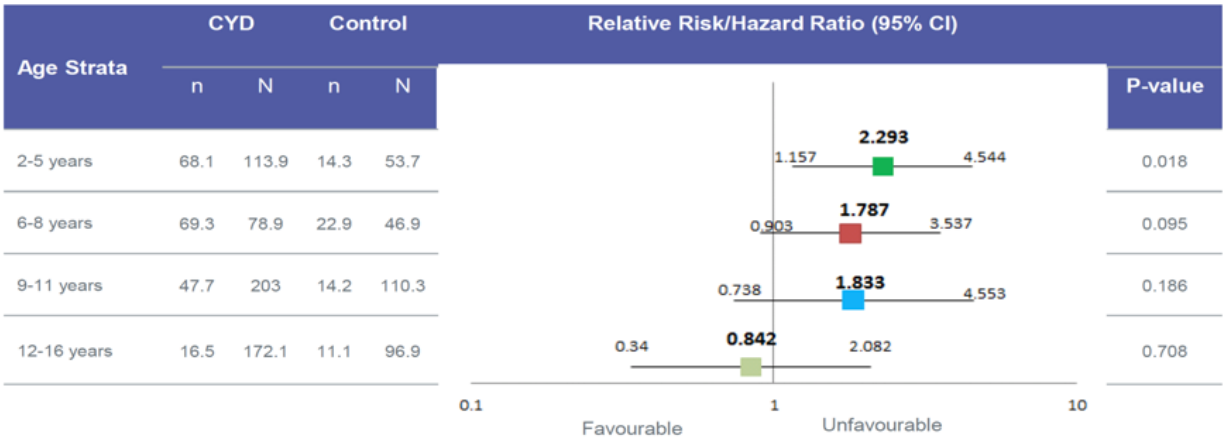


Figure 8. Risk of hospitalized VCD in seronegative participants in CYD14, CYD15, and CYD57 by age-strata by Multiple Imputation (M0 onwards).

5.2 Cumulative incidence of hospitalized VCD by time since first dose (0-66 months after first dose)

Figure 9 shows the cumulative risk of hospitalized dengue by time since the first dose, in different age groups and for seronegative and seropositive participants, according to vaccination status.

In seropositive participants, the cumulative risk of hospitalized VCD over 60 months was lower among vaccine recipients than controls throughout the observation period of 60 months in all age groups.

In seronegative participants, there was an excess risk of hospitalized VCD in vaccine recipients compared to controls from M30 in 9–16-year-olds, and from M18 in 2–8-year-olds. In seronegative participants aged 9-16 years, the cumulative risk of hospitalized VCD was similar to that in seropositive unvaccinated participants. In seronegative participants aged 2-8 years, the cumulative risk of hospitalized VCD approached that for seropositive unvaccinated subjects over the follow-up period.

5.3 Hazard Ratio (HR) by year after first vaccination, in seronegative trial participants

Based on multiple imputation methods, HRs of hospitalized VCD per year of study were calculated, for the active follow-up phase (first two years), Year 1 and 2 of hospitalization phase, and >Year 2 of hospitalization phase for participants aged 9-16 years (Figure 10) and aged 2-8 years (Figure 11). The HR of hospitalized VCD in seronegative subjects was highest in Year 3 after first vaccination, eg in the first year of the hospital phase.

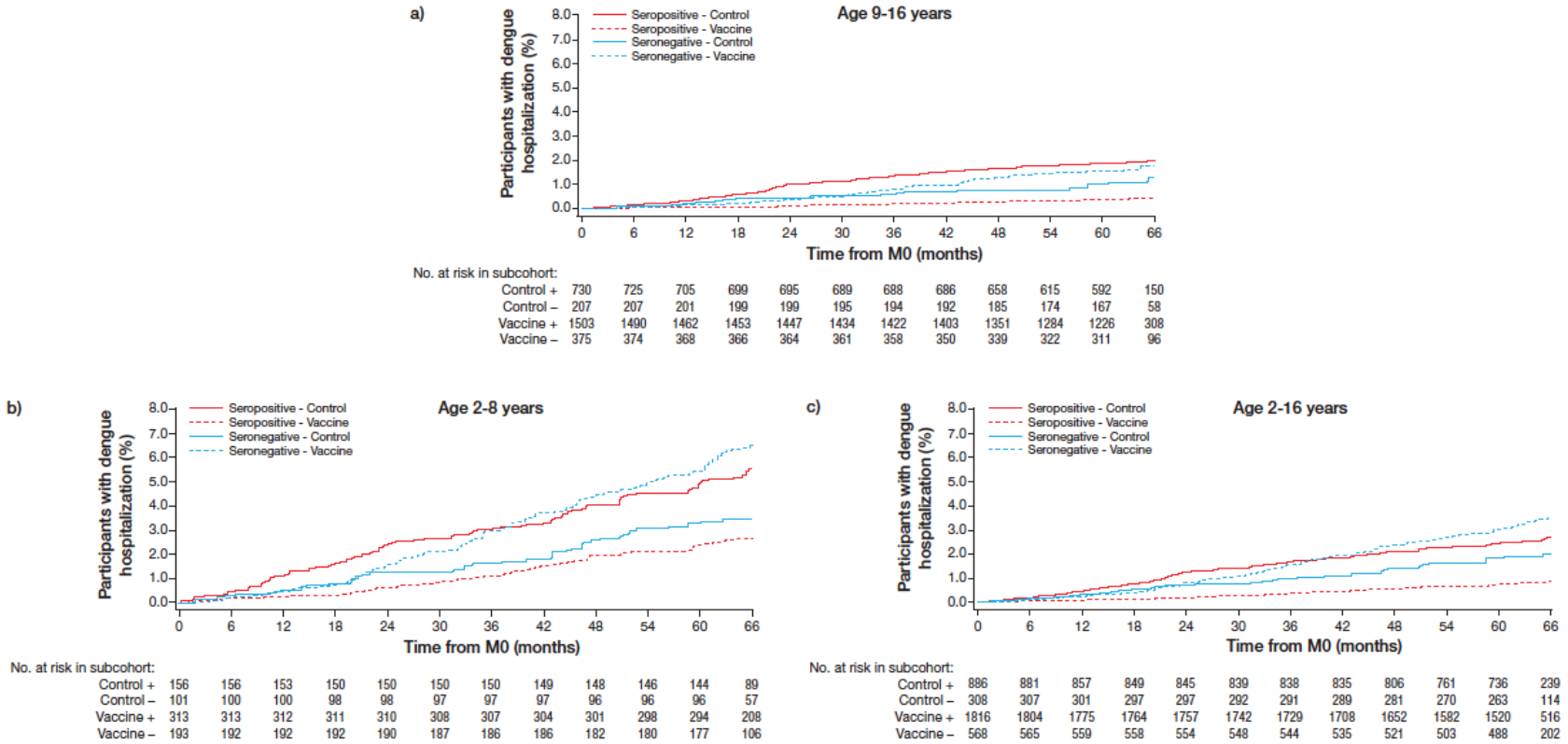


Figure 9. Cumulative incidence of dengue hospitalizations from M0 by baseline serostatus (MI method) and vaccination status, in participants aged 9-16 years (a), 2-8 years (b) and 2-16 years (c). Data represents pooled analysis of CYD14, CYD15 and CYD23/57 trials. The cumulative incidence curves are curtailed at M66 to ensure at least 20% of subjects remaining at risk in each sub-cohort.

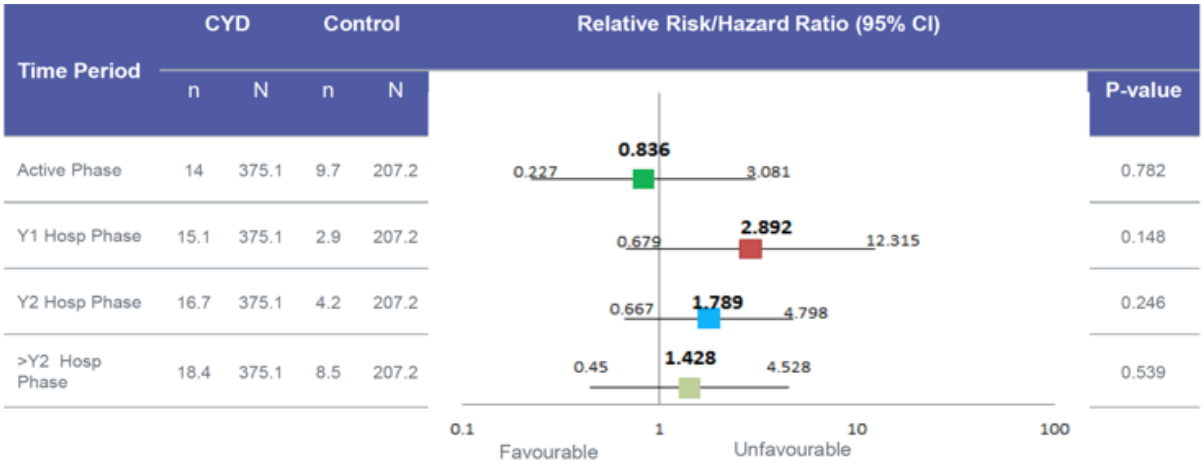


Figure 10. Hospitalized VCD in seronegative participants in CYD14, CYD15, and CYD57, age 9-16 years, by year of study by multiple imputation (M0 onwards).

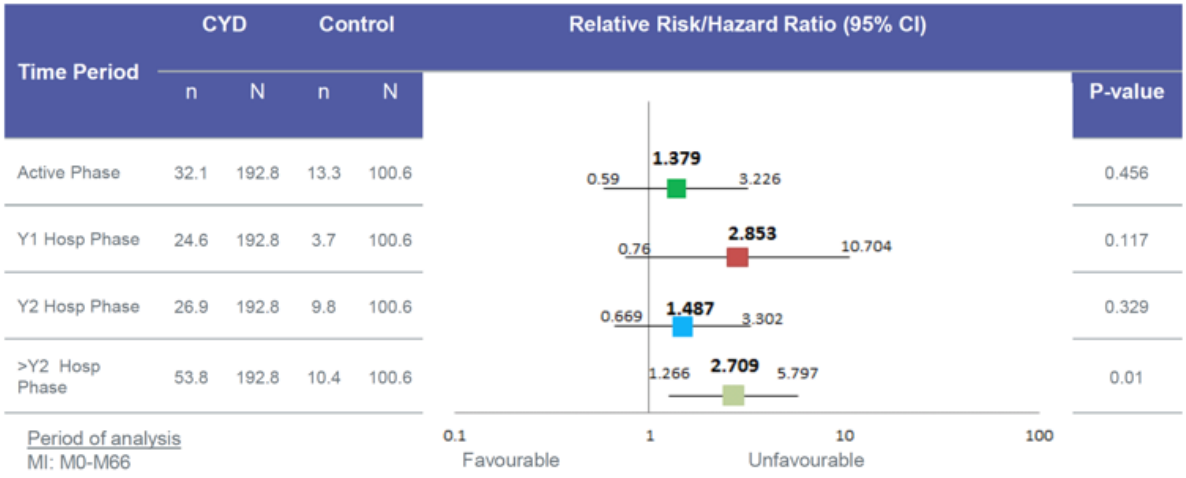


Figure 11. Hospitalized VCD in seronegative participantsin CYD14, CYD15, and CYD57, age 2-8 years, by year of study by Multiple Imputation (M0 onwards).

5.4 Attributable risk (AR) and cumulative incidence estimates

The AR is calculated as the difference in the cumulative incidence rates of hospitalised dengue in vaccinated and control participants. Over five-years of follow-up, the AR for seronegative vaccine recipients 9-16Y of age was 4.78 (95%CI: −13.99, 24) for hospitalized VCD and 2.30 (95%CI: −7.0,10.67) for severe VCD per 1,000 subjects. The corresponding ARs for seropositive vaccinees were −15.08 (95%CI: −25.44,−4.97) and −4.05 (95%CI: −9.59,0.63) per 1,000 subjects, respectively. In other words, based on the average seroprevalence and annual incidence as observed in the trial settings, during the 5-year follow-up after vaccination, there was a reduction of about 15 cases of hospitalized dengue and 4 cases of severe dengue per 1,000 seropositive persons 9-16Y of age vaccinated.

For 1,000 seronegative persons 9-16Y of age vaccinated, there was an increase of about 5 cases of hospitalized dengue and 2 cases of severe dengue.

Table 2. Attributable risk and cumulative incidence estimates in subjects aged 9–16 years according to baseline serostatus (Multiple Imputation Methods)

Endpoint	Incidence in non-vaccinated (per 1,000)	95% CI	Incidence in vaccinated (per 1,000)	95% CI	Attributable risk (per 1,000)	95% CI
Seropositive at baseline						
Dengue Hospitalization	18.83	(15.36,23.07)	3.75	(2.63,5.35)	-15.08	(-25.44,-4.97)
Severe Dengue	4.80	(3.35, 6.88)	0.75	(0.34, 1.65)	-4.05	(-9.59, 0.63)
Seronegative at baseline						
Dengue Hospitalization	10.93	(5.26, 22.65)	15.71	(11.25, 21.93)	4.78	(-13.99, 24.00)
Severe Dengue	1.74	(0.36, 8.34)	4.04	(2.18,7.49)	2.30	(-7.00, 10.67)

Data pooled from the CYD14, CYD15 and CYD23/57 studies. Subjects are categorized as seropositive or seronegative by Multiple Imputation approach (M0 onwards to M60).

5.5 Absolute risk of hospitalized VCD and severe VCD by serostatus and vaccination status

The risk depends on the yearly incidence of dengue. Based on the incidence in the epidemiological settings of the trials, for persons aged 9 years and above, the new analysis indicates that the 5-year risk of severe dengue in vaccinated seronegative persons (4 per 1,000 seronegative persons vaccinated) approaches the risk of severe dengue in unvaccinated seropositive subjects (4.8 per 1,000 seropositive persons unvaccinated). The risk of severe dengue is lower in unvaccinated seronegative persons (1.7 per 1,000 unvaccinated seronegative subjects). The risk of severe dengue in vaccinated seropositive participants is the lowest (less than 1 per 1,000 vaccinated seropositive subjects).

5.6 Comparison of clinical severity of hospitalized VCD in seropositive vaccinated and unvaccinated, and seronegative vaccinated and unvaccinated trial participants

The clinical manifestations and laboratory parameters in all hospitalized VCD cases occurring after M13 up to March 2017 in the case-cohort study from CYD14, CYD15 and CYD23/57 are presented below categorized by serostatus defined by anti-NS1 (threshold 9) and intervention group, eg there were four groups: vaccinated and unvaccinated (control) seronegative subjects, vaccinated and unvaccinated (control) seropositive subjects. The data are presented for subjects 2-16 years of age, 9-16 years of age and 2-8 years of age.

Table 3. Summary of clinical signs and symptoms of all hospitalized VCD episodes occurring after M13 in seronegative (NS1 Th9) subjects ≥9 years of age classified as seropositive and seronegative by NS1 at M13 (threshold 9) - CYD14/CYD15/CYD23/57.

	Seronegative Vaccine group	Seronegative Control group	Risk Ratio of seronegative CYD vs placebo (95% CI)	Seropositive Vaccine group	Seropositive Control group	Risk Ratio of seropositive CYD vs placebo (95% CI)
Number VCD episodes, n	56	20		49	110	
Duration of clinical symptoms, days Median (min-max)	8 (3-29)	7.5 (4-14)		8 (2-13)	8 (4-18)	
Duration of fever, days Median (min-max)	5 (1-10)	5 (2-8)		4 (1-9)	5 (1-17)	
Hospitalized VCD episodes						
Serotype 1, n	24	9		14	32	
Serotype 2, n	19	5		18	42	
Serotype 3, n	11	6		13	16	
Serotype 4, n	3	2		4	21	
Median duration of hospitalization, days (min-max)	4 (1-8)	4 (2-6)		4 (1-10)	5 (2-12)	
Any haemorrhage	22/56 (39.3%)	9/20 (45.0%)	0.873 (0.39; 2.15)	15/49 (30.6%)	46/110 (41.8%)	0.732 (0.38; 1.34)
Any visceral manifestation	0/56 (0.0%)	1/20 (5.0%)	0.000 (0.00; 13.93)	2/49 (4.1%)	7/110 (6.4%)	0.641 (0.07; 3.37)
Plasma Leakage						
Any	20/56 (35.7%)	2/20 (10.0%)	3.571 (0.87; 31.51)	17/49 (34.7%)	46/110 (41.8%)	0.830 (0.45; 1.47)
With clinical signs	2/56 (3.6%)	0/20 (0.0%)		4/49 (8.2%)	17/110 (15.5%)	0.528 (0.13; 1.62)
Hematocrit increase>=20%	20/56 (35.7%)	2/20 (10.0%)	3.571 (0.87; 31.51)	14/49 (28.6%)	39/110 (35.5%)	0.806 (0.40; 1.52)
Thrombocytopenia						
Platelet count <= 50x10^9/L	23/56 (41.1%)	3/20 (15.0%)	2.738 (0.83; 14.25)	23/49 (46.9%)	60/110 (54.5%)	0.861 (0.51; 1.41)
Platelet count <= 100x10^9/L	43/56 (76.8%)	14/20 (70.0%)	1.097 (0.59; 2.17)	39/49 (79.6%)	94/110 (85.5%)	0.931 (0.62; 1.37)
Shock	0/56 (0.0%)	0/20 (0.0%)		2/49 (4.1%)	2/109 (1.8%)	2.224 (0.16; 0.69)

Table 4. Summary of clinical signs and symptoms of all severe VCD episodes occurring after M13 in seronegative (NS1 Th9) subjects of any age classified as seropositive and seronegative by NS1 at M13 (threshold 9) - CYD14/CYD15/CYD23/57.

	Seronegative Vaccine group	Seronegative Control group	Risk Ratio of seronegative CYD vs placebo (95% CI)	Seropositive Vaccine group	Seropositive Control group	Risk Ratio of seropositive CYD vs placebo (95% CI)
Number VCD episodes, n	37	5		31	44	
Duration of clinical symptoms, days Median (min-max)	10 (5-29)	7 (6-10)		9 (4-15)	10 (5-18)	
Duration of fever, days Median (min-max)	4 (2-10)	5 (3-7)		4 (2-7)	5 (2-17)	
Hospitalized VCD episodes						
Serotype 1, n	14	4		10	11	
Serotype 2, n	16	2		8	17	
Serotype 3, n	6	0		12	8	
Serotype 4, n	1	0		1	8	
Median duration of hospitalization, days (min-max)	5 (1-8)	4 (3-6)		5 (2-10)	5 (3-11)	
Any haemorrhage	29/37 (78.4%)	4/5 (80.0%)	0.980 (0.34; 3.84)	22/31 (71.0%)	34/44 (77.3%)	0.918 (0.51; 1.62)
Any visceral manifestation	1/37 (2.7%)	0/5 (0.0%)		3/31 (9.7%)	9/44 (20.5%)	0.473 (0.08; 1.90)
Plasma Leakage						
Any	37/37 (100.0%)	5/5 (100.0%)	1.000 (0.39; 3.26)	29/31 (93.5%)	44/44 (100.0%)	0.935 (0.56; 1.53)
With clinical signs	6/37 (16.2%)	0/5 (0.0%)		6/31 (19.4%)	19/44 (43.2%)	0.448 (0.15; 1.17)
Hematocrit increase>=20%	37/37 (100.0%)	5/5 (100.0%)	1.000 (0.39; 3.26)	27/31 (87.1%)	38/44 (86.4%)	1.008 (0.59; 1.70)
Thrombocytopenia						
Platelet count <= 50x10^9/L	25/37 (67.6%)	1/5 (20.0%)	3.378 (0.55; 138.71)	17/31 (54.8%)	31/44 (70.5%)	0.778 (0.40; 1.45)
Platelet count <= 100x10^9/L	37/37 (100.0%)	5/5 (100.0%)	1.000 (0.39; 3.26)	29/31 (93.5%)	44/44 (100.0%)	0.935 (0.56; 1.53)
Shock	3/37 (8.1%)	0/5 (0.0%)		4/31 (12.9%)	1/44 (2.3%)	5.677 (0.56; 279.60)

Among hospitalized VCD cases in subjects 9-16 and 2-8 years of age, the median duration of fever, symptoms and hospitalization were comparable between cases in the seronegative vaccine and seronegative control groups. A pattern of increased frequency of plasma leakage and severe thrombocytopenia (platelet count <50x109/L) was observed in the seronegative vaccine group compared to the seronegative control group, with the seronegative vaccine group exhibiting similar features as the unvaccinated seropositive group.

5.7 Possible Reasons for the excess cases of severe dengue in the vaccinated seronegative population

It is clear, from the analyses summarised above, that the vaccine causes seronegative recipients to be at higher risk of hospitalised and severe dengue than unvaccinated controls. A plausible hypothesis is that the vaccine acts as a silent infection, so that the first breakthrough natural infection in seronegative recipients is then "secondary-like", with an associated higher chance of severe disease. This hypothesis is illustrated in the Figure 12 below and is what was assumed in the mathematical modelling undertaken for the original SAGE consideration of CYD-TDV. However, other mechanisms of action are possible, and there is no definitive explanation of the excess risk as yet. Of note, it is not the vaccine itself that causes excess cases, but rather that the vaccine induces an immune status that increases the risk that subsequent infections be more severe.

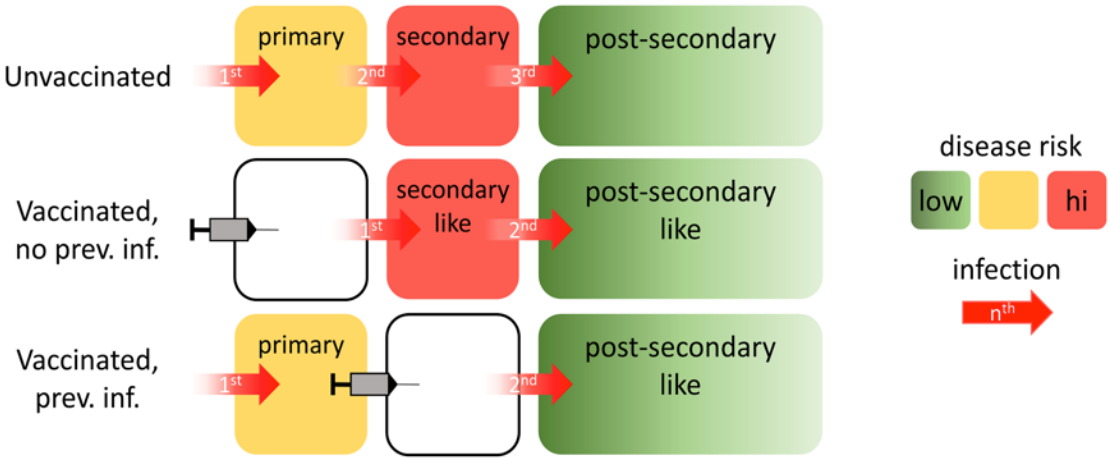


Figure 12. Plausible explanation for the excess cases of severe dengue in vaccinated seronegative individuals.

Image from: Flasche S, Jit M, Rodriguez-Barraquer I, Coudeville L, Recker M, Koelle K, et al. The Long-Term Safety, Public Health Impact, and Cost-Effectiveness of Routine Vaccination with a Recombinant, Live-Attenuated Dengue Vaccine (Dengvaxia): A Model Comparison Study. PLoS Med. 2016;13:1–19. doi:10.1371/ journal.pmed.1002181.

An excess risk of severe dengue in seronegative recipients was seen in all age groups, but was more pronounced in trial participants below the age of 9 years. Vaccine efficacy was higher in the older age groups, and the onset of the increased relative risk for hospitalized dengue in seronegatives started later in older children. Previous studies of the natural history of dengue suggest that younger children are more susceptible to more severe infection, perhaps due to higher capillary fragility in younger age groups(10). The relative risk of severe dengue was most pronounced in year 3 after the first dose of vaccine. The fact that vaccination of seronegative individuals may represent an attenuated subclinical primary infection means that in the efficacy trials, such a primary infection has been temporally clustered in vaccinated individuals due to the condensed enrolment periods of the trials, whereas subjects who received the placebo are exposed to a primary wild-type infection over a longer period of time(11).

6. NON-DENGUE SERIOUS ADVERSE EVENTS STRATIFIED BY SEROSTATUS

An overview on safety data was published in 2016(12). In the pooled analysis of safety that included subjects aged 9-60 years, the serious adverse events (SAEs) reported mostly corresponded to common medical conditions expected in each age group. There was no evidence of any excess of any SAEs attributable to vaccination.

Non-dengue SAE were re-analyzed stratified by serostatus, and are presented in Table 5. There is no evidence of an excess risk in either seronegative or seropositive vaccinated participants.

Table 5. Non-dengue SAEs in CYD14 (2-14Y) and CYD15 (9-16Y) from day 0 to year 5 by baseline dengue serostatus defined by measured $PRNT_{50}$ in immunogenicity subset.

Baseline serostatus	Adverse event	CYD14 % (95%CI)		CYD15 % (95%CI)	
		CYD	Control	CYD	Control
Seronegative	**SAE**	11.5% (8.7,15.0)	14% (9.6,19.3)	11.2% (7.7,15.7)	10.7% (6.3,16.9)
	Fatal SAE	0% (0.0,0.9)	0% (0.0,1.7)	0% (0.0,1.4)	0% (0.0,2.4)
Seropositive	**SAE**	11.7% (9.6,13.9)	10.1% (7.5,13.3)	11.4% (9.5,13.4)	12.9% (10.1,16.1)
	Fatal SAE	0.1% (0.0,0.6)	0.0% (0.0,0.8)	0.5% (0.2,1.1)	0.6% (0.1,1.7)

Virologically confirmed dengue reported as dengue fever SAE are removed from the analysis.

The Clopper-Pearson method is used for the 95% CI for a single proportion.

Dengue non-immune subjects at baseline are defined as subjects with titers < 10 (l/dil) against all four serotypes at baseline.

Dengue immune subjects at baseline are defined as subjects with titers >= 10 (l/dil) against at least one dengue serotype at baseline.

6.1 Adverse events of special interest

The following adverse events of special interest (AESIs) have been defined by the manufacturer for CYD: allergic reactions within 7 days after vaccination, acute viscerotropic or neurotropic disease (AVD, AND) with 30 days after vaccination, and serious dengue disease at any time during the study.

No immediate anaphylactic shock has been reported post-vaccination. Five subjects receiving CYD have experienced a serious potential allergic reaction: 4 subjects with asthma/asthmatic crisis (all had medical history), and 1 urticaria (with history of allergic rhinitis). In the placebo group, there was one serious adverse event suggestive for allergic reaction (asthma in a subject with a history of asthma).

As CYD-TDV is based on YF vaccine backbone, the risk of very rare severe reactions associated with YF vaccine was monitored during its clinical development for YF vaccine-associated viscerotropic disease (YFV-AVD) and YFV vaccine-associated neurotropic disease (YFV-AND).

YFV-AVD: clinical signs and symptoms resemble those of wild-type yellow fever infection and disease and include a rapid onset, within 2-5 days of vaccination after first vaccination after yellow fever vaccine. Laboratory confirmation is usually required to fulfill the case definition of AVD. Large amounts of yellow fever viral antigen are found in the liver, the heart and other affected organs(13).

YFV-AND: three categories of YEL-AND can be distinguished: 1 - encephalitis, 2 - neurotropic auto-immune disease with central nervous system involvement, 3 - neurotropic auto-immune disease with peripheral nervous system involvement. The median of onset is 11 days (range from 2 to 23 days) after yellow fever vaccination.

There have been no confirmed AVD or AND cases in any of the >30,000 trial participants to date.

6.2 Pregnancy

In the licensed indication, pregnancy and lactation are contraindications. A total of 615 pregnancies (404 in the CYD group and 211 in the placebo group) were reported from all CYD dengue vaccine trials (SP personal communication). They were mainly reported during CYD15. Among the 404 pregnancies reported in the CYD group, 22 pregnant women were inadvertently exposed to CYD-TDV (i.e. vaccinated 7 days after LMP or 7 days before estimation of conception or later during pregnancy). Of these, 17 resulted in a live birth, 1 resulted in an abortion (spontaneous and unspecified), 1 resulted in elective termination, 1 still birth, 1 death in utero, and 1 unknown. Of 211 pregnancies reported in the placebo group, 12 pregnant women were exposed, of which all 12 resulted in a live birth. An update of pregnancy analyses will be performed at the end of the hospital phase.

7. IMMUNOGENICITY BY SEROSTATUS

In vaccinees seropositive before vaccination, neutralizing antibodies titres were higher following vaccination compared to the seronegative vaccinees. The Geometric Mean Titres (GMTs) measured by the $PRNT_{50}$ assay increased mainly after the first dose among participants who were seropositive at baseline; however, a more gradual increase after each dose was observed for serotypes 1–3 among those who were seronegative (14). The GMTs post-dose 3 for serotypes 1–4, respectively, were 580, 741, 827 and 341 for participants who were seropositive at baseline and 34.6, 101, 174 and 119 for those who were seronegative (Figure 13). After the third injection, serotype-specific seropositivity rates were 94.2% or higher, and 100%, 98.6% and 93.4% of participants were baseline seropositive for at least 2, at least 3 and all 4 serotypes, respectively. A lower seropositivity rate for all 4 serotypes was observed in seronegative participants (77.9%) compared with those who were seropositive (97.6%).

The $PRNT_{50}$ assay does not allow for reliable differentiation between monotypic and heterotypic (temporarily cross-protective) antibodies, hence all the GMT titres may be a mixture of long-lasting monotypic and transient heterotypic antibodies, neutralizing and non-neutralizing antibodies. Statistical analysis suggested that dengue serotype 4 (DENV4) was immunodominant after the first dose (15). No correlate of protection for dengue has been established to date, although some correlation has been described between vaccine-induced neutralizing antibody titres and protection from VCD for a given serotype (16, 17).

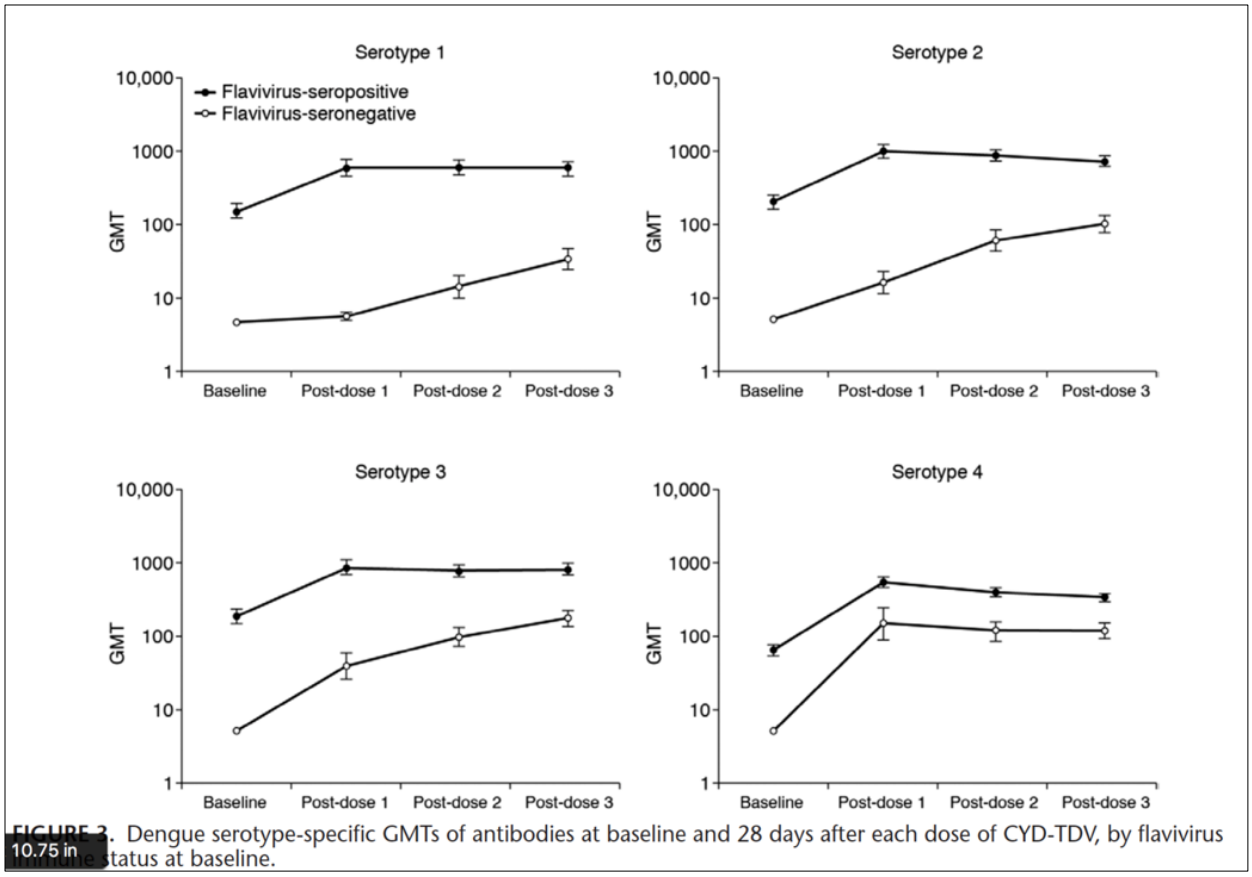


FIGURE 3. Dengue serotype-specific GMTs of antibodies at baseline and 28 days after each dose of CYD-TDV, by flavivirus immune status at baseline.

Figure 13. GMTs after one, two and 3 doses by serotype and serostatus in subjects 9-16Y in Latin America (extracted from (14)).

7.1 Persistence of Immunogenicity by serostatus

GMTs remained higher in seropositive participants aged ≥ 9 y than those aged <9 y throughout follow-up of 3 years as reported by Vigne et al (18). Dengue neutralizing antibody persistence data in 2 studies (CYD22 and CYD28) with longer follow-up to 4 y post-dose 3 (Year 4 of follow-up) also show that GMTs remain 1.2–3.2-fold higher than baseline.

In summary, in seropositive subjects immunogenicity appears to be as high after one dose as after 3 doses. This fits with findings in the Phase III trials that VE between the first and second dose, and second and third doses, was similar to VE after the third dose, in the overall trial population. However, no long-term efficacy data for one or two dose schedules exist because the compliance rates (e.g. completion rate of 3 doses) was very high in the trials. There is an urgent need to study one or two dose vaccination schedules in order to enhance the programmatic use of CYD-TDV.

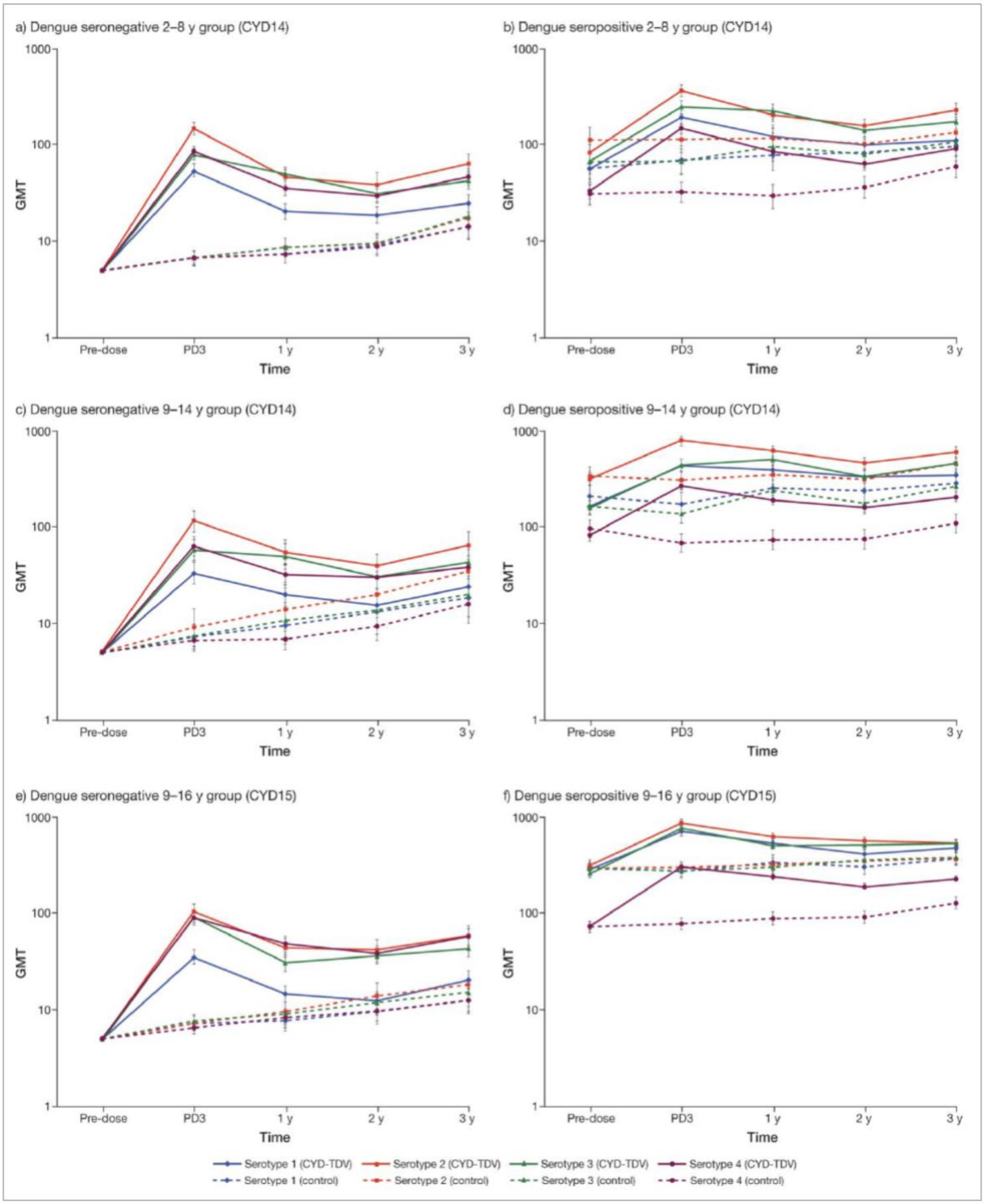


Figure 14. GMTs (95% CI) for each dengue serotype over time (years after the last dose) in children aged 2–8 y or ≥ 9 y in the CYD14 and CYD15 studies, as extracted from (18).

8. POPULATION BENEFIT VERSUS INDIVIDUAL RISK

The new NS1 assay-based data confirms previous findings that, overall, vaccinated trial participants had a reduced risk of virologically-confirmed dengue disease, hospitalizations due to dengue, and severe dengue. Trial participants who were inferred to be seropositive at the time of first vaccination had a durable protection against hospitalized and severe dengue during the 5-year observation period. However, trial participants who were inferred to be seronegative at time of first vaccination had, overall, a significantly higher risk of hospitalized and severe dengue compared with unvaccinated participants, regardless of age at time of vaccination, although some age effect was still observed. The risk persisted over the trial follow up period of about 5 years after the first dose.

The cases of hospitalised and severe disease in seropositive subjects substantially outnumbered those precipitated in seronegative participants. A trade-off therefore exists between the population benefit conferred by vaccination, and the enhanced risk experienced by a subset of seronegative vaccine recipients.

The population and individual impacts of a dengue vaccination programme – on the expected incidence of hospitalized/severe dengue cases –depends primarily on three factors:

(1) The level of dengue seroprevalence in the target age group for vaccination: this determines the proportion of vaccine recipients who will be seropositive when they receive vaccine, but is also an indicator of the level of dengue exposure in the population.
(2) The level of dengue incidence that can vary significantly from year-to-year.
(3) The time horizon considered for assessing the impact of vaccination.

Based on the incidence in the epidemiological settings of the trials (which spanned a range of moderate to high transmissions settings), for persons aged 9 years and above, the new analysis indicates that the 5-year risk of severe dengue in vaccinated seronegative persons (4.04 per 1,000 seronegative persons vaccinated) is similar to the risk of severe dengue in unvaccinated seropositive persons (4.8 per 1,000 seropositive persons unvaccinated). The risk of severe dengue is lower in unvaccinated seronegative persons (1.7 per 1,000 seronegative persons unvaccinated). The risk of severe dengue in vaccinated seropositive persons is the lowest (less than 1 per 1,000 seropositive persons vaccinated). Thus over 5 years, there was a reduction of about 15 cases of hospitalized dengue and 4 cases of severe dengue per 1,000 seropositive persons vaccinated (Table 2 above). For 1,000 seronegative persons vaccinated, there was an increase of about 5 cases of hospitalized dengue and 2 cases of severe dengue.

The similar incidence of hospitalized and severe dengue in vaccinated seronegative trial participants and unvaccinated seropositive participants is consistent with the hypothesis that vaccination in seronegative individuals causes a primary-like infection.

Since dengue incidence varies substantially by geographic setting and over time, it is difficult to translate these absolute estimates of incidence reduction into predictions of programmatic impact in particular settings without using mathematical models. However, given that approximately 80% of trial participants were seropositive, we can estimate the averted numbers if 1,000,000 children over 9 years of age were vaccinated with the same distribution of ages (>9) in the settings as seen in the trials.

If 1,000,000 children were vaccinated under such settings:

- 11,000 hospitalized dengue cases would be averted (12,000 averted in seropositives, 1,000 excess cases in seronegatives)
- 2,800 severe dengue cases would be averted (3,200 averted in seropositives, 460 excess cases in seronegatives).

Dynamic transmission models are required to predict the potential population and individual impacts of vaccination programmes in a wider range of transmission settings, or for a period longer than 5 years. The NS1 antibody assay study provided the opportunity to revisit modelling analyses originally undertaken by eight WHO-coordinated modelling groups in 2015. These models were fitted to the phase III trial data and all models made the assumption that the vaccine acts as a 'silent' first infection, leaving seronegative vaccinated individuals at increased risk of severe dengue when they experience their first natural dengue infection, but at very low risk thereafter (having effectively had two infections). In contrast, unvaccinated seronegatives are at low risk of severe dengue disease when they experience their first natural infection, then have an increased risk of severe dengue when they experience a second infection, and at very low risk thereafter. Thus, vaccination brings forward the risk period for severe dengue (associated with a natural second infection) but does not increase the lifetime risk of severe dengue except in low transmission settings where not everyone is likely to experience two natural dengue infections in their lifetime.

However, from an individual perspective, an important consideration is that the period of risk experienced by seronegative vaccine recipients precedes the hypothesised period of eventual benefit. This ordering has the consequence that the rare individual who experiences fatal severe dengue infection during the period of risk has, mathematically speaking, no opportunity to benefit later. 'Bringing forward' a period of enhanced risk of severe dengue disease therefore may potentially increase overall life-years lost from dengue disease, even if overall numbers of deaths stay constant or even decline.

Whether seronegative vaccine recipients eventually benefit from vaccination depends on the transmission intensity of dengue in their residence location. In high transmission settings, the great majority of people experience two natural dengue infections, and furthermore, mass vaccination in such settings is predicted to cause small reductions in dengue transmission (due to the large impact of vaccination in seropositive recipients) which will benefit seronegative recipients. In addition, the time-period between infections reduces as transmission intensity increases, so the expected long-term benefit of vaccination in seronegatives will be seen sooner in very high transmission settings than in lower (but still high) transmission settings. However, it should be emphasised that the new data still do not validate the assumption that seronegative vaccinees who experience a first natural infection are thereafter at very low risk of severe dengue (akin to an unvaccinated individual who has experienced two natural infections); we have only seen the period of enhanced risk so far in trial data up to 66 months.

Preliminary and still unpublished work independently undertaken by the modelling groups at Sanofi Pasteur and Imperial College indicate that the new data provides new evidence of age-specific effects of vaccination, independent of serostatus. Fitting models to the new data, risk enhancement in seronegative recipients is estimated to be higher in younger age groups (particularly those below the age of 5) than in older age groups (though is present in all age groups), while vaccine efficacy in seropositive recipients is estimated to be higher in older age groups (>9 years) than in younger groups. However, this age-dependence makes relatively little difference to predicted impacts of vaccination in 9 year-old or older children, or to conclusions about population versus individual benefits of mass vaccination.

9. ETHICAL CONSIDERATIONS

The ethical tension between personal and population benefit in vaccination programmes is not new. Vaccines are given to healthy members of society to prevent illness, and thus the tolerance for vaccine adverse events is very low. Vaccines, like all medical products, are associated with some individual risk, even if generally extremely low, and greatly outweighed by the benefits to both individuals and communities. In the case of conflict between the goal to promote societal benefit and the goal to promote individuals' interests/wellbeing, neither goal should be thought to supersede, or have absolute priority over the other. It is widely accepted that it might sometimes be ethically appropriate to take actions that compromise the wellbeing or interests of individuals (i.e. put individuals at some level of risk) when necessary to promote the greater good of society; but it is also widely accepted that it would be inappropriate to compromise individuals' interests and wellbeing *whenever* this would be necessary to benefit population health. The relative magnitude of societal benefits and individual risks is an important consideration when evaluating the acceptability of added risk, together with other key considerations such as public acceptance. For example, it is known that rotavirus vaccination is associated with a very small risk of inducing intussusception, but this is greatly outweighed by the protective effective effect of the vaccine against severe rotavirus disease.

Although in high dengue transmission settings both the population and individuals may eventually benefit from vaccination, it is important to note that there are no data from the trials yet showing the long-term benefit to seronegatives. Even if there is such long-term benefit, other issues related to the timing and cause of risk/harm that might make population-based dengue vaccination programmes ethically problematic and have adverse implications for trust and the long-term success of public health programmes. While most vaccinated individuals (and population health in general) might be expected to ultimately benefit from mass vaccination in high transmission settings, it is easy to imagine scenarios where some cases of severe dengue that result would end up (rightly or wrongly) getting attributed to the vaccine—and thus damage the reputation of the vaccine programme.

Furthermore, an important difference from the rotavirus vaccine cited above, is in that situation it is not possible to predict which vaccinated children will develop intussusception (or indeed who will have a case of severe rotavirus disease averted), but with respect to the dengue vaccine, it is possible to identify a subgroup of the those vaccinated (the seronegative) who will be at increased risk of severe dengue (at least the short-term), even though with current diagnostic tests it may be programmatically difficult to vaccinate large populations while at the same time ensuring that seronegatives are not vaccinated.

Testing and vaccinating only seropositive individuals is also not without ethical tensions. This strategy avoids risk of harm to seronegatives and promotes population health. However, questions of feasibility to develop a sensitive and specific rapid test as well as cost-effectiveness may mean that the vaccine cannot be used for several years; thus, there would be a cost in terms of forgone benefits for seropositives, and the entire community in high transmission settings, if vaccination was delayed.

Some ethicists have drawn a distinction between harms resulting from acts (e.g. harms resulting from vaccinating someone—i.e. the harms to seronegatives vaccinated), and those resulting from omission (e.g. harms resulting from not vaccinating someone—i.e., the harms to seropositives not vaccinated). If a medical product causes harm, someone can be sued. There is less obvious liability if someone doesn't get the product. But there is no widely accepted absolute ethical principle according to which harms from acts outweigh harms from omissions, or where the balance between these two harms lies (i.e. how many cases must be prevented for every case induced). It can

be argued that if one can bring about the prevention of a harm and fails to do so, that can arguably be worse than actively bringing about harms of smaller magnitude, but what the ratio of those harms should be is uncertain.

Much depends on whether the harms in question are avoidable—and thus, in context of dengue vaccine, whether a suitable serological test exists. If it is not feasible and cost effective to test, then would mass vaccination necessarily be wrong (in high prevalence settings) given that no individuals/groups who are (in practice) identifiable would be harmed as a result? As present, most doubt that testing would be feasible in the short-term. At some point in the future, it is hoped that better tests will become available—and relevant research and development appears to be in progress. Thus, perhaps a key question is whether testing is practical logistically and economically in the context of immunization programs.

10. PROGRAMMATIC CONSIDERATIONS

To maximize the public health benefit and minimize harm to individuals, the WG considered two strategies – the population seroprevalence criteria without individual screening and pre-vaccination screening. The WG considered the advantages and disadvantages of each strategy, including programmatic considerations and achievable vaccine coverage.

10.1 Population seroprevalence criteria

The rationale for this strategy is that vaccination based on high seroprevalence criteria would result in a substantially larger number of severe and hospitalized dengue cases prevented in seropositive individuals than the number of excess cases resulting from priming seronegatives through vaccination. In this strategy, first a population survey would be undertaken to identify areas where seroprevalence thresholds are high enough to maximize public impact and minimize harm, followed by a mass vaccination targeted towards an optimal age.

10.1.1 Population serosurveys to determine seroprevalence

There are multiple sources of epidemiologic data that could be used as evidence of high pre-existing immunity to dengue, such as nationally representative surveillance data. However, surveillance data alone can be unreliable, as clinically apparent cases represent a variable fraction of all dengue infections, typically estimated to be around 25%, healthcare seeking for dengue can vary greatly based on access to care, and outbreaks may occur in low seroprevalence areas. Because surveillance data can be unreliable, population-based seroprevalence studies are the only way to reliably measure the proportion of seropositive individuals in a population.

Serosurveys are needed to determine seroprevalence rates. A serosurvey involves collecting and testing blood specimens from a defined population to estimate the proportion positive for DENV immunoglobulin G (IgG) antibodies as a measure of population immunity. Age-stratified serosurveys should be recent (within the last 3–5 years) in a geographically relevant location and capturing the likely vaccine target age range.

WHO has provided recommendations on designing and implementing cross-sectional serosurveys to estimate age-specific dengue seroprevalence: “Informing vaccination programs: a guide to the design and conduct of dengue serosurveys” (http://www.who.int/immunization/research/development/Dengue_Serosurveys_020617.pdf). This guidance document includes recommendations for methods for planning and conducting serosurveys, including

survey design, specimen collection, laboratory testing, data analysis, and the interpretation and reporting of results.

10.1.2 Considerations for serosurveys to determine population seroprevalence

Introducing CYD-TDV in high seroprevalence settings could maximize the public health and follows other models for subnational vaccinations programs based on incidence (e.g. TBE, cholera). However, a potentially identifiable subpopulation of seronegatives will experience harm, despite the overall significant population level benefit. The decision on the cut-off of such seroprevalence thresholds will depend not only on the optimal seroprevalence for public health impact, but also on the risk perceptions, public confidence and communication strategies. Higher seroprevalence thresholds, e.g. 85%, may be considered more acceptable to policy makers and the public. However, with higher seroprevalence thresholds, the parts of the country suitable for vaccination becomes smaller, and the effort required to conduct serosurveys to identify these populations, becomes larger.

Mathematical modelling predicts that even seronegative individuals would benefit from vaccination in as little as 6 years in very high transmission settings where >90% of 9 year-olds would be expected to be seropositive. However, dengue transmission intensity maps (https://mrcdata.dide.ic.ac.uk/ dengue/dengue.php) derived from serological and age-specific reported dengue incidence data suggest that no country would meet such a high threshold for transmission intensity by the age of 9. Eventual positive benefits of vaccination in seronegatives are still expected, based on the modelling, in slightly lower transmission settings but such benefit takes longer to be seen. However, even if a 10-year timescale for evaluating benefits is used, modelling indicates that vaccine should only be used in settings where seroprevalence in 9 year-olds exceeds 80%. Such a high threshold would effectively exclude the great majority of dengue endemic countries from vaccine introduction. Table 6 shows how the seroprevalence threshold varies with the target age for vaccination. If one chooses 80% for 9 year olds, then conservatively one would want to pick ~90% for 16 year olds in order to be fairly confident that seronegative recipients would benefit within 10 years.

Table 6. Optimal target age in relation to seroprevalence thresholds for predicted benefit in seronegative recipients within 10 years (Table provided by Neil Ferguson, Imperial College)

Target age for vaccination (years)	Seroprevalence in target age group required (model incorporating best-fit age-specific vaccine effects)	Seroprevalence in target age group required (model with more limited age-specific vaccine effects)
9	80	80
10	81	83
11	82	86
12	82	88
13	83	90
14	85	92
15	87	93
16	88	94
17	90	95
18	91	96

Dengue transmission intensity shows marked geographic heterogeneity even over relatively small distances (a few km) driven by environmental and socioeconomic factors(19). Hence, decisions to introduce vaccination based on transmission intensity exceeding a fixed threshold need to be made at subnational level. Seroprevalence data are not currently available in any country at the relatively fine level of geographic resolution that is required to ensure that we minimize harm to seronegative individuals. Large-scale serosurveys with relatively complex sampling designs would be needed characterize transmission intensity (e.g. seroprevalence in 9 year-olds above 80%) at fine geographic scales. It is therefore possible that the cost of implementing rigorous population serosurveys may exceed that of a "screen and vaccinate " strategy. Limiting vaccination introduction to small-scale areas within a country that meet the a seroprevalence cut-off (in 9 year-olds) of between 80% and 90% will also likely result in very low overall vaccine coverage, and hence a low population impact of vaccination.

Figure 15 shows some seroprevalence settings in different countries to illustrate the wide variation between countries by age stratification.

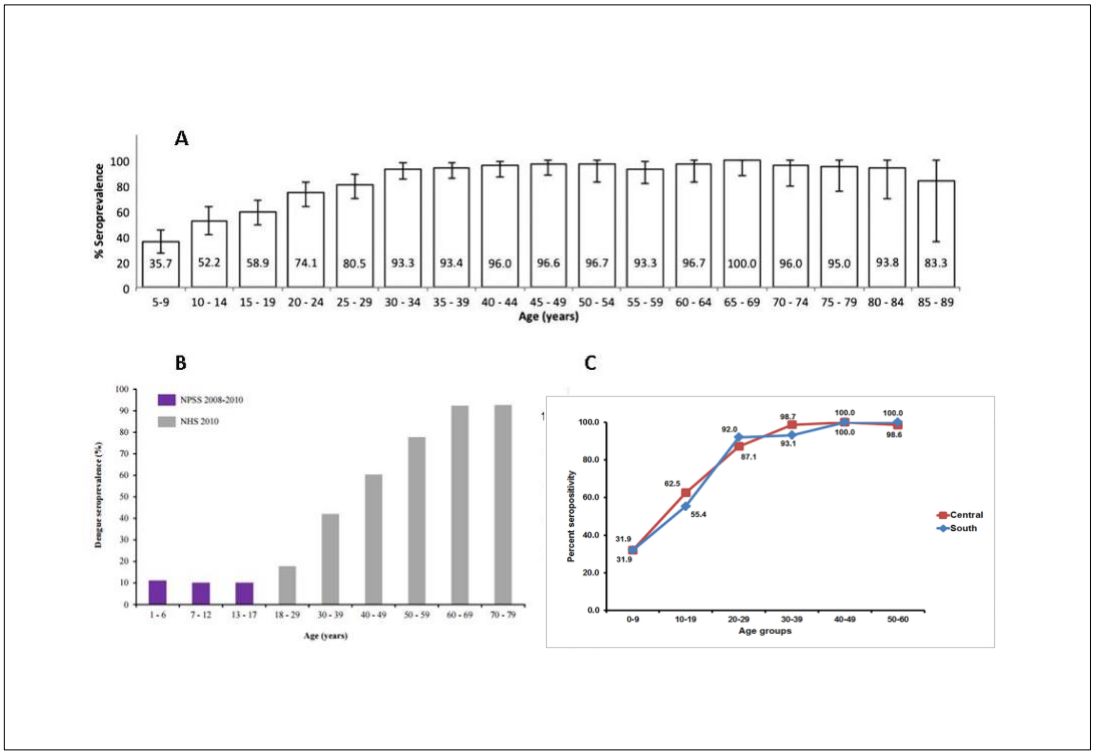


Figure 15. Examples of seroprevalence by age from localities in A) Mexico (20), B) Singapore (21), and C) Thailand (22).

Figure 16 illustrates the extent of spatial heterogeneity within a country, with Brazil as example.

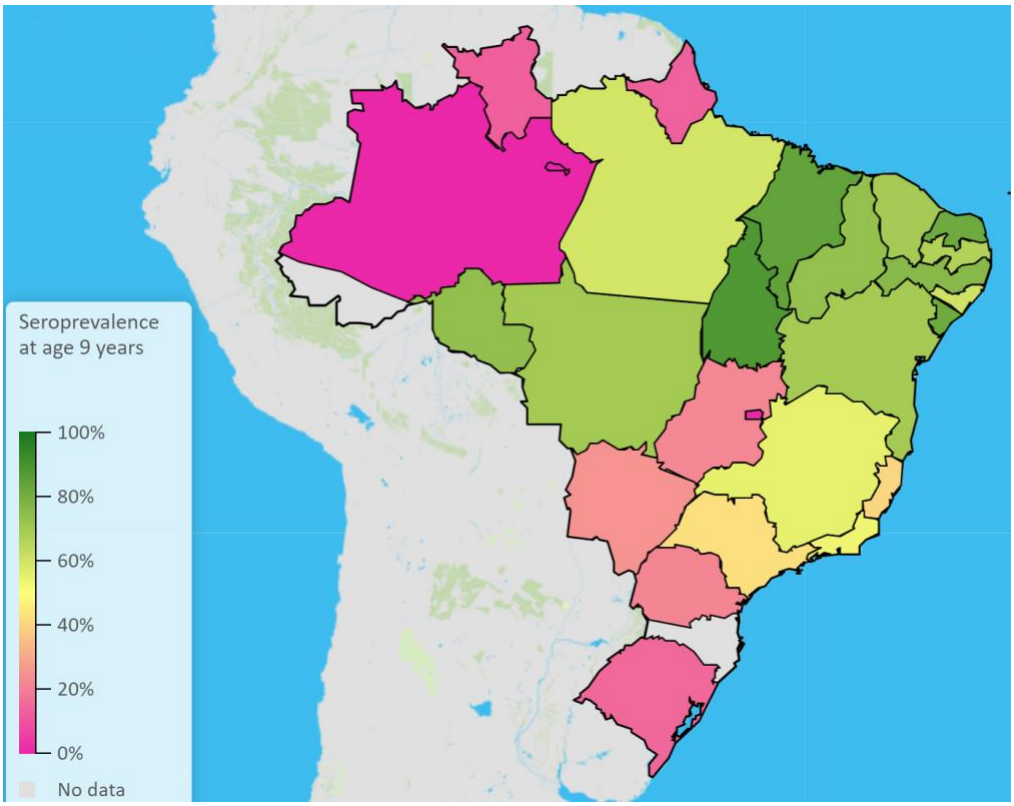


Figure 16. Spatial heterogeneity of seroprevalence at age 9 years in Brazil (Source: https://mrcdata.dide.ic.ac.uk/_dengue/dengue.php)

For countries where sufficient surveillance data were available, a preliminary assessment was made of the likely proportion of the population that would be eligible for vaccination using seroprevalence criteria (>80%) versus a "pre-vaccination screening" strategy. This assumed that seroprevalence thresholds and consequent mass vaccination decisions would be made at the first administrative unit level (admin 1) within individual countries. From Table 7, it can be seen that no level 1 administrative unit in a selected list of dengue endemic countries listed would be expected to reach a threshold of 90% seroprevalence in 9 year-olds, and that even with 85% or 80% thresholds, expected vaccine coverage would be much lower than might be achieved with an individual test-and-vaccinate policy.

Table 7. Preliminary assessment of predicted coverage of mass-vaccination with seroprevalence threshold versus screen-and-vaccinate policies for countries with dengue force of infection estimates for 5 or more admin 1 units, based on unpublished data. Seroprevalence estimated from force of infection estimates derived from routinely reported age-specific dengue case incidence data. Denominator is total population of admin 1 units for which data were available to estimate force of infection (provided by Neil Ferguson, Imperial College, UK)

Country	Number of admin1 units	Proportion of admin 1 units with data available to allow estimation of force of infection	Predicted coverage* with 80% seroprevalence threshold in 9 year-olds applied at admin 1 level	Predicted coverage* with 85% seroprevalence threshold in 9 year-olds applied at admin 1 level	Predicted coverage* with 90% seroprevalence threshold in 9 year-olds applied at admin 1 level	Predicted coverage* with screen and vaccinate policy
Brazil	27	93%	7%	1%	0%	50%
Colombia	32	88%	4%	0%	0%	64%
India	36	19%	44%	17%	0%	64%
Mexico	32	84%	0%	0%	0%	24%
Philippines	81	69%	17%	1%	0%	67%
Thailand	77	94%	0%	0%	0%	57%
Venezuela	25	96%	59%	24%	0%	79%

*proportion of 9 year-olds receiving vaccine

10. 2. Pre-vaccination screening strategy

Screening and vaccinating those tested seropositive offers the potential of retaining much of the benefits of vaccination for seropositive individuals while largely eliminating the risks experienced by seronegative recipients. Such "screen and vaccinate" strategies are not entirely new, with test-based targeting having also been undertaken in some populations for Hepatitis B, BCG and other vaccines. A pre-vaccination screening strategy involves the use of a rapid diagnostic (or screening) test to determine dengue serostatus. Those with a documented history of laboratory confirmed dengue would not need to be screened.

10.2.1 Screening tests

Various tests that can be used to determine serostatus; each test has its advantages and disadvantages. The test with the highest sensitivity and specificity to diagnose seropositivity would be the desirable option. Low sensitivity would result in missing truly seropositive persons; while low specificity would lead to falsely classifying seronegative as seropositive persons. Hence, low sensitivity would decrease the benefit of the vaccine in truly seropositives, low specificity would increase the potential harm. To facilitate programmatic use, the test should be simple and at point of care, and should be affordable.

Table 8. Overview of diagnostic tests that could be used for screening for serostatus

Diagnostic Test	Advantage	Disadvantage
Plaque reduction neutralisation test (PRNT)	• PRNT is specific for detecting dengue specific seropositivity	• Time-consuming • Expensive • Requires high level of expertise and for these reasons, it has remained a research tool
Dengue immunoglobulin G (IgG) enzyme-linked immunoassay (ELISA)	• Anti-DENV IgG ELISA is relatively fast (2-3 hours) • inexpensive ($4-10 USD/test).	• Lab-based assay, so screen and vaccinate policy would require separate visits for testing and vaccination • Cross-reactivity
Rapid diagnostic tests (RDT) for point-of-care tests (POCT)	• Results within half an hour	• Suboptimal sensitivity and/or specificity currently less than PRNT or ELISA

<u>Dengue IgG ELISA</u>

Although PRNT assays were used in the Sanofi Pasteur clinical trials and are viewed as the current gold standard for dengue serological testing, they are time-consuming, expensive and require expertise, and are therefore limited to research settings. IgG ELISA is comparable to PRNT with high sensitivity and specificity of 91% and 98% respectively(23) (study done prior to the emergence of Zika as a public health problem in dengue endemic countries in Latin America). Dengue IgG ELISA requires taking a venous blood sample to obtain serum, about 2.5 hours of laboratory time, excluding the time for sample transportation to the laboratory and reporting results to

the clinician. ELISAs are formatted such that multiple specimens are tested simultaneously thus laboratories often batch samples before starting an ELISA. Hence, the lag time between the availability of IgG ELISA result to the clinician (and the individual) is usually at least a day, more often a week. Therefore, dengue IgG ELISA would require two visits before deciding whether or not to administer the first vaccine dose, thereby adding a level of inconvenience to the potential vaccinee and additional burden to the health care system.

Rapid diagnostic tests

Point-of care testing (POCT) using rapid diagnostic tests (RDT) provides the vaccine recipient a result within 15-30 minutes and can be done in an outpatient or outreach setting such as schools and care facilities using a finger prick sample. Thus a decision on vaccination eligibility can be determined during the same visit. POCT is the most feasible option to ensure a reasonable vaccine uptake, reduces outpatient visits and hence costs to the vaccinee and the health care system. Current POCTs generally have lower sensitivity and specificity than dengue IgG ELISA. However, this needs to be weighed up against the speed of testing, lower cost and accessibility outside specialized laboratories.

Cross-reactivity with available tests

Dengue IgG tests, both RDT or ELISA, could cross-react (i.e. give a false positive test result) with other flaviviruses, acquired through natural infection or vaccination(24). If a dengue IgG ELISA is to be used in areas where JEV or YFV vaccination occur, individual-level vaccine history should be collected and analyses should be stratified to assess for cross-reactivity in the assay. All comparisons of commercial diagnostic assays and evaluations of sensitivity and specificity for dengue IgG were done before Zika became a widespread problem. Hence, the extent of IgG cross reactivity in Zika endemic countries will need to be assessed in prospective studies. Dengue IgG will also be falsely positive in individuals that have already received a dengue vaccine.

Future prospects for RDTs

A number of RDTs were tested by Sanofi Pasteur, some of which exhibited favourable performance characteristics, but as of now, all have limitations due to either cross reactivity with other flaviviruses or due to modest sensitivity. The company is engaging with diagnostic test manufacturers to expeditiously develop, test and register one or more new tests for this indication.

To increase the sensitivity of dengue RDTs in detecting past dengue infection, several modifications could be contemplated, one of which would be ‘recalibration’ by changing the concentration of the IgG capture antigen and/or detection reagent to lower the limit anti-dengue IgG detection. For tests that also exhibit cross-reactivity with other flaviviruses, particularly Zika, other modifications must be considered to improve specificity.

Possibly 2 years might be required to develop, register, manufacture and deploy a suitable dengue RDT.

10.2.2 Optimizing the impact of a “pre-vaccination screening” strategy

If only a single round of screen and vaccinate is to be offered to each birth cohort, it will be optimal to target the age at which monotypic seroprevalence (the proportion of people who have experienced only one infection) peaks. Routine hospital surveillance data should be able to be used to identify this age group, since the secondary dengue infections are thought to be responsible for the great majority of severe dengue disease. Thus the age at which severe dengue disease incidence is highest will be approximately equal to the age at which monotypic

seroprevalence peaks. For maximal impact, vaccination age should be tuned at a subnational level, given the high level of spatiotemporal variation in dengue transmission intensity.

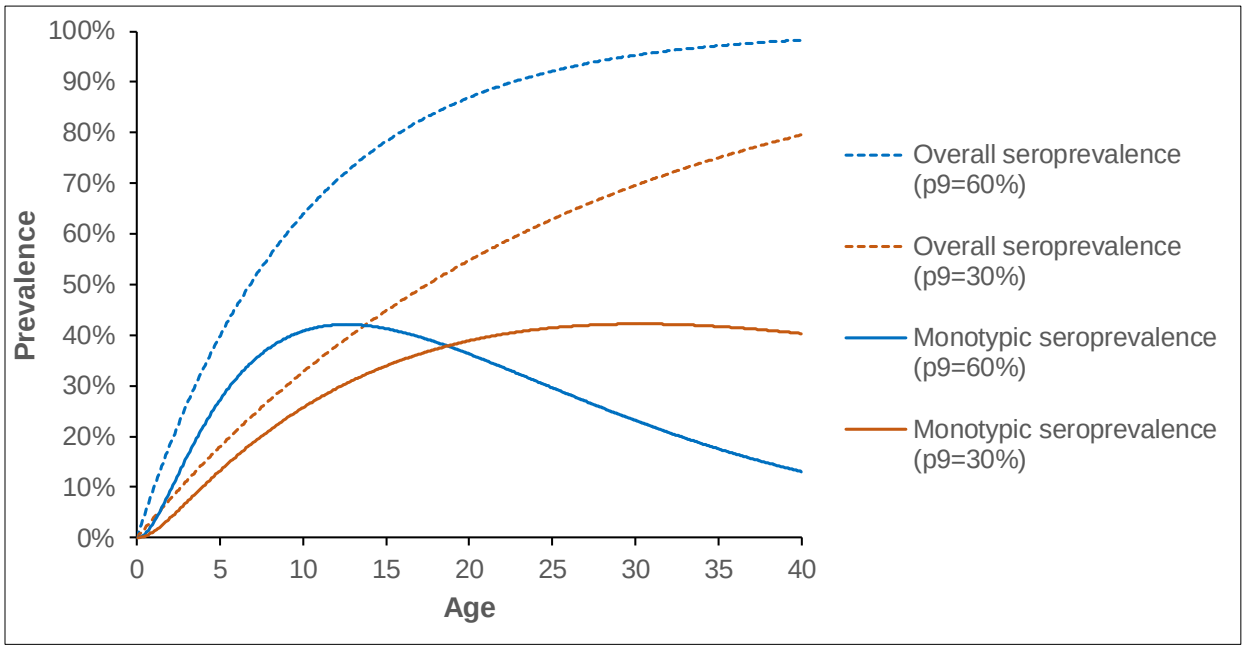


Figure 17. Illustrative profiles of overall seroprevalence (1 or more past dengue infection) by age (dashed lines) and monotypic seroprevalence (only one prior dengue infection) by age (solid lined) for two transmission settings, corresponding to seroprevalence in 9 year-olds of 60% (blue) and 30% (orange). Single round screen and vaccinated policies need to target the age of peak monotypic seroprevalence for maximal impact (Figure prepared by Neil Ferguson).

If multiple rounds of screen-and-vaccinate campaigns are envisaged to target single cohorts at multiple ages, the coverage will increase but so will the complexity of the programme. However, preliminary (unpublished) modelling suggests that a single round of screen-and-vaccinate per annual birth cohort can achieve similar levels of population impact in moderate or high transmission settings as mass vaccination might achieve in high transmission settings, if test sensitivity is high.

10.2.3. Communication with regards to pre-vaccination screening

Given that no assay will be 100% specific, occasionally truly seronegative individuals may be unintentionally vaccinated based on a false positive test result. Furthermore, although the efficacy against dengue infections in seropositive individuals is high, it is still not complete. Therefore transparent communication is needed to inform vaccinees that they may still be at risk of dengue and the need of adhering to other disease preventive measures.

10.2.4 Cost-effectiveness

Implementing individual level testing to determine past dengue infection with the objective to only vaccinate seropositive individuals is associated with added costs related to the diagnostic assay itself, the need for blood taking, waiting for the POCT result, or even adding a second visit to obtain the IgG ELISA result. Cost-effectiveness studies are needed to support countries` decisions to adopt a “screen and vaccinate” strategy.

10.2.5 Implementing the "pre-vaccination screening" strategy

Various settings could potentially be targeted.

Schools

Schools have a clear potential for population-based delivery and provide an opportunity to "screen and vaccinate" to increase coverage. School-based delivery strategies will likely lead to high vaccination coverage when there is high school attendance and either a strong school health system or a strong collaboration between the ministries of health and education. In general, countries need to be aware that school-based programmes tend to be more costly than health-facility based strategies and require significant preparation and coordination with school authorities. WHO has produced a School Vaccination Readiness Assessment Tool in relation to HPV vaccination: http://www.who.int/immunization/hpv/plan/school_readiness_assessment_tool_who_2013.pdf.

The current schedule of the CYD-TDV candidate vaccine (0/6/12 months) may necessitate (an) additional vaccination contact(s) in most programmes. While HPV or TT-containing vaccines could be co-administered based on age indication, there are currently no co-administration data. Thus, countries may elect to stagger HPV and CYD-TDV, either requiring new vaccination visits or targeting different age groups during the same campaigns. Experiences with new visits/school-based campaigns suggest substantial programmatic costs, unless integrated with existing school-based programs (http://amp-vaccinology.org/activity/dengue-vaccination-program-toolkit)

Health facility-based delivery

Health facility based HPV vaccine delivery to school age adolescents has been successful in several countries and could be considered for dengue vaccine. In general, health facility-based delivery in this age group has worked best in countries with fairly strong health systems.

Campaigns

Where the target age for the CYD-TDV vaccine is outside the school-age group, a possible option may be to deliver the vaccines through campaigns. Although many EPI programmes have significant experience with conducting large-scale and wide-age range campaigns with injectable vaccines (e.g. measles and Men A vaccines), there is limited experience with repeating such campaigns every six months. Other considerations for a campaign mode delivery include the added cost of *per diems* and other logistics, the additional trained manpower that may be needed, and the need to pay attention to how doses are recorded for individual vaccinees (especially those who may have missed the first or second waves of vaccination campaigns). Although the initial coverage may be high, with the build-up of new unvaccinated cohorts, issues of sustainability of the campaign approach will need to be addressed.

Outpatient settings

As all seropositive individuals with a reasonable likelihood of only having had one primary infection in the past will benefit from vaccination with CYD-TDV to reduce the risk of severe dengue during any subsequent wild type infection, private clinics, government clinics or any outpatient setting would provide opportunities for the individual use of CYD-TDV. Furthermore, patients with documented lab-confirmed past dengue infection could benefit from the opportunity to be vaccinated at outpatient settings.

Whether given at the health centre or through school-based campaigns or through campaigns, a three-dose vaccine given six months apart will require use of a vaccine registry maintained by the MOH and vaccination record for each vaccinee to ensure vaccinees receive all three doses. The majority of countries with dengue endemicity may need to build or strengthen such a tracking system.

Hospital settings

For patients hospitalized with laboratory confirmed dengue, vaccination with CYD-TDV could be offered at time of discharge. However, further studies may be needed to document that a very recent dengue illness (resulting in homotypic and heterotypic antibodies) does not suppress the immunogenicity of CYD-TDV.

Travel medicine settings

With increasing global travel including repeated travel to dengue endemic countries, travellers from dengue non-endemic countries may also increasingly have had a past exposure to a dengue infection. Such seropositive travellers may be concerned about repeat travel to a dengue endemic country for fear of severe dengue. However, the current 3-dose schedule renders the use of CYD-TDV in a travel medicine setting difficult, and the results of studies on alternative schedules would need to be available before this approach becomes more widely available. Furthermore, CYD-TDV is currently only registered in dengue endemic countries.

11. PLANNED POST-APPROVAL EVALUATION BY THE MANUFACTURER

The manufacturer has identified important areas for post-approval evaluation: YF vaccine-associated viscerotropic disease (AVD) and YF vaccine-associated neurotropic disease (AND), allergic reactions (including anaphylactic reactions), waning efficacy over time, co-administration with other vaccines, amongst others. Table 9 provides an update of the current status of studies to address these identified risks and research questions.

Table 9. Summary of Risk Management Plan (RMP) proposed by the manufacturer.

Type of Activity	Description	Status	Planned date for final report submission
Post-marketing pharmacovigilance (PV) activities	Routine PV monitoring Evaluate capacity building/Expand AE reporting awareness /Training	Ongoing	N/A
	Enhanced safety surveillance Reinforce AE/safety information Exchange between MoH/MAH and independent review by WHO	Ongoing	N/A
Long Term Monitoring of Efficacy studies	Surveillance expansion CYD 14&CYD 15 5year FU post dose 3 for CYD14 & CYD 15	Studies ongoing Yearly interim reports	Final reports: Q4 2018 (CYD 14) Q1 2019 (CYD 15)
	5 year-FU post dose 3 for CYD 57 (follow-up of CYD23)	Study completed	Final report released in Q4 2016
Active surveillance	DNG15.PASS-Cohort Event Monitoring	Ongoing	2025*
	DNG16-PASS- Pregnancy registry	Planned to start in 2018*	2023*
	DNG11: Background incidence rate of conditions mimicking viscerotropism and neurotropism	Completed	Final report released in Q4 2017
Effectiveness studies §	CYD52 in Mexico (Yucatan)	Planned condition on mass vaccination campaigns	Dependent on study start
	CYD70 in Brazil (Goiana & Sao Paolo)		
	CYD 53 in Malaysia		
	CYD 69 in Philippines	Planned to start in 2018*	2023*
	DNG10042 in Brazil (Parana)	Ongoing	2020
Additional clinical studies	Booster studies (CYD63, CYD64 and CYD65)	Ongoing	2019 (CYD63 and CYD64), 2020 (CYD65)
	Study in clinically-stable HIV+ subjects in Latin America (CYD50)	Planned to start in 2019	2021, if starts in 2019
	Co-administration studies (with HPV vaccines, Tdap) (CYD66, CYD67, CYD71	Ongoing	2020
Risk minimization activities	Routine: Product Information Update	Submitted**	N/A
	Additional: Direct HealthCare Professional letter HealthCare Professional guide	Submitted/implemented In preparation	N/A

* Study start and finish date may vary depending on the vaccine availability and introduction through mass vaccination programs, and other external factors

** This labelling update was submitted through a safety labelling variation (LCR F2017-724546 for CCDS version 4.0 dated 17 November 2017)

§ Effectiveness studies preceded by preparation studies: DNG25 in Mexico, DNG28 in Brazil, DNG13 in Malaysia

Vaccine schedules

A study was initiated to look at immunogenicity and safety in approximately 1,000 participants 9-50 years of age who received either 1, 2, or 3 doses of the vaccine, and a booster dose at 12-24 months after the last dose (NCT02628444). After the start of the study, the protocol was amended according to IDMC recommendations related to the results of additional exploratory analyses (NS1 study) in order to stop any further vaccination of seronegative individuals. Based on these recommendations, booster vaccinations are planned only in seropositive individuals, and the results will be presented only in seropositive subjects.

Co-Administration

Three Phase 3b, open-label, observer-masked co-administration studies have been identified as high priority given the indicated age range: HPV (tetravalent and bivalent) and Tdap. These studies will assess the impact of co-administration on immunogenicity of each vaccine, as well as safety and reactogenicity. The initial clinical trial protocols of these 3 studies have been amended based on the recommendations from the IDMC after the review of the results of the additional NS1 studies. All subjects included in these trials have received at least one injection of the CYD-TDV. Baseline serostatus will be made available for all subjects included in the trials. Once the protocol amendment is approved, only the subjects assessed as seropositive for dengue before the first injection will proceed with the remaining injections. As a consequence, the number of subjects who will receive the 3 injections will be lower compared to the initial plan and the outcome of the studies could be only descriptive (as the number of subjects needed for statistical testing may not be reached). The three studies are currently on-hold and will resume once the protocol amendments, currently being reviewed by Ethics Committees and Health Authorities, are approved. This will have an impact on the availability of the results of the co-administration studies: the clinical study report describing the results obtained up to 28 days after the first injection in CYD66 (co-administration with Tdap) will be available in Q4 2018. The final clinical study reports of the three studies will be available in Q1 2020.

Booster dose

Two studies that capitalize on vaccinated recipients from previous Phase 1 and Phase 2 trials are mentioned under the RMP, one study in Asia in a low endemic region (CYD 63), and one in Latin America (CYD64) (Mexico, Honduras, Puerto Rico, Colombia and Brazil). Following a gap of 4-5 years after the primary series of CYD-TDV, a single booster dose of CYD-TDV or placebo will be assessed in terms of non-inferiority of the antibody response.

In interim results from the study conducted in Latin America (NCT02623725) among subjects 9-16 years of age, regardless of serostatus, non-inferiority of the immune response measured 28 days after the CYD dengue vaccine booster injection compared to the third injection of the primary series was demonstrated for each serotype and overall in interim results. The superiority of the booster injection compared to the third injection of the primary was demonstrated for serotypes 1, 2 and 4. This study demonstrated that the anti-Dengue neutralizing antibody levels measured 28 days after booster vaccination can reach levels at least as high as or higher than after the 3rd dose through the stimulation of immunological memory with a CYD-TDV dose 4-5 years after the standard 3-dose vaccination schedule.

Safety

In the study conducted in Latin America, the overall safety profile of the CYD dengue vaccine booster injection was comparable to the controls in terms of frequency, duration and severity of AEs (Coronel D, Garcia E, Rivera M, et al. Dengue Vaccine Booster in Healthy Adolescents and Adults 4 to 5 years after a 3-Dose Primary Schedule in Latin America. Poster presented at: XVII Congreso SLIPE; 2017 Nov 8-11; Cancun, Mexico)

12. SUMMARY OF CRITICAL ASSESSMENTS

12.1 Vaccine efficacy and long-term safety

a) Seropositive trial participants

Table 10 summarizes the efficacy against symptomatic VCD in the first 25 months after first vaccination, and the long-term safety follow up to 66 months, expressed as Hazard Ratio (HR) against hospitalized dengue and severe dengue in inferred baseline seropositive subjects 9-16 years of age. Vaccine efficacy based on the NS1 antibody assay likely underestimates the true efficacy (due to misclassification issues as explained under "Study Design"). Based on the PRNT results in the immunogenicity subset, vaccine efficacy was (81.9%, 95%CI 67.2-90.0) among seropositive participants and 52.5% (95%CI 5.9-76.1) among participants who were seronegative at baseline.

No data beyond 25 months are currently available to assess the long-term efficacy of symptomatic VCD, which presents an evidence gap.

Table 10. Vaccine efficacy and cumulative long-term safety in seropositive trial participants. n represents the number of subjects fulfilling the item listed and N represents the total number of subjects selected in sub-cohort; n and N are average numbers from 10 iterations of multiple imputations

	Number of Subjects with Cases				
	Vaccine Group n (N)	**Placebo Group n (N)**	**Vaccine Efficacy (%)**	**95% Confidence Interval**	**p-value**
Symptomatic VCD (M0-M25)	192.7 (1441.4)	372.1 (697.3)	76	(63.9, 84.0)	<0.001
	Number of Subjects with Cases				
	Vaccine Group n (N)	**Placebo Group n (N)**	**Hazard Ratio**	**95% Confidence Interval**	**p-value**
Hospitalized dengue (M0-M60-72)	58.8 (1502.9)	137.7 (729.8)	0.21	(0.138, 0.307)	<0.001
Severe dengue (M0-M60-72)	11.2 (1502.9)	33.4 (729.8)	0.16	(0.068, 0.371)	<0.001

b) Seronegative trial participants

Table 11 summarizes the efficacy against symptomatic VCD in the first 25 months after first vaccination, and the long-term safety follow up to 66 months, expressed as Hazard Ratio against hospitalized dengue and severe dengue in inferred baseline seronegative subjects 9-16 years of age.

Table 11. Estimates in seronegative subjects 9-16 years of age with Multiple Imputation M0 onwards. n represents the number of subjects fulfilling the item listed and N represents the total number of subjects selected in sub-cohort; n and N are average numbers from 10 iterations of multiple imputations

	Number of Subjects with Cases				
	Vaccine Group n (N)	**Placebo Group n (N)**	**Vaccine Efficacy (%)**	**95% Confidence Interval**	**p-value**
Symptomatic VCD (M0-M25)	174.3 (353.6)	148.9 (193.7)	39	(-1, 63)	0.054
	Number of Subjects with Cases				
	Vaccine Group n (N)	**Placebo Group n (N)**	**Hazard Ratio**	**95% Confidence Interval**	**p-value**
Hospitalized dengue (M0-M60-72)	64.2 (375.1)	25.3 (207.2)	1.41	(0.74, 2.68)	0.287
Severe dengue (M0-M60-72)	14.8 (375.1)	3.6 (207.2)	2.44	(0.47, 12.56)	0.283

- The HRs for the entire trial population (aged 2-16) for hospitalized VCD and severe VCD in seronegative children were 1.65 (95%CI: 1.047-2.614; p=0.031) and 2.997 (95% CI 1.102-8.148; p=0.032), respectively, over 66 months.

- The excess risk was apparent from month 30 of the trial (17 months after the 3rd dose) in seronegatives aged 9 years and above and persisted throughout the 66 months of available observation time. The excess risk was apparent from month 18 in children <9 years of age.

- The magnitude of risk was higher in younger children. The HRs for hospitalized VCD and severe VCD in seronegative children aged 2-8 were 1.95 (95%CI: 1.19;3.19, p=0.008) and 3.31 (95%CI: 0.87;12.54, p=0.077), respectively, over 66 months.

- Clinical manifestations of severe dengue were similar in vaccinated seronegative persons compared to unvaccinated seropositive persons, consistent with the working hypothesis that CYD-TDV vaccination mimics a primary-like dengue infection.
- The majority of severe cases were classified as DHF I and DHF II and all recovered.

12.2 Assessment of modelled long-term benefit in seronegative subjects

Mathematical modelling, based on plausible assumptions on the mode of action of the vaccine, predicts that the harm in seronegatives following vaccination over time will be balanced by excess cases of severe disease in the unvaccinated seronegatives at later time periods in areas of high incidence where nearly all individuals will be infected with dengue at least twice in their lifetime.

- Risk increase in seronegatives occurs relatively soon after vaccination (from month 30 onwards in those aged 9 years and above)

- Predicted benefit in seronegative (reduction in long-term cumulative risk of hospitalised dengue) takes longer to accumulate and depends on dengue transmission intensity
- Timescale over which cumulative risk excess falls to zero is sensitive to assumptions about vaccine action (and statistical uncertainty)
- Excess risk can take >30 years to reach zero (if ever achieved) in lower seroprevalence settings
- For positive benefit in seronegative 9 year-olds in <10 years, need >80% seropositivity in that age group (>90% for benefit in 6 years)
- Risk in seronegatives is clear from the data; benefit (or at least reduction of relative risk over time) is predicted from modelling, but yet to be proven

12.3 Assessment of 3-dose schedule

A 3-dose schedule given 6 months apart is not optimal from a programmatic perspective. Immunogenicity in seropositives is high after the first dose and does not increase with subsequent doses. Phase 3 trial data suggest protection from the vaccine begins with the first dose. However, due to the high vaccine series completion rate in the trial, there are insufficient data to evaluate efficacy during the 25 follow up period by dose received, other than in the 6 months following each dose. Therefore, until additional data are available on fewer than three doses through vaccine effectiveness studies, or until an immune correlate of protection is available, the protection seen in the trial can only be assured through use of a 3-dose schedule.

12.4 Assessment of population seroprevalence criteria to introduce mass vaccination without individual screening

While it is recognized that targeting vaccination based on high seroprevalence criteria would result in a substantially larger number of severe and hospitalized dengue cases prevented in seropositive individuals than the number of such cases induced by priming seronegatives through vaccination, several major challenges have been highlighted in previous sections of the background paper.

Challenge 1: spatiotemporal heterogeneity of dengue transmission

- Transmission intensity varies over fine geographic scales
- Requires very large scale serosurveys to characterise

Challenge 2: coverage/impact

- Very few locations have seroprevalence > 80% in 9 year olds
- Almost no locations globally where seroprevalence in 9 year olds is >90%

Challenge 3: communication/uncertainties

- Long-term benefit in seronegatives not (yet) demonstrated in trial data
- Risk occurs before benefit, and is quantifiable

The optimal indication would be seroprevalence rates in a population or subpopulation exceeding 80% by the age of 9. In this setting the public health impact would be highest, and the harm to seronegatives lowest. It is important to note that if one increases the target age group, the seroprevalence threshold above which seronegatives see benefit also increases, explained by the fact that a certain average force of infection is being targeted. A setting with an average force of infection of 18% per year would be expected to have 80% seroprevalence in 9 year olds and 94% seroprevalence in 16 year olds. Changing the threshold seroprevalence affects the timescale over which benefit would be expected in seronegatives.

Cost-effectiveness analyses that incorporate the costs of high-resolution serosurveys to identify subnational areas of seroprevalence clearly above 80% have not been untertaken to date. Country-specific analyses will be needed to assess cost-effectiveness with locally relevant parameters.

12.5 Assessment of pre-vaccination screening

The advantages of a "pre-vaccination screening" strategy is that risk associated with vaccinating seronegatives can be minimized, while maximizing benefit from targeting seropositives only. One advantage of the pre-vaccination screening strategy over a "population seroprevalence criteria mass vaccination" is that the former strategy may also be considered in low to moderate transmission settings. Preliminary modelling predicts that more people would be eligible for vaccination using the pre-vaccination screening strategy than the seroprevalence based strategy refer to "programmatic use"). However, there are also some major challenges:

Challenge 1: age-targeting

- Too young: a high proportion of the population is still seronegative
- Too old: high proportion of the population will already have had 2 infections

Challenge 2: test performance

- High specificity required to minimise risk
- But consequence may be low sensitivity – and hence reduced impact

Challenge 3: policy design

- Mass vaccination – single age, or multiple ages?
- Private use – communicating context-specific benefits

The public health impact of the "screen and vaccinate" strategy depends on test sensitivity. High sensitivity ensures that eligible persons receive the vaccine. High specificity ensures that the risk to seronegatives is minimized. High specificity is more important in lower transmission settings. In a high transmission area with high seroprevaelnce, although high specificity is always desirable, the proportion of misclassified seronegatives will be small even with suboptimal specificty. In Table 12 the reduction in dengue incidence in a vaccinated cohort calculated from the age of vaccination onwards, versus vaccinating without serotesting, is represented. As the impact is dependent on underlying seroprevalence in the population, three scenarios are presented (seroprevalence 70, 80 and 90%).

Table 12. Expected number and proportion of dengue events prevented in a cohort of 100,000 vaccinated individuals over a 5-year follow-up with and without serotesting (Table provided by Sanofi Pasteur)

Cases prevented*										
Dengue seroprevalence	**Events**	**Vaccinate without serotesting**			**Screen and vaccinate**					
					Sensitivity 90%, Specificity 99%			**Sensitivity 69%, Specificity 98%**		
		Sero+	**Sero-**	**All**	**Sero+**	**Sero-**	**All**	**Sero+**	**Sero-**	**All**
90%	**Hospitalized cases**	1357 (80,1%)	-48 (-43,7%)	**1309 (72,6%)**	1221 (72,1%)	0 (-0,4%)	**1221 (67,7%)**	936 (55,2%)	-1 (-0,9%)	**935 (51,8%)**
	Severe cases	364 (84,3%)	-23 (132,2%)	**341 (75,9%)**	328 (75,9%)	0 (-1,32%)	**328 (72,9%)**	251 (58,2%)	0 (-2,6%)	**251 (55,8%)**
80%	**Hospitalized cases**	1206 (80,1%)	-96 (-43,7%)	**1110 (64,4%)**	1085 (72,1%)	-1 (-0,4%)	**1084 (62,9%)**	832 (55,2%)	-2 (-0,9%)	**830 (48,1%)**
	Severe cases	324 (84,3%)	-46 (132,2%)	**278 (66,3%)**	291 (75,9%)	0 (-1,32%)	**291 (69,5%)**	223 (58,2%)	-1 (-2,6%)	**222 (53,1%)**
70%	**Hospitalized cases**	1055 (80,1%)	-143 (-43,7%)	**912 (55,4%)**	950 (72,1%)	-1 (-0,4%)	**948 (57,6%)**	728 (55,2%)	-3 (-0,9%)	**725 (44,1%)**
	Severe cases	1357 (80,1%)	-48 (-43,7%)	**1309 (72,6%)**	1221 (72,1%)	0 (-0,4%)	**1221 (67,7%)**	195 (58,2%)	-1 (-2,6%)	**194 (50%)**

**Compared to no vaccination, negative numbers correspond to excess cases.*

- Numbers reflect cases prevented compared to no vaccination.
- Percentage in brackets are proportion increase or decrease compared to no vaccination setting
- Incidence is based on cumulative incidence over the first 5 years following dose 1observed in 9-16 years old in clinical trials (pooled studies), Multiple Imputation approach from M0

Age-targeting:

Transmission intensity will determine the most optimal age for the "screen and test" strategy. A good proxy for the optimal target age for a single round vaccination is the age when hospitalizations due to dengue peak.
Table 13 shows the preliminary modeling results on both optimal age and estimated population based long-term reduction in total burden of hospitalised dengue over 30 years based on the "pre-vaccination screening" policy. In contrast to the reduction of burden in the vaccinated cohort (Table 12), the model results in Table 13 estimate the reduction of the overall burden of hospitalised dengue in the population.

Table 13. Preliminary modelling results on both optimal age and estimated population based long-term reduction in total burden of hospitalised dengue over 30 years based on the "pre-vaccination screening" strategy (prepared by Neil Ferguson, Imperial College)

Transmission setting (seroprevalence in 9 year-olds)	Optimal age for screen and vaccinate	30yr reduction in total burden of hospitalised dengue with 80% coverage of screen and vaccinate policy, assuming: • Test sensitivity of 90% • Test specificity of 95% • Targeted at optimal age within range 9-18	30yr reduction in total burden of hospitalised dengue with 100% coverage of screen and vaccinate policy, assuming: • Test sensitivity of 100% • Test specificity of 100% • Targeted at optimal age within range 9-18
40	>18	12%	18%
45	>18	13%	20%
50	18	14%	21%
55	17	15%	21%
60	16	15%	21%
65	15	15%	21%
70	13	15%	21%
75	11	15%	21%
80	9	15%	21%
85	8	15%	21%
90	7	14%	20%

If programmatically feasible, repeated RDT testing in vaccination-naïve individuals from early childhood might increase the overall impact of screen and vaccinated policies, albeit at considerable additional cost and diminishing returns after the first round.

12.6 Comparison of "pre-vaccination screening" with "population seroprevalence criteria"

Both the "pre-vaccination screening" and the "population seroprevalence criteria" approach are logistically challenging and associated with additional costs beyond those associated with a more typical blanket vaccination programme. A significant advantage of the "screen and vaccinate" strategy is that it can also be used in moderate transmission settings with similar levels of expected impact, so long as the age of vaccination is tuned for maximal impact. Table 14 summarises the different aspects to be considered in the choice of the population seroprevalence criteria versus pre-vaccination screening.

Table 14. Comparison of the two strategies: population seroprevalence criteria versus individual pre-vaccination screening

	Population Seroprevalence Criteria without Screening	Pre-Vaccination Screening
Benefits and harm	Overall substantial population benefit in areas with high seroprevalence predicted. An identifiable subset of the population will be put at increased risk of severe dengue, at least in the short to medium term.	Maximizing the benefit (high efficacy and good safety) in seropositive while avoiding harm in correctly identified seronegatives. Some seronegative individuals will be put at increased risk of severe dengue if vaccinated due to a false positive screening test result.
Proportion of vaccinated population that will be put at increased risk of severe dengue	Dependent on seroprevalence criteria chosen: if vaccine is introduced in a setting with 80% seroprevalence, 20% of the vaccinated population will be put at risk.	Dependent on the specificity of the screening test. In a setting with 80% seroprevalence and a test with 80% specificity, 20% of true seronegatives will be unintentionally vaccinated. That is, 4% of the total population would be unintentionally vaccinated. In a setting with 80% seroprevalence and a test with 98% specificity, 0.4% of the population would be unintentionally vaccinated.
Population eligible for vaccination	Subnational areas with seroprevalence >80% in 9 year olds are predicted by modelling to be rare, those with seroprevalence >90% by the age of 9 very rare.	Modelling predicts vaccine eligibility will be higher on a population basis compared to the seroprevalence criteria strategy, as all seropositive persons in the population are eligible. Strategy can be used in both high and moderate transmission settings, although pre-test probability will be higher in high transmission settings.
Risk perceptions	Loss in vaccine confidence (dengue vaccines and possibly other vaccines). Inability of vaccinees to know own serostatus may lead to increased vaccine hesitancy.	Risk of false positive test: seronegative individuals will be misclassified as seropositive and unintentionally vaccinated as no test will be 100% specific.
Challenges for implementation	Dengue transmission exhibits a high spatiotemporal heterogeneity. To identify subnational areas with seroprevalence above 80% by age 9 years, multiple small-scale age stratified seroprevalence studies need to be conducted. Limitations of available tests require additional validation work to estimate seroprevalence. Providing appropriate information to those eligible for vaccination of the potential risks and benefits will be more challenging than for other vaccines.	Pre-vaccination blood sampling may lead to decreased acceptance of the vaccination programme No RDT has been validated or licensed for the indication of screening for past dengue infection. Unlikely that any test will have a 100% specificity, thereby still putting some truly seronegatives at risk. Tests with high sensitivity are needed to ensure that a large proportion of seropositives will benefit from CYD-TDV.
Population impact	Given that areas with seroprevalence above 80% by age 9 are predicted to be rare, population impact is likely to be low.	Population impact on reduction of hospitalized dengue modelled at approximately 20% over 30 years

Continued on next page

	Population Seroprevalence Criteria without Screening	Pre-Vaccination Screening
Age	Seroprevalence threshold in target age group increases for higher target ages. So while 80% seroprevalence required for a target age of 9 years, a seroprevalence threshold of 90% or more is required if 16 year olds are targeted.	Seropositive individuals of any age as indicated in the label can be targeted. As monotypic seropositives would be the target group that will benefit most from CYD-TDV, the optimal age for vaccine introduction will depend on dengue transmission intensity and can be informed by the age at which dengue hospitalisations due to severe dengue peaks.
Cost effectiveness	Cost effectiveness studies not done for scenarios of >80% seroprevalence. Cost effectiveness studies done in 2016 for seroprevalence threshold at 70% can be found in(7) Cost-effectiveness studies need to take into account the costs required to conduct population serosurveys to identify sub-national areas with seroprevalence above 80%.	No cost-effectiveness studies have been conducted to date. Cost-effectiveness studies need to take into account cost associated with identifying seropositives.

12.7 Indirect effect of vaccination with CYD-TDV

Since vaccination only transiently reduces the risk of infection and the main effect of vaccination is to modify the risk of disease, mathematical modelling predicts that the indirect effect of vaccination on DENV transmission will be limited(8). This explains why the predicted impacts of routine vaccination (whether positive or negative) scale almost linearly with vaccine coverage. The only empiric data available to date on the reduction of asymptomatic infections is based on a study between months 13 and 25 after the first dose and was not stratified by serostatus.(25). The efficacy of CYD-TDV against asymptomatic dengue virus infection was assessed using pooled data for 3736 individuals in the phase 3 trials who received either CYD-TDV or placebo and found a vaccine efficacy of 33.5% (95% CI, 17.9%–46.1%) against asymptomatic infection. The annual incidence of asymptomatic dengue virus infection in this age group was 14.8%, which was 4.4 times higher than the incidence for symptomatic dengue (3.4%).

12.8 Non-dengue serious adverse events

Data from Phase 2 and Phase 3 trials have not signalled any safety concern other than the dengue-related signal described above. With regard to traditional safety considerations (reactogenicity, serious adverse events, etc.), CYD-TDV is well-tolerated. Due to the hypothetical risk of viscerotropic (AVD) and neurotropic disease (AND), the sponsor identified these events as adverse events of special interest and has initiated studies to assess background rates of AVD/AND-like disease, followed by post-licensure cohort event monitoring. To date, no cases of viscerotropic or neurotropic disease have been reported. The licensed Japanese encephalitis vaccine using the same ChimeriVax technology, IMOJEV®, is similarly being evaluated, with no signal to date.

12.9 CYD-TDV in the context of the dengue control program

CYD-TDV is a partially efficacious vaccine and vector control must remain a critical component of dengue control programs. Furthermore, the mosquito vectors of dengue transmit other important viruses, including Yellow Fever, Chikungunya, and Zika virus. Vaccination should be viewed as part of an integrated strategy to control dengue(26).

12.10 Second-generation dengue vaccines

CYD-TDV is the only vaccine licensed against dengue at this point in time. Two other candidate vaccines are currently being evaluated in large Phase 3 trials(27, 28). The data obtained from these trials are needed before the vaccines may be licensed by national regulatory authorities. No conclusions can be drawn from the data generated from CYD-TDV onto these two candidate vaccines.

WHO convened a technical consultation in June 2017 to guide dengue vaccine developers on trial design and duration of observation to enable broader public health recommendations for second-generation dengue vaccines(29). The clinical development of second generation vaccines would be greatly facilitated if established correlates of protection were available(30). Both correlates of protection and correlates of enhancement are needed (29, 31).

13. KEY RECOMMENDATIONS

The WG came to the overall conclusion that CYD-TDV still has a potential public health role, in the absence of currently available alternative solutions to combat the expanding problem of the global dengue burden. The challenge is how best to use CYD-TDV to maximize the public health impact, and minimize harm. In these deliberations, two main approaches were considered if the vaccine were to be further used in public programs:

- Subnational or national mass vaccination strategy based on population seroprevalence criteria, and
- Pre-vaccination screening whereby only those tested seropositive will be vaccinated

<u>Population Seroprevalence Criteria</u>

While implementing vaccination based on high seroprevalence criteria would result in a substantially larger number of severe and hospitalized dengue cases prevented in seropositive individuals than the number of excess cases resulting from priming seronegatives through vaccination, several major challenges warrant consideration:

(1) To minimize harm in seronegatives, high seroprevalence thresholds of 80% and above in 9-year olds would be required.
(2) Very few locations have seroprevalence > 80% in 9 year olds, and even fever have locations with seroprevalence >90% in 9 year olds.
(3) The spatiotemporal heterogeneity of dengue transmission combined with the need for high seroprevalence thresholds would necessitate large scale serosurveys to identify suitable areas at micro scale, thus adding complexity and cost to any public vaccination programme.
(4) Given the limited areas with such high seroprevalence rates, national coverage rates would be low and hence the overall public health impact potentially limited.
(5) A potentially identifiable subpopulation of seronegative persons would be put at increased risk of severe dengue, at least for a period of time
(6) Communication around a strategy where a subpopulation would be put at risk for the sake of overall population level benefit would be challenging, and may undermine vaccine confidence in general.

Recognizing the hurdles of individual testing, combined with the documented overall population benefit of CYD-TDV in very high transmission settings, the use of CYD-TDV without individual pre-vaccination testing could be considered by countries with subnational areas with very high transmission intensity, as defined by

seroprevalence in 9-year olds of 80% and above. It is expected that only a very small proportion of subnational areas in most endemic countries will meet this criterion. Local, recent, age-stratified seroprevalence studies would have to be used to guide decision-making and introduction at subnational levels. Such programmes would need to take into account the feasibility and cost of seroprevalence studies, public confidence in national vaccination programmes, and perceptions of ethical considerations with regard to population level benefit versus individual level risk. Communication would have to ensure due regard for appropriate and full disclosure of risks of vaccination with regards to unknown serostatus.

Pre-vaccination Screening

With this strategy, only persons with evidence of a past dengue infection would be vaccinated (based on a screening test, or in some cases based on a documented laboratory confirmed dengue infection in the past). This approach would maximize the benefit from the vaccine by targeting seropositives, and minimize the risk associated with vaccinating seronegative persons. The pre-test probability of an individual being seropositive will be higher in settings with high endemic transmission and thus a "pre-vaccination screening" strategy would likely be more cost effective in such settings than in areas of lower endemicity. The advantage of the "pre-vaccination screening strategy" over "population seroprevalence criteria" is that this strategy may also be considered in low to moderate transmission settings. Preliminary mathematical modelling shows that the population level coverage rates achieved by the "screen and vaccinate" strategy would be higher than that achieved by the seroprevalence criteria based strategy. Individuals who only had one past dengue infection (monotypic past infection) will benefit most from CYD-TDV. The likelihood of having had two or more dengue infections increases with age and with the transmission intensity in any given country. The age group in which the highest dengue hospitalizations occur in a given area, based on surveillance, would be the modelled optimum age target for vaccination.

Despite the advantages of the "Pre-vaccination screening" strategy, major challenges remain:

(1) Screening tests would need to be highly specific to avoid harm in seronegative persons, and would need to be highly sensistive to ensure that the vast majority of seropositive persons would benefit.
(2) Such tests would preferentially need to be deliverable at point-of-care as rapid diagnostic tests (RDT).
(3) To date, no RDTs has been validated and licensed for the indication of screening for past dengue infection (seropositivity).
(4) Pre-vaccination screening poses significant hurdles in large-scale vaccination programmes.

The WG concluded that both "Population Seroprevalence Criteria" and "Pre-vaccination screening" are imperfect approaches for achieving high population protection from dengue because they are each programmatically difficult, for different reasons and with different consequences.

Proposed Recommendations

For countries considering vaccination as part of their dengue control program, a "pre-vaccination screening strategy" would be the preferred option, in which only dengue-seropositive persons are vaccinated.

Conventional serological testing for dengue virus IgG (e.g. dengue IgG ELISA) could be used to identify persons who have had previous dengue infections. Sensitivity and specificity of dengue IgG ELISA should be assessed in a local context, and will depend on the prevalence of other flaviviruses, and past use of flavivirus vaccines (such as Japanese encephalitis and yellow fever vaccines).

Currently available rapid diagnostic tests - despite their lower sensitivity and specificity to detect past dengue infection compared with conventional dengue IgG ELISA - could be considered in high transmission settings until better tests are available. In settings with high dengue transmission (high numbers of seropositives), a test with lower specificity might be acceptable.

The pre-test probability of an individual being seropositive will be higher in settings with high transmission. However, a pre-vaccination screening strategy may also be considered in low to moderate transmission settings. In settings with low transmission (high numbers of seronegatives) a test with high specificity is needed.

Given that no assay will be 100% specific, some truly seronegative individuals may be vaccinated due to a false positive test result. Furthermore, although the efficacy against dengue infections in seropositive individuals is high, it is still not complete. Hence, the limitations of CYD-TDV will need to be clearly communicated to populations offered vaccination.

There is a continued need to adhere to other disease preventive measures and to seek prompt medical care in the event of dengue-like symptoms, regardless of whether vaccinated or not. Vaccination should be considered as part of an integrated dengue prevention and control strategy together with well-executed and sustained vector control and the best evidence-based clinical care for all patients with dengue.

Decisions about implementing a "pre-vaccination screening" strategy with the currently available tests will require careful assessment at the country level, including consideration of the sensitivity and specificity of available tests and of local priorities, dengue epidemiology, country-specific dengue hospitalization rates, and affordability of both CYD-TDV and screening tests.

Age

Whether there are age-specific effects, independent of serostatus, is the subject of ongoing research. Currently, the vaccine should be used within the indicated age range, which is typically 9 to 45 years of age. The age to target for vaccination depends on the dengue transmission intensity in a given country, and will be lower in countries with high transmission, and higher in countries with low transmission. The optimal age group to be targeted is the age at which severe dengue disease incidence is highest, and this can be ascertained from national and subnational routine hospital surveillance data.

Schedule

In the absence of data on vaccine efficacy and safety with fewer than three doses, CYD-TDV is recommended as a three dose series given 6 months apart. Should a vaccine dose be delayed for any reason, it is not necessary to restart the course and the next dose in the series should be administered.

Booster

There are currently no data on the use of booster doses. Additional studies to determine the utility of a booster dose and its best timing are under way. Accordingly, there is no current recommendation for a booster dose.

Research priorities

Development of a highly sensitive and specific rapid diagnostic test to determine serostatus, and assessment of simplified immunization schedules and booster needs should be prioritized.

Special settings and populations:

Outbreak response

CYD-TDV should not be considered as a tool for outbreak response. A dengue outbreak is a signal that an improved dengue control strategy is needed. When an outbreak occurs in an area that meets the criteria for routine introduction in relation to transmission intensity, vaccination with the 3-dose schedule as part of an overall dengue control strategy may be considered.

Special populations

Pregnant women: CYD-TDV is contraindicated in pregnant and lactating women because insufficient data have so far been gathered on its use in pregnancy. However, based on limited data generated from inadvertent pregnancies that occurred during clinical trials, there are no data to warrant termination of an inadvertent pregnancy should the vaccination have occurred anytime during pregnancy. If a woman becomes pregnant before all three doses have been administered, the remaining doses should be administered after lactation.

Immunocompromised: CYD-TDV is contraindicated in immunocompromised individuals. More data will be available from upcoming studies in HIV-infected individuals.

Travellers: In travellers who have already been previously infected with dengue, vaccination for travel to high dengue transmission settings may be beneficial.

Surveillance

Dengue surveillance should be strengthened, particularly in the context of emerging infections with clinical similarities to dengue. In areas of the world for which there is a paucity of data, further characterization of the burden of dengue, which appears to be growing, is needed. Harmonized case-definitions are encouraged to enhance data sharing and comparisons across regions.

Using surveillance data to monitor population impact of a vaccination program may be challenging as the year-to-year variability in dengue transmission may be greater than the expected vaccine impact. Long-term monitoring for severe dengue in vaccinated subjects to assess long-term effects of vaccination should be done in selected areas.

14. RESEARCH PRIORITIES

Tables 15 and 16 summarize the research priorities for CYD-TDV and beyond.

Table 15. Research questions to be addressed in the Risk Management Programme (RMP) by Sanofi Pasteur and other research questions beyond the RMP.

Research Question	Priority	Addressed in RMP?	Notes
Improved point of care (POC) tests to identify seropositive/ seronegative individuals	**Critical**	Dedicated studies are needed. Not addressed by RMP, but Sanofi Pasteur has expressed their intent to co-develop rapid diagnostic tests	Improved POC tests to identify past dengue infection
Duration of protection / need for booster doses	**Critical**	CYD14 and CYD15 long-term follow up will inform duration of protection, and booster dose studies are underway by the manufacturer.	Post-licensure monitoring will need to contribute to follow up for time periods beyond the 6 years planned in the clinical trials.
Vaccine effectiveness with fewer than three doses	**Critical**	Vaccine effectiveness studies are included in RMP.	
Cost-effectiveness of "screen and vaccinate" strategies	**Critical**	Out of scope of RMP	Cost-effectiveness based on seroprevalence and heterogeneity of seroprevalence in a given country
Novel diagnostic assays to diagnose past or recent dengue infections in vaccinated individuals	High	Out of scope of RMP	
Co-administration with age-appropriate vaccines	High	Co-administration studies are planned by the manufacturer.	Of particular interest are co-administration with HPV vaccines and Tdap
Health impact assessment of vaccination program	High	Planned as part of RMP	
Long-term transmission dynamics (serotype/ genotype selection)	High	Out of scope of RMP	As seen for other vaccine preventable diseases, serotype replacement is a real risk and should be monitored. Dedicated studies are needed.

Table 16. Research priorities for the dengue vaccine field identified by the SAGE Working Group on Dengue Vaccines.

General Research Areas	Priority	Notes
Second-generation vaccines that include characteristics such as improved protection against all four dengue serotypes, single-dose, for use in younger age groups	**Critical**	Two Phase 3 trials are ongoing; results to be expected by Q1 2019
Immune correlate of protection, immune correlates of disease enhancement	High	Broader efforts that could potentially be extrapolated to other/all dengue vaccines are needed. Dedicated studies are needed.
Implementation strategies for "screen and vaccinate" policies	High	Operational research
Optimal integrated dengue control strategy (vector control strategies together with vaccination for maximum public health impact)	High	Dedicated studies are needed to understand the effectiveness of vector control and optimal integrated strategies.
Development of simple mathematical modelling tools for country use in decision-making with consideration of the local context.	High	Dedicated efforts are needed.
Research on dengue burden in Africa	High	Dedicated studies are needed.

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