BACKGROUND PAPER ON DENGUE VACCINES

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

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1. EXECUTIVE SUMMARY

Dengue is the most extensively spread mosquito-borne virus. In the last 60 years the incidence of cases of clinical dengue reported to WHO has increased 30-fold, with a much increased geographic range and expansion from urban to rural settings. 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 and large scale trials are lacking. The world requires a safe and efficacious dengue vaccine.

The first dengue vaccine, CYD-TDV (Dengvaxia®) has now been licensed by several dengue-endemic countries in Asia and Latin America for use in 9-45 or 9-60 year-olds, and it is under regulatory review in several others. To support licensure, CYD-TDV was evaluated in two parallel Phase 3 clinical trials, known as CYD14 and CYD15. 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. In the trials the vaccine was evaluated with a 3-dose schedule given at 0/6/12 months.

In the trials, the vaccine showed partial protection against virologically-confirmed dengue in the two years after the first dose, during which time there was active surveillance for symptomatic dengue of any severity. Vaccine efficacy over 25 months from the first dose among 9-16 year-olds, pooled from both CYD14 and CYD15 (post-hoc analysis), was 65.6% (95%CI 60.7-69.9). Protection was evident following the first dose and showed little variation up to one year following the third dose. Vaccine efficacy in these first 25 months varied by infecting serotype (higher protection against DENV 3 and 4), age (higher protection in 9-16 year age group), and severity (higher protection against hospitalized and severe dengue). Most notably, vaccine efficacy was high among participants 9 years of age or older who were seropositive (i.e., had previous exposure to dengue) at baseline (81.9%, 95%CI 67.2-90.0), and lower 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 80% in both Phase 3 trials.

After these first 25 months of follow up, participants were monitored for dengue disease on the basis of hospitalizations only. In most age groups, there was continued partial protection through the ongoing 5th year of follow up. In those first vaccinated at ages 2-5 years in Asia, a statistically significant increased risk of hospitalized dengue was seen in vaccine recipients in the third year after the first dose. The increased risk diminished and was not statistically significantly elevated compared to controls in the 4th and 5th years. Considering follow up from the beginning of the trial to date, there is an excess of cases of hospitalized dengue among vaccinated children in the 2-5 year age group, which is not statistically significant. No other safety signals have been identified in any age group. Aggregated across all efficacy trials with over 4 years of follow up, there was evidence that CYD-TDV was partially protective against hospitalized dengue in those aged older than 5 years at first vaccination. These findings led to the current indication, the intention being to set it conservatively, starting at 9 years of age.

Mathematical modelling suggests 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. The modelling predicted that the vaccine would be less beneficial in low transmission settings, due to the higher proportion of seronegative individuals, among whom the vaccine may have limited protective effect.

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

Given the predicted variable impact of the vaccine according to transmission intensity, the modelling indicated that it is a better use of resources to target vaccination to areas with higher transmission. As with many mosquito-borne diseases, dengue transmission is highly heterogeneous and may vary substantially across small geographical areas, suggesting a potential benefit to subnational, targeted introduction.

While there are currently no data to indicate an increased risk of hospitalization due to dengue in vaccine recipients in the indicated age range of 9-45 years, *there is a theoretical possibility that vaccination may be ineffective or may even increase that risk in those who are seronegative at the time of first vaccination*. Targeted studies, in parallel to vaccine implementation, are needed to address these questions, otherwise it will remain a controversial issue and could compromise public confidence in the vaccine program.

Proposed Recommendations

Countries should consider introduction of CYD-TDV in geographic settings (national or subnational) with high dengue transmission, i.e. seroprevalence of approximately 70% or greater in the age group targeted for vaccination but not below 50%.[2]

Where possible, assessment of dengue transmission intensity should be supported by geographically relevant seroprevalence studies. Seroprevalence estimates should guide decision-making and introduction at subnational levels while noting that these are not precise indicators. Work is needed to identify routinely collected epidemiologic indicators that can be used to infer likely seroprevalence.

Decisions about introduction require careful assessment at the country level, including consideration of local priorities, subnational dengue epidemiology, predicted impact and cost-effectiveness with country-specific hospitalization rates and costs, as well as affordability and budget impact. Vaccination should be considered as an integrated strategy together with well-executed and sustained vector control and the best evidence-based clinical care for all patients with dengue.

CYD-TDV is recommended as a three dose series given 6 months apart. While protection has been documented after administration of the first dose, completion of the three-dose scheduled is recommended to assure the protection demonstrated in the 5-year period of trial follow up so far. 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. Because of the duration of the vaccine schedule and to enable better vaccine monitoring, countries should have systems in place for tracking vaccination.

The target age for routine vaccination should be defined by each country based on an assessment of dengue endemicity and programmatic feasibility of targeting particular ages. The age to target to optimize impact likely varies by transmission setting.[3] Although only immunogenicity (not vaccine efficacy) has been studied in clinical trials of 17-45 year-olds, in principle these age groups could be targeted for vaccination. At this stage, insufficient data are available to permit a recommendation for use above the age of 45 years. No vaccination is recommended under age 9 years due to the potential safety concern signalled in children 2-5 years of age in the Phase 3 trial.

[2] Mathematical modelling suggests optimal public health and economic impact in these transmission settings. Seroprevalence of 50% was at the lower end of the range of participants in Phase 3 trial sites. The overall seroprevalence in 9-16 year-old trial participants in the Phase 3 studies was approximately 80%. Modelling cautions against CYD-TDV use in lower transmission settings in early adolescence.

[3] Mathematical modelling found 9 years of age was optimal only in very high transmission settings (seroprevalence of 90% in that age group). In other settings with moderate to high transmission, vaccination between 11 and 13 years is predicted to maximize impact, although the variability in impact with age of vaccination was not great.

Risk of dengue hospitalization has been monitored for up to 4 years post-dose 3 in the Phase 3 trials. In the age group currently part of the indication (9-16 years), there is evidence of decreasing protection against dengue hospitalization over this time period. Ongoing follow up from the Phase 3 trials will provide information on the duration of protection, and it is possible that booster doses may be necessary to maintain protection. Currently there is no recommendation for a 4th dose.

Co-administration is not recommended until data are available on the safety and immunogenicity of CYD-TDV when co-administered with other age-appropriate vaccines.

CYD-TDV should be introduced as part of a routine immunization program in appropriate settings. Catch-up campaigns targeting priority age groups defined by local epidemiology can be considered for a greater immediate impact. While adding age cohorts will give progressively better disease control, mathematical modelling of catch-up campaigns in 10-17 year-olds does not suggest a significant impact on dengue transmission (i.e. herd immunity). Future research will study a possible impact of the vaccine delivered through the routine system plus catch up on disease transmission.

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: CYD-TDV has not formally been licensed for use in travellers. In travellers who have already been previously infected with dengue, vaccination for travel to high transmission settings may be beneficial. Extrapolation of data from the Phase 3 trials suggests that in such persons there may be some protection after the first dose, but completion of the full 3-dose schedule is still recommended. In travellers unlikely to have already had dengue, vaccination may be substantially less beneficial (and there is a theoretical risk that it may be harmful), analogous to seronegative individuals living in endemic settings. Co-administration with other travel vaccines is not recommended.

Health care workers: There are no specific recommendations for health care workers.

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.

Other aspects

Due to the partial efficacy of the vaccine against dengue of any severity, careful communication is needed to inform vaccinees that they may still be at risk of dengue and of the importance of receiving all three doses and of adhering to other disease preventive measures.

An assessment of vaccine effectiveness, and the durability of that effectiveness, is a priority. Current data suggest substantially lower benefit of vaccination in seronegative individuals 9-45 years of age. There is a theoretical possibility that vaccination could do harm in this population. Although theoretical risks not supported by data should not impede rollout of this vaccine, it is critical to evaluate as soon as possible whether there is any risk to this population.

Research recommendations may be found in Section 11.7.

2. BACKGROUND

2.1 Epidemiology

Dengue is a major public health problem with every WHO Region affected by dengue. Dengue viruses (DENVs) are members of the genus Flavivirus, within the family Flaviviridae. There are four serotypes (termed DENV-1 to DENV-4). All four serotypes circulate globally, with most endemic countries reporting circulation of all four serotypes in recent years [1].

Dengue is the most extensively spread mosquito-borne virus. In the last 60 years the incidence of clinical cases of dengue reported to WHO has increased 30-fold, with a much increased geographic range, including the expansion from predominantly urban to rural settings. Approximately 3.5 billion people live in dengue endemic countries; dengue is endemic in Asia and Latin America, and large parts of Africa, although data for Africa are sparse. The number of cases reported annually to WHO ranged from 0.4 to 1.3 million in the decade 1996–2005, and in 2010 was 2.2 million [2]. There is substantial under-reporting of dengue within health systems, and also underreporting to WHO [3]. A recent prediction based on available incidence and prevalence data and modelled globally estimated 390 million dengue infections per year in 2010 (95% credible interval 284–528 million), of which about 25%, 96 million (67–136 million), manifest clinically (with any severity of disease) [4]. The greatest number of infections was estimated to have occurred in Asia (204 million), followed by Africa (48 million), and the Americas (40 million)(Figure 1). WHO has estimated 500,000 hospitalizations for dengue annually, of which about 12,000 are fatal [5]. The case-fatality rate (CFR) is now low (<1%) due to advances in case management, although it varies according to location and how well severe dengue is managed medically. The number of people who are affected by dengue leads to tremendous burden on health care infrastructure as well as financial costs to the health sector, particularly during outbreaks when hospitals may become full or over capacity, and, in some cases, catastrophic household expenditures.

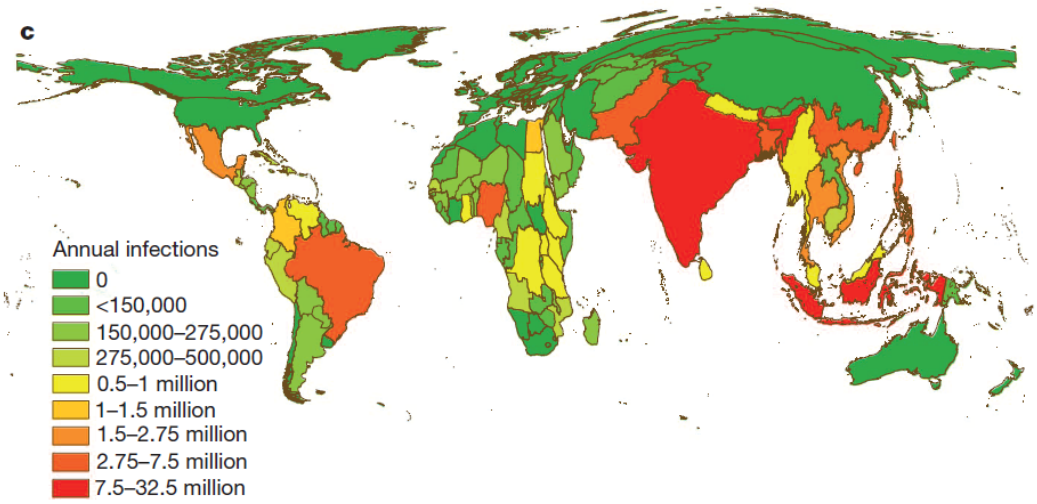


Figure 1 Cartogram of the annual number of infections in 2010 for all ages as a proportion of national or subnational geographical area [4].

Dengue viruses are primarily maintained in a human-to-mosquito-to-human cycle. The primary vector is the *Aedes aegypti* mosquito, which is highly domesticated. *Aedes albopictus* can also sustain DENV transmission. The spread of vectors following urbanization and the decline in vector-control efforts has partially contributed to the increased incidence of DENV infection. Additionally, factors such as population growth, globalization and travel, and climate change facilitate increased transmission of dengue.

Mosquito populations and their ability to transmit dengue appear to be highly dependent on climatic factors such as temperature and rainfall. Based on a review of nearly two decades of dengue surveillance data, a recent study found fluctuations in dengue transmission in 8 countries in South-East Asia closely following temperature patterns, with high incidence in 1997-1998 coinciding with elevated temperatures throughout the region and the strongest El Niño episode of the century [6].

Although reports of what were likely dengue outbreaks occurred as early as the mid-17th century, dengue could first be diagnosed definitively in the mid-1940s when the virus was able to be isolated [7]. Efforts shortly thereafter to eradicate the *Ae. aegypti* vector in the Americas to control Yellow Fever were successful in many countries, leading to reduced circulation of dengue and other mosquito-borne viruses. However, eradication across the continent fell short. As a result of a loss of political priority, DDT resistance, and other factors, mosquito control programs deteriorated and *Aedes* re-emerged in a broader geographic area. A number of dengue outbreaks were reported in the 1970s and 1980s, and despite renewed attempts to control the vector in the PAHO region, cases have continued to rise.

Transmission intensity as well as population structure and demographics can affect the age distribution of dengue infections and cases. Although there are many metrics used to measure transmission intensity, seroprevalence surveys are important for understanding age-specific infection rates, as many infections are clinically inapparent. Endemic settings are highly variable with respect to average age of infection. Figure 2 shows age-specific seroprevalence data from three settings, from low endemicity in Singapore (~10% seroprevalence by age 9 years) to high endemicity in Papua New Guinea (>90% seroprevalence at age 9 years).

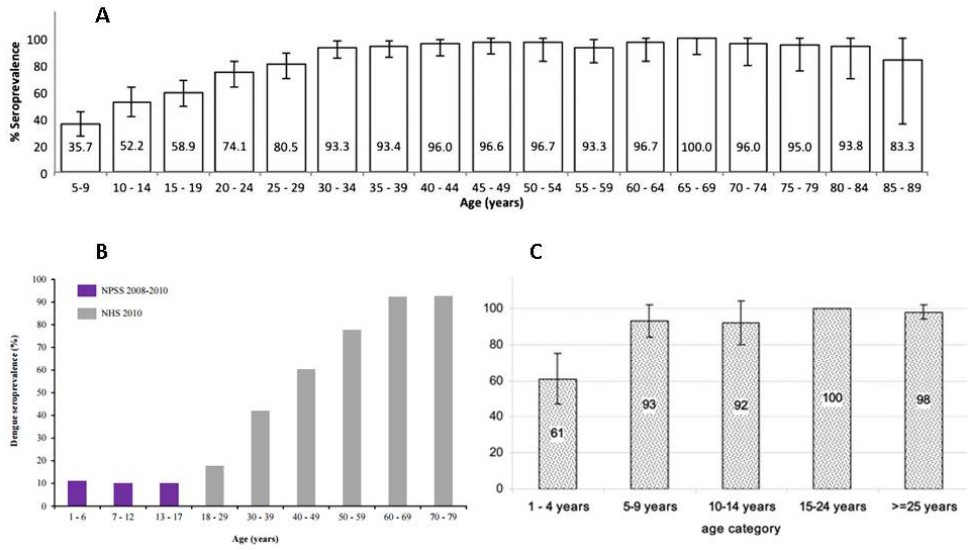


Figure 2 Examples of seroprevalence by age from localities in A) Mexico [8], B) Singapore [9], and C) Papua New Guinea [10].

Age distributions of infection are not static but change over time; in one province in Thailand, in 1980 96% of the population had been infected by dengue by age 11 years; in 2010, 65% of the population were infected by 11 years [11]. Similar variations in the ages at infection or of dengue disease have been seen in other settings [12], potentially due to demographic changes [13].

In addition to heterogeneity of transmission between countries and over time, heterogeneity at a local level makes country-wide generalizations difficult. Such heterogeneity could be based on geographic factors, such as elevation, or demographic factors, such as population density. While large differences may be seen in neighbouring municipalities (Figure 3), even further heterogeneity may be important at smaller spatial scales [14].

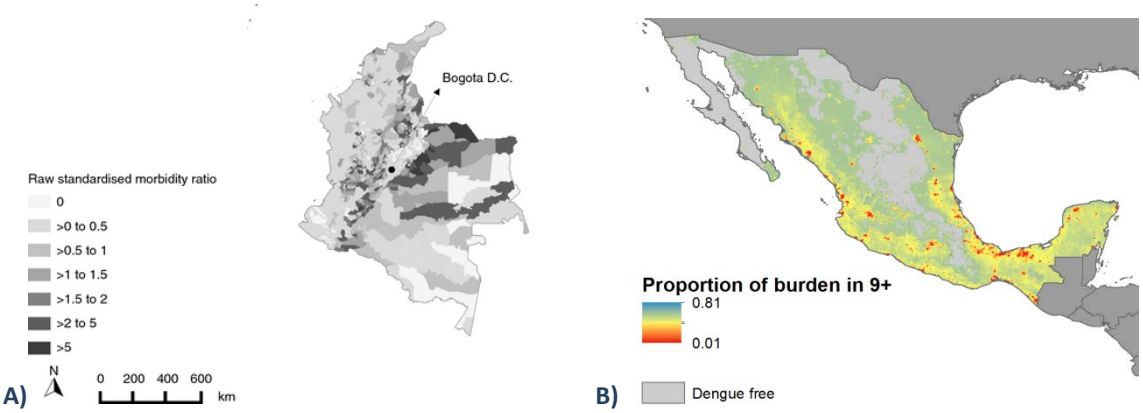


Figure 3 Heterogeneity in national patterns of dengue in A) Colombia, based on notified dengue cases by municipality[15], and B) Mexico, based on modelled proportion of dengue infections occurring in the 9 years of age and older population at fine spatial scale (Courtesy of O. Brady, Oxford University).

2.2 Disease and Diagnosis

The majority of DENV infections are either asymptomatic or mild. The incubation period is usually 4-7 days but can range from 3-14 days. The most common presentation is the sudden onset of fever accompanied by headache, pain behind the eyes, generalized myalgia and arthralgia, flushing of the face, anorexia, abdominal pain and nausea. Rash is frequently seen on the trunk, on the insides of the arms and thighs, and on plantar

and palmar surfaces and can be macular, maculopapular, morbilliform, scarlatiniform or petechial. Laboratory abnormalities may include leukopenia and thrombocytopenia. For the purpose of clinical management, WHO classifies dengue illness as (i) dengue with or without warning signs for progression towards severe dengue and (ii) severe dengue (Figure 4). Warning signs of severe dengue include abdominal pain or tenderness, persistent vomiting, clinical fluid accumulation, mucosal bleeding, lethargy or restlessness, liver enlargement of >2 cm, or an increase in haematocrit concurrent with a rapid decrease in platelet count. Criteria for severe dengue include any sign of severe plasma leakage leading to shock or fluid accumulation with respiratory distress, severe bleeding, or severe organ impairment. A detailed clinical case classification of dengue is provided in the WHO Dengue Guidelines [16].

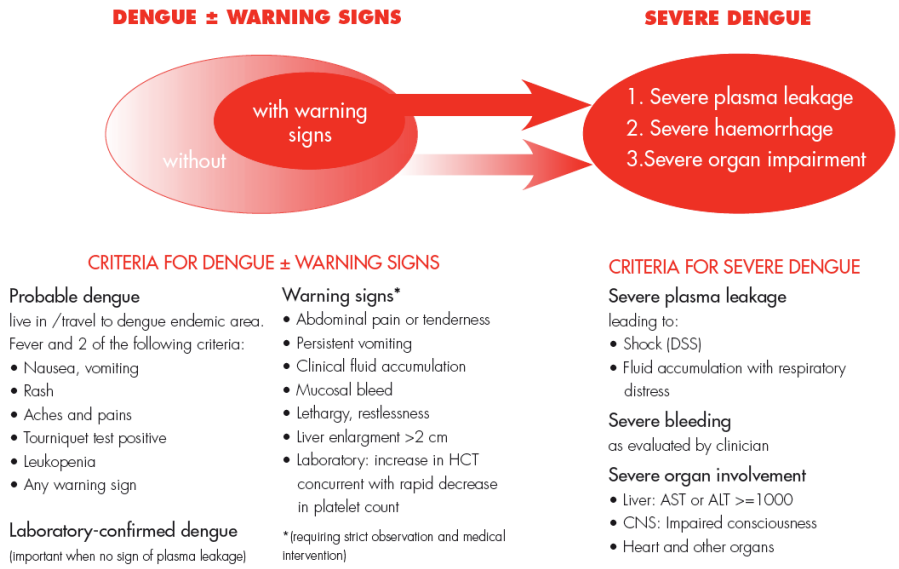


Figure 4 WHO dengue case classification and levels of severity [16].

There is no specific anti-viral treatment for dengue. Clinical management is based on supportive therapy, primarily judicious monitoring of intravascular volume replacement. Improvements in case management have reduced the case fatality rate of hospitalized dengue to less than 1%, whereas historically they were as high as 20% [17, 18].

Laboratory-confirmed dengue is diagnosed either by virus isolation, serology (MAC-ELISA, IgG ELISA, PRNT), or molecular methods (RT-PCR). Diagnosis by serology typically does not allow for serotyping the infecting virus (except by PRNT), and is also susceptible to cross-reactivity, variable sensitivity by timing of specimen collection, and the need for multiple samples (IgG acute and convalescent samples). PCR and detection of NS1 antigen offer more specific and early diagnosis (for PCR, 80-90% sensitivity and 95% specificity if applied in the appropriate time window).

2.3 Dengue pathogen and pathogenesis

Flaviviruses encompass a very dynamic and diverse group of species, and many are human pathogens. Flaviviruses are lipid-enveloped, positive-sense, single-stranded RNA viruses, approximately 55 nm in diameter. The virion RNA encodes a single open reading frame that is flanked by a 5' untranslated region (UTR) and a 3' UTR. Three structural proteins are derived by cleavages of the amino-terminal one third of the polyprotein: the capsid or core protein forms a "nucleocapsid" complex with virion RNA that lies within the lipid envelope. The premembrane (prM) and envelope (E) proteins are embedded in the lipid envelope via carboxy-terminal transmembrane domains and are displayed on the surface of virions. Cleavage of the carboxy-terminal two thirds of the polyprotein yields seven non-structural (NS) proteins: NS1, NS2A, NS2B, NS3, NS4A, NS4B and NS5.

NS1 plays various roles in the virus replication cycle while NS2A, NS2B, NS4A and NS4B are all small hydrophobic proteins with the central region of NS2B required for the functioning of the NS3 protease. The four DENV serotypes only share about 60-75% identity at the amino acid level, making them diverse viruses [19].

Following infection, resulting from the bite of an infected mosquito, the virus replicates in local dendritic cells. Subsequent infection of macrophages and activation of lymphocytes is followed by entry into the bloodstream. DENV primarily infect cells of the myeloid lineage, including macrophages, monocytes, and dendritic cells. There is also evidence of infection of hepatocytes and endothelial cells, although there is disagreement on the latter. Haematogenous spread is the likely mechanism for seeding of peripheral organs and the occasional reports of central nervous system infections.

2.4 Immune response to dengue infection and natural history of disease

Immune responses to dengue virus are only partially understood and complicated by the inter-relatedness of host responses to the four distinct serotypes. Dengue infection induces high-titered neutralizing antibody. Following a primary infection with one DENV, protection against the infecting serotype (homotypic protection) is believed to be life-long. Temporary cross-protection is induced to the other serotypes (heterotypic protection), lasting an average of around 2 years [20, 21]. Following waning of cross-neutralizing antibodies, the host-immune response may increase the severity of subsequent DENV infections with different serotypes. It is well accepted that severe disease is more likely to occur after a second dengue infection than after the first dengue infection with a relative risk of approximately 7 [14], although other studies have found higher [22, 23] or lower [24] relative risks. Following recovery from a second infection, broadly neutralizing antibody is induced (multitypic protection), such that severe disease with tertiary and quaternary infections is considered rare. The mechanism for more severe disease associated with a second infection is not well understood although antibody-dependent enhancement, cytokine storm, or cross-reactive T cells are hypothesized.

2.5 Dengue control measures

At present, the only method to control or prevent the transmission of dengue virus is through interventions directed at the vector. While no specific method is recommended, WHO recommends integrated vector management (IVM), which is defined as “a rational decision-making process for the optimal use of resources for vector control” [16]. A variety of approaches have been used in dengue control programs. There are many studies showing reductions in entomological indicators following vector control; however, there is a paucity of data to show an effect of vector control interventions on the incidence of human dengue cases [25]. Recent evidence from cluster-randomized trials in Nicaragua and Mexico suggest that community-based prevention efforts could have an effect on reducing dengue infection in children (as measured by paired saliva samples for IgG seroconversion) [26]. Few controlled studies have been conducted; thus many vector control interventions are undertaken without a strong evidence base for effectiveness. Some common interventions include:

- preventing mosquitoes from accessing egg-laying habitats by environmental management and modification, such as disposing of solid waste properly and removing artificial man-made mosquito habitats;
- covering, emptying and cleaning of domestic water storage containers on a weekly basis;
- applying appropriate insecticides or predators to outdoor water storage containers;
- using personal and household protection such as window screens, long-sleeved clothes, insecticide or repellent treated materials, coils and vaporizers;
- improving community participation and mobilization for sustained vector control;
- applying insecticides using space sprays during outbreaks as one of the emergency vector-control measures;

Vector control is best utilized as a routine preventive measure rather than as outbreak response. However, even for routine dengue control, the general consensus in the field of vector control for dengue is that current tools are difficult to standardize and evaluate, and their application requires a trained workforce, as well as inter-sectoral and community participation. Though countries such as Singapore and Cuba have been able to implement very high levels of vector control and have to some extent moderated endemicity and outbreaks, problems are faced with widespread implementation, sustainability and cost. Many current tools require a robust evaluation against clinical endpoints (rather than entomological endpoints) to assess their impact on disease. For new vector control tools, such as RIDL (Release of Insects with Dominant Lethality (sterile males)) and Wolbachia (a bacteria found in many insects that reduces mosquitoes ability to transmit dengue by multiple mechanisms), there are plans in place to evaluate the effectiveness against dengue. There are also ongoing efforts to conduct such evaluations for traditional vector control tools.

However, given their importance to dengue control programs, and the fact that these vectors carry other viruses (e.g. Zika and Chikungunya), the use of any new tools, such as vaccination, would be in the context of existing vector control measures. Better data on the effectiveness of vector control against dengue are needed to be able to redesign dengue control programs to optimize the package of interventions, also in consideration of disease transmission of different *Aedes* circulated pathogens.

3. DENGUE VACCINES

3.1 Clinical pipeline

There have been efforts to develop dengue vaccines for decades, but it has proven to be one of the more difficult pathogens against which to develop a vaccine for a variety of reasons. Importantly, it has been difficult to develop a vaccine that induced balanced protection without immunologic interference following simultaneous vaccination against all four dengue serotypes; this is not necessarily a prerequisite but has been considered highly desirable given the immune pathology resulting from sequential natural infections. There is no good animal model for dengue; non-human primates develop some viraemia but no clinical disease. There is no established correlate of protection, and the assay used to measure neutralizing antibodies (PRNT) is limited in its relevance to thresholds of protection. Both quantitative and qualitative aspects of the immune response are likely to be important; a single measurement may be insufficient, protective levels may vary by serotype, and/or be vaccine-specific. Because there is no specific antiviral treatment for dengue, the use of human infection models to evaluate vaccine candidates have been controversial, although there are attenuated challenge strains approved under US FDA Investigational New Drug (IND) that will soon be used for vaccine candidate profiling. Theoretical concerns about immune enhancement following waning immunity have necessitated relatively long follow up of clinical trial participants [27].

In the dengue vaccine clinical pipeline there is one vaccine registered (developed by Sanofi Pasteur and the focus of this background paper) and at least five candidates in clinical development but not yet licensed. The two most advanced candidates under clinical development are live attenuated (recombinant) vaccines developed by the U.S National Institutes of Health (NIH) and licensed to several manufacturers, and by Takeda.

TV003 and TV005 (which are identical vaccine candidates except for the dosing level of the DEN2 component) were developed by the US NIH and are based on wild-type strains with targeted mutations to attenuate the virus [28]. Vaccine virus serotypes 1, 3, and 4 are based on complete viruses, while serotype 2 is a recombinant virus based on the serotype 4 vaccine strain with the structural proteins replaced by those of serotype 2. TV003 or TV005 has been licensed to several manufacturers, including Butantan, VaBiotech, Panacea, Serum Institute of India and Merck. Phase 2 studies are underway in Brazil and Thailand. Butantan has started a Phase 3 trial.

Takeda is also developing a live recombinant vaccine, TDV (formerly DENVax). This tetravalent candidate includes a whole attenuated DEN2 virus and recombinant DEN1, DEN3, and DEN4 using the DEN2 backbone. There have been a number of ongoing and completed Phase 1 and Phase 2 trials in both endemic and non-endemic settings, evaluating different dosing schedules and a variety of formulations and routes of administration (including traditional needle-syringe mechanism, a needle-less injector, and a needle-free Pharmaject Injector). A multicenter Phase 3 study is being planned.

Other candidates and approaches have been evaluated, or are currently under evaluation, in Phase 1 trials, include a tetravalent purified inactivated vaccine (GSK/Walter Reed Army Institute of Research), a tetravalent recombinant subunit vaccine based on the dengue wild-type pre-membrane and truncated envelope protein (Merck), a monovalent plasmid DNA vaccine (US Navy Medical Research Center), and an inactivated vaccine/live attenuated vaccine heterologous prime boost (Walter Reed Army Institute of Research).

3.2 Technical Specifications of CYD-TDV (Dengvaxia®)

CYD-TDV (Dengvaxia®) is a prophylactic, tetravalent, live attenuated viral vaccine developed by Sanofi Pasteur. The indication from the first licenses (Mexico, Philippines, Brazil, El Salvador, and Paraguay) is for the prevention of dengue disease caused by dengue virus serotypes 1, 2, 3, and 4 in individuals 9 through 45 or 60 years of age (depending on the license), living in dengue endemic areas. The vaccination schedule consists of 3 injections of 0.5 mL administered at 6-month intervals by the sub-cutaneous route. A time window of +/- 20 days was specified as acceptable for doses 2 and 3.

The active substances contained in the CYD dengue vaccine are 4 live attenuated viral recombinants representing serotypes 1, 2, 3, and 4. Each monovalent CYD recombinant is obtained separately by replacing the genes encoding the pre-membrane (prM) and envelope (E) proteins of the structural proteins in the attenuated yellow fever (YF) 17D virus genome with the corresponding genes of the 4 wild type dengue serotypes 1, 2, 3 and 4. The final formulation contains 4.5-6.0 log10 median cell-culture infectious doses ($CCID_{50}$) of each live, attenuated, dengue serotype 1, 2, 3 and 4 viruses.

CYD-TDV is presented in a single-dose vial or in a 5-dose multi-dose vial. It is a sterile, freeze-dried product to be reconstituted before injection with either a sterile solution of 0.4% sodium chloride for the single-dose presentation or a sterile solution of 0.9% sodium chloride for the 5-dose presentation. After reconstitution, one dose (0.5 mL) is to be administered by the subcutaneous (SC) route. The diluent is provided as a pre-filled syringe for single-dose presentation, or in a vial for the multi-dose presentation.

The CYD-TDV dengue vaccine contains no adjuvant or preservatives. No material of biological origin (animal or human) is used in the manufacturing process of the CYD dengue virus seed lot system, Vero cell banking system and CYD Drug Substance (DS) and Drug Product (DP). Extraneous agent tests (in vivo tests on animals, in vitro tests on several cell substrates, molecular biology) were carried out along the manufacturing process of the seed lots, cell banks and DS and none showed the presence of adventitious agents.

Based on the package inserts vaccination is contraindicated in: 1) individuals with a history of severe allergic reaction to any component of the dengue vaccine or after prior administration of the dengue vaccine or a vaccine containing the same components; 2) individuals with congenital or acquired immune deficiency that impairs cell-mediated immunity; 3) individuals with symptomatic Human Immunodeficiency Virus (HIV) infection or with asymptomatic HIV infection when accompanied by evidence of impaired immune function; and 4) pregnant or breastfeeding women. Administration should be postponed in individuals suffering from moderate to severe febrile or acute disease.

3.3 Development of CYD-TDV

CYD-TDV has been under development for the last two decades. The platform used for CYD-TDV is the same as that used for the Japanese encephalitis vaccine, IMOJEV®, which was first licensed by Australia in 2010. A number of non-clinical assessments were undertaken with YF17D recombinant flavivirus vaccines against dengue viruses, West Nile Virus, and Japanese encephalitis virus to evaluate theoretical environmental risks related to vaccine virus transmission through mosquitoes, reversion to virulence, and recombination [29].

These recombinant vaccines induce no or low viraemia in human recipients, which is considered below the threshold for transmission to mosquitoes. No oral infection of mosquitoes was induced, and no transmission was observed when infected directly. Despite being a RNA virus, the YF17D vaccine genome was found to be very stable. Natural recombination (intragenetic or intergenetic) is considered unlikely, and artificial recombinants produced in the laboratory were still attenuated. Full genome sequences of the four recombinant dengue vaccine viruses were established for premaster seed lots, master seed lots, bulk, and bulk+10 passages. High genomic stability was seen, with only 9 mutations across all four vaccine strains. All except one were in the non-structural region. The 8 non-silent mutations occurred early in the process and were conserved moving forward.

A number of Phase 1 and 2 studies have been conducted around the world, and, including the Phase 3 studies, more than 25,000 individuals have received at least 1 dose of vaccine (Table 1). The development program was consistent with that recommended by WHO [27].

Following Phase 1 and 2 studies to select formulation, dose, and schedule, a proof-of-concept Phase 2b efficacy study was conducted in Thailand (CYD23/57), which provided initial estimates of efficacy. The primary objective of the phase 2b study was to assess the efficacy of CYD-TDV in preventing dengue disease, after completion of the vaccination schedule of three doses given 6 months apart. Additional objectives included the evaluation of vaccine safety and immunogenicity. The study population consisted of 4,002 children aged 4 to 11 years in Ratchaburi Province, Thailand. The definition of fever, precipitating a diagnostic test for dengue, was slightly different to that used in the Phase 3 trials. The trial included 2 years of active follow up, and then 4 years of hospital-based follow up. Due to the wealth of data from the Phase 3 trials, which are larger and across varied settings, and thus allow for greater interrogation of the data, results from the Phase 3 trials are emphasized.

Table 1 Clinical database; Number of persons who received at least one vaccine dose, by age and endemicity. Provided by manufacturer on request.

	<9 years*	9-16 years	17-45 years	46-60 years**
Non-endemic settings	Safety: Not Done (N.D.) Immunogenicity: N.D. Efficacy: N.D.	Safety: N.D. Immunogenicity: N.D. Efficacy: N.D.	Safety: 638 Immunogenicity: 632 Efficacy: N.D.	Safety: 241 Immunogenicity: 241 Efficacy: N.D.
Endemic settings	Safety: 5,689 Immunogenicity: 1,296 Efficacy: 5,166	Safety: 19,120 Immunogenicity: 2,810 Efficacy: 18,262	Safety: 668 Immunogenicity: 294 Efficacy: N.D.	Safety: N.D. Immunogenicity: N.D. Efficacy: N.D.

<9 years*: Outside of claimed age indication

46-60 years**: Outside of the licensed indication in some countries

3.4 Overview of Phase 3 Trials on CYD-TDV

CYD-TDV has been evaluated in two parallel Phase 3 clinical trials, known as CYD14 and CYD15. 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. In each of these trials, participants were randomized to vaccine and placebo (0. 9% solution of

sodium chloride) in a 2:1 ratio. Because the physical appearance of the vaccine and placebo was different, unmasked trial staff was responsible only for preparation and administration of injections and were not involved in the follow-up of trial participants. For the ascertainment of trial endpoints the trials were observer-masked. All serology testing was also performed in a blinded manner. The dosing schedule and trial design were identical in the two Phase 3 studies, and each was designed to have similar statistical power to assess vaccine efficacy, based on the expected disease incidence in the study locations. Together, these trials included over 30,000 participants aged 2 to 16 years.

Table 2 Overview of Phase 3 Trials design and status.

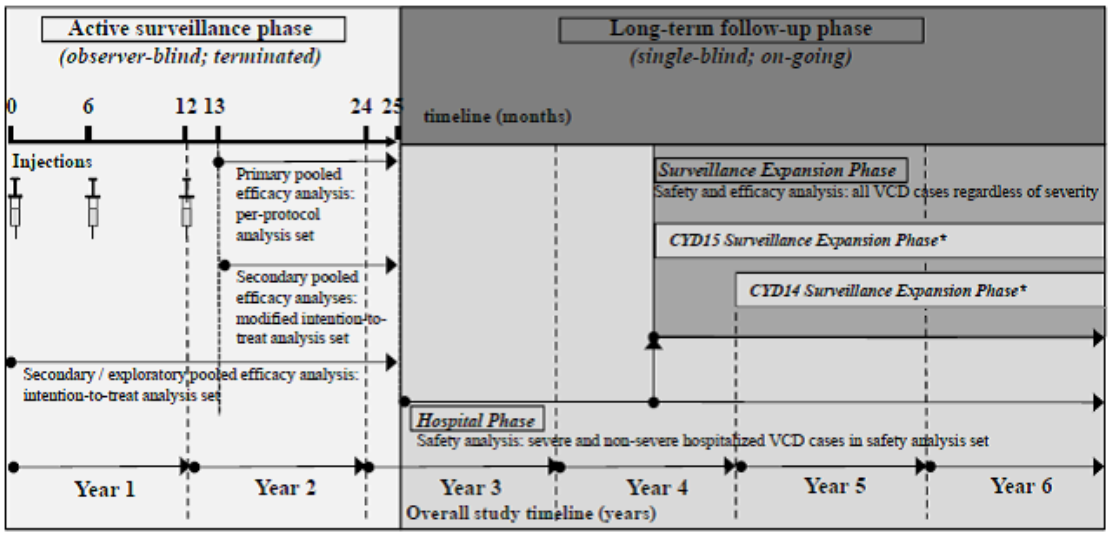
	CYD14	CYD15
Trial size	10,275	20,869
Randomization CYD:Placebo	2:1	2:1
Ages included	2-14 years	9-16 years
Countries participating	Indonesia, Malaysia, Philippines, Thailand, and Vietnam	Brazil, Colombia, Honduras, Mexico, and Puerto Rico (US)
Primary endpoint (per protocol)	Vaccine efficacy after 3 vaccinations at 0, 6, and 12 months (VE measured from 28 days after the 3rd dose) in preventing symptomatic virologically-confirmed dengue cases, regardless of the severity, due to any of the four serotypes up to 13 months pose-dose 3.	Vaccine efficacy after 3 vaccinations at 0, 6, and 12 months (VE measured from 28 days after the 3rd dose) in preventing symptomatic virologically-confirmed dengue cases, regardless of the severity, due to any of the four serotypes up to 13 months pose-dose 3.
Study start date	June 2011	June 2011
End of Active Phase for primary endpoint	December 2013	April 2014
Estimated completion date	November 2017	April 2018

The study protocols included an active phase of follow-up for 13 months after the last dose of vaccine in the series (i.e. 25 months from dose 1) for the primary efficacy endpoint and included a hospital-based follow-up period of four additional years for safety evaluation, which is ongoing.

During the Active Phase of surveillance (Years 1-2), participants attended five visits at months 0, 6, 12 (for vaccination) and months 13 and 25 for follow-up. During the 2-year period children were monitored for febrile illnesses through weekly contact with participants or their parent/guardian, and in CYD14 by school absenteeism as well. For participants with an acute febrile illness, blood samples were taken for diagnosis. Virologically-confirmed dengue was defined as acute febrile episode (temperature ≥38°C on ≥2 consecutive days) and a positive NS1 or rtPCR test.

During the Hospital Phase (Years 3+) participants who were admitted to hospital with a febrile illness (temperature ≥38°C on ≥2 consecutive days) were tested for dengue infection (as described above) but children with febrile illnesses who were not admitted to hospital were not monitored. Thus, relative risks against hospitalized and severe dengue could be estimated (but not the milder forms identified through active surveillance in Years 1-2). Study investigators, parent/guardians, and participants will all remain masked to vaccination status until the hospital phase of the trial is complete.

A Surveillance Expansion Phase (SEP) was initiated in Years 4 and 5 of the Phase 3 trials. The SEP, for which re-consenting of participants is currently ongoing, will transition to an active surveillance follow up among participants who consent (those unwilling are still followed in the Hospital Phase follow up).



VCD: virologically-confirmed dengue; Per-protocol analysis set VCD from D28 post injection 3 to M25; Modified intention-to-treat analysis set: VCD from D28 after all 3 injections, regardless of protocol deviations; Intention-to-treat analysis set: VCD from D0 to M25 after ≥1 injection; Safety analysis set: participants who received ≥1 dose: participants analyzed according to the first dose treatment received
*As of February 2016, re-consenting process for the Surveillance Expansion Phase is still ongoing

Figure 5 Summary of Phase 3 trial design. Provided by manufacturer on request.

Severe dengue was classified based on clinical characteristics in two ways: 1) met criteria for the 1997 WHO classification for dengue haemorrhagic fever (DHF), or 2) met criteria set forth by the Independent Data Monitoring Committee (IDMC)[4]. For the purposes of the SAGE review, Working Group emphasis has been placed on severe disease as assessed by the IDMC due to its consideration of broader organ impairment.

Blood samples were taken from all trial participants at month 13 (one month post-dose 3). Pre-vaccination and month 7 blood samples were taken in a subset of participants in each trial, the analysis set for immunogenicity (immunogenicity subset) to test concentrations of dengue neutralizing antibody measured by the Vero cell based plaque reduction neutralisation test ($PRNT_{50}$). In CYD14 (immunogenicity subset N=1983) and CYD15 (immunogenicity subset N=1944), participants who were enrolled the early part of the trials in each country were included in the immunogenicity and reactogenicity subsets.

Serostatus at baseline was assessed for those in the immunogenicity subset. While $PRNT_{50}$ is non-diagnostic, participants with $PRNT_{50} \geq 10$ against one or more serotypes were considered seropositive at baseline, which was interpreted as having been exposed to at least one dengue virus prior to vaccination. All other participants

[4] IDMC classified dengue cases as severe using the following criteria: Virologically-confirmed dengue fever, i.e. temperature ⩾38°C on ⩾2 consecutive days and virological confirmation, and at least one of the following:

- Platelet count ⩽$100x10^9$/L and bleeding (tourniquet, petechiae or any bleeding) and plasma leakage (effusion on chest x-ray or clinically apparent ascites including imaging procedures or hematocrit >20% above baseline recovery level or standard for age if only one reading).
- Shock (pulse pressure ⩽ 20 mmHg in a child or adolescent, or hypotension [⩽ 90mmHg] with tachycardia, weak pulse and poor perfusion).
- Bleeding requiring blood transfusion
- Encephalopathy i.e., unconsciousness or poor conscious state (Glasgow Coma Scale (GCS) score) or convulsions not attributable to simple febrile convulsion or focal neurological signs.
- Liver impairment (AST >1000 U/L or prothrombin time, international normalized ratio >1.5)
- Impaired kidney function (serum creatinine ⩾1.5 mg/dL)
- Myocarditis, pericarditis or heart failure (clinical heart failure) supported by chest X ray, echocardiography, electrocardiogram or cardiac enzymes where they were available

were considered seronegative, which was interpreted as dengue non-immune. Age-specific seropositivity proportions are presented in Table 3.

Table 3 Proportion of CYD14 and CYD15 participants testing positive for neutralizing antibodies to one or more dengue serotype by $PRNT_{50}$ [30, 31].

Age group	CYD14	CYD15
2-5 years	51%	NA
6-11 years	72%	75%**
12-16 years	81%*	84%
Total Trial Population	68%	79%

* 12-14 years ** 9-11 years

4. CYD-TDV VACCINE EFFICACY IN THE ACTIVE FOLLOW-UP

4.1 Vaccine efficacy against VCD from Phase 3 trials during the period of active follow-up

Vaccine efficacy against virologically-confirmed dengue (VCD) of any severity was designed to be evaluated only during Years 1 and 2 of the efficacy trials, when active surveillance was in place. The per protocol analysis of vaccine efficacy was based on follow up time from Month 13 to Month 25 (1 month post-dose 3, for 12 months). The per protocol vaccine efficacy is shown in Table 4.

Table 4 Vaccine efficacy during the active phase of surveillance, by serotype (pre-specified analyses, per protocol population, duration of follow up: study months 13-25) [30-32].

Outcome	CYD14	CYD15	Pooled
VCD-DENV1-4	56.5% (43.8-66.4)	60.8% (52.0-68.0)	59.2% (52.3-65.0)
VCD-DENV1	50.0% (24.6-66.8)	50.3% (29.1-65.2)	50.2% (35.6-61.5)
VCD-DENV2	35.0% (-9.2-61.0)	42.3% (14.0-61.1)	39.6% (18.7-55.2)
VCD-DENV3	78.4% (52.9-90.8)	74.0% (61.9-82.4)	74.9% (65.1-82.0)
VCD-DENV4	75.3% (54.5-87.0)	77.7% (60.2-88.0)	76.6% (65.0-84.4)

Vaccine efficacy against dengue of any serotype was 56.5% (95%CI 43.8-66.4) in CYD14, and 60.8% (95%CI 52.0-68.0) in CYD15. In both trials, vaccine efficacy was lower against serotypes 1 and 2 than against serotypes 3 and 4. Vaccine efficacy estimates were similar across the two Phase 3 trials despite variable epidemiological settings and ages at vaccination (2-14 years in CYD14 and 9-16 years in CYD15).

Aside from the vaccine efficacy estimates reported above, the manufacturer calculated all other secondary outcome vaccine efficacy parameters using the intention-to-treat (ITT) population for efficacy (follow up starting with administration of dose 1, Month 0-Month 25). These are displayed in Table 5.

Table 5 Vaccine efficacy (intention to treat population) against VCD of any severity during the active phase of surveillance, by serotype, serostatus, (pre-specified analyses), duration of follow up: study months 0-25) [30-32]. VE estimates in those >9 years pooled are post-hoc analysis for CYD14, pre-specified analyses CYD15.

Outcome	Study Population	CYD14	CYD15	Pooled	Pooled ≥ 9 years
VCD-DENV1-4	All	54.8% (46.8-61.7)	64.7% (58.7-69.8)	60.3% (55.7-64.5)	65.6% (60.7-69.9)
	2-5 years	33.7% (11.7-50.0)	NA	NA	NA
	6-11 years	59.5% (48.9-68.0)	61.7% (52.3-69.3)**	Not published	Not published
	12-16 years	74.4% (59.2-84.3)*	67.6% (59.3-74.3)	Not published	Not published
	Seropositive	74.3% (53.2-86.3)	83.7% (62.2-93.7)	78.2% (65.4-86.3)	81.9% (67.2-90.0)
	Seronegative	35.5% (-27.0-66.6)	43.2% (-61.6-80.0)	38.1% (-3.4-62.9)	52.5% (5.9-76.1)
VCD-DENV1	Full	54.5% (40.9-64.9)	54.8% (40.2-65.9)	54.7% (45.4-62.3)	58.4% (47.7-66.9)
VCD-DENV2	Full	34.7% (10.4-52.3)	50.2% (31.8-63.6)	43.0% (29.3-53.9)	47.1% (31.3-59.2)
VCD-DENV3	Full	65.2% (43.3-78.9)	74.2% (63.9-81.7)	71.6% (63.0-78.3)	73.6% (64.4-80.4)
VCD-DENV4	Full	72.4% (58.5-81.7)	80.9% (70.9-87.7)	76.9% (69.5-82.6)	83.2% (76.2-88.2)

*12-14 years , **9-11 years

Vaccine efficacy estimates against VCD for all serotypes were similar in the per protocol analysis (56.5% and 60.8% for CYD14 and CYD15) and in the ITT analyses (54.8% and 64.7% for CYD14 and CYD15, respectively). The overall pooled estimate for CYD14 and CYD15 combined for VCD of any serotype in the 2 years post-dose 1 was 60.3% (95%CI 55.7-64.5). Vaccine efficacy was lower in the youngest age group of 2-5 years (CYD14 only) at 33.7%, and it was highest in the oldest age groups (VE 74.4% in CYD14 and 67.6% in CYD15 among participants 12-14 or 12-16 years of age, respectively). Vaccine efficacy was higher in individuals who were seropositive at baseline (pooled VE against dengue of any serotype was 78.2%) compared to those who were seronegative at baseline (pooled VE against dengue of any serotype was 38.1%, the confidence interval for which included 0%). The limited number of individuals in the immunogenicity subset, for which serostatus at baseline was known, makes it difficult to interpret analyses further stratifying this group (e.g. by age).

The summary vaccine efficacy estimates reported above have included children of all ages in the Phase 3 trials, including those <9 years who are not included in the currently indicated age ranges for licensing. An analysis was done limited to those ≥9 years of age in CYD14 (post-hoc) and CYD15 (full trial population in CYD15, pre-specified). Pooled efficacy estimates in the 2 years following dose 1 are similar to those for the full trial population. Vaccine efficacy was 65.6% (95%CI 60.7-69.9) against VCD of any serotype in the ≥9 years population, and in the subset for whom baseline serostatus was assessed the efficacy of 81.9% (95%CI 67.2-90.0) in those seropositive at baseline and 52.5% (95%CI 5.9-76.1) in those seronegative at baseline. Vaccine efficacies among those seropositive and seronegative at baseline who were <9 years were 70.1% (95%CI 32.3-87.3) and 14.4% (95%CI -111-76.1), respectively [32].

When age is modelled as a continuous variable, VE against VCD is relatively stable in the indicated age range (9-16 years) from Month 0 to Month 25 (no data on VCD beyond Month 25 due to change in from active to hospital-based surveillance in the trial) (Figure 6).

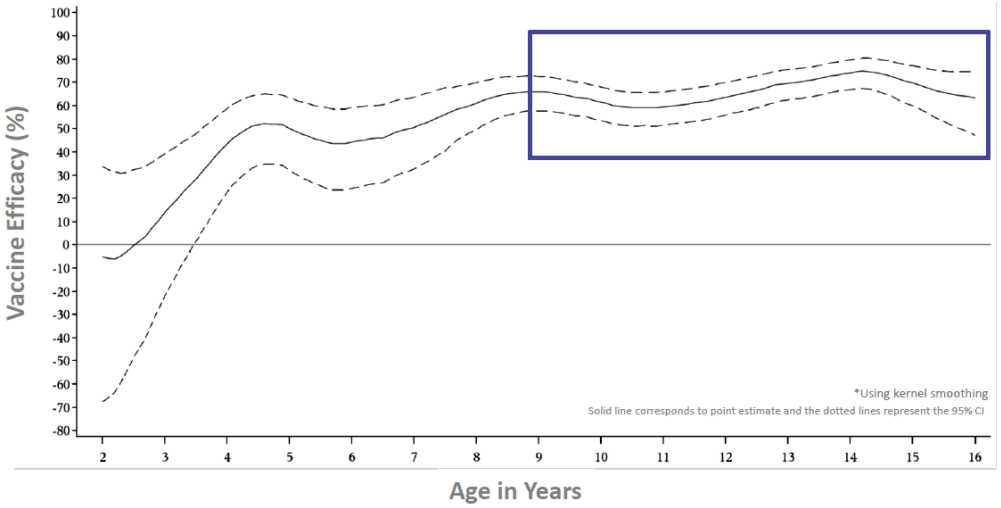


Figure 6 VE against symptomatic virologically-confirmed dengue cases during the whole Active Phase due to any of the 4 serotypes according to age, using kernel smoothing - CYD14 and CYD15 (2-16 years) [33].

Vaccine efficacy estimates varied by infecting serotype, serostatus at baseline, and age (although age and serostatus are highly correlated). Serotype distribution and transmission intensity varied across trial sites. Thus, vaccine efficacy estimates in the trials at the country level vary at least in part due variations in these characteristics between countries (Table 6). For example, vaccine efficacy was high in Brazil (77.5% against VCD of any serotype), where about 75% of the population was seropositive at baseline and there was a DENV4 outbreak, against which serotype the vaccine efficacy was high. Vaccine efficacy was lowest in Mexico, where only about 50% were seropositive at baseline, and there was a high burden of DENV1 and DENV2, against which serotypes the VE was lower. However, such correlations were not as clear in CYD14.

Table 6 Seropositivity and distribution of dengue serotypes in among trial participants by country and vaccine efficacy (ITT population of all ages included in trial, follow up from study month 0-25) [30, 31] and provided by manufacturer on request.

Study	Country	N (% of total in trial)	Baseline dengue seropositivity	DENV-1 cases in placebo	DENV-2 cases in placebo	DENV-3 cases in placebo	DENV-4 cases in placebo	VE
CYD14 (2-14 years)	Indonesia	1870 (18%)	80.9%	11	19	8	4	54.3% (28.0-71.0)
	Malaysia	1401 (14%)	47.0%	5	5	3	2	79.0% (52.3-91.5)
	Philippines	3501 (34%)	78.1%	87	22	17	33	53.9% (41.7-63.6)
	Thailand	1170 (11%)	67.7%	16	17	11	2	51.8% (25.3-68.9)
	Vietnam	2333 (23%)	54.2%	7	11	4	26	51.1% (26.1-67.6)
CYD15 (9-16 years)	Brazil	3548 (17%)	73.5%	9	0	0	72	77.5% (66.5-85.1)
	Colombia	9743 (47%)	92.2%	58	33	67	9	67.5% (58.3-74.7)
	Honduras	2799 (13%)	85.7%	6	20	39	0	71.1% (57.0-80.7)
	Mexico	3464 (17%)	53.1%	25	30	0	1	31.3% (1.3-51.9)
	Puerto Rico	1315 (6%)	56.2%	11	1	0	1	57.6% (-2.5-82.8)

In CYD23 (Phase 2b trial in Thailand), the vaccine efficacy estimate against VCD of any serotype in the ITT analysis was 34.9% (95% CI 6.7% to 54.3%) but was not statistically significant in the per protocol analysis, 30.2%

(95% CI -13.4% to 56.6%) [34]. Statistically significant efficacy estimates were reported for three of the four dengue virus serotypes (DENV1, DENV3, and DENV4) after at least one vaccine dose (ITT), but not after three doses (per protocol). These results are consistent with the lower vaccine efficacy generally seen against DENV2 (per protocol vaccine efficacy against DENV2 was 9.2%, 95%CI -75.0-51.3); around half of the cases of dengue in the placebo group in this trial were DENV2.

4.2 Vaccine efficacy against hospitalization for dengue and severe dengue during the period of active follow-up

Vaccine efficacy against VCD resulting in hospitalization, as well as against severe dengue, was higher in the 25 months following dose 1 than for VCD of any severity (Table 7). Across all ages, pooled VE against hospitalized dengue was 72.7% (95%CI 62.3-80.3), and 80.8% (95%CI 70.1-87.7) in participants first vaccinated ≥ 9 years of age. Vaccine efficacy against hospitalization for VCD was higher across all serotypes than VCD (Table 5 and Table 7). Notably, hospitalization rates in the placebo arm varied substantially across countries, ranging from 4.9% of VCD episodes in Brazil to 45.5% in Indonesia [35]. Vaccine efficacy against severe dengue was 79.1% (95%CI 60.0-89.0) in the first 25 months of follow up in the two trials combined, and it was 93.2% (95%CI 77.3-98.0) in participants ≥9 years of age.

The number of severe or hospitalized episodes was too small to undertake meaningful analyses stratifying by other factors.

Table 7 Vaccine efficacy against hospitalized or severe VCD during the active phase of surveillance (pre-specified analyses, intention to treat population, duration of follow up: study months 0-25)[32].

Outcome	CYD14	CYD15	Pooled	Pooled ≥ 9 years
Severe (IDMC) VCD	70.0% (35.7-86.6)	95.5% (68.8-99.9)	79.1% (60.0-89.0)	93.2% (77.3-98.0)
Hospitalized VCD	67.4% (50.6-78.7)	80.3% (64.7-89.5)	72.7% (62.3-80.3)	80.8% (70.1-87.7)
Hospitalized VCD-DENV1	71.5% (44.1-86.0)	73.2% (27.8-91.0)	72.1% (52.9-83.4)	Not published
Hospitalized VCD-DENV2	50.2% (-12.7-78.0)	80.1% (45.7-93.7)	65.7% (39.3-80.6)	Not published
Hospitalized VCD-DENV3	73.2% (27.6-90.9)	83.4% (33.6-97.1)	77.4% (52.2-89.3)	Not published
Hospitalized VCD-DENV4	77.9% (20.8-95.0)	91.7% (31.8-99.8)	83.5% (54.5-94.0)	Not published

4.3 Vaccine efficacy up to two years post randomisation, by dose

The indicated vaccine schedule is three doses administered 6 months apart. Completion of the 3-dose series in the Phase 3 trials was very high (over 90%), such that it is not possible to estimate efficacy after each dose, except in the 6 months following each dose. In the pooled analysis in the indicated age range (≥ 9 years*)*, VE between doses 1 and 2 was 70.8% (95%CI 58.1-79.6), 66.6% (95%CI 54.5-75.5) between doses 2 and 3, and 62.4% (95%CI 51.4-70.9) between dose 3 and 6 months post-dose 3 (data provided by manufacturer on request). The overall VE during the full active phase was 65.6% (95%CI 60.7-69.9). The rapid protective effect of 1 dose can be seen in the Kaplan-Meier curves, showing the accumulation of cases for vaccinated and control children. The curves start to diverge within a short period of the first dose (Figure 7).

The protective effect of doses 1 and 2 beyond 6 months after these doses, is unknown, nor is the additional protection derived from doses 2 and 3 known. Doses after the first may influence the duration of efficacy and may have different effects in those seropositive or seronegative at baseline. These remain research questions.

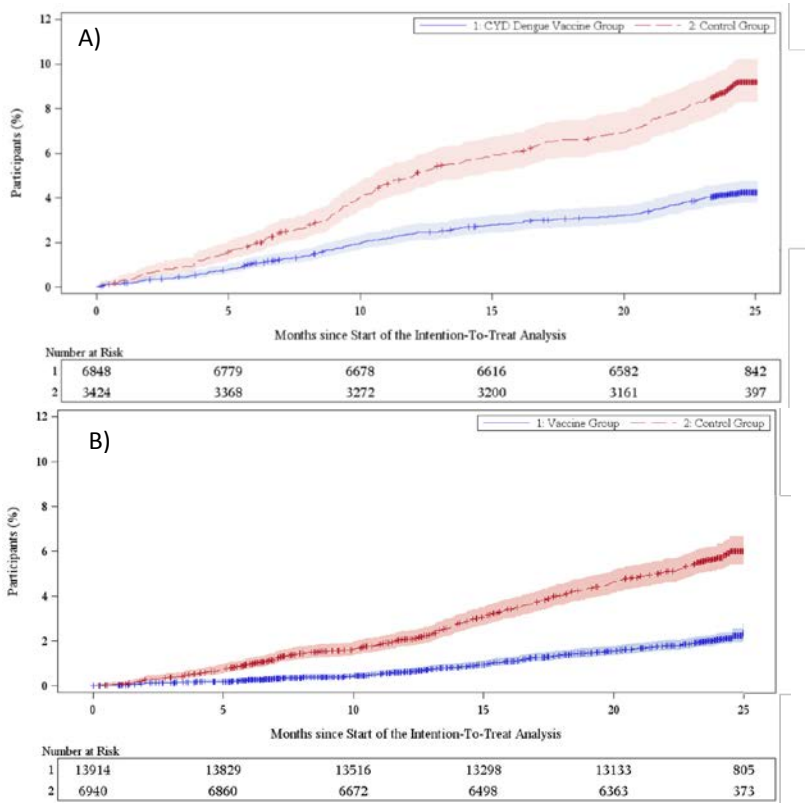


Figure 7 Cumulative incidence curve for virologically-confirmed dengue during the active phase due to any serotype (ITT population, follow up from study month 0-25), A) CYD14 and B) CYD15. Modified from [30, 31].

5. DENGUE AND DURATION OF PROTECTION BEYOND 2 YEARS OF FOLLOW-UP

The data presented so far have covered the active follow-up phase of the trials, months 0-25. Following this period, the participant follow up switched to hospital-based (as planned in the trial protocol for years 3-6). Thus, in this period it was no longer possible to assess VE against VCD (though will be with the surveillance expansion phase currently initiated). The continuing follow up for hospitalized and severe dengue was undertaken as a safety endpoint. To make clear this distinction, vaccine effects are reported as relative risks (rather than as VEs).

The long term follow-up data presented in this section rely on analyses performed by the manufacturer as an ongoing safety management supporting the IDMC evaluation of the safety. It contains the first 2 complete years of hospital phase from CYD14 (Study Years 3 and 4, abstract submitted to 5th Pan American Dengue Research Network Meeting; Panama 20-14 April 2016: Long-Term Safety of a CYD-TDV Dengue Vaccine in Asia Dengue Endemic Countries), Year 3 from CYD15 and Years 3 and 4 from CYD57 [32]. In addition, data provided by manufacturer upon request are also presented for CYD14 (partial Year 5), CYD15 (partial Year 4 and Year 5), and CYD57 (Year 5 complete and partial Year 6). Finally, cumulative Relative Risks over the entire study are also provided (data provided by manufacturer upon request).

5.1 Effects on dengue hospitalizations more than 2 years after trial entry

During the course of the hospital-based surveillance, a signal emerged from the youngest age group (2-5 years, an age group only included in CYD14). During both Years 1 and 2 of active follow-up, the RR of hospitalized dengue in the 2-5 year age group was 0.6 (not statistically significant). During Year 3, there were 15 hospitalized cases in the CYD group compared to 1 hospitalized case in the placebo group (2:1 randomization), a RR of 7.45 (95%CI 1.15-313.80) (Table 8). During Year 4 and Year 5, the relative risks diminished to 1.424 (95%CI 0.58-3.99) and 1.495 (95%CI 0.27-15.15), respectively. The cumulative relative risk during the entire trial period to date is 1.256 (95%CI 0.76-2.13). The 2-5 year age group was not included in CYD15.

Table 8 Vaccine effect on hospitalized dengue of any severity (ITT population) over time for CYD14, CYD15, and CYD23/57. [32] and provided by manufacturer on request.

		CYD14			CYD15			CYD23/57		
Age Group	**Time Period**	**CYD cases**	**Control cases**	**RR (95%CI)**	**CYD cases**	**Control cases**	**RR (95%CI)**	**CYD cases**	**Control cases**	**RR (95%CI)**
2-5 Years CYD14 N=2451 CYD23/57 (starting at 4yrs) N=623	Year 1 (Active)	8	6	0.644 (0.20-2.32)	Not included in trial population			1	2	0.239 (0.00-4.58)
	Year 2 (Active)	9	7	0.641 (0.21-2.02)				3	1	1.413 (0.11-74.17)
	Year 3 (Hospital)	15	1	7.45 (1.15-313.80)				5	1	2.443 (0.27-115.54)
	Year 4 (Hospital)	20	7	1.424 (0.58-3.99)				5	3	0.814 (0.16-5.24)
	Year 5 (Hospital/SEP)	6	2	1.495 (0.27-15.15)				4	0	+inf (0.32- +inf)
	Year 6 (Hospital)	NA	NA	NA				11	4	1.344 (0.40-5.76)
	Cumulative to date	**58**	**23**	**1.256 (0.76-2.13)**				**29**	**11**	**1.274 (0.62-2.83)**
6-8 Years CYD14 N=2791 CYD23/57 N=1513	Year 1 (Active)	5	12	0.209 (0.06-0.64)	Not included in trial population			4	3	0.670 (0.11-4.57)
	Year 2 (Active)	8	9	0.446 (0.15-1.3)				18	13	0.705 (0.33-1.57)
	Year 3 (Hospital)	4	5	0.400 (0.08-1.86)				14	5	1.401 (0.48-4.97)
	Year 4 (Hospital)	18	9	1.000 (0.43-2.53)				8	9	0.445 (0.15-1.30)
	Year 5 (Hospital/SEP)	5	3	0.833 (0.16-5.37)				3	1	1.498(0.12-78.66)
	Year 6 (Hospital)	NA	NA	NA				15	4	1.873 (0.60-7.75)
	Cumulative to date	**40**	**37**	**0.541 (0.34-0.87)**				**62**	**35**	**0.890 (.058-1.39)**
9-11 Years CYD14 N=2618 CYD15 N=8436 CYD23/57 N=1311	Year 1 (Active)	5	5	0.502 (0.12-2.18)	2	8	0.125 (0.01-0.63)	3	2	0.759 (0.09-9.08)
	Year 2 (Active)	2	13	0.077 (0.01-0.34)	6	14	0.214 (0.07-0.59)	3	9	0.169 (0.03-0.68)
	Year 3 (Hospital)	6	3	1.009 (0.22-6.23)	10	9	0.554 (0.20-1.54)	3	5	0.308 (0.05-1.58)
	Year 4 (Hospital)	12	3	2.013 (0.54-11.11)	6	5	0.601 (0.15-2.49)	3	5	0.308 (0.05-1.58)
	Year 5 (Hospital/SEP)	3	2	0.755 (0.09-9.04)	1	1	0.498 (0.01-39.12)	1	3	0.171 (0.00-2.13)
	Year 6 (Hospital)	NA	NA	NA	NA	NA	NA	11	5	1.126 (0.36-4.14)
	Cumulative to date	**28**	**26**	**0.542 (0.31-0.96)**	**25**	**37**	**0.337 (0.19-0.58)**	**24**	**29**	**0.422 (0.24-0.75)**
12-16 Years CYD14 N=2309 (up to 14 yrs) CYD15 N=10174	Year 1 (Active)	2	5	0.139 (0.02-1.22)	3	7	0.214 (0.04-0.94)	Not included in trial population		
	Year 2 (Active)	1	7	0.071 (0.00-0.55)	7	14	0.250 (0.09-0.66)			
	Year 3 (Hospital)	2	4	0.249 (0.02-1.74)	6	6	0.501 (0.13-1.87)			
	Year 4 (Hospital)	7	10	0.348 (0.11-1.01)	0	2	0.000 (0.00-2.67)			
	Year 5 (Hospital/SEP)	1	2	0.249 (0.00-4.79)	0	0	NC (NC)			
	Cumulative to date	**13**	**27**	**0.240 (0.11-0.48)**	**16**	**29**	**0.276 (0.14-0.52)**			

N= denominator of evaluable subjects for the RR calculation for the entire study.
SEP=Surveillance expansion phase

Consistent results were seen in those aged 4-5 in CYD23/57. In the 4-5 year age group, there were 5 hospitalized cases in Year 3 in the CYD group compared to 1 in the placebo group, a RR of 2.44 (95%CI 0.27-115.54). In Year 4, this excess was no longer apparent (5 cases in CYD group and 3 cases in the placebo group, a RR of 0.81 (95%CI 0.16-5.24), although in Year 5 there were 4 cases in the CYD group and 0 cases in the placebo group, and in Year 6 there were 11 cases in the CYD group and 4 cases in the placebo group.

In contrast, across older age groups (6-8, 9-11, and 12-16 years), an elevated risk was not seen consistently across the trials (Table 8). The relative risk point-estimate of hospitalized dengue was always below 1 in the ages included in the indication with two exceptions: in Year 4 of CYD14 for those first vaccinated aged 9-11 years, the relative risk was 2.013 (95%CI 0.54-11.11), and in Year 6 of CYD23/57 for those vaccinated at 9-11 years, the relative risk was 1.126 (95%CI 0.36-4.14). In comparison, the relative risk during Year 4 in the 9-11 year-olds in CYD15 was 0.601 (95%CI 0.15-2.49) and in CYD23/57 was 0.308 (95%CI 0.05-1.58). No Year 6 data are yet available from CYD14 or CYD15. In the older age groups, the relative risk over the full trial period to date (Years 1-5 in CYD14 and CYD15, Years 1-6 in CYD23/57) was always statistically significantly protective. Based on a smoothing of vaccine efficacy by age performed by the manufacturer, the point-estimate of the relative risk for hospitalization due to dengue crosses 1.0 between 6 and 7 years of age and remains below 1.0; the 95% confidence interval remains above 1.0 until between 12 and 13 years of age (Figure 8). It should be noted these relative risk estimates are based on a small number of cases, and the relative risk estimates often change markedly with the addition/subtraction of even just 1 case.

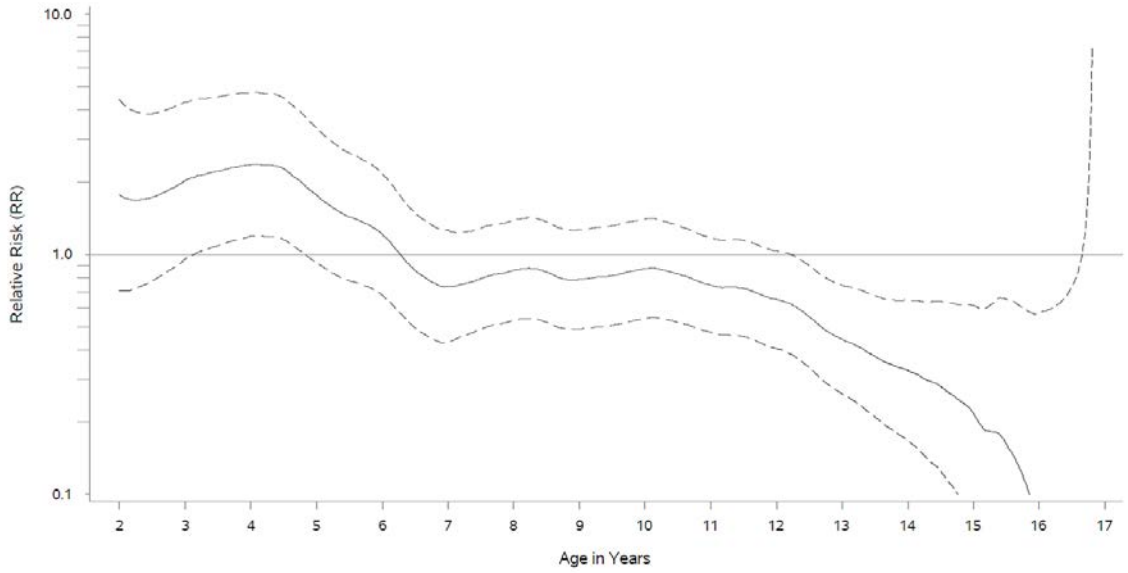
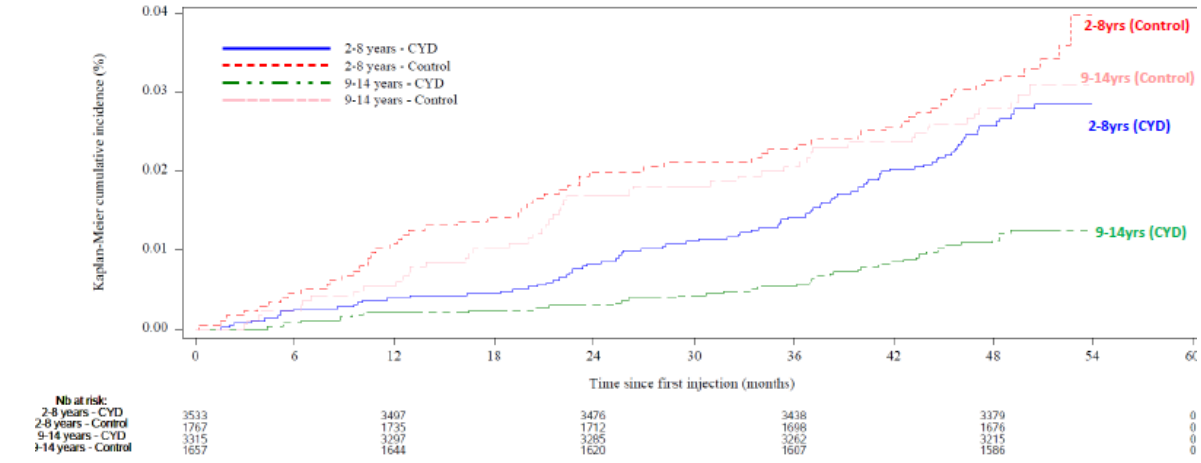


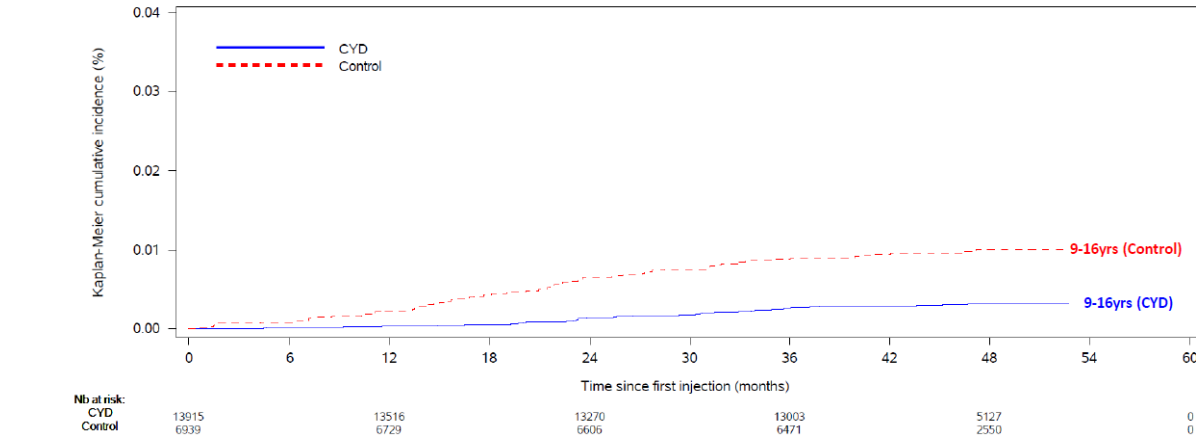
Figure 8 Relative risk (and 95%CI) against hospitalized symptomatic VCD in the Hospitalization Phase/Surveillance Expansion Phase due to any serotype by age in CYD14 and CYD15. Provided by the manufacturer on request.

In light of the signal that emerged in the 2-5 year age group, extensive profiling of these dengue cases was undertaken by the manufacturer. There was no apparent difference in the clinical severity of severe cases, either in the hospital phase compared to the active phase, or in the vaccinees compared to the controls [32]. There was no apparent difference in viraemia levels or cytokine profiles, including by age group, which has been argued to be counter to an immune enhancement hypothesis [36].

When considering 42 months of follow-up from the first dose, and an age stratification at 9 years, there is still an overall positive benefit overall in the CYD group 2-8 years of age (Figure 9). However, when further stratified by pre-existing age groups, the 2-5 year age group exhibits no benefit compared to the placebo group; the overall effect is negative, but does not reach statistical significance (Table 8).



A)



B)

Figure 9 Cumulative incidence of hospitalized VCD due to any serotype from first dose in A) CYD14 stratified by age groups, and B) CYD15 entire trial population. Provided by the manufacturer on request.

The Global Advisory Committee on Vaccine Safety (GACVS) reviewed longer-term follow up data through Year 3 of CYD14 and CYD15 [37]. GACVS noted the increased relative risk in the 2-5 year old population and highlighted the importance of understanding the potential factors associated with this signal that may be in addition to, or instead of, age. At the time of the data review, GACVS was unable to fully assess the risk in the youngest age group, currently excluded from the indication. GACVS emphasized the importance of further monitoring the risk of dengue requiring hospitalization (particularly severe dengue) in older individuals who are seronegative at the time of vaccination.

5.2 Severe dengue

A proportion of hospitalized dengue cases were classified as severe (IDMC definition). Due to the small numbers, case counts were combined over Years 1 and 2 (Active Phase) and Years 3-5 (Hospital Phase and Surveillance Expansion Phase) for CYD14 and CYD15 (Table 9). The results for severe dengue mirror those for hospitalized dengue. In the 2-5 year age group (2:1 randomization), in Years 1 and 2 there were 7 severe cases in the CYD group and 5 in the placebo group for a relative risk of 0.697 (95%CI 0.19-2.79). In Years 3-5, there were 13 severe cases in the CYD group and 1 case in the placebo group in Years 3-5 for a relative risk 6.473 (95%CI 0.97-275.1). In this age group, over the full trial period to date, there was a higher incidence in the

vaccinated group than in the placebo group, but the excess is not statistically significant. For the population above 9 years of age, the point estimates for relative risk against severe dengue were always below one with one exception in CYD14 (in the 9-11 year age group in Years 3-5, the relative risk of severe dengue was 3.525 (95%CI 0.45-158.86); this was not seen in CYD15 (relative risk 0.832, 95%CI 0.16-5.36) during the same time period). The point estimate of the cumulative relative risk over the full trial period to date was below 1 in the 6-8, 9-11, and 12-14 year age groups.

Table 9 Risk of severe (IDMC definition) hospitalized VCD by age group during full study period in CYD14 and CYD15. Provided by the manufacturer on request.

		CYD14			CYD15		
Age Group	**Time Period**	**CYD cases**	**Control cases**	**RR (95%CI)**	**CYD cases**	**Control cases**	**RR (95%CI)**
2-5 Years CYD14 N=2451	Year 1-2 (Active)	7	5	0.697 (0.19-2.79)	Not included in trial population		
	Year 3-5 (Hospital/SEP)	13	1	6.473 (0.97-275.1)			
	Year 1-5	**20**	**6**	**1.660 (0.64-5.05)**			
6-8 Years CYD14 N=2791	Year 1-2 (Active)	3	4	0.376 (0.06-0.22)	Not included in trial population		
	Year 3-5 (Hospital/SEP)	8	5	0.800 (0.23-3.11)			
	Year 1-5	**11**	**9**	**0.612 (0.23-1.67)**			
9-11 Years CYD14 N=2618 CYD15 N=8436	Year 1-2 (Active)	2	8	0.126 (0.01-0.63)	0	3	0.000 (0.00-1.21)
	Year 3-5 (Hospital/SEP)	7	1	3.525 (0.45-158.86)	5	3	0.832 (0.16-5.36)
	Year 1-5	**9**	**9**	**0.503 (0.18-1.43)**	**5**	**6**	**0.416 (0.10-1.64)**
12-16 Years CYD14 N=2309 CYD15 N=10174	Year 1-2 (Active)	0	3	0.000 (0.00-1.20)	1	8	0.062 (0.00-0.47)
	Year 3-5 (Hospital/SEP)	1	3	0.166 (0.00-2.07)	1	2	0.250 (0.00-4.81)
	Year 1-5	**1**	**6**	**0.083 (0.00-0.68)**	**2**	**10**	**0.100 (0.01-0.47)**

5.3 Potential explanations for signal in 2-5 year age group

The manufacturer has described interrelated working hypotheses as possible explanations for the signal seen [38]. The following is an excerpt from their paper:

> *The risk of developing severe disease is higher for individuals with a secondary heterotypic infection than for those with a primary infection. This may be mimicked by CYD-TDV vaccination of seronegative individuals, whereby vaccination represents a 'primary-like' infection dominated by one or a few serotypes, and diminishing responses lead to only short-term cross-protection. As cross-protection wanes (potentially rapidly, owing to low antibody titres), so vaccine efficacy is reduced, as discussed above. Furthermore, vaccinated individuals could be at greater risk of developing a severe or symptomatic 'secondary-like' infection the first time they contract DENV: the vaccine could act as their primary infection, and the subsequent true primary wild-type DENV infection (which would otherwise be typically less severe) could simulate a secondary wild-type infection (which is typically more severe).This situation is also more likely to occur in younger vaccinated individuals.[38]*

Related, the manufacturer has proposed three interrelated hypotheses, also described in the paper.

- Hypothesis 1: waning protection leads to reduced efficacy, particularly in seronegative individuals…*Humoral immunity is likely to wane more rapidly in seronegative than in seropositive vaccinated individuals, as the recall response in seropositive vaccinated individuals gives rise to a stronger immune response than is seen in their seronegative counterparts. Given that younger age groups have a higher chance of being seronegative than older age groups (as the likelihood of being exposed to a primary infection increases with age), waning immunity is more probable in the youngest vaccinated individuals. Consequently, their neutralizing responses are more likely to rapidly fall below protective thresholds for all four DENV serotypes and to present a monotypic pattern that is less likely to be cross-protective.*
- Hypothesis 2: younger vaccinated individuals are more susceptible to severe infection. *Age-related differences in vaccine efficacy may also be explained by differences in physiology that influence susceptibility to severe infection. For example, age differences at the microvascular and vascular levels could be associated with higher chances of plasma leakage, which is thought to contribute to severe disease. In addition, younger children could be less able to recover from dengue-induced disorders, increasing their chances of requiring hospitalization. Furthermore, some qualitative differences at the immunological level were seen between children 5–10 years of age and those who were older. These differences may affect innate immune responses, the diversity of the repertoire of B cells and T cells that are mobilized or the affinity of B cell clones, thus influencing the duration and quality of the CYD-TDV-induced specific responses in younger children versus older children. In agreement with there being an independent age effect, pooled efficacy analyses showed a significant vaccine efficacy in seronegative individuals 9 years of age or older, whereas the vaccine was not significantly effective in younger seronegative individuals.*
- Hypothesis 3: susceptibility in vaccinated individuals is temporally clustered. *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. This clustering occurred in a short period of time because of 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. Therefore, differences in seasonality and endemicity may mean that the primary infection and the subsequent secondary exposure to a heterologous serotype (with a potentially more severe outcome) are more spread out in time for control subjects than for vaccinated individuals. As a consequence, during a given period of time, one would observe more dengue-related hospitalizations for vaccinated individuals than for controls; however, this imbalance may be only temporary, occurring during a limited period of time, after which more severe cases would be accrued in placebo recipients.*

The hypotheses will require further data and follow up time to lend support or refute. The diminishing relative risk in Years 4 and 5 in the 2-5 year age group in CYD14 may support to some extent the cluster hypothesis. For policy considerations, with the data currently available, a key question is whether individuals who are seronegative at vaccination but above 9 years of age could be at increased overall risk of hospitalized or severe dengue. A further consideration is whether, if there is an increased risk at certain periods after vaccination in this population, there is simply no overall benefit, early protection being balanced out by a later excess of cases among vaccinated, or whether there is overall harm. Current data do not show an increased risk on hospitalized or severe dengue at any time point in seronegatives over 9 years of age, although data are very limited by the number of cases of hospitalized and severe dengue that occurred in the immunogenicity subset, for which baseline serostatus was known.

5.4 Duration of Protection

Vaccine efficacy against VCD of any severity has been measured in Years 1-2. The Surveillance Expansion Phase, started in Years 4 and 5 in response to the increased risk seen in children 2-5 years of age in Year 3, will collect data on virologically-confirmed dengue of any severity. Thus, the ability to make inferences about duration of protection against dengue of any severity are currently limited, but will be informed by future data generated from the ongoing clinical trials.

Data on hospitalized dengue has been collected throughout the trial period, though with different surveillance systems in the Active and Hospital Phases. With the limitations of this change in surveillance and that the CYD and placebo groups have different histories of dengue exposure at the start of later time intervals, it is one source of data available now to assess protection over the period of the trial.

For hospitalized dengue in ages included in the indication (9-16 years), the point estimate of relative risk of hospitalized dengue remains below 1, suggesting a sustained protective effect (Table 8). The point estimates year-by-year are variable, although in many instances the point estimate becomes closer to 1 as time progresses. In all age groups, the relative risk of severe dengue among vaccinated compared to controls is lower during the Active Phase than during the Hospital Phase (Table 9). These data may suggest potential (though unconfirmed) waning protection across all age groups.

6. IMMUNOGENICITY

6.1 Immune response induced by CYD-TDV

CYD-TDV induces neutralizing antibodies against all 4 serotypes, as measured by $PRNT_{50}$. In seronegative vaccinees, responses to the 3-dose regimen are mostly homotypic, usually (but not exclusively) to DENV4, while responses to the other serotypes are largely based on cross-reactive antibodies [38, 39]. T cell responses against structural antigens of DENV are also induced, as well as against non-structural antigens of the yellow fever vaccine virus. In vaccinees seropositive before vaccination, neutralizing antibodies titers are higher following vaccination (Figure 10 and Figure 11). Vaccination may boost previous natural immunity; responses due to vaccination are specific to the original infection serotype and cross-reactive against all serotypes as seen upon secondary wild type infection. Responses specific to other serotypes are also induced. A broader T cell response is also induced in seropositives compared to seronegatives. In addition, T cell responses against non-structural antigens of the dengue viruses are recalled in vaccinees seropositive before vaccination [40].

In multivariate regression analysis of phase 2 immunogenicity data from various trials in Latin America and South East Asia, two major predictors of post-vaccination titres were identified: baseline immune status (negative, mono-, multivalent) and trial location [41]. Age and gender were not predictors.

In the Phase 3 trials, GMT increased post-dose 2 (no post-dose 1 samples were taken), and did not increase post-dose 3 (Figure 10 and Figure 11). GMT were higher in those vaccinated who were seropositive at baseline compared to seronegative at baseline. GMT were higher in CYD15 compared to CYD14: in the CYD group (regardless of serostatus), GMT after dose 3 were 166, 355, 207, and 151 for serotypes 1, 2, 3, and 4, respectively, in CYD14 [30], and they were 395, 574, 508, and 241 for serotypes 1, 2, 3, and 4, respectively, in CYD15 [31]. It should be noted that baseline seropositivity, as well as age, was higher in CYD15 (79%) compared to CYD14 (68%) (Table 3).

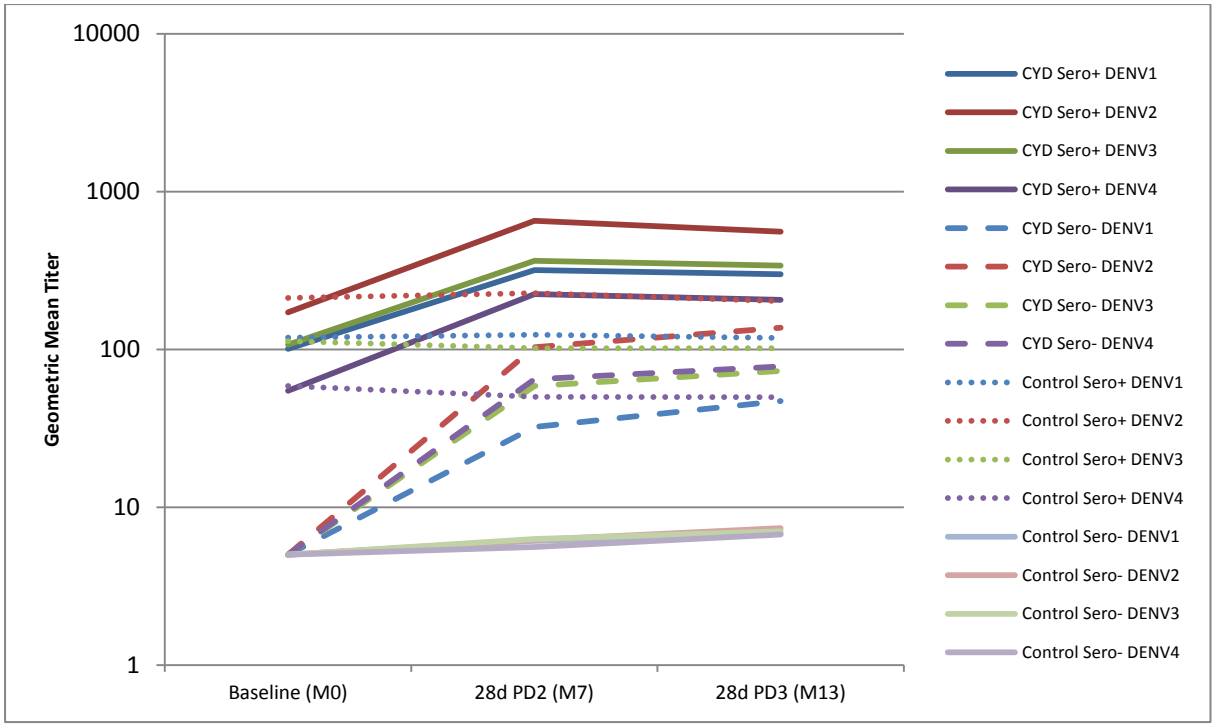


Figure 10 Geometric mean titers (GMT) as measured by PRNT50 in CYD14, by serostatus in CYD group (seropositive and seronegative combined in control group). Provided by the manufacturer on request.

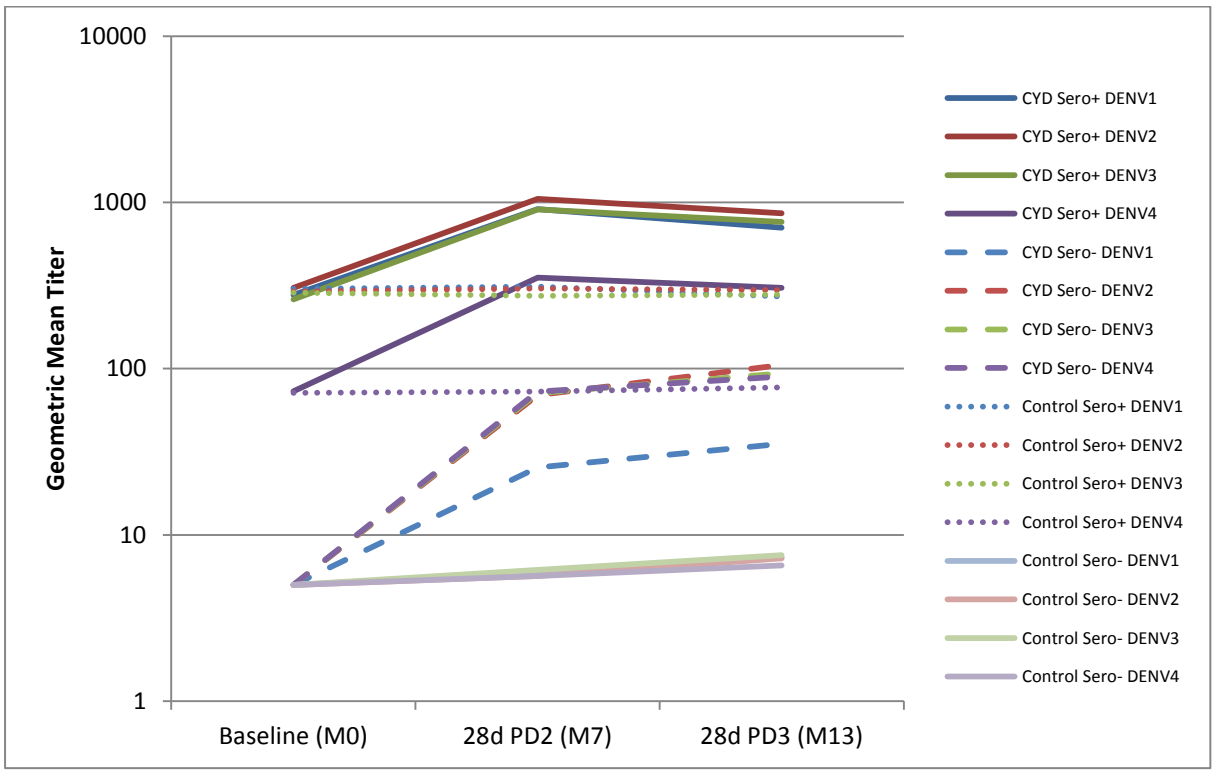


Figure 11 Geometric mean titers (GMT) as measured by PRNT50 in CYD15, by serostatus in CYD group (seropositive and seronegative combined in control group)[31] and manufacturer provided on request.

No correlate of protection for dengue has been established to date, although some correlation has been described between vaccine-induced neutralizing antibody titers and protection from VCD for a given serotype [42].

6.2 Immunologic rationale for vaccine schedule

Before vaccine efficacy data were available from the Phase 2b and Phase 3 trials, immunogenicity based on tetravalent seroconversion (in the absence of a correlate of protection) was an important factor in determining the number of doses to be included in the vaccination series. However, it is unclear how seroconversion, either against all four serotypes or fewer, relates to protection against disease.

Among subjects seropositive at baseline (to at least one serotype), many had a tetravalent response, even prior to receiving any vaccination, at baseline (Figure 12 and Figure 13). Following two doses, the majority of seropositive subjects had a tetravalent response in both trials. A subsequent dose increase the proportion of subjects with tetravalent responses. The range from studies in Latin America is smaller than in Asia, with, generally, a higher proportion for tetravalent responders in Latin America.

In seronegative subjects, the proportion with a tetravalent response by dose is lower than in the seropositive subjects. The 3-dose series again increased the proportion of subjects with a tetravalent response, although there was still a range across ages, with between 38% and 100% of subjects with a tetravalent response following three doses in the 18-45 year age group in Asia.

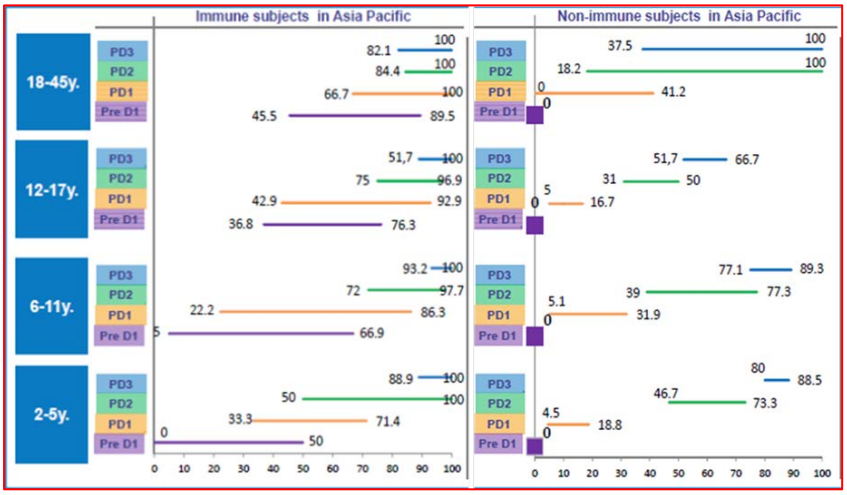


Figure 12 Range of percentage of subjects seroconverted to four serotypes ($PRNT_{50}\geq10$) by dose, age, and serostatus from Phase 2 trials in Asia. Provided by the manufacturer on request.

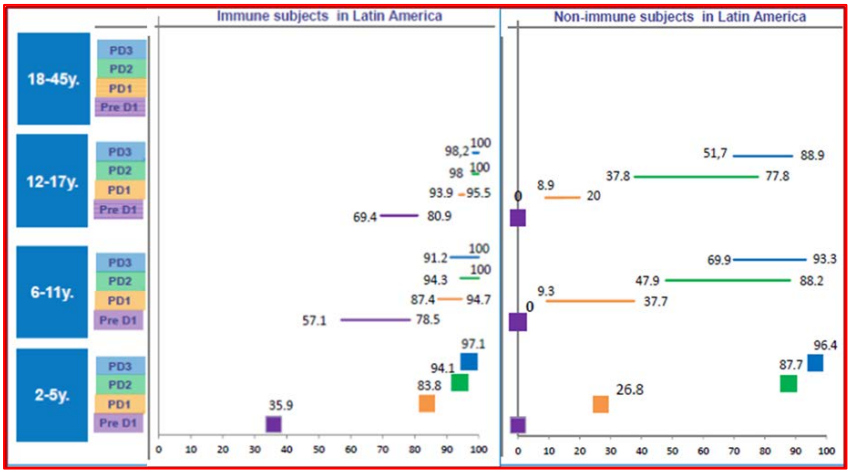


Figure 13 Range of percentage of subjects seroconverted to four serotypes ($PRNT_{50}\geq10$) by dose, age, and serostatus from Phase 2 trials in Latin America. Provided by the manufacturer on request.

Considerations of vaccine efficacy by dose were described in Section 4. While the vaccine efficacy estimates between doses were comparable to post-dose 3 vaccine efficacy estimates, these are pooled populations with about 70% seropositive subjects. Vaccine efficacy with fewer than 3 doses could vary by serostatus, as was seen after 3 doses.

6.3 Bridging vaccine efficacy beyond the age groups included in efficacy trials

At the time of writing, NRAs from the five countries that have registered the vaccine approved an indication in individuals 9-45 or 9-60 years of age, although vaccine efficacy data were available only up to 16 years of age. The age groups included in the efficacy trials were selected based on the high incidence. Safety and immunogenicity studies were undertaken in 294 individuals aged 18-45 in endemic settings (Table 1). Although there is no correlate of protection to be used for bridging, it has been shown that serostatus at baseline is associated both with age and with higher titers post vaccination. Comparing post-dose 3 titers from the vaccine efficacy studies to post-dose 3 titers from immunogenicity studies in Vietnam (N=20 aged 18-45) and India (N=126 aged 18-45), titers in adults in endemic settings were typically statistically significantly higher than in the older children and adolescent trial population (Sanofi Pasteur, personal communication). Given efficacy was established in this younger population, it was extrapolated that efficacy would also be similar or better in comparable adult populations.

6.4 Challenges interpreting immunogenicity data

Although neutralization antibodies are believed most likely to be a correlate of protection (as is the case for Japanese encephalitis, yellow fever and tick-borne encephalitis vaccines), limitations in the $PRNT_{50}$ assay and assumptions about needed titer levels for protection across 4 different serotypes make interpreting immunogenicity results difficult. With regards to the neutralization assay, there has been interassay and inter-laboratory variation demonstrated [43]. With additional variability induced by different of viral challenge strains and cell lines used, numerical values across vaccine developers/labs should be compared with caution. Even within a single laboratory, interassay variation may be as much as 2- or 3-fold different [44]. There is also cross-reactivity with other flaviviruses, making the characterization of an individual's flavivirus exposure history very difficult.

The traditional $PRNT_{50}$ is performed in Vero or LLC-MK2 cells, which do not include Fcγ receptors or produce antiviral interferon, in contrast to the human dengue target cells (i.e. monocytes, macrophages, and myeloid dendritic cells) [43]. The $PRNT_{50}$ assay also does not allow for differentiation between monotypic and heterotypic (temporarily cross-protective) antibodies, and may result in higher GMTs than in a different cell substrate more similar to the human *in vivo* experience. Until the first vaccine efficacy data were available in 2012, it was assumed that seroconversion would correlate with protection from disease. Although CYD-TDV induced a balanced antibody response by $PRNT_{50}$, vaccine efficacy by serotype varies. This could be due to qualitative differences in antibodies or potentially variable thresholds of antibody required to neutralize each dengue virus serotype. Depletion assays are useful to assess the relative contribution of monotypic and heterotypic responses across serotypes. New assays that address the limitations of the traditional $PRNT_{50}$, as well as a better understanding of the contribution of cellular immunity, will enhance the use of immunogenicity results in the absence of efficacy data to evaluate vaccine performance.

7. VACCINE SAFETY (NON-DENGUE)

7.1 Reactogenicity

Safety data across multiple studies that used the final formulation and final vaccination schedule have been pooled for the age range of 9-60 years, both in endemic and non-endemic areas. CYD was more reactogenic than placebo, although the percentage of subjects was comparable. Among solicited injection site reactions, the most common was pain, reported by 45.2% of subjects aged 18-60 years and 49.2% in subjects ages 9-17 years [45]. Of all solicited injection site reactions, less than 1% were Grade 3. Over 60% of participants reported a solicited systemic reaction, of which approximately 10% were Grade 3, most related to headache

and fever. The most common solicited systemic reactions were headache (>50%), malaise (>40%), and myalgia (>40%). Fever occurred in 5% and 16% of participants in the adults 18-60 and subjects 9-17, respectively. A review of safety outcomes by serostatus and by age group (9-17 years and 18-60 years) did not identify any signals of concern (data not shown).

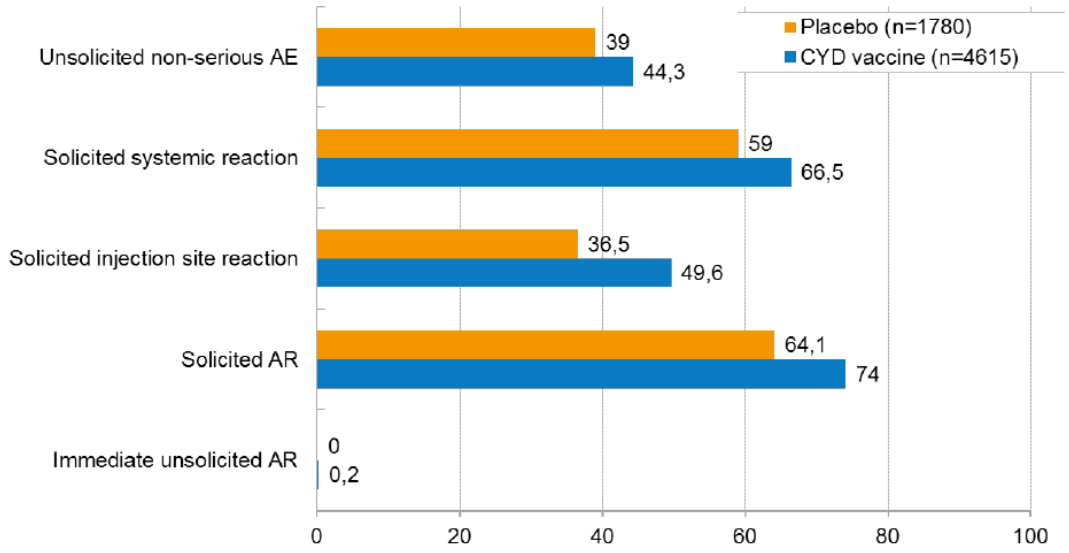


Figure 14 Percentage of subjects presenting with at least 1 reaction or event – subjects aged 9-60 years (pooled across multiple studies)[45].

Table 10 Percentage of participants in CYD14 and CYD15 experiencing safety outcomes [30, 31]. i.e. at least one SAE and death reported from baseline to month 25 (safety analysis set) and reactogenicity events reported within 28 days after any injection (subset analysis).

Adverse Health Outcome	CYD14 % (95%CI)		CYD15 % (95%CI)	
	CYD	Control	CYD	Control
SAE	5% (4.7-5.7)	6% (5.6-7.3)	4.1% (3.7-4.4)	4.4% (4.0-4.9)
Death	<1% (0.0-0.1)	0% (0.0-0.1)	<1% (TBC)	<1% (TBC)
Immediate unsolicited non-serious AEs	0% (0.0-0.3)	0% (0.0-0.6)	0.2% (0.0-0.7)	0.2% (0.0-0.8)
Solicited injection-site reaction	47% (44.8-50.2)	43% (39.2-46.9)	50.8% (48.1-53.6)	42.4% (38.6-46.3)
Solicited systemic reaction	57% (54.3-59.7)	55% (51.5-59.2)	68.4% (65.9-70.9)	69.5% (65.8-73.0)
Unsolicited non-serious AE	37% (34.1-39.3)	40% (36.7-44.3)	44.6% (41.9-47.4)	44.0% (40.2-47.8)
Unsolicited non-serious AR	1% (0.9-2.2)	<1% (0.3-2.0)	1.2% (0.7-1.9)	0.8% (0.2-1.7)
Unsolicited non-serious injection site AR	<1% (0.3-1.3)	<1% (0.0-1.1)	0.7% (0.3-1.3)	0.5% (0.1-1.3)
Unsolicited non-serious systemic AE	37% (34.1-39.3)	40% (36.7-44.3)	44.6% (41.9-47.4)	44.0% (40.2-47.8)
Unsolicited non-serious systemic AR	<1% (0.4-1.4)	<1% (0.2-1.5)	0.5% (0.2-1.1)	0.3% (0.0-1.1)

All but SAE and death are based on reactogenicity subset

No deaths were vaccine related. AE=adverse event. AR=adverse reaction. SAE=serious adverse event.

*Includes SAEs due to virologically confirmed dengue.

7.2 Serious adverse events

In the Phase 3 trials, the number of serious adverse events (SAEs) was similar between CYD and placebo group. Related SAEs up to 28 days after a CYD injection occurred in 6 subjects (headache and polymyalgia rheumatic in adults, and allergic urticaria, asthma, acute polyneuropathy, and tension headache in 9-17 year-old participants). An additional SAE was classified as related by the investigator in the 28 days to 6 months post CYD injection (blighted ovum), and 1 SAE of convulsion was judged to be related by the sponsor (not the Investigator).

7.3 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). There have been no confirmed AVD or AND cases in the studies. Severe dengue disease was discussed in Section 5.

7.4 Pregnancy

In the licensed indication, pregnancy and lactation are contraindications. A total of 613 pregnancies (402 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 402 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.

8. ESTIMATED VACCINE IMPACT

In April 2015 WHO initiated an open call for mathematical modellers to participate in a consortium called “Comparative modelling of dengue vaccine public health impact” (CMDVI). The purpose of the consortium was to generate model-based predictions of the potential population-level public health and economic impact of CYD-TDV, a primary goal of which was to inform SAGE recommendations on CYD-TDV. Eight modelling groups participated. The full results of this effort is an accompanying document (Flasche S. *et al*., Comparative modelling of dengue vaccine public health impact (CMDVI), SAGE Yellow Book).

The vaccine mode of action and introduction strategies were agreed to in collaboration with the SAGE Working Group in order to maximize relevance of CMDVI to SAGE deliberations. The models adopted, with small variations, the most parsimonious vaccine mode of action that matched the observed trial data; namely, that vaccination, similarly to natural infection, induces transient, heterologous protection against infection with any serotype. Furthermore vaccination acts like a silent natural infection in that a subsequent natural breakthrough infection in a vaccinated individual has the same pathogenicity as the latter of two natural infections in the same individual if she was unvaccinated. All results were generated for a range of transmission intensities, characterized by the proportion of 9 year olds that are seropositive (referred to as SP9, applied at seropositivity rates of 10%, 30%, 50%, 70% and 90%). Case definitions for symptomatic and hospitalized cases followed the clinical trial definitions.

All models predicted that routine vaccination of 9 year-olds with CYD-TDV at 80% vaccine coverage would cause an overall reduction in dengue disease in moderate to high transmission intensity settings (SP9≥50%). This range of transmission intensity covers all the sites selected for the phase 3 trials of CYD-TDV. The impact of vaccination was greatest in high transmission intensity settings (SP9≥70%), where the reduction in dengue-related hospitalizations predicted by the models ranged from 10% to 30%. Predicted impact on all symptomatic dengue disease were generally comparable to impact on hospitalised disease in these transmission settings.

Most models predicted that in very low transmission intensity settings (SP9=10%), vaccination was likely to increase dengue hospitalization rates. This was due to a key assumption used by the models, that vaccination primes seronegative recipients to have a 'secondary-like' infection when they are exposed for the first time, which thus can increase incidence of symptomatic and hospitalized dengue in low transmission settings. In the absence of vaccination, when transmission intensity is low, a high proportion of individuals never experience a natural secondary dengue infection.

In settings with slightly higher (but still low) transmission intensity (SP9=30%) there was less consensus between the predictions of different models; those models which better reproduced the risk increase in 2-5 year age group in the longer-term follow-up tended to predict that vaccination at age 9 years would increase hospitalizations in this setting, while other models predicted a beneficial effect of vaccination.

For all levels of transmission intensity, the predicted impact of vaccination scaled approximately linearly with the number of people vaccinated when different coverage levels were examined and when the potential impact of a catch-up campaign was explored.

All models predicted that as transmission intensity increased, the optimal age for routine vaccination decreased. Within the age range considered in the exercise (9-18y), vaccination at 9 years of age was optimal for the highest transmission intensity setting (SP9=90%). Vaccination at between 11 and 13 years of age was near-optimal for the SP9=70% setting for most models. The optimal age range increased to 14-18 years in the SP9=50% moderate transmission setting, and to 16-18 year olds for the SP9=30% low transmission intensity setting. All models predicted a positive impact on dengue disease in all settings with SP9≥30% if vaccination targeted children aged 14 years or older.

Vaccination was predicted to be potentially cost-effective in settings with SP9=30-90%, if the vaccine can be purchased and delivered cheaply enough. However, the results derived indicated that vaccination will only be cost-effective using the public payer perspective if the total cost of fully vaccinating one person is below $40 ($15 at SP9=30%). Given that the recurrent costs of delivering three doses of HPV vaccine in a similar age group in low and middle income countries lies in the range $1 - $16, this suggests that vaccination may not be cost-effective in the SP9=30% setting, and that the vaccine would have to be competitively priced and/or co-administered with other vaccines in higher transmission settings. Vaccination is more cost-effective if a societal perspective is adopted or a higher value is placed on averting a DALY. It should be noted, however, that the CMDVI results are only indicative and should not be used as a substitute for more targeted analyses to inform country-specific decisions.

9. PROGRAMMATIC CONSIDERATIONS

As part of the deliberations on the use of any new vaccine, the programmatic implications and operational feasibility of the proposed vaccination schedule are important issues to be considered. The following section outlines some of the programmatic considerations specific to the licensed dengue vaccine (indicated in several endemic countries for individuals 9-45 or 9-60 years of age living in endemic settings), drawing lessons from recent HPV vaccine introductions in adolescents as well as from routine infant immunization.

In the absence of a SAGE recommendation and WHO position, this section serves to provide some preliminary thoughts based on the knowledge and experience of immunization programme experts. If appropriate, a

broader consultative process with partners and country programmes will be undertaken to design and plan for the introduction of the CYD-TDV vaccine.

Recently, the EPI programmes in most countries have accumulated limited but significant experience with delivering injectable vaccines to individuals outside the traditional EPI age group of less than one year, including TT, HPV, rubella, Men A and seasonal influenza vaccines. The 0/6/12 month schedule of the CYD-TDV vaccine could pose a potential new challenge in some settings. Nonetheless, given the high awareness about dengue disease in affected countries (compared to awareness of the target condition for some other recently introduced vaccines), a dengue vaccine is more likely to lead to very high societal demand. As such, the efforts to overcome the delivery challenges listed above should be interpreted in this context.

9.1 Vaccine strategies

Serostatus: Based on the performance of CYD-TDV in clinical trials, the vaccine is more protective amongst individuals who have already been exposed to dengue infection than in those who are dengue non-immune (seronegative). There is a theoretical possibility that vaccination may be ineffective or may even increase the risk of severe and/or hospitalized dengue in those who are seronegative at the time of first vaccination, regardless of age. As a result, the greatest benefit would be expected in those who are seropositive at the time of vaccination. Currently, there is no rapid, point-of-care test to establish serostatus in order to allow for this kind of targeted vaccination. In the absence of ascertainment of serostatus at the time of vaccination, any use of the vaccine in a routine program would need to consider serostatus at the population level. Any requirement to conduct seroprevalence studies prior to vaccine implementation will be new to the EPI programme and will need careful communication to health workers as well as the general population.

Geographically targeted strategies: Given the dependency of vaccine performance on serostatus at baseline, as well as the heterogeneity in transmission intensity in small geographic areas, it is possible that subnational, localized vaccine introduction would be most cost-effective. This may lead to challenges in implementation if vaccination schedules are heterogeneous across districts or regions. Key considerations for a localized introduction should include population and health worker mobility, potential for disease to spread across initially defined boundaries over time (for example due to climatic changes and changes in vector prevalence/infection rate), public perceptions of inequity, as well as need for ongoing training of health workers as they move across districts. Individual countries can best assess their capacity for subnational introduction, including within political boundaries if appropriate.

Adding new vaccination contacts: The current schedule of the CYD-TDV candidate vaccine (0/6/12 months) will likely 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. Experience with new visits/school-based campaigns suggest substantial programmatic costs. Whether given at the health centre or through school-based 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.

Delivery strategy: Vaccination schedules targeting school age children and adolescents (e.g. 9-17 years) may be administered either through health facilities or through school-based programs. Both strategies have been effective at achieving high coverage of HPV vaccine in different settings. 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.

Similarly, 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, among other factors. WHO has produced a School Vaccination Readiness Assessment Tool to assist with planning and preparations.

Vaccination schedules targeted at adults or the out-of-school population would likely require alternate strategies. While some countries have some experience with influenza vaccine in adult populations, coverage rates are traditionally low. Countries would need to consider strategies to reach populations when there is not a ready platform (e.g. school health platform) and vaccination status would need to be carefully tracked to ensure compliance with the three-dose schedule.

Vaccine delivery through 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.

Integration with other interventions: Experience with the HPV vaccine has shown that new contacts with health care professionals during the adolescent period provide potential opportunities for integrating a variety of health interventions (e.g. sexual health, WASH, vision and dental assessments, tobacco counselling, menstrual hygiene, etc.). In practice, maximizing the potential value of such opportunities continues to be a challenge. Given the expected wide acceptability of a dengue vaccine, opportunities for integration with other health services and commodities should be sought at the onset. Experience suggests that for a successful integration, discussions among departments and ministries should commence as early as possible. It is important to note, however, that in situations where CYD-TDV is offered only to specific geographic locations, issues of equity and fairness with regard to the additional services/commodities will need to be addressed.

Vector control is an important intervention against all vector-borne diseases. There could be additive or synergistic effects when using vaccination and carefully implemented vector control together. Furthermore, community-based vector control interventions, such as COMBI (Communication for Behavioural Impact) and social mobilization for source reduction can serve as an opportunity to educate the public about vaccination. Furthermore, vaccination can serve as a platform to reinforce messages about community-based efforts.

Vaccine management and logistics: CYD-TDV is available both as a single- and multi-dose (5) vial. The multi-dose presentation requires less cold-chain capacity. However, per WHO recommendations [46], any reconstituted doses remaining at the end of the session would need to be discarded within 6 hours of opening/reconstitution or at the end of a session, whichever comes first. Although this is well-suited for vaccination campaign delivery (including school-based campaigns), multi-dose vials may lead to high wastage rates in the routine setting compared to a single-dose vial. On the other hand, single dose vials will require much greater cold-chain capacity, and the resource implications of expanding the cold chain should be given due considerations during the planning phase.

Coverage monitoring: Given the long interval between the first and final dose (12 months) and the need to ensure full vaccination with all three doses, countries will need to consider use of a vaccine registry maintained by the Ministry of Health and vaccination record for each vaccinee. Similarly, considerations for assessing the size of the target population for calculating administrative coverage will require careful review at the onset.

9.2 Co-administration

There are currently no data available from co-administration studies within the age indication for licensure from endemic settings, but three small co-administration studies were previously conducted in toddlers with YF, DTaP-IPV/Hib, and MMR. These studies were undertaken in Colombia/Peru, Mexico, and the Philippines, respectively. In adults, one study has been conducted in the US - a non-endemic setting (YF, different CYD schedule than sought for licensure). From these small studies it was concluded that there were no safety concerns (data were comparable when vaccines were co-administered or given alone), and that the immunogenicity profile was satisfactory both for CYD and for co-administered vaccines. The one exception to this was a lower response to serotype 4 in the study in US adults. In the labelling, there are no data with co-administration included because the toddler age group and non-endemic population are outside the first indication.

9.3 Outbreak response

CYD-TDV has not been evaluated in the context of a response to an identified outbreak. There are programmatic considerations for use in an outbreak response including factors such as size of the outbreak, timeliness possible of the response, population affected, transmission intensity and background serostatus of the target population, and programmatic capacity. Further discussion on the potential use in the context of an outbreak is provided in the proposed recommendations.

10. PLANNED POST-APPROVAL EVALUATION BY THE MANUFACTURER

The manufacturer has identified important potential risks (some basis for suspicion of an association with the product, but where association not confirmed): allergic reactions (including anaphylactic reactions, YF vaccine-associated viscerotropic disease and YF vaccine-associated neurotropic disease, increase in the severity of dengue disease from the start of vaccination, and waning protection against dengue disease over time.

Table 11 Summary of Risk Management Plan proposed by the manufacturer

Type	Activities
Post-marketing pharmacovigilance activities	• Routine pharmacovigilance monitoring • Enhanced safety surveillance
Long-term monitoring of ongoing efficacy studies	• Surveillance expansion in CYD14 and CYD15 (return to active surveillance currently in progress) • 5 year follow-up post-dose 3
Safety studies	• Background rates of conditions that can mimic viscerotropism and neurotropism • Cohort event monitoring • Pregnancy registry
Effectiveness studies	• Community-based studies to evaluate impact on disease transmission • Facility-based studies to evaluate impact on hospitalization and severe dengue (with annual bleeding) • Monitor potential waning immunity over time
Additional clinical studies	• Booster studies • Clinical stable HIV+ subjects • Co-administration studies (HPV, Tdap)
Risk minimization	• Product information / labelling and packaging

CYD14 and CYD15 will be maintained for follow up until 5 years after the 3rd dose. Protocol amendments have been submitted for active surveillance to be re-instated (through SEP), which will allow for assessment of

efficacy against VCD of any severity. Because blood samples will be taken at the time of re-enrolment, the relationship between dengue antibody level at that time and further subsequent VCD can be evaluated.

Vaccine schedules:

A study is planned to look at immunogenicity and safety in approximately 1,000 participants 9-50 years of age who receive either 1, 2, or 3 doses of the vaccine. A booster dose is also planned 12-24 months after the last dose (NCT 02628444).

Co-Administration:

Two co-administration studies have been identified as high priority given the indicated age range: HPV (tetravalent and bivalent) and Tdap. These are planned as Phase 3b, open-label, observer-masked studies and will assess the impact of co-administration on immunogenicity of each vaccine, as well as safety and reactogenicity.

Booster dose:

A multicentre study is planned that capitalizes on vaccinated recipients from previous Phase 1 and Phase 2 trials. Following the primary series of CYD-TDV, a 4-5 year gap will have occurred between the primary series of CYD-TDV and a single booster dose of CYD-TDV or placebo. There will be no comparison with age-matched subjects who have not received the primary series previously. Non-inferiority will be assessed, as will there be qualitative assessments of the immune response, and safety will be assessed (NCT02623725). Durability of the immune response up to 2 years post-booster will also be assessed.

11. OVERALL ASSESSMENT AND KEY RECOMMENDATIONS FOR SAGE CONSIDERATION

The first dengue vaccine has been thoroughly evaluated in two Phase 3 trials in Asia and Latin America and NRAs from several endemic countries have licensed the vaccine. The indicated age range for the vaccine based on current regulatory approvals is 9-45 years or 9-60 years. The trials were executed to a very high quality and the sponsor has proactively shared key results to allow for a robust assessment of the vaccine. Because there were two comparable large Phase 3 trials as well as the Phase 2b trial, it is possible to look for consistencies and differences. Vaccine effects during the Hospital Phase were based on relatively small numbers of hospitalized and severe cases, and thus these comparisons are particularly useful when there is a suggestion of a year-to-year aberration in one of the trials. When an unfavourable relative risk was seen, it was valuable to compare effects in the other two trials.

11.1 Assessment of vaccine efficacy and vaccine schedule

The primary endpoints were met in both Phase 3 trials. At a population level, the vaccine confers partial protection against virologically-confirmed dengue of any serotype. Secondary and exploratory analyses demonstrated vaccine efficacy in the first 25 months after the first dose is higher against serotypes 3 and 4 than against serotypes 1 and 2, vaccine efficacy is higher against severe and hospitalized dengue, vaccine efficacy is higher among older trial participants, and vaccine efficacy is higher amongst those who had already been exposed to dengue prior to vaccination.

Vaccine efficacy estimates produced in the trials represent averages over different ages and countries, which includes variable year-to-year dengue transmission, variable serotype transmission, and variable participant characteristics, including serostatus at baseline. Vaccine efficacy varied by country, probably due, at least in part, to variations in these factors, and suggests that impact can be optimized in settings defined by key characteristics.

Importantly, the protection conferred by CYD-TDV was substantially higher among trial participants who were seropositive at the time of vaccination. Among trial participants included in the indication (9-16 years), vaccine efficacy among seropositives was 81.9% (95%CI 67.2-90.0), and vaccine efficacy in seronegatives was 52.5% (5.9-76.1). In seropositive individuals, there is a clear and important benefit against dengue of any severity. The strong effect seen in seropositives may be because the vaccine acts as a booster (or silent post-primary infection) that elicits broadly cross-reactive neutralizing antibodies against all serotypes, just as is seen with natural infection. In seronegatives, the lower bound of the 95% confidence interval was above 0, though the wide confidence interval, low GMTs, and suggestions of waning call into question whether there is any substantial cumulative benefit in this group.

While it would be preferable to target vaccination in those who are seropositive, appropriate point-of-care tests do not exist at this time, and thus age and the history of dengue in the target communities will need to serve as surrogate measures for vaccinating those who will benefit most from vaccination. The optimal age group will reflect the underlying disease transmission, with the goal for a majority of those vaccinated to be seropositive at the time of vaccination. If a majority of vaccine recipients are expected to be seropositive at vaccination, given the high incidence of dengue, the impact could be substantial in terms of absolute numbers of cases averted.

A 3-dose schedule given 6 months apart is not optimal from a programmatic perspective; however, high compliance with this schedule was achieved in the trials and experience gained with vaccine delivery for older children and adolescents indicates that it is likely to be possible to deliver a vaccine on this schedule to the 9-11 year age group, and likely to older school-age children as well (acknowledging school drop-out rates increase with age). Phase 3 trial data suggest protection from the vaccine begins with the first dose. However, due to the high course completion rate in the trial, it is not possible within the trial to look at efficacy by doses received during the 25 follow up period, other than in the 6 months following each dose. Furthermore, whether the duration of protection is affected by the number of doses received also not known. Based on immunogenicity data, it is clear that the immune response in seronegatives is improved with doses 2 and 3. 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. Additionally, host factors such as serostatus will need to be considered in dosing regimens, as different schedules may protect some individuals but not others.

11.2 Assessment of risk of hospitalized and severe dengue over time and duration of protection

In the ages included in the indication, there was protection against hospitalized and severe dengue across the Phase 3 trials and up to the latest available follow up data (Year 5 for CYD14 and CYD15). The relative risks generated during the course of the Phase 3 trials were used as a safety endpoint, not an efficacy endpoint. However, there is evidence that the relative risks of hospitalized and severe dengue among those vaccinated moved closer towards 1 in years 3-5 compared with years 1-2, potentially indicating waning immunity (Table 9). Data generated in Year 5 with the Surveillance Expansion Phase will allow for comparison of vaccine efficacy against virologically-confirmed dengue generated in Years 1 and 2. When these data become available, potential waning immunity and booster needs can be better assessed, as can the overall benefit anticipated over time from vaccination.

An increased risk of hospitalized and severe dengue was seen in the 3rd year of follow up in 2-5 year-olds in CYD14. This increased risk was large (7.45 in Year 3), but diminished in Years 4 and 5. The Phase 2b trial in Thailand, CYD23/57, found similar effects. It could not be evaluated in CYD15 due to the absence of this age group in the trial. The 2-5 year age group also has the highest proportion of seronegatives. Thus, a key question is to what extent the increased risk seen in the 2-5 year age group is due to age, serostatus, or a combination of the two. Looking across the trials in the older age groups, there was a lack evidence of an

increased risk at any point during follow up. Only in the 9-11 year age group in CYD14 was a relative risk above one in Years 4 of follow up; however, as the relative risk was below 1 in this same age group in CYD15 and CYD23/57, it is not interpreted as a signal.

There are few data to support or refute any risk in seronegatives greater than 9 years of age. In CYD14 and CYD15, over 70% of the population in this age group was seropositive, and this increased with age up to 16 years. The relative risks were below 1 over time in this age group (consisting of both seropositives and seronegatives). Within the immunogenicity subset, among seronegatives, there is no indication that the same effect is observed in the 9-16 year-olds as was seen in the younger age groups (Appendix 3). Current data are compatible with no reduction in disease risk among vaccinated seronegatives. However, it cannot be excluded that in the years following vaccination, seronegatives may be at an increased risk of dengue. Of note, there is a theoretical risk even in seropositives that as immunity wanes, they could too be at increased risk of severe and hospitalized dengue some years in the future.

The explanation for these findings in the 2-5 year age group is unclear based on available data. The hypotheses put forward by the Sponsor (Section 5.3) are plausible, in particular the suggestion that the immunological mode of action of the vaccine is to move individuals along the infection line. The clustering hypothesis may also help explain the initial elevated relative risk 7.45 in Year 3 that diminished to 1.4-1.5 with further follow-up. An age effect independent of serostatus, which would reduce the theoretical risk of predisposing older seronegative vaccinees to more severe forms of dengue, would also be compatible with the available data but requires further investigation.

11.3 Assessment of impact predicted by mathematical modelling

The positive benefit of vaccination provided in moderate-to-high transmission settings of seroprevalence at 9 years of age of 50% or higher across 8 different mathematical models provides reassurance that use of the vaccine in these contexts will result in a population-level reduction in dengue, including for hospitalizations, which present an important burden on the health system. A reduction of 10-30% in dengue-hospitalizations was predicted over 30 years. Notably, impact was highest in transmission settings of 70% or higher seroprevalence at age 9 years. The variability in model outputs at low and very low transmission settings urges some caution in vaccine use in such settings. Importantly, these are population-level outputs that do not directly reflect individual-level effects, i.e. individual risk of hospitalized or severe dengue among vaccinated seronegatives, and some models do predict negative impact among seronegatives even in the 50% seropositivity setting (because in this transmission setting in the absence of vaccination, many seronegatives would not have experienced two dengue infections in their lifetime). However, additional data and follow up are needed to better characterize this risk in seronegatives in this age group to better understand the risk profile.

The optimal ages for vaccination vary by transmission setting; 9 years of age is only optimal in the highest transmission settings from the perspective of disease impact, although there may be programmatic reasons why 9 years of age may be preferable in settings with lower than 90% seropositivity in this age group. Impact variability by age was not substantial in the moderate (SP9=50%) to high (SP9=70%) transmission settings.

With the introductions scenarios modelled, which were chosen to be realistic in representing what most countries would consider, neither catch-up vaccination nor higher coverage in a routine program impacted transmission (i.e. little or no indirect effects). Cost-effectiveness analyses, evaluated using the CMDVI settings that were not country-specific, suggest that vaccination could be potentially cost-effective in moderate-to-high transmission settings, if the vaccine can be purchased and delivered cheaply enough. Importantly, country-specific analyses will be needed to assess cost-effectiveness with locally relevant parameters.

The modelling comparison is an important tool to translate point-estimates generated from the trial, which varied by infecting serotype, age, serostatus, and severity, into predicted program impact. While there was a high level of consistency across the models, there are a number of uncertainties in the model assumptions, including the mode of action of vaccination and duration of protection, which may vary by factors such as serostatus, that remain unknown. Empirical data remain critical. Modelling predictions will continue to be important tools as they are informed by newly generated data that address key remaining questions with respect to vaccine performance.

11.4 Assessment on other aspects of vaccine safety

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 AVD and 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. Spontaneous reporting should also emphasize these outcomes to help assess whether there is any risk. The licensed Japanese encephalitis vaccine using the same ChimeriVax technology, IMOJEV®, is similarly being evaluated, with no signal to date.

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

Vector control is the backbone of dengue control programs. 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.

There are a number of strategies employed by control programs to reduce mosquito populations, and designing a dengue control program that optimizes allocation of resources is a priority. Many vector control interventions have been shown to be effective against entomologic indicators. However, given the lack of an established correlation between entomologic indices and epidemiologic outcomes, dengue control programs could be improved through the better evaluation of vector control and its effect on dengue disease. Vector control is a key strategy, but maintenance of a sustained impact of this intervention is a concern. Therefore, vaccination as a complementary to vector control will further strengthen dengue control programme in countries.

Countries will need to make decisions about vaccine introduction and use based on their own epidemiological setting and local resources and priorities. Given the complexity of the disease and the vaccine performance in different populations, mathematical models are a useful tool to predict potential impact of a vaccination program with local considerations. Additional work in developing modelling tools using local data that can be reasonably attained would assist in designing country immunization strategies.

11.6 Post-licensure data needs

The sponsor has submitted to NRAs a global Risk Management Plan to address a number key issues, including vaccine effectiveness, co-administration and booster needs, and traditional vaccine safety monitoring. NRAs have accepted this RMP. In addition, countries that introduce the vaccine need to conduct their own post-licensure monitoring and evaluation. It is important to bear in mind that, when considering empirical data for evaluating vaccine impact at the population level, dengue transmission is often highly variable year-to-year: a 20% change in dengue in either direction is within expected year-to-year variation. Policy-makers should be careful when interpreting surveillance data to infer vaccine impact or its absence.

One important research question remains that will not be adequately addressed in the RMP, which is to understand vaccine effects in individuals in the indicated age range who are seronegative at vaccination. There are different approaches that might be taken to evaluate risk in seronegatives; further consideration should be given to assess this hypothetical risk in parallel to vaccine introduction. Targeted studies in parallel to implementation are needed to answer this question definitively, otherwise it will remain a controversial issue and could compromise public confidence in the vaccine program.

11.7 Key conclusions and recommendations for SAGE consideration

Countries should consider introduction of CYD-TDV in geographic settings (national or subnational) with high dengue transmission, i.e. seroprevalence of approximately 70% or greater in the age group targeted for vaccination but not below 50%.[5]

Where possible, assessment of dengue transmission intensity should be supported by geographically relevant seroprevalence studies. Seroprevalence estimates should guide decision-making and introduction at subnational levels while noting that these are not precise indicators. Work is needed to identify routinely collected epidemiologic indicators that can be used to infer likely seroprevalence.

Decisions about introduction require careful assessment at the country level, including consideration of local priorities, subnational dengue epidemiology, predicted impact and cost-effectiveness with country-specific hospitalization rates and costs, as well as affordability and budget impact. Vaccination should be considered as an integrated strategy together with well-executed and sustained vector control and the best evidence-based clinical care for all patients with dengue.

CYD-TDV is recommended as a three dose series given 6 months apart. While protection has been documented after administration of the first dose, completion of the three-dose scheduled is recommended to assure the protection demonstrated in the 5-year period of trial follow up so far. 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. Because of the duration of the vaccine schedule and to enable better vaccine monitoring, countries should have systems in place for tracking vaccination.

The target age for routine vaccination should be defined by each country based on an assessment of dengue endemicity and programmatic feasibility of targeting particular ages. The age to target to optimize impact likely varies by transmission setting.[6] Although only immunogenicity (not vaccine efficacy) has been studied in clinical trials of 17-45 year-olds, in principle these age groups could be targeted for vaccination. At this stage, insufficient data are available to permit a recommendation for use above the age of 45 years. No vaccination is recommended under age 9 years due to the potential safety concern signalled in children aged 2-5 years of age in the Phase 3 trial.

Risk of dengue hospitalization has been monitored for up to 4 years post-dose 3 in the Phase 3 trials. In the age group currently part of the indication (9-16 years), there is evidence of decreasing protection against dengue hospitalization over this time period. Ongoing follow up from the Phase 3 trials will provide information on the duration of protection, and it is possible that booster doses may be necessary to maintain protection. Currently there is no recommendation for a 4th dose.

[5] Mathematical modelling suggests optimal public health and economic impact in these transmission settings. Seroprevalence of 50% was at the lower end of the range of participants in Phase 3 trial sites. The overall seroprevalence in 9-16 year-old trial participants in the Phase 3 studies was approximately 80%. Modelling cautions against CYD-TDV use in lower transmission settings in early adolescence.

[6] Mathematical modelling found 9 years of age was optimal only in very high transmission settings (seroprevalence of 90% in that age group). In other settings with moderate to high transmission, vaccination between 11 and 13 years is predicted to maximize impact, although the variability in impact with age of vaccination was not great.

Co-administration is not recommended until data are available on the safety and immunogenicity of CYD-TDV when co-administered with other age-appropriate vaccines.

CYD-TDV should be introduced as part of a routine immunization program in appropriate settings. Catch-up campaigns targeting priority age groups defined by local epidemiology can be considered for a greater immediate impact. While adding age cohorts will give progressively better disease control, mathematical modelling of catch-up campaigns in 10-17 year-olds does not suggest a significant impact on dengue transmission (i.e. herd immunity). Future research will study a possible impact of the vaccine delivered through the routine system plus catch up on disease transmission.

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: CYD-TDV has not formally been licensed for use in travellers. In travellers who have already been previously infected with dengue, vaccination for travel to high transmission settings may be beneficial. Extrapolation of data from the Phase 3 trials suggests that in such persons there may be some protection after the first dose, but completion of the full 3-dose schedule is still recommended. In travellers unlikely to have already had dengue, vaccination may be substantially less beneficial (and there is a theoretical risk that it may be harmful), analogous to seronegative individuals living in endemic settings. Co-administration with other travel vaccines is not recommended.

Health care workers: There are no specific recommendations for health care workers.

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.

Other aspects

Due to the partial efficacy of the vaccine against dengue of any severity, careful communication is needed to inform vaccinees that they may still be at risk of dengue and of the importance of receiving all three doses and of adhering to other disease preventive measures.

An assessment of vaccine effectiveness, and the durability of that effectiveness, with fewer than 3 doses is a priority. Current data suggest substantially lower benefit of vaccination in seronegative individuals 9-45 years of age. There is a theoretical possibility that vaccination could do harm in this population. Although theoretical risks not supported by data should not impede rollout of this vaccine, it is critical to evaluate as soon as possible whether there is any risk to this population.

Research Priorities

Table 12 Research priorities related to CYD-TDV identified by the SAGE Working Group on Dengue Vaccines.

CYD Research Question	Priority	Addressed in RMP?	Notes
Risk of severe/hospitalized dengue over time in vaccinated seronegatives	**Critical**	Post-licensure studies in RMP will not test serostatus at the time of vaccination, although serostatus from yearly surveys will be known.	This is a critical research question that needs to be addressed with carefully considered research protocols. Dedicated studies are needed.
Duration of protection / need for additional doses	**Critical**	CYD14 and CYD15 long-term follow up will inform duration of protection, and booster dose studies are planned 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	High	VE studies are included in RMP.	
Dosing requirements by serostatus	High	Post-licensure studies in RMP will not test serostatus at the time of vaccination.	Different dosing schedules may be warranted for seronegative vs. seropositive subjects at baseline. Until a POC test is available, a single schedule that optimizes vaccine performance in all groups should be used. Dedicated studies are needed.
Co-administration with age-appropriate vaccines	High	Co-administration studies are planned by the manufacturer.	
Health impact assessment of vaccination program	High	Planned as part of RMP.	
Long-term transmission dynamics (serotype/ genotype selection)	High	No: 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.
Development of simple mathematical modelling tools for country use in decision-making with consideration of the local context.	High	No: out of scope of RMP.	Dedicated efforts are needed.

Table 13 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**	Dedicated studies are needed.
Immune correlate of protection	High	Broader efforts that could potentially be extrapolated to other/all dengue vaccines are needed. Dedicated studies are needed.
Improved POC diagnostics to identify seropositive/ seronegative individuals	High	Dedicated studies are needed.
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 burden of dengue in Africa	High	Dedicated studies are needed.

12. ACKNOWLEDGEMENTS

The Working Group would like to acknowledge the openness and responsiveness of the manufacturer in providing data requested and identified by the Working Group to be important for global recommendations. The Working Group would also like to acknowledge the contributions of the comparative modelling of dengue public health vaccine impact (CMDVI) modelling groups and WHO consultants for their collaboration and inputs.

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APPENDIX 1. SAGE WORKING GROUP ON DENGUE VACCINES MEMBERSHIP

SAGE members

- Terry Nolan, (Co-Chair of the Working Group), Melbourne School of Population and Global Health, Australia
- Piyanit Tharmaphornpilas, Ministry of Public Health, Thailand

Experts

- Jeremy Farrar, (Co-Chair of the Working Group), Wellcome Trust, UK
- Ananda Amarasinghe, Ministry of Health, Sri Lanka (resigned from Working Group 29 February 2016)
- Alan Barrett, University of Texas Medical Branch, USA
- Anna Durbin, Johns Hopkins Bloomberg School of Public Health, USA (resigned from Working Group 31 December 2015)
- Elizabeth Ferdinand, University of the West Indies, Barbados
- Maria Guzman, Pedro Kouri Tropical Medicine Institute, Cuba
- Maria Novaes, Universidade de São Paulo, Brazil
- Lee Ching Ng, National Environment Agency, Singapore
- Amadou Sall, Institut Pasteur de Dakar, Senegal
- Peter Smith, London School of Hygiene and Tropical Medicine, UK
- Wellington Sun, U.S. Food and Drug Administration, USA (resigned from Working Group 1 February 2016)
- Stephen Thomas, Walter Reed Army Institute of Research, USA

WHO secretariat

- Joachim Hombach
- Kirsten Vannice

Declaration of interests

All members completed a declaration of interests. Six members reported any relevant interests. It was concluded that all members could take part in full in all of the discussions. The reported relevant interests are summarized below:

Terence Nolan

- He received consultancy fees for participating in meetings and for data analysis and interpretation as member of Data and Safety Monitoring Board (DSMB) and Independent Data Monitoring Committee (IDMC) on Human Papilloma Virus vaccine from GSK. The consultancy was ceased by the 17th October 2012. This interest was assessed as personal, non-specific and financially significant*.
- In the time from 2008-2012 his institution received research support for vaccine trials implemented in Australia from a number of companies (including GSK, Wyeth, Novartis Vaccines, sanofi pasteur and CSL Ltd).These trials concern a number of vaccines (MenACWY, MenB, MenC, HibMenC Adult and peadiatric TIV, H1N1 and H5N1 vaccine and DTPa-Hib-hepB-IPV-MenC vaccine). This interest was assessed as non-personal, non-specific and financially significant*.
- His institution receives research support to conduct a follow-up clinical trial on a birthdose of Pertussis Vaccination from GSK. This interest was assessed as non-personal, non-specific and financially significant*.

- His institution receives research support to conduct a Meningococcal ACWY vaccine clinical trial from GSK. This interest was assessed as non-personal, non-specific and financially significant*.
- He serves as principal investigator for a clinical trial assessing the antibody response and persistence following MenACWY-TT funded by GSK and Murdoch Childrens Research Institute. This interest was assessed as personal, non-specific and financially significant*.

Piyanit Tharmaphornpilas

- She received in 2011 a travel grant from a joint venture of the Thai Government Pharmaceutical Organization - Merieux Biological Product to attend the Re-invigorating Immunization Policy Implementation and Success: From Parent to Partner and from Broad to Engagement. This interest was assessed as personal, non-specific and financially significant*.

Alan Barrett

- His institution holds a contract funded by the U.S. National Institutes of Health to conduct a phase I clinical trial of the Takeda dengue vaccine candidate. This interest was assessed as non-personal, specific, and financially significant*.
- His institution participates in collaborative projects with Hawaii Biotech/Merck, two of which study recombinant flavivirus immunogens (tick-borne encephalitis). This interest was assessed as non-personal, non-specific, and financially significant*.
- He is co-investigator of a contract funded by the U.S. National Institutes of Health to test dengue drugs and vaccines in mouse models. This interest was assessed as personal, specific, and financially significant*.

Anna Durbin (resigned from Working Group in December 2015)

- She is co-investigator of a contract funded by the U.S. National Institutes of Health to test flavivirus vaccines, including the U.S. National Institutes of Health dengue vaccine candidate, in clinical trials. This interest was assessed as personal, specific, and financially significant*.
- She has provided expertise to Vabiotech and the Instituto Butantuan in relation to the U.S. National Institutes of Health dengue vaccine, funded by the German Federal Ministry of Education and Research (BMBF) through a grant to the Dengue Vaccine Initiative. This interest was assessed as personal, specific, and financially significant*.

Wellington Sun (resigned from Working Group in February 2015)

- He is a co-inventor of one U.S. patent (#6638514) for WRAIR's live attenuated dengue vaccine, which is no longer being developed commercially, and co-inventor on another EU patent (#2462930) for the strategy of prime-boost in dengue vaccines. This interest was assessed as personal, specific, and financially insignificant*.

Stephen Thomas

- His institution, the U.S. Army, has cooperative agreements with Sanofi Pasteur, GSK, and Takeda guiding the co-development of dengue vaccine development activities, that may include in kind financial support for travel or other support provided to the US Army. This interest was assessed as non-personal, specific, and financially significant*.

Peter Smith

- He is a member of the Independent Data Monitoring Committee for Sanofi Pasteur’s dengue vaccine clinical trials. This interest was assessed as personal, specific, and financially significant*.

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* According to WHO's Guidelines for Declaration of Interests (WHO expert), an interest is considered "personal" if it generates financial or non-financial gain to the expert, such as consulting income or a patent. "Specificity" states whether the declared interest is a subject matter of the meeting or work to be undertaken. An interest has "financial significance" if the honoraria, consultancy fee or other received funding, including those received by expert's organization, from any single vaccine manufacturer or other vaccine-related company exceeds 5,000 USD in a calendar year. Likewise, a shareholding in any one vaccine manufacturer or other vaccine-related company in excess of 1,000 USD would also constitute a “significant shareholding”.

APPENDIX 2. EVIDENCE TO RECOMMENDATIONS TABLE AND GRADE TABLES

SAGE EVIDENCE TO RECOMMENDATIONS TABLE

More evidence that was made available to SAGE to support their recommendations on dengue vaccine can be found in this background paper of the Working Group.

Question: *Should the dengue vaccine be recommended, over no vaccination, to be administered to immunocompetent individuals (≥9years of age) in dengue-endemic countries to mitigate burden of severe dengue disease?*

Population: *Immunocompetent individuals (≥9years of age)*

Intervention: *Three doses of dengue vaccine in the context of routine dengue control interventions*

Comparison(s): *No vaccination in the context of routine dengue control interventions*

Outcome: *Hospitalized or severe dengue*

Background:

Dengue is a mosquito-borne virus with extensive distribution in the tropics and subtropics. Dengue is a high incidence disease, and hospitalized and severe dengue cause significant burden on health systems. The most common presentation of dengue is the sudden onset of fever accompanied by headache, pain behind the eyes, generalized myalgia and arthralgia, flushing of the face, anorexia, abdominal pain and nausea. Rash is frequently seen on the trunk. Criteria for severe dengue include any sign of severe plasma leakage leading to shock or fluid accumulation with respiratory distress, severe bleeding, or severe organ impairment. There is no specific anti-viral treatment for dengue. Due to advanced clinical case management, the case-fatality rate is <1%. At present, the only method to reduce the transmission of dengue virus is through vector control. There is a paucity of data showing an effect of vector control interventions on the incidence of human dengue cases.

The first dengue vaccine was licensed in December, 2015, and has now been licensed or submitted for licensure in several dengue-endemic countries. It is a three-dose vaccine administered 6 months apart and is indicated for use in individuals 9 years to either 45 years or 60 years, depending on the country.

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL INFORMATION
PROBLEM	Is the problem a public health priority?	*No* ☐ *Uncertain* ☐ *Yes* ☒ *Varies by setting* ☐	Dengue is a major public health problem, with every WHO Region affected by dengue. In the last 60 years the incidence of clinical cases of dengue reported to WHO has increased 30-fold, with a much increased geographic range, including the expansion from predominantly urban to rural settings. Approximately 3.5 billion people live in dengue endemic countries. A recent prediction, based on available incidence and prevalence data and modelled globally, estimated 390 million dengue infections per year in 2010 (95% credible interval 284–528 million), of which about 25%, 96 million (67–136 million), manifest clinically (with any severity of disease)(Bhatt et al. 2013). WHO has estimated 500,000 hospitalizations for dengue annually, of which about 12,000 are fatal (SAGE Background Paper on Dengue Vaccines)	There have been efforts to develop dengue vaccines for decades, but it has proven to be one of the more difficult pathogens against which to develop a vaccine for a variety of reasons (SAGE Background Paper on Dengue Vaccines).
BENEFITS & HARMS OF THE OPTIONS	<u>Benefits of the intervention</u> Are the desirable anticipated effects large?	*No* ☐ *Uncertain* ☐ *Yes* ☐ *Varies* ☒	Vaccine efficacy over 25 months from the first dose among 9-16 year-olds, pooled from both CYD14 and CYD15 (post-hoc analysis), was 65.6% (95%CI 60.7-69.9). Protection was evident following the first dose and showed little variation up to one year following the third dose. VE against hospitalized dengue was 80.8% (95%CI 70.1-87.7) in participants first vaccinated > 9 years of	Vaccine efficacy in these first 25 months varied by infecting serotype (higher protection against DENV 3 and 4), age (higher protection in 9-16 year age group), and severity (higher protection against hospitalized and severe dengue). Most notably, vaccine efficacy was high among participants 9 years of age or older who were seropositive (i.e., had

			age. VE against severe dengue in the first 25 months of follow up in the two trials combined was 93.2% (95%CI 77.3-98.0) in participants >9 years of age. (SAGE Background Paper on Dengue Vaccines). Mathematical modelling suggests that in high 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. The modelling predicted that the vaccine would be less beneficial in low transmission settings, due to the higher proportion of seronegative individuals, among whom the vaccine may have limited protective effect.	previous exposure to dengue) at baseline (81.9%, 95%CI 67.2-90.0), and lower 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. There are no POC diagnostic tests that could be used to identify seropositives and seronegatives at the time of vaccination.
	<u>Harms of the intervention</u> Are the undesirable anticipated effects small?	*No* ☐ *Uncertain* ☐ *Yes* ☐ *<u>Varies</u>* ☒	Data from Phase 2 and Phase 3 trials have not signaled any safety concern with regard to traditional safety considerations (reactogenicity, serious adverse events, etc.). CYD-TDV is well-tolerated. An increased risk of hospitalized and severe dengue was seen in the 2-5 year-olds in the Phase 3 trial in which this age group was included. This increased risk was large (relative risk 7.45 in Year 3), but diminished in Years 4 and 5. The Phase 2b trial in Thailand, CYD23/57, found similar effects in children under 6 years. The 2-5 year age group also has	There is a theoretical possibility that vaccination may be ineffective or may even increase that risk in those who are seronegative at the time of first vaccination. Because these subgroups cannot be identified, there cannot be separate recommendations for subgroups in an immunization program.

			the highest proportion of seronegatives. There are no data from the Phase 3 trials to suggest a similar increased risk in those aged 9 years or above, but most of these children were seropositive when first vaccinated.	
	Balance between benefits and harms	*Favours intervention* ☒ | *Favours comparison* ☐ | *Favours both* ☐ | *Favours neither* ☐ | *Unclear* ☐	The benefits of the dengue vaccine have been measured in Phase 3 efficacy trials. The potential harms in the seronegative population aged 9 years and above are theoretical. From a population perspective, there is clear evidence of a positive impact of vaccination on severe and hospitalized dengue when the vaccine is used in a high transmission setting. For seronegative individuals, it is possible that the vaccine has no effect or theoretically could do harm, if their (lifetime) population risk of dengue was such that they would likely only receive one natural infection (which would then place them at a higher risk of severe or hospitalized dengue). However, the vaccine performance among seronegatives age 9 years and above requires further characterization to quantify risks and benefits. As serostatus cannot be easily determined at the time of vaccination, it is difficult to make individual-level decisions about vaccination based on serostatus in a population-based vaccination programme.	

	What is the overall quality of this evidence for the critical outcomes?	*No included studies* ☐ | *Very low* ☐ *Low* ☒ *Moderate* ☐ *High* ☒ Effectiveness of the intervention *No included studies* ☐ | *Very low* ☐ *Low* ☒ *Moderate* ☒ *High* ☐ Safety of the intervention	GRADE high quality evidence for vaccine efficacy. Grade low quality of evidence for duration of protection beyond 2 years from first dose. Grade low quality of evidence for risk of severe/hospitalized dengue in seronegatives Grade moderate quality of evidence for risk of serious (non-dengue)adverse events following dengue vaccination	
VALUES & PREFERENCES	How certain is the relative importance of the desirable and undesirable outcomes?	*Important uncertainty or variability* ☐ *Possibly important uncertainty or variability* ☒ *Probably no important uncertainty or variability* ☐ *No important uncertainty or variability* ☐ | *No known undesirable outcomes* ☐	No data on public attitudes about desirable and undesirable outcomes.	Both demonstrated desirable and theoretical undesirable outcomes are based on risk of dengue. Thus, the outcomes are equally important. Whether some individuals are concerned about the theoretical risk in seronegatives to such an extent as to refuse vaccination is unknown.

	Values and preferences of the target population: Are the desirable effects large relative to undesirable effects?	*No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☒ *Yes* ☐ *Varies* ☐	No evidence was retrieved on the values and preferences of the target population with respect to the demonstrated benefit in the trials and theoretical risks. In general, the target population is expected to be very supportive of a dengue vaccine.	In the context of implementation, it would need to be considered the most appropriate communication strategies for informed decision-making about vaccination.
RESOURCE USE	Are the resources required small?	*No* ☐ *Uncertain* ☒ *Yes* ☐ *Varies* ☐	The price of the dengue vaccine has not yet been communicated. In terms of additional resources, the vaccine could be delivered through existing school-based immunization programs, if they are in place. Stress on the supply chain needs to be assessed. Additional contacts may be required, leading to a possible increase in operational costs to the health system.	Given the price of the vaccine and budget affordability, countries will need to consider whether the dengue vaccine is a priority intervention to fund.
	Cost-effectiveness	*No* ☐ *Uncertain* ☒ *Yes* ☐ *Varies* ☐	Vaccination was predicted to be potentially cost-effective in settings with a seroprevalence at 9 years of age of 30-90%, if the vaccine can be purchased and delivered cheaply enough.	Countries should do cost-effectiveness assessments based on their own context, including country-specific hospitalization rates and costs.

EQUITY	What would be the impact on health inequities?	*Increased* ☐ *Uncertain* ☐ *Reduced* ☐ Varies ☒	There has been no specific evaluation on how the dengue vaccine implementation may contribute to reducing health inequities. Dengue does primarily effect low and middle income countries, and reducing the disease burden would improve equity. Reducing the burden of catastrophic expenditures related to dengue disease in low-income families could reduce inequities within countries.	If the vaccine is not paid for by a government program, there is high risk that low-income families cannot afford vaccination, thus increasing health inequity.
ACCEPTABILITY	Which option is acceptable to key stakeholders (Ministries of Health, Immunization Managers)?	*Intervention* ☒ *Comparison* ☐ *Both* ☐ *Neither* ☐ *Unclear* ☐	Countries should assess whether adequate resources can be allocated to implement and sustain dengue vaccination in the routine immunization schedule. This especially applies to low and middle income countries with limited resources, where dengue vaccination might be competing with other important public health interventions.	
	Which option is acceptable to target group?	*Intervention* ☒ *Comparison* ☐ *Both* ☐ *Neither* ☐ *Unclear* ☐	Given the high burden of morbidity, it is presumed that the vaccination would be acceptable to the target group if the costs are covered by the health care provider.	

FEASIBILITY	Is the intervention feasible to implement?	*No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☐ *Yes* ☒ | *Varies* ☐		The intervention is feasible, as has been demonstrated with vaccines administered in similar age groups.	If the vaccine is not paid for by a government program, there is high risk that low-income families cannot afford vaccination.	
Balance of consequences	Undesirable consequences *clearly outweigh* desirable consequences in most settings ☐	Undesirable consequences *probably outweigh* desirable consequences in most settings ☐	The balance between desirable and undesirable consequences *is closely balanced or uncertain* ☐	Desirable consequences *probably outweigh* undesirable consequences in most settings ☐	Desirable consequences *clearly outweigh* undesirable consequences in most settings[7] ☒	
Type of recommendation	We recommend the intervention ☐	We suggest considering recommendation of the intervention ☐ Only in the context of rigorous research ☐ Only with targeted monitoring and evaluation ☒ Only in specific contexts or specific (sub)populations		We recommend the comparison ☐	We recommend against the intervention and the comparison ☐	

[7] When considered at the population level and in settings meeting the criteria outlined in the recommendation

Recommendation (text)	Countries should consider introduction of CYD-TDV in geographic settings (national or subnational) with high dengue transmission, i.e. seroprevalence of approximately 70% or greater in the age group targeted for vaccination but not below 50%. Where possible, assessment of dengue transmission intensity should be supported by geographically relevant seroprevalence studies. Seroprevalence estimates should guide decision-making and introduction at subnational levels while noting that these are not precise indicators. Work is needed to identify routinely collected epidemiologic indicators that can be used to infer likely seroprevalence. Decisions about introduction require careful assessment at the country level, including consideration of local priorities, subnational dengue epidemiology, predicted impact and cost-effectiveness with country-specific hospitalization rates and costs, as well as affordability and budget impact. Vaccination should be considered as an integrated strategy together with well-executed and sustained vector control and the best evidence-based clinical care for all patients with dengue.
Implementation considerations	Due to the partial efficacy of the vaccine against dengue of any severity, careful communication is needed to inform vaccinees that they may still be at risk of dengue and of the importance of receiving all three doses and of adhering to other disease preventive measures.
Monitoring and evaluation	Monitoring of immunization coverage and disease surveillance, including risk of dengue over time in vaccinated individuals and duration of protection.
Research priorities	A number of research priorities specific to CYD-TDV and general to the dengue vaccine field are listed in section 11.7. The following were assessed as critical, to be addressed as soon as possible: • Risk of severe/hospitalized dengue over time in vaccinated seronegatives • Duration of protection / need for additional doses • Second-generation vaccines that include characteristics such as improved protection against all four dengue serotypes, single-dose, for use in younger age groups

GRADE TABLE 1

What is the efficacy of 3 doses of CYD-TDV in preventing clinical dengue in individuals 9-16 years of age in the first year following vaccination?

Population: 9-16 year-olds living in dengue endemic areas

Intervention: 3 doses of CYD-TDV administered 6 months apart

Comparison: Placebo

Outcome: Virologically-confirmed dengue occurring ≤ 12 months of completion of 3 doses

What is the efficacy of 3 doses of CYD-TDV in preventing clinical dengue in individuals 9-16 years of age in the first year following vaccination?				
			Rating	Adjustment to rating
Quality Assessment	No. of studies/starting rating		2 RCT[1]	4
	Factors decreasing confidence	Limitation in study design	None serious	0
		Inconsistency	None serious	0
		Indirectness	None serious[2]	0
		Imprecision	None serious	0
		Publication bias	None serious	0
	Factors increasing confidence	Large effect	Not applicable[3]	0
		Dose-response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
	Final numerical rating of quality of evidence			**4**
Summary of Findings	**Statement on quality of evidence**			**Evidence supports a high level of confidence that the true effect lies close to that of the estimate of effect on health outcome.**
	Conclusion			**CYD-TDV demonstrates statistically significant vaccine efficacy against virologically-confirmed dengue in the first 12 months following vaccination with three doses, although the degree of protection varies by age, infecting serotype, serostatus at baseline, and dengue severity.**

[1] CYD-TDV has been evaluated in two parallel Phase 3 clinical trials, known as CYD14 and CYD15. CYD14 was conducted in 5 countries in Asia (Indonesia, Malaysia, Philippines, Thailand, and Vietnam), with 5,234 participants aged 9-14 years at first vaccination (10,275 participants in the full trial population aged 2-14 years). 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. In each of these trials, participants were randomized to vaccine and placebo in a 2:1 ratio. Because the

physical appearance of the vaccine and placebo was different, unmasked trial staff were responsible only for preparation and administration of injections and were not involved in the follow-up of trial participants. For the ascertainment of trial endpoints the trials were observer-masked. All serology testing was also performed in a blinded manner. In the per-protocol analysis (full trial populations monitoring from 1 month after the 3rd dose for 12 months), vaccine efficacy against dengue of any serotype was 56.5% (95%CI 43.8-66.4) in CYD14, and 60.8% (95%CI 52.0-68.0) in CYD15. In the 25 months following 1 doses of CYD-TDV (ITT analysis), vaccine efficacy against virologically-confirmed dengue pooled across the two studies was 59.2% (95%CI 52.3-65.0) and was consistent across studies. In both trials, vaccine efficacy was lower against serotypes 1 and 2 than against serotypes 3 and 4, was lower in individuals seronegative at baseline compared to seropositive at baseline, and was higher against more severe forms of dengue. Vaccine efficacy in those <9 years of age was lower than in those ≥9 years of age. While the endpoint led to variable vaccine efficacy estimates, the estimates were highly consistent for the same outcomes across trials. Vaccine efficacy was also measured in a Phase 2b study, CYD23/57, in 4,002 children aged 4 to 11 years in Ratchaburi Province, Thailand. The definition of fever, precipitating a diagnostic test for dengue, was slightly different to that used in the Phase 3 trials.

[2]Vaccine efficacy has been assessed only the 9-16 year population within the indicated age range of 9-45 or 9-60 years. SAGE recommendations focus on the younger 9-16 year-old population, which is more relevant for high endemicity settings. Licensure has been granted by regulatory authorities in the 17+ population based on immunological bridging, although there is no accepted correlate of protection. It has been shown that serostatus at baseline is associated both with age and with higher titers post vaccination. The confidence in the estimate of effect for the 17-45 population would be downgraded by 1 for indirectness.

[3]A large effect is noted 59.2% (95%CI 52.3-65.0), although currently the score is not eligible for upgrade at the maximum score.

GRADE TABLE 2

What is the duration of protection in individuals 9-16 years of age vaccinated with CYD-TDV?

Population: 9-16 year-old individuals living in dengue endemic areas

Intervention: 3 doses of CYD-TDV administered 6 months apart

Comparison: Placebo

Outcome: Virologically-confirmed dengue occurring > 12 months of completion of 3 doses

What is the duration of protection in individuals 9-16 years of age vaccinated with CYD-TDV?				
			Rating	Adjustment to rating
Quality Assessment	No. of studies/starting rating		2 RCT[1]	4
	Factors decreasing confidence	Limitation in study design	Very serious[2]	-2
		Inconsistency	None serious	0
		Indirectness	None serious	0
		Imprecision	None serious	0
		Publication bias	None serious	0
	Factors increasing confidence	Large effect	Not applicable	0
		Dose-response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
	Final numerical rating of quality of evidence			**2**
Summary of Findings	**Statement on quality of evidence**			**Evidence supports a low level of confidence that the true effect lies close to that of the estimate of effect on health outcome.**
	Conclusion			**There is insufficient data from the Phase 3 trials to assess waning immunity against virologically-confirmed dengue. Further assessment is required.**

[1]CYD-TDV has been evaluated in two parallel Phase 3 clinical trials, known as CYD14 and CYD15. CYD14 was conducted in 5 countries in Asia (Indonesia, Malaysia, Philippines, Thailand, and Vietnam), with 5,234 participants aged 9-14 years at first vaccination (10,275 participants in the full trial population aged 2-14 years). 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. In each of these trials, participants were randomized to vaccine and placebo in a 2:1 ratio. Because the physical appearance of the vaccine and placebo was different, unmasked trial staff were responsible only for preparation and administration of injections and were not involved in the follow-up of trial participants. For the ascertainment of trial endpoints the trials were observer-masked.

[2]The study design of CYD14 and CYD15 included 25 months of active surveillance followed by hospital-based surveillance. Thus, duration of protection against VCD cannot be assessed. However, active surveillance is currently being reinstated. Data on hospitalized dengue has been collected throughout the trial period, though with different surveillance systems in

the Active and Hospital Phases. With the limitations of this change in surveillance and that the CYD and placebo groups have different histories of dengue exposure at the start of later time intervals, it is one source of data available now to assess protection over the period of the trial.

For hospitalized dengue in ages included in the indication (9-16 years), the point estimate of relative risk of hospitalized dengue remains below 1, suggesting a sustained protective effect. The point estimates year-by-year are variable, although in many instances the point estimate becomes closer to one as time progresses. In all age groups, the relative risk of severe dengue among vaccinated compared to controls is lower during the active phase than during the hospital phase. These data may suggest potential (though unconfirmed) waning protection across all age groups.

GRADE TABLE 3

What is the risk of other serious adverse events (non-dengue) in individuals 9-16 years of age vaccinated with CYD-TDV?

Population: 9-16 year-old individuals living in dengue endemic areas

Intervention: 3 doses of CYD-TDV administered 6 months apart

Comparison: Placebo

Outcome: Serious adverse events (non-dengue)

What is the risk of other serious adverse events (non-dengue) in individuals 9-16 years of age vaccinated with CYD-TDV?				
			Rating	Adjustment to rating
Quality Assessment	No. of studies/starting rating		2 RCT[1]	4
	Factors decreasing confidence	Limitation in study design	None serious	0
		Inconsistency	None serious	0
		Indirectness	None serious[2]	0
		Imprecision	Serious[3]	-1
		Publication bias	None serious	0
	Factors increasing confidence	Large effect	Not applicable	0
		Dose-response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
	Final numerical rating of quality of evidence			**3**
Summary of Findings	**Statement on quality of evidence**			**Evidence supports a moderate level of confidence that the true effect lies close to that of the estimate of effect on health outcome.**
	Conclusion			**There is no evidence of an association between CYD-TDV and non-dengue serious adverse events based on clinical trials.**

[1] CYD-TDV has been evaluated in two parallel Phase 3 clinical trials, known as CYD14 and CYD15. CYD14 was conducted in 5 countries in Asia (Indonesia, Malaysia, Philippines, Thailand, and Vietnam), with 5,234 participants aged 9-14 years at first vaccination (10,275 participants in the full trial population aged 2-14 years). 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. In the Phase 3 trials conducted in 2-16 year-olds, the number of serious adverse events (SAEs) was similar between CYD and placebo group.

Safety data have also been generated in the course of multiple Phase 1 and 2 trials (11 additional contributing studies to the 9-60y pool are: CYD12, 13, 22, 24, 28, 30, 47, 23, 17, 32, 51). Related SAEs up to 28 days after a CYD injection occurred in 6 subjects (headache and polymyalgia rheumatic in adults, and allergic urticaria, asthma, acute polyneuropathy, and tension headache in 9-17 year-old participants). An additional SAE was classified as related by the investigator in the 28 days to 6 months post CYD injection (blighted ovum), and 1 SAE of convulsion was judged to be related by the sponsor (not

the Investigator). No immediate anaphylactic shock has been reported post-vaccination.

[2]There are a limited number of trial participants beyond 16 years of age to assess the risk of serious adverse events in the 17-45 year population. For consideration of the risk of SAEs in the 17-45 year-old population based on extrapolation from the Phase 3 trials, the quality of the evidence would need to be further downgraded by 1 for indirectness.

[3]Even large Phase 3 clinical trials are limited in their ability to detect rare SAEs. The GRADE score was thus downgraded by 1 for imprecision.

GRADE TABLE 4

What is the risk of hospitalized and severe dengue over time in in individuals 9-16 years of age vaccinated with CYD-TDV who are seronegative at baseline?

Population: 9-16 year-old individuals with $PRNT_{50}$<10 against all four serotypes, living in dengue endemic areas

Intervention: 3 doses of CYD-TDV administered 6 months apart

Comparison: Placebo

Outcome: Hospitalized or severe dengue occurring > 12 months after completion of the first three doses

What is the risk of hospitalized and severe dengue over time in adolescents and adults 9-16 years of age vaccinated with CYD-TDV who are seronegative at baseline?				
			Rating	Adjustment to rating
Quality Assessment	No. of studies/starting rating		3 RCT[1]	4
	Factors decreasing confidence	Limitation in study design	None serious	0
		Inconsistency	None serious	0
		Indirectness	Serious[2]	-1
		Imprecision	Serious[3]	-1
		Publication bias	None serious	0
	Factors increasing confidence	Large effect	Not applicable[4]	0
		Dose-response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
	Final numerical rating of quality of evidence			**2**
Summary of Findings	**Statement on quality of evidence**			**Evidence supports a low level of confidence that the true effect lies close to that of the estimate of effect on health outcome.**
	Conclusion			**There are insufficient data to inform whether seronegative individuals 9 years of age or older who are vaccinated may be at some point in time at higher risk of severe or hospitalized dengue than those do not receive vaccine.**

[1]CYD-TDV has been evaluated in two parallel Phase 3 clinical trials, known as CYD14 and CYD15. CYD14 was conducted in 5 countries in Asia (Indonesia, Malaysia, Philippines, Thailand, and Vietnam), with 5,234 participants aged 9-14 years at first vaccination (10,275 participants in the full trial population aged 2-14 years). 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. In each of these trials, participants were randomized to vaccine and placebo in a 2:1 ratio. Because the physical appearance of the vaccine and placebo was different, unmasked trial staff were responsible only for preparation and administration of injections and were not involved in the follow-up of trial participants. Risk of hospitalized and severe dengue was also assessed in the Phase 2b trial in Thailand (CYD23/57). For the ascertainment of trial endpoints the trials

were observer-masked. All serology testing was also performed in a blinded manner. After 2 years of active phase of follow up, participants were followed for hospitalized and severe dengue using an enhanced passive surveillance system. Only a subset of trial participants were included in the immunogenicity subset, for which baseline serostatus was known. During the course of the hospital-based surveillance, a signal emerged from the youngest age group (2-5 years, an age group only included in CYD14). During both Years 1 and 2 of active follow-up, the RR of hospitalized dengue in the 2-5 year age group was 0.6. During Year 3, there were 15 hospitalized cases in the CYD group compared to 1 hospitalized case in the placebo group (2:1 randomization), a RR of 7.45 (95%CI 1.15-313.80). During Year 4 and Year 5, the cumulative relative risk for Year 3 onwards diminished to 1.424 (95%CI 0.58-3.99) and 1.495 (95%CI 0.27-15.15), respectively. The cumulative relative risk during the entire trial period to date is 1.256 (95%CI 0.76-2.13). In contrast, across older age groups (6-8, 9-11, and 12-16 years), an elevated risk was not seen consistently across the trials.

[2]Given the small numbers of participants in the immunogenicity subset and thus the numbers of cases that occur in this small population is insufficient to characterize well the risk in seropositive individuals. In CYD14 the immunogenicity subset was 1983 children and in CYD15 the immunogenicity subset was 1944 children, across all ages in the trials and CYD and placebo groups. Among trial participants 9 years of age or older, seropositivity was approximately 80%, thus there were few hospitalized dengue cases that occurred among seronegatives 9 years of age or older who were also included in the immunogenicity subset. Some inference may be drawn from the 2-5 year trial population in CYD14, which had a higher proportion of seronegatives. However, this is downgraded for indirectness.

[3]In CYD14 the immunogenicity subset was 1983 children and in CYD15 the immunogenicity subset was 1944 children. The confidence intervals for effect are very wide due to the small numbers in the immunogenicity subset, and so this is downgraded for imprecision.

[4]A large effect is noted in the 2-5 year age group (RR hospitalized dengue in Year 3 7.45(95%CI 1.15-313.80)), however as it is an indirect measure of serostatus, the score was not upgraded.

APPENDIX 3. DATA ADDENDUM TO BACKGROUND PAPER

The following data were added to the Background paper on May 6, 2016. These data were discussed by the SAGE Working Group on Dengue Vaccines and Vaccination and also presented to SAGE on April 14, 2016, and may be found on slide 42 of the presentation given by Peter Smith (available at http://www.who.int/immunization/sage/meetings/2016/april/2_Smith_Clinical_Trial_Results_SAGE.pdf).

Table A3.1 Number of Hospitalized and/or severe VCD cases by age group and dengue immune status at baseline. Pool of CYD14, CYD15, and CYD57.

		Active phase cases/N (%)		Hospital phase-SEP† cases/N (%)		Cumulative cases/N (%)	
Age group	Serostatus	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)

*Includes only subjects from the Full Analysis Set for Immunogenicity; † Includes all subjects from the Safety Analysis Set for Efficacy; SEP: Surveillance Expansion Phase