

## APPENDIX 1: SAGE WORKING GROUP ON DENGUE VACCINES AND VACCINATION (DECEMBER 2017 TO AUGUST 2018)

### Terms of Reference

The reconvened Dengue Working Group is asked to review new data on the long-term follow-up of dengue vaccine recipients. This includes data generated by further laboratory testing and analysis related to the long-term safety and efficacy of CYD-TDV Phase 3 trial participants. In particular, the group is asked to review the differential performance of the CYD-TDV vaccine (also known as Dengvaxia®) in subjects seronegative versus seropositive at the time of vaccination. The group is asked to advise on a revision of WHO's current vaccine recommendations as published in July 2016. The review at SAGE is tentatively scheduled for April 2018. This will lead to the publication of an amended WHO position paper on the use of a dengue vaccine, which will replace the interim recommendation issued by WHO on 22 Dec 2017 ([WHO interim position on the use of Dengvaxia®](#))

The Working Group will specifically be asked to review data relating to:

- the long-term safety, efficacy, immunogenicity profile and benefit/risk assessment of CYD-TDV (Dengvaxia®) stratified by serostatus
- the schedule, age of administration, and potential vaccination strategies for targeting vaccination to individuals seropositive to dengue at the time of vaccination
- additional critical issues that need to be considered in drafting amended recommendations to SAGE

### Composition

The working group is composed of its previous members, and additional ad hoc experts in accordance to the terms of reference.

#### SAGE members

- Terry Nolan, (Co-Chair of the Working Group), Melbourne School of Population and Global Health, Australia
- Kate O'Brien, Johns Hopkins International Vaccine Access Center (IVAC), Baltimore, USA

#### Experts

- Jeremy Farrar, (Co-Chair of the Working Group), Wellcome Trust, UK
- Piyanit Tharmaphornpilas, Ministry of Public Health, Thailand
- Alan Barrett, University of Texas Medical Branch, USA
- 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
- Peter Smith, London School of Hygiene and Tropical Medicine, UK

#### Ad hoc experts

- Stefan Flasche, London School of Hygiene and Tropical Medicine, UK
- In-Kyu Yoon, International Vaccine Institute, South Korea

## **WHO secretariat**

- Annelies Wilder-Smith
- Joachim Hombach

## **Declaration of interests**

All members completed a declaration of interest. 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:

### **Terry 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 paediatric 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\*.

### **Kate O'Brien**

- Serves as technical expert consultant for Astellas Pharma, SutroVax, Merck, ClearPath, Affinivax and PATH on pneumococcal vaccination. This interest was assessed as non-personal, specific and financially insignificant\*.
- Serves as technical expert consultant for Sanofi Pasteur on RSV. This interest was assessed as non-personal, non-specific and financially insignificant\*.
- Served as member of DSMB on malaria RTS,S vaccine funded by PATH-Malaria Vaccine Initiative. This ceased in 2014. This interest was assessed as non-personal, non-specific and financially significant\*.
- Received funding for travel costs for a GSK Grand Convergence Meeting in 2015. This interest was assessed as non-personal, non-specific and financially insignificant\*.
- Her institution currently receives research grants from GSK, Gavi, JSI Research & Training Institute, Inc., BMGF, Pfizer and Yale regarding pneumococcal, rotavirus vaccines, biomarkers of vaccination status, vaccine coverage, programmatic impact of multi-dose vaccines, vaccine demand support, PCV impact evaluation and/or pneumonia etiology. This interest was assessed as personal, specific and financially significant\*.
- Her institution receives research grants from the National Institutes of Health (NIH) regarding pneumococcal epidemiology and vaccines. This interest was assessed as personal, specific and financially significant\*.
- Her institution received research grants from Merck on adult vaccines until June 2016. This interest was assessed as non-personal, non-specific and financially significant\*.
- Her institution received research grants from BMGF regarding a disease surveillance, country support of pneumococcal and rotavirus vaccines, vaccine demand approaches, technical country support and decision making on pneumococcal/rotavirus vaccine, PCV policy optimization and pneumococcal, Hib

and meningococcus etiology work (disease burden estimates). This interest was assessed as personal, specific and financially significant\*.

- Her institution received research grants from Gavi regarding scientific communication support and PCV product assessment. This interest was assessed as personal, specific and financially significant\*.
- Her institution received research grants from the Pfizer Foundation regarding monitoring of routine immunization coverage in Pakistan. This interest was assessed as personal, non-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\*.

#### **In-Kyu Yoon**

- His institution receives unrestricted grants from Sanofi Pasteur and other vaccine companies. This interest was assessed as non-personal, non-specific and financially significant\*. He served once on a Scientific Advisory Board for Merck on dengue vaccines. This interest was assessed as personal, specific, and financially non-significant\*.

#### **Alan Barrett**

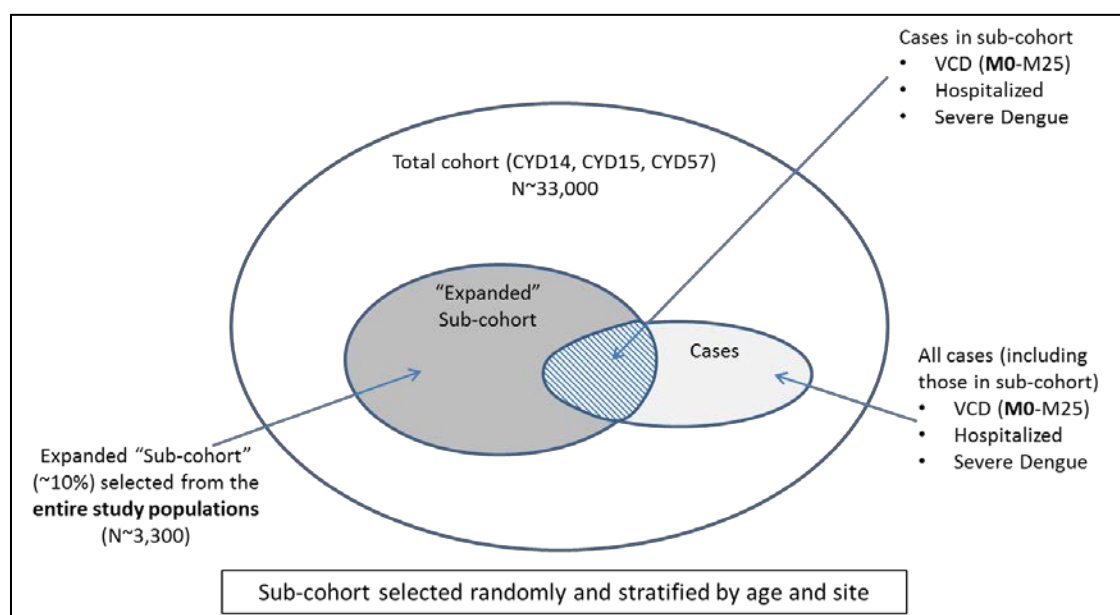
- His institution holds a contract funded by the U.S. National Institutes of Health to conduct a phase I clinical trial of the Takeda dengue vaccine candidate. This interest was assessed as non-personal, specific, and financially significant\*.
- His institution holds a contract funded by Merck to conduct a phase I clinical trial of the Merck 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\*.

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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: STUDY DESIGN AND METHODS TO RETROSPECTIVELY DETERMINE BASELINE SEROSTATUS

A case-cohort study was undertaken to re-assess all cases of symptomatic virologically-confirmed dengue (VCD), hospitalized VCD and severe VCD by serostatus from the three efficacy trials. A sub-cohort of 10% of all participants from each trial was randomly selected after stratifying by age-group and trial site. In this study, all cases of hospitalized VCD and severe VCD over the follow-up period (60-72 months), and all cases of symptomatic VCD in the first 25 months were included. Three methods utilizing anti-NS1 IgG ELISA titers measured at M13 were used to infer baseline dengue serostatus at the time of vaccination, namely Logistic regression for the Multiple Imputation approach, SuperLearner for the TMLE approach and the NS1 Threshold 9. The proportion of subjects in the sub-cohort classified as seronegative was similar across the methods used; 24.5% were classified seronegative by the MI method, 24.0% by SuperLearner and 23.4% by NS1 Th9. Estimates based on the MI approach from M0 onwards (MI-M0) is presented below as the MI approach is more commonly used for handling missing data issues and as estimates using the different analytical approaches were generally consistent with each other. Analysis from M0 is presented as it accounts for potential vaccine protection against M0–13 events in cumulative efficacy and risk estimates and maximizes benefit of randomization.



**Figure A2.1.** Diagrammatic representation of case-cohort design

The primary objective was to assess the risk of hospitalization for dengue in vaccinated seronegative participants aged  $\geq 9$  years at enrollment. Additional objectives included assessment of the risk across all age groups and among those aged  $< 9$  years at enrolment, the risk against severe dengue (based on the definition by the Independent Data Monitoring Committee), the risk over time and estimated efficacy against symptomatic VCD up to 25 months. All these endpoints were also assessed in dengue seropositive participants (3-5).

A hospitalized virologically-confirmed dengue case was defined as:

- Acute febrile illness i.e., temperature  $\geq 38^{\circ}\text{C}$  on at least two consecutive days (for CYD14 and CYD15) and acute febrile illness lasting for at least one day, temperature  $\geq 37.5^{\circ}\text{C}$  measured at least twice with an interval of at least four hours (for CYD57)
- Virologically-confirmed by dengue reverse transcriptase-polymerase chain reaction (RT-PCR) and/or dengue non-structural protein (NS) 1 enzyme-linked immunosorbent assay (ELISA) antigen (Ag) test
- In-patient hospitalization, involving at least one overnight stay.

Definition of severe virologically-confirmed dengue and dengue hemorrhagic fever:

An Independent Data Monitoring Committee (IDMC) was involved in the regular review of safety data and confirmed dengue cases, including assessment of severity of virologically confirmed dengue (VCD) cases to ensure consistency in classification. The IDMC classified dengue cases as severe using the following criteria:

- Virologically-confirmed dengue fever, i.e. temperature  $\geq 38^{\circ}\text{C}$  on  $\geq 2$  consecutive days and virological confirmation, and at least one of the following:
- Platelet count  $\leq 100 \times 10^9/\text{L}$  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  $\leq 20$  mmHg in a child or adolescent, or hypotension [ $\leq 90$  mmHg] 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  $\geq 1.5$  mg/dL)
- Myocarditis, pericarditis or heart failure (clinical heart failure) supported by chest X- ray, echocardiography, electrocardiogram or cardiac enzymes where they were available.

Severity of the dengue episodes was also assessed using the following 1997 WHO criteria for defining dengue hemorrhagic fever (DHF), since clinicians are more familiar with this definition: The following must be present:

- Fever, or history of acute fever, lasting 2-7 days, occasionally biphasic.
- Hemorrhagic tendencies, evidenced by at least one of the following:
  - a positive tourniquet test;
  - petechiae, ecchymoses or purpura;
  - bleeding from the mucosa, gastrointestinal tract, injection sites or other locations;
  - hematemesis or melena.
- Thrombocytopenia ( $100,000$  cells per  $\text{mm}^3$  or less).
- Evidence of plasma leakage due to increased vascular permeability, manifested by at least one of the following:
  - a rise in the hematocrit  $\geq 20\%$  above average for age, sex and population;
  - a drop in the hematocrit following volume-replacement treatment  $\geq 20\%$  of baseline;
  - signs of plasma leakage such as pleural effusion, ascites and hypoproteinemia.

DHF was graded as follows:

- Grade I: Fever accompanied by non-specific constitutional symptoms; the only hemorrhagic manifestation is a positive tourniquet test;
- Grade II: Spontaneous bleeding in addition to the manifestations of Grade I patients, usually in the form of skin and/or other hemorrhages;

- Grade III: Circulatory failure manifested by rapid and weak pulse, narrowing of pulse pressure (20 mmHg or less) or hypotension, with the presence of cold clammy skin and restlessness;
- Grade IV: Profound shock with undetectable blood pressure and pulse.

### **Anti-NS1 IgG ELISA assay**

The underlying principle of the Anti-NS1 IgG ELISA assay is that CYD-TDV's non-structural proteins code for yellow fever vaccine proteins, and therefore an assay measuring responses to dengue non-structural proteins could differentiate between immune responses due to past dengue infection from those due to vaccination. Thus, testing samples collected after vaccination with the anti-NS1 IgG ELISA assay could enable baseline serostatus to be retrospectively inferred.

The dengue anti-NS1 IgG ELISA assay was used to quantitate human IgG antibodies against dengue virus NS1 in human sera. The method involves the detection of IgG antibodies present in human sera that specifically react with recombinant dengue NS1 antigen adsorbed to the surface of individual microtiter test plate wells. The amount of IgG antibody bound to the dengue NS1 antigen coated wells is determined by a colorimetric substrate reaction following incubation and detection using anti-human IgG antibody-enzymatic conjugate. The optical density of the signal (OD) is measured by reading the plate on a 96-well microtiter plate reader. The concentration of IgG in serum is then derived by extrapolation from a standard curve, generated from multiple dilutions of a reference standard serum with defined IgG units (ELISA units/mL).

The quantitative anti-NS1 IgG titers obtained on subjects in the case-cohort was used as a continuous variable (among other variables) in imputation models to predict baseline PRNT50 serostatus. In addition, two exploratory assessments using a threshold of anti-NS1 titers to categorise serostatus were conducted. First, using a conservative threshold at the lower limit of quantitation of the assay to minimize the false seronegativity rate, subjects with titers  $\geq 9$  EU/mL were classified as seropositive.. Second, an alternative threshold for classifying subjects as seropositive, anti-NS1 titers  $\geq 20$  EU/mL was used. This second analysis allows mitigation of the misclassification of seronegative subjects as seropositive and the potential bias resulting from it, while also limiting the inclusion of dengue exposed individuals into the seronegative estimates.

The proportion of subjects correctly classified as seropositive or seronegative by the anti-NS1 IgG assay using a threshold of 9 depends on the sensitivity and specificity of the assay as well as on the prevalence of the condition of interest. The estimates of efficacy in seropositives based on the method using NS1 threshold 9 to determine serostatus is likely to underestimate vaccine efficacy (i.e. disfavours the vaccine) as a proportion of individuals truly dengue unexposed will have been classified as seropositive by the anti-NS1 IgG assay. The underestimation of the beneficial effect is likely to be more pronounced in younger age groups compared to older age groups (as a higher prevalence of truly dengue unexposed is likely in younger age-groups).

The estimates of risk of hospitalized dengue in seronegatives based on the method using NS1 threshold 9 to determine serostatus are likely to be underestimated (i.e., favours the vaccine) as a proportion of individuals truly dengue exposed will have been classified as seronegative by the anti-NS1 IgG assay. The underestimation of the risk is likely to be more pronounced in the older age groups compared to the younger age groups (as a higher prevalence of truly dengue exposed is likely in older age groups).

In addition to the misclassification due to the assay performance, an excess misclassification of about 8% of seronegative subjects as seropositive (anti-NS1 assay threshold of 9 EU/ml) was observed in vaccine recipients compared to placebo recipients.

This excess misclassification may affect estimates obtained in those seropositive, as seronegative individuals are included in those assessments and vaccine efficacy is known to be lower in those seronegative. However,

due to the large predominance of seropositive individuals in the study populations, the overall impact on seropositive estimates is likely to be small.

Risk and efficacy estimates using an anti-NS1 threshold are estimated from M13 onwards and does not account for vaccine effect in the first 12 months. Hence, there was a need for additional methods. The principal methods utilized in the case-cohort study were based on measured (for subjects in the case-cohort with baseline samples) or imputed (for subjects in the case-cohort with missing baseline samples) PRNT at M0. Two imputation methods were used: Logistic regression for the Multiple Imputation (MI) analysis and SuperLearner(32) for the Targeted Minimum Loss-based Estimator (TMLE).

### **Multiple Imputation Method**

Multiple imputation with 10 iterations was used to predict missing baseline PRNT50 serostatus for subjects in the case-cohort (seropositive or seronegative) using a logistic regression model. Anti-NS1 readouts as a continuous variable, treatment group and other variables were used in the prediction model. In each of the 10 iterations of multiple imputations, Prentice's modified Cox regression model was used to estimate the hazard ratio or vaccine efficacy which was then combined using Rubin's rule to obtain the final estimate of the hazard ratio or vaccine efficacy.

### **SuperLearner/TMLE methodology**

A nonparametric statistical approach was also considered. This approach used machine learning (SuperLearner2) to select among a library of candidate algorithms for estimating the probability that a subject has a given baseline serostatus conditional on M13 anti-NS1 titers, M13 PRNT50 titers (if observed), vaccination status, age, and country. To estimate the risk of dengue hospitalization and severe dengue and vaccine efficacy against VCD, a doubly robust targeted minimum loss-based estimator (TMLE7,8) was used. This estimator makes use of both the predicted baseline serostatus probabilities obtained from SuperLearner and estimates of missingness probabilities, where these probabilities account for missing values both by experimental design and by chance.

## APPENDIX 3. 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 ( $\geq 9$  years of age) in dengue-endemic countries to mitigate burden of severe dengue disease?*

**Population:** *Immunocompetent individuals ( $\geq 9$  years 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. Following licensure in some countries, WHO issued its position on the use of CYD-TDV in July 2016, based on recommendations provided by



SAGE in April 2016. On 29 November 2017, Sanofi Pasteur announced the results of additional studies they had conducted to better describe the benefit-risk in seronegative individuals. While the new analyses from the long-term safety follow up indicate the overall population level benefit remains substantial, an overall higher risk of severe dengue and hospitalizations from dengue was observed in vaccinated seronegative trial participants of all ages compared to unvaccinated seronegative trial participants.

Key Reference for this table: SAGE Background Paper on Dengue Vaccines - Amendment

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL INFORMATION
PROBLEM	Is the problem a public health priority?	<div> <div>No</div> <div>Uncertain</div> <div>Yes</div> <div><u>Varies by setting</u></div> </div> <div> <input type="checkbox"/> <input type="checkbox"/> <input checked="" type="checkbox"/> <input type="checkbox"/> </div>	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.	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.

BENEFITS & HARMS OF THE OPTIONS	<u>Benefits of the intervention</u>  Are the desirable anticipated effects large?	No <input type="checkbox"/>	Uncertain <input type="checkbox"/>	Yes <input type="checkbox"/>	Varies <input checked="" type="checkbox"/>	<p>Vaccine efficacy was high among participants 9 years of age or older who had a previous dengue infection before vaccination (seropositives) 76% (95%CI: 63.9, to 84.0), but low among participants who were seronegative at baseline (38.8%, 95%CI: -0.9 to 62.9%) in the first 25 months after the first dose of vaccine.</p> <p>Mathematical modelling suggests population-level impact with use of the vaccine in high transmission settings. Individual-level benefit depends on the serostatus of the vaccinee.</p>	<p>In seropositive participants aged 9-16 years, Hazard Ratios (HRs), that is, the ratio of incidence rates in vaccinated and control participants (Hazard Ratios (HRs)), for hospitalized VCD and severe VCD were 0.21 (95%CI: 0.14;0.31, <math>p&lt;0.001</math>) and 0.16 (95%CI: 0.07;0.37, <math>p&lt;0.001</math>), respectively (Figure 6, MI method). Cumulative incidences of hospitalized VCD and severe VCD through to M60 in vaccine recipients were 0.38% (95%CI: 0.26;0.54) and 0.08% (95%CI: 0.03;0.17), respectively, and 1.88% (95%CI: 1.54;2.31) and 0.48% (95%CI: 0.34;0.69) in controls.</p> <p>Based on the incidence in the epidemiological settings of the trials, for those aged 9 years and above, the new analysis indicates that the risk of severe dengue over 5 years was as follows:</p> <p>1,0 per 1,000 seropositive vaccinated persons versus 4.8 per 1,000 unvaccinated seropositive persons (benefit)</p>
	<u>Harms of the intervention</u>	No <input type="checkbox"/>	Uncertain <input type="checkbox"/>	Yes <input type="checkbox"/>	Varies <input checked="" type="checkbox"/>	<p>Data from Phase 2 and Phase 3 trials have not signaled any safety concern with regard to traditional safety</p>	<p>Clinical manifestations of severe dengue were similar in vaccinated seronegative persons compared to unvaccinated</p>

	Are the undesirable anticipated effects small?		<p>considerations (reactogenicity, serious adverse events, etc.). CYD-TDV is well-tolerated.</p> <p>In the 5- year follow-up period after the first dose of vaccine, an overall higher risk of severe dengue and hospitalizations from dengue was observed in vaccinated seronegative trial participants of all ages compared to unvaccinated seronegative trial participants. The excess risk was apparent from year 3 and persisted throughout the 5 years observation time.</p>	<p>seropositive persons.</p> <p>The HRs for hospitalized VCD and severe VCD in seronegative participants were 1.41 (95%CI: 0.74;2.68, p=0.29) and 2.44 (95%CI: 0.47;12.56, p=0.28), respectively. Cumulative incidences of hospitalized VCD and severe VCD through to M60 were 1.57% (95%CI: 1.13;2.19) and 0.40% (95%CI:0.22; 0.75) in vaccine recipients, respectively, and 1.09% (95%CI: 0.53;2.27) and 0.17% (95%CI: 0.04;0.83) in controls.</p> <p>The absolute risk of severe dengue in the vaccinated and unvaccinated trial populations by serostatus depends on the annual dengue incidence. Based on the incidence in the epidemiological settings of the trials, for those aged 9 years and above, the new analysis indicates that the risk of severe dengue over 5 years was as follows:</p> <p>4,0 per 1,000 seronegative vaccinated persons versus 1.7 per 1,000 unvaccinated seronegative persons (harm)</p>
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	<p>Balance between benefits and harms</p>	<p> <i>Favours intervention</i>  <input type="checkbox"/> </p> <p> <i>Favours comparison</i>  <input type="checkbox"/> </p> <p> <i>Favours both</i>  <input checked="" type="checkbox"/> </p> <p> <i>Favours neither</i>  <input type="checkbox"/> </p> <p> <i>Unclear</i>  <input type="checkbox"/> </p>	<p>CYD-TDV is favoured for individuals who are seropositive vaccinees, and the comparator (no vaccine) is favoured for individuals who are seronegative. How to balance benefits to seropositives and harms to seronegatives will depend on the vaccination strategy.</p>	<p>These new analyses suggest that if the vaccine is administered in a population with a high proportion of seropositives, there is an overall substantial benefit in terms of reduction of severe dengue and reduction of hospitalizations due to dengue. That is, the number of cases prevented in those who are seropositive is substantially greater than the excess number induced in seronegatives. The extent of the population benefit depends on the dengue seroprevalence.</p> <p>Harms may be minimized with a screen and vaccinate strategy is used that vaccinates only individuals who are seropositive.</p>
	<p>What is the overall quality of this evidence for the critical outcomes?</p>	<p>Effectiveness of the intervention</p> <p> <i>No included studies</i>  <input type="checkbox"/> </p> <p> <i>Very low</i>  <input type="checkbox"/> </p> <p> <i>Low</i>  <input type="checkbox"/> </p> <p> <i>Moderate</i>  <input checked="" type="checkbox"/> </p> <p> <i>High</i>  <input checked="" type="checkbox"/> </p> <p>Safety of the intervention</p> <p> <i>No included studies</i>  <input type="checkbox"/> </p> <p> <i>Very low</i>  <input type="checkbox"/> </p> <p> <i>Low</i>  <input type="checkbox"/> </p> <p> <i>Moderate</i>  <input checked="" type="checkbox"/> </p> <p> <i>High</i>  <input type="checkbox"/> </p>	<p>GRADE high quality evidence for vaccine efficacy in seropositive vaccinees.</p> <p>GRADE moderate quality evidence for vaccine efficacy in seronegative vaccinees.</p> <p>GRADE moderate evidence for risk of severe/hospitalized dengue in seropositive vaccinees.</p> <p>GRADE moderate evidence for risk of severe/hospitalized dengue in</p>	

							<p>seronegative vaccinees.</p> <p>Grade moderate quality of evidence for risk of serious (non-dengue) adverse events following dengue vaccination in seropositive vaccinees.</p> <p>Grade moderate quality of evidence for risk of serious (non-dengue) adverse events following dengue vaccination in seronegative vaccinees.</p>	
VALUES & PREFERENCES	How certain is the relative importance of the desirable and undesirable outcomes?	<p><i>Important uncertainty or variability</i></p> <p><input type="checkbox"/></p>	<p><i>Possibly important uncertainty or variability</i></p> <p><input checked="" type="checkbox"/></p>	<p><i>Probably no important uncertainty or variability</i></p> <p><input type="checkbox"/></p>	<p><i>No important uncertainty or variability</i></p> <p><input type="checkbox"/></p>	<p><i>No known undesirable outcomes</i></p> <p><input type="checkbox"/></p>	<p>The desirable outcome (preventing dengue) and the undesirable outcome (inducing dengue) are both understood to be very important to the public as they are the same disease. However, there are no data, only anecdotal experiences, to inform the relative importance of preventing cases of dengue and inducing cases of dengue, and how many would need to be prevented in order to accept an induced case.</p>	<p>The experience in the some countries rolling out the vaccine suggests the importance of the undesirable outcomes is greater than the desirable outcomes. However, it may be different in different contexts. What is acceptable in some settings may by unacceptable in others.</p>

	Values and preferences of the target population: Are the desirable effects large relative to undesirable effects?	<div> <div>No</div> <div>Probably No</div> <div>Uncertain</div> <div>Probably Yes</div> <div>Yes</div> <div>Varies</div> </div> <div> <input type="checkbox"/> <input type="checkbox"/> <input checked="" type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> </div>	No studies were retrieved on the values and preferences of the target population with respect to the demonstrated benefit in seronegatives and harm in seropositives. The anecdotal experience in one country suggests the desirable effects are not large relative to the undesirable effects, although this may not be representative.	Beyond direct harm to seronegatives, there may be inadvertent harm to vaccine confidence more broadly.
RESOURCE USE	Are the resources required small?	<div> <div>No</div> <div>Uncertain</div> <div>Yes</div> <div>Varies</div> </div> <div> <input checked="" type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> </div>	The price of the dengue vaccine has not yet been communicated. Serosurveys or individual tests would also require additional resources, and this will depend on the price of tests.	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	<div> <div>No</div> <div>Uncertain</div> <div>Yes</div> <div>Varies</div> </div> <div> <input type="checkbox"/> <input checked="" type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> </div>	Cost-effectiveness evaluations with the new evidence, with consideration of seroprevalence criteria or the test-vaccinate strategy, have not been completed.	Countries should do cost-effectiveness assessments based on their own context, including country-specific hospitalization rates and costs of program implementation.

EQUITY	What would be the impact on health inequities?	<div> <div>Increased</div> <input type="checkbox"/> <div>Uncertain</div> <input type="checkbox"/> <div>Reduced</div> <input type="checkbox"/> <div>Varies</div> <input checked="" type="checkbox"/> </div>	There has been no specific evaluation on how the dengue vaccine implementation may contribute to reducing health inequities. This may depend on the vaccination strategy used.	<p>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.</p> <p>If individual testing is not offered free of cost, it may only be accessible to higher income families, thus increasing inequities. On the other hand, there may be higher seropositivity amongst lower income families, and an accessible vaccination program could then decrease inequity.</p>
ACCEPTABILITY	Which option is acceptable to key stakeholders (Ministries of Health, Immunization Managers)?	<div> <div>Intervention</div> <input type="checkbox"/> <div>Comparison</div> <input type="checkbox"/> <div>Both</div> <input type="checkbox"/> <div>Neither</div> <input type="checkbox"/> <div>Unclear</div> <input checked="" type="checkbox"/> </div>	It is currently unclear whether key stakeholders will support further use of CYD-TDV and under what conditions. Either of the two strategies (seroprevalence or screen and vaccinate) may seem prohibitive with respect to feasibility for a public immunization program.	
	Which option is acceptable to target group?	<div> <div>Intervention</div> <input type="checkbox"/> <div>Comparison</div> <input type="checkbox"/> <div>Both</div> <input type="checkbox"/> <div>Neither</div> <input type="checkbox"/> <div>Unclear</div> <input checked="" type="checkbox"/> </div>	It is unclear whether CYD-TDV would be acceptable to the target group given the new evidence of harm in seronegative vaccinees. The acceptability may vary by setting and by vaccine strategy.	The “screen and vaccinate” strategy may be more acceptable to the target group, although there are currently no evidence to inform this question.

FEASIBILITY	Is the intervention feasible to implement?	<div> <div>No</div> <div>Probably No</div> <div>Uncertain</div> <div>Probably Yes</div> <div>Yes</div> <div>Varies</div> </div> <div> <input type="checkbox"/> <input type="checkbox"/> <input checked="" type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> </div>					It is uncertain whether a vaccination program is feasible based on seroprevalence criteria above 80% or a test vaccinate strategy with imperfect tests. Whether either one or both strategies are feasible may depend on the setting.		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 <i>clearly outweigh</i> desirable consequences in most settings	Undesirable consequences <i>probably outweigh</i> desirable consequences in most settings	The balance between desirable and undesirable consequences <i>is closely balanced or uncertain</i>	Desirable consequences <i>probably outweigh</i> undesirable consequences in most settings	Desirable consequences <i>clearly outweigh</i> undesirable consequences in most settings				
Type of recommendation	We recommend the intervention	We suggest considering recommendation of the intervention		We recommend the comparison	We recommend against the intervention and the comparison					
	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>					
		<input type="checkbox"/> Only in the context of rigorous research <input type="checkbox"/> Only with targeted monitoring and evaluation <input checked="" type="checkbox"/> Only in specific contexts or specific (sub)populations								



Recommendation (text)	For countries considering vaccination as part of their dengue control program, a “screen and vaccinate strategy” would be the preferred option, in which only persons with evidence of a past dengue infection are vaccinated (based on a documented laboratory confirmed dengue infection in the past, or screening tests).
Implementation considerations	<p>Decisions about implementing a “screen and vaccinate” strategy with the currently available assays will require careful assessment at the country level, including consideration of the sensitivity and specificity of available tests and of local priorities, dengue epidemiology, country-specific dengue hospitalization rates and costs, and affordability of both CYD-TDV and screening tests.</p> <p>Conventional serological testing for dengue virus IgG (dengue IgG ELISA) could be used to identify persons who have had previous dengue infections in order to select those to be offered vaccination. Sensitivity and specificity of dengue IgG ELISA should be assessed in a local context, depending on the prevalence of other flaviviruses, and past use of other flavivirus vaccines (Japanese encephalitis and yellow fever).</p> <p>Currently available RDTs, despite their lower sensitivity and specificity to detect past dengue infection compared with conventional dengue IgG ELISA, could be considered in high transmission settings until better tests are available. In settings with high numbers of seropositives and relatively low numbers of seronegatives, the population level benefit would be high and the individual risk low even with imperfect tests.</p>
Monitoring and evaluation	Monitoring of immunization coverage and disease surveillance, including and duration of protection and alternative schedules. Program evaluation and cost-effectiveness.
Research priorities	Development of a highly sensitive and specific RDT, simplified immunization schedules, and assessment of booster needs should be prioritized.

**GRADE TABLE 1a:** What is the efficacy of 3 doses of CYD-TDV in preventing clinical dengue in **seropositive** individuals 9-16 years of age in the first year following vaccination?

**Population:** 9-16 year-olds living in dengue endemic areas **seropositive** at vaccination

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

**Comparison:** Placebo

**Outcome:** Virologically-confirmed dengue occurring < 25 months of completion of the first dose (13 months post dose 3)

What is the efficacy of 3 doses of CYD-TDV in preventing clinical dengue in <b>seropositive</b> individuals 9-16 years of age in the 25 months following the first vaccination?				
			Rating	Adjustment to rating
Quality Assessment	No. of studies/starting rating		2 RCT <sup>1</sup>	4
	Factors decreasing confidence	Limitation in study design	None serious	0
		Inconsistency	None serious <sup>2</sup>	0
		Indirectness	None serious <sup>3</sup>	0
		Imprecision	None serious	0
		Publication bias	None serious	0
	Factors increasing confidence	Large effect	Not applicable <sup>4</sup>	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 25 months after the first vaccination among trial participants 9-16 years of age who were <b>seropositive</b> at the time of vaccination.

<sup>1</sup> 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. Based on the immune subset, vaccine efficacy amongst seropositives was 74.3% (95%CI 53.2-86.3) in CYD14, 83.7% (95%CI 62.2-93.7) in CYD15, 78.2% (65.4-86.3%) in the two trials pooled, and 81% (95%CI 67.2-90.0) in the two trials pooled with the age limited to 9-16 years. Data based on the new analysis affirms high vaccine efficacy in seropositives with point estimates ranging from 71-75%, depending on the method, and tight confidence intervals.

<sup>2</sup> With the new analyses, there is an indication of variability by age, depending on the analysis. At the extreme, vaccine efficacy in seropositives aged 9-16 years based on the multiple imputations analysis was 76% (95%CI 64-84), while seropositives aged 2-8 years it was 57% (95% CI 38-70). For other analyses, the difference in estimates by age was less pronounced. Because the vaccine is not currently licensed in the 2-8 year-old population, the confidence is not downgraded.

<sup>3</sup> 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. The confidence in the estimate of effect for the 17-45 **seropositive** population may be downgraded by 1 for indirectness.

<sup>4</sup> A large effect is noted (VE point estimate of 74.3%-83.7%, depending on the analysis) although currently the score is not eligible for upgrade at the maximum score.

**GRADE TABLE 1b:** What is the efficacy of 3 doses of CYD-TDV in preventing clinical dengue in **seronegative** individuals 9-16 years of age in the first year following vaccination?

**Population:** 9-16 year-olds living in dengue endemic areas **seronegative** at vaccination

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

**Comparison:** Placebo

**Outcome:** Virologically-confirmed dengue occurring < 25 months of completion of the first dose (13 months post dose 3)

What is the efficacy of 3 doses of CYD-TDV in preventing clinical dengue in <b>seronegative</b> individuals 9-16 years of age in the 25 months following the first vaccination?				
			Rating	Adjustment to rating
Quality Assessment	No. of studies/starting rating		2 RCT <sup>1</sup>	4
	Factors decreasing confidence	Limitation in study design	None serious <sup>2</sup>	0
		Inconsistency	None serious	0
		Indirectness	None serious <sup>3</sup>	0
		Imprecision	None serious <sup>4</sup>	-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		CYD-TDV demonstrates consistently positive (>0) point estimates of vaccine efficacy against virologically-confirmed dengue in the first 25 months after the first vaccination among trial participants 9-16 years of age who were <b>seronegative</b> at the time of vaccination.	

<sup>1</sup> 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. Based on the immune subset, vaccine efficacy amongst seronegatives was 35.5% (95%CI -27.0-66.6) in CYD14, 43.2% (95%CI -61.6-80.0) in CYD15, 38.1% (95%CI -3.4-62.9) in the two trials pooled, and 52.5% (95%CI 5.9-76.1) in the two trials pooled with the age limited to 9-16 years. There were few seronegatives in the immune subset, making it hard to estimate vaccine efficacy with precision. The confidence is downgraded in the category of imprecision, although it does reflect a flaw in the study design.

Data based on the new analysis provides variable point estimates for seronegatives. In 9-16 year-olds, vaccine efficacy is estimated at 39% (95%CI -1-63) using the multiple imputation method, 45% (95%CI 26-58) using the TMLE method, and 18% (95%CI -18-43) using the NS1 method.

<sup>2</sup> The methods used for re-analysis of the Phase 3 trial data are based on assays and statistical methods that are associated with misclassification of serostatus at baseline, which vary by assay. The false-negative rate (misclassifying seropositives as seronegatives) is low, and for this analysis there is to be limited bias due to misclassification.

<sup>3</sup>Based on the best assay for serostatus in the immune subset, the confidence intervals are very wide. All cross zero except when the analysis is limited to 9-16 year-olds. The imprecision remains for most new analyses, with the lower bound of the 95%CI crossing 0 for the multiple imputation method and NS1 method.

<sup>4</sup> 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 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. The confidence in the estimate of effect for the 17-45 **seronegative** population would be downgraded by 1 for indirectness.

**GRADE TABLE 2a:** What is the **duration of protection/risk** in **seropositive** 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/risk in <b>seropositive</b> individuals 9-16 years of age vaccinated with CYD-TDV?				
			Rating	Adjustment to rating
Quality Assessment	No. of studies/starting rating		2 RCT <sup>1</sup>	4
	Factors decreasing confidence	Limitation in study design	Very serious <sup>2</sup>	-1
		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			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			CYD-TDV is associated with statistically significant protection against severe and hospitalized dengue in seropositive participants 9-16 years of age

<sup>1</sup>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. Active surveillance of participants lasted only until study month 25, after which surveillance was hospital-based. Thus, it is not possible to evaluate the duration of protection against virologically-confirmed dengue of any severity. However, since severe outcomes are also of interest and importance from a public health perspective, the confidence is not downgraded.

Based on participants with serostatus derived from the new analyses, in seropositive participants aged 9-16, Hazard Ratios (HRs) up to study month 60 for hospitalized VCD and severe VCD were 0.21 (95%CI: 0.14;0.31,  $p<0.001$ ) and 0.16 (95%CI: 0.07;0.37,  $p<0.001$ ), respectively, and point estimates were  $<1$  with all methods in pooled analyses and in individual trials.

<sup>2</sup>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.

The methods used for re-analysis of the Phase 3 trial data are based on assays and statistical methods that are associated with misclassification of serostatus at baseline, which vary by assay. The false-positive rate (misclassifying seronegatives as seropositives) is high (31%), which would bias the result towards the null. Thus the protective effect in seropositives may be greater than that estimated in these analyses.

**GRADE TABLE 2b:** What is the **duration of protection/risk** in **seronegative** individuals 9-16 years of age vaccinated with CYD-TDV?

**Population:** 9-16 year-old **seronegative** 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/risk in <b>negative</b> individuals 9-16 years of age vaccinated with CYD-TDV?				
			Rating	Adjustment to rating
Quality Assessment	No. of studies/starting rating		2 RCT <sup>1</sup>	4
	Factors decreasing confidence	Limitation in study design	Very serious <sup>2</sup>	-1
		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			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			CYD-TDV is associated with an increase in severe and hospitalized dengue in seronegative participants 9-16 years

<sup>1</sup>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. Active surveillance of participants lasted only until study month 25, after which surveillance was hospital-based. Thus, it is



not possible to evaluate the duration of protection against virologically-confirmed dengue of any severity. However, since severe outcomes are also of interest and importance from a public health perspective, the confidence is not downgraded.

Based on participants with serostatus derived from the new analyses, in seronegative participants aged 9-16, The HRs for hospitalized VCD and severe VCD in seronegative participants were 1.41 (95%CI: 0.74;2.68, p=0.29) and 2.44 (95%CI: 0.47;12.56, p=0.28), respectively, with point estimates >1 for all methods in pooled analyses. The effect suggested the effect could vary by age, although the confidence intervals for each estimate were wide and overlapped. The HR against hospitalized VCD amongst seronegative 9-16 year-olds was 0.836 (95%CI 0.227-3.081) during the active phase of study years 1 and 2, 2.892 (95%CI 0.679-12.315) during study year 3, 1.789 (95%CI 0.667-4.798) during study year 4, and 1.428 (95%CI 0.45-4.528) during study year 5 and beyond. Thus, the trend in the point estimate for HR in this age group is declining with time, although the confidence intervals all overlap.

<sup>2</sup>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.

The NS1 method used for re-analysis of the Phase 3 trial data are based on assays and statistical methods that are associated with misclassification of serostatus at baseline. The false-negative rate (misclassifying serpositives as seronegatives) is low (4.7%), and would have limited effect in the interpretation of the data.

**GRADE TABLE 3a:** What is the risk of other serious adverse events (non-dengue) in **seropositive** individuals 9-16 years of age vaccinated with CYD-TDV?

**Population:** 9-16 year-old **seropositive** 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 <b>seropositive</b> individuals 9-16 years of age vaccinated with CYD-TDV?				
			Rating	Adjustment to rating
Quality Assessment	No. of studies/starting rating		2 RCT <sup>1</sup>	4
	Factors decreasing confidence	Limitation in study design	None serious	0
		Inconsistency	None serious	0
		Indirectness	None serious <sup>2</sup>	0
		Imprecision	Serious <sup>3</sup>	-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 in seropositive participants based on clinical trials.

<sup>1</sup> 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 proportion of participants with serious adverse events (SAEs) and fatal AEs was similar between seropositive participants in the CYD and placebo group based on the immune subset. In CYD14, the proportion with an SAE was 11.7% and 10.1% in the CYD and placebo groups, respectively, and the proportion with a fatal SAE was 0% in both groups. In CYD15,

the proportion with an SAE was 11.4% and 12.9% in the CYD and placebo groups, respectively, and the proportion with a fatal SAE was 0.5% and 0.6% in the CYD and placebo groups, respectively.

<sup>2</sup>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.

<sup>3</sup>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 3b:** What is the risk of other serious adverse events (non-dengue) in **seronegative** individuals 9-16 years of age vaccinated with CYD-TDV?

**Population:** 9-16 year-old **seronegative** 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 <b>seronegative</b> individuals 9-16 years of age vaccinated with CYD-TDV?				
			Rating	Adjustment to rating
Quality Assessment	No. of studies/starting rating		2 RCT <sup>1</sup>	4
	Factors decreasing confidence	Limitation in study design	None serious	0
		Inconsistency	None serious	0
		Indirectness	None serious <sup>2</sup>	0
		Imprecision	Serious <sup>3</sup>	-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 in seronegative participants based on clinical trials.

<sup>1</sup> 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 proportion of participants with serious adverse events (SAEs) and fatal AEs was similar between seronegative participants in the CYD and placebo group based on the immune subset. In CYD14, the proportion with an SAE was 11.5% and 14% in the CYD and placebo groups, respectively, and the proportion with a fatal SAE was 0% in both groups. In CYD15,

the proportion with an SAE was 11.2% and 10.7% in the CYD and placebo groups, respectively, and the proportion with a fatal SAE was 0% in both groups.

<sup>2</sup>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.

<sup>3</sup>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.