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

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

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

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

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

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

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

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

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

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

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

It is important to understand the extent of risk at a population level. Based on the incidence in the epidemiological settings of the trials, for those aged 9 years and above, the new analysis indicates that the risk of severe dengue over 5 years stratified by serostatus was as follows:
• In those seropositive prior to vaccination, the incidence of severe dengue was 1.0 per 1,000 in those vaccinated and 4.8 per 1,000 in those not vaccinated (benefit).
• In those seronegative prior to vaccination, the incidence of severe dengue was 4.0 per 1,000 in those vaccinated and 1.7 per 1,000 in those not vaccinated (harm).

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

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

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

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

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

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

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

**Population Seroprevalence Criteria:**

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

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

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

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

Pre-vaccination Screening

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

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

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

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

Proposed Recommendations

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

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

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

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

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

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

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

**Age**

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

**Schedule**

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

**Booster**

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

**Research priorities**

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