SAGE Evidence to recommendation framework[i]

Detailed documentation related to the evidence to recommendation table can be found in the background papers presented to the Strategic Advisory Group of Experts (SAGE) on Immunization in April 2018[1] The framework presented here only refers to CYD-TDV, the first licensed dengue vaccine.

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

Population: Immunocompetent individuals (≥9 years of age)
Intervention: Three doses of CYD-TDV
Comparison(s): No vaccination with CYD-TDV
Outcome: Symptomatic dengue illness, hospitalized dengue and severe dengue

Background:

Dengue is the most extensively spread mosquito-borne virus. Dengue is caused by any one of the four dengue virus serotypes (serotypes 1-4). Infection by one serotype is thought to provide lifelong immunity against that particular serotype, but susceptibility remains to the other three viruses. The second infection by a different serotype to the first is associated with a higher risk of severe dengue. Fatality rates are around 0.1% to 1% in hospitalized cases that receive appropriate intensive care. Dengue often requires hospitalization, thereby challenging already fragile health care systems.

In the last 50 years, the incidence of dengue reported to WHO has increased manifold, with outbreaks of increasing frequency and magnitude, and continuing geographic expansion. Vector control is an important component of a comprehensive dengue control strategy; however, as a single strategy, it has been difficult to demonstrate its effectiveness in reducing the human dengue burden. There is no specific antiviral therapy to mitigate severity of disease. As such, a vaccine is critical and must protect against the four different serotypes of dengue viruses (i.e. be tetravalent).

CYD-TDV was first licensed in December 2015, and is now licensed in a number of 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 of licensure. Other dengue vaccines

[1] Working Group report, available at http://www.who.int/immunization/sage/meetings/2018/april/en/ , accessed April 2018.

are currently under development.
Key Reference for this table: SAGE Background Paper on Dengue Vaccines[2]

	CRITERIA	JUDGEMENTS				RESEARCH EVIDENCE	ADDITIONAL INFORMATION
PROBLEM	Is the problem a public health priority?	*No* ☐	*Un-certain* ☐	*Yes* ☒	*Varies by setting* ☐	Dengue is a major public health problem, with every WHO Region reporting cases. In the last 50 years the incidence of dengue reported to WHO has increased manifold, with an expanded geographic range. Approximately 3.5 billion people live in dengue endemic countries. A recent estimate suggest 390 million dengue infections per year in 2010 (95% CI 284–528 million), of which about 25%, 96 million (95% CI 67–136 million), manifest clinically (with any severity of disease).[3] WHO has estimated 500 000 hospitalizations as a result of dengue annually, of which about 10 000 to 50 000 are fatal[2].	There have been efforts to develop dengue vaccines for decades. A tetravalent vaccine is needed with a balanced efficacy against all four dengue serotypes.
BENEFITS & HARMS OF THE	<u>Benefits of the intervention</u> Are the desirable anticipated effects large?	*No* ☐	*Un-certain* ☐	*Yes* ☐	*Varies* ☒	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.	Individual-level benefit depends on the serostatus of the vaccinee.

[2] SAGE Working Group Background Document. Available at http://www.who.int/immunization/sage/meetings/2018/april/2_DengueBackgrPaper_SAGE_Apr2018.pdf?ua=1, accessed April 2018.
[3] Bhatt S et al. The global distribution and burden of dengue. Nature. 2013 Apr 25;496(7446):504-7.

					In seropositive participants aged 9-16 years, Hazard Ratios (HRs) for hospitalized virologically confirmed dengue (VCD) and severe VCD were 0.21 (95%CI: 0.14;0.31) and 0.16 (95%CI: 0.07;0.37), respectively. Cumulative incidences of hospitalized VCD and severe VCD through to month 60 after the first dose 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. Based on the dengue incidence and seroprevalence rates in the epidemiological settings of the trials, for those aged 9 years and above, the reduction of severe dengue over 5 years was as follows: 1.0 per 1 000 seropositive vaccinated persons versus 4.8 per 1,000 unvaccinated seropositive persons (benefit).[2]	
	<u>Harms of the intervention</u> Are the undesirable anticipated effects small?	*No* ☐	*Un-certain* ☐	*Yes* ☐	*Varies* ☒	CYD-TDV is well-tolerated. There have been no safety concerns with regard to traditional safety considerations. However, excess cases of hospitalized and severe dengue were observed in those individuals who were seronegative prior to vaccination. The HRs for hospitalized VCD and severe VCD in seronegative participants were 1.41 (95%CI: 0.74; 2.68) and 2.44 (95%CI:	Clinical manifestations of severe dengue were similar in vaccinated seronegative persons compared to unvaccinated seropositive persons, supporting the hypothesis the vaccine behaves like a silent primary infection. The absolute risk of severe dengue in the vaccinated and unvaccinated trial populations

			0.47;12.56), respectively. Cumulative incidences of hospitalized VCD and severe VCD through to months 60 after the first dose 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. The excess risk was apparent from year 3 of observation post vaccine receipt and persisted throughout the 5 years observation time, although a gradual decline was observed. 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: 4.0 per 1 000 seronegative vaccinated persons versus 1.7 per 1 000 unvaccinated seronegative persons experienced a higher risk of severe dengue over 5 years in the seroprevalence settings of the trials.	by serostatus depends on the annual dengue incidence. The overall population level benefit remains substantial in setting with high seroprevalence.
	Balance between benefits and harms	*Favours inter-vention*: ☐ *Favours com-parison*: ☐ *Favours both*: ☒ *Favours neither*: ☐ Unclear: ☐	At a population level, in areas with a high proportion of seropositives (=high seroprevalence), 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.	CYD-TDV is favoured for individuals who are seropositive vaccinees, and the comparator (no vaccine) is favoured for individuals who are seronegative. Balancing benefits to seropositives and harms to seronegatives will depend on the vaccination strategy used.

			At an individual level, those who are seronegative (no serological evidence of past dengue infection) are at increased risk of hospitalizations due to dengue and of severe dengue.	The extent of the population benefit depends on the dengue seroprevalence.
	What is the overall quality of this evidence for the critical outcomes?	Effectiveness of the intervention *No included studies* ☐ *Very low* ☐ *Low* ☐ *Mod-erate* ☒ *High* ☐ Safety of the intervention *No included studies* ☐ *Very low* ☐ *Low* ☐ *Mod-erate* ☒ *High* ☐	The evidence presented below is based on analyses done retrospectively from blood samples taken from all trial participants at month 30 of the trial. There is high quality evidence for vaccine efficacy for those who are seropositive for prevention of hospitalization and severe disease, but not sufficient quality evidence for long-term efficacy (beyond 25 months) of symptomatic virologically confirmed dengue infection of any severity. There is moderate quality of evidence for very low efficacy in seronegative individuals in the first 25 months. After 25 months, an increased risk of hospitalized and severe dengue is observed.	
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* ☐	The desirable outcome (preventing severe dengue) is clearly important in affected communities. The undesirable outcome (sensitizing seronegative vaccinees to severe dengue) is of major concern.	The perception of the relative importance of the undesirable versus desirable outcomes may be different in different contexts. What is acceptable in some settings may be unacceptable in others.

	Values and preferences of the target population: Are the desirable effects large relative to undesirable effects?	*No* ☐ *Probably No* ☐ *Uncertain* ☒ *Probably Yes* ☐ *Yes* ☐ *Varies* ☐	The desirable effects are large relative to undesirable effects in high seroprevalence settings, but low in low seroprevalence settings. No studies have been conducted to date on the values and preferences of the target population with respect to the demonstrated benefit in seronegatives and harm in seropositives.	Beyond direct harm to seronegatives, there may be inadvertent harm to vaccine confidence more broadly. Individual versus population level perspectives need to be considered.
RESOURCE USE	Are the resources required small?	*No* ☒ *Uncertain* ☐ *Yes* ☐ *Varies* ☐	The cost of the dengue vaccine remains unknown, and may differ between countries. The vaccine cost is likely to be substantive. In addition, cost-effectiveness studies need to consider the cost of risk minimization strategies (diagnostic testing, seroprevalence surveys).	Given the budget implications – cost of the vaccine, communications etc, countries will need to consider whether the dengue vaccine is a priority intervention to fund.
	Cost-effectiveness	*No* ☐ *Uncertain* ☒ *Yes* ☐ *Varies* ☐	Cost effectiveness studies have not yet been conducted.	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.

EQUITY	What would be the impact on health inequities?	*Increa-sed* ☐ *Un-certain* ☐ *Re-duced* ☐ *Varies* ☒	Dengue affects all populations. There have been no specific evaluations on how the dengue vaccine implementation may contribute to reducing health inequities. This may depend on the vaccination strategy used and how it is implemented. (See table 2)	
ACCEPTABILITY	Which option is acceptable to key stakeholders (Ministries of Health, Immunization Managers)?	*Inter-vention* ☐ *Com-parison* ☐ *Both* ☐ *Neither* ☐ *Un-clear* ☒	Acceptability will depend on a combination of various factors including burden of dengue in a given country, cost effectiveness, risk assessment, risk management and communication, demand for vaccine programmatic feasibility and vaccine strategy.	
	Which option is acceptable to target groupsBo?	*Inter-vention* ☐ *Com-parison* ☐ *Both* ☐ *Neither* ☐ *Un-clear* ☒	It is unclear whether CYD-TDV would be acceptable to the target group given the evidence of harm in seronegative vaccinees. The acceptability may vary by setting and by implementation strategy. (see table 2)	
FEASIBILITY	Is the intervention feasible to implement?	*No* ☐ *Probably No* ☐ *Un-certain* ☐ *Probably Yes* ☐ *Yes* ☐ *Varies* ☒	Both the pre-vaccination screening strategy and the seroprevalence criteria will be difficult to implement because of the additional need for screening tests, and the complexities of programmatic and communication issues.	

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 ☐
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 ☐
Recommendation (text)	The live attenuated dengue vaccine CYD-TDV has been shown in clinical trials to be efficacious and safe in persons who have had a dengue virus infection in the past (seropositive individuals), but carries an increased risk of severe dengue in those who experience their first natural dengue infection after vaccination (seronegative individuals). Countries should consider introduction of the dengue vaccine CYD-TDV only if the minimization of risk can be assured.				

Implementation considerations	Implementation considerations will depend on the strategy chosen. (see table 2)
Monitoring and evaluation	Monitoring of immunization coverage and disease epidemiology, including duration of protection.
Research priorities	Research is needed to evaluate vaccine schedules with fewer doses, and to assess the need for booster doses. Locally applicable cost-effectiveness studies are needed to underpin policy decisions. The development of safe, effective, and affordable dengue vaccines for use irrespective of serostatus remains a priority.

[i] [i]This Evidence to Recommendation table is based on the DECIDE Work Package 5: Strategies for communicating evidence to inform decisions about health system and public health interventions. Evidence to a recommendation (for use by a guideline panel). http://www.decide-collaboration.eu/WP5/Strategies/Framework