SAGE Evidence to recommendations framework[i] Table 2

Detailed evidence 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]

Question: Should countries considering introduction of CYD-TDV to reduce the burden of dengue use a pre-vaccination screening or population seroprevalence based criteria?

Population: Populations living in dengue endemic countries
Intervention: Pre-vaccination screening to determine serostatus and then only vaccinate those found to be seropositive
Comparison(s): Introducing the vaccine based on population seroprevalence criteria without individual screening
Outcome: Symptomatic dengue of any severity (including hospitalizations due to dengue and severe dengue)

Background:

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 (referred to as "seropositive"), but carries an increased risk of severe dengue in those who experience their first dengue infection after vaccination, i.e. seronegative individuals. Countries should therefore consider introduction of the dengue vaccine CYD-TDV only if the minimization of risk can be assured. From a programmatic point of view, two strategies could be considered by countries considering vaccination with CYD-TDV vaccine as part of their dengue control program:

Strategy 1 (intervention = pre-vaccination screening): screen individuals for seropositivity prior to vaccination and vaccinate only seropositive individuals. The rationale for this strategy is that screening and vaccinating only those testing seropositive offers the potential of retaining the benefits of vaccination while substantially reducing the risks experienced by seronegative recipients.

Strategy 2 (comparator strategy = population seroprevalence threshold criteria, without individual screening): use CYD-TDV only in populations with very high seroprevalence rates (defined as 80% and above). 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, a population serosurvey would be undertaken first to identify population groups among whom seroprevalence levels are high enough to ensure substantial public health impact, followed by implementation of mass vaccination.

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

Key Reference for this table: SAGE Background Paper on Dengue Vaccines[2] and Table 1.

	CRITERIA	JUDGEMENTS				RESEARCH EVIDENCE	ADDITIONAL INFORMATION
PROBLEM	Is the problem a public health priority?	*No* ☐	*Un-certain* ☐	*Yes* ☒	*Varies by setting* ☐	Dengue is a public health priority (see Table 1). Based on the new data that indicates an increased risk of hospitalized and severe dengue in seronegative vaccine recipients, a balance between population level benefit and individual risk needs to be considered. Hence, countries could consider two main strategies on how to introduce CYD-TDV: "pre-vaccination screening" or "population seroprevalence criteria".	
BENEFITS & HARMS OF THE OPTIONS	<u>Benefits of the intervention</u> Are the desirable anticipated effects large?	*No* ☐	*Un-certain* ☐	*Yes* ☐	*Varies* ☒	Pre-vaccination screening would identify seropositive individuals for which CYD-TDV is efficacious and safe, and exclude seronegative individuals for whom CYD-TDV may trigger excess cases of severe dengue when these individuals encounter their first natural dengue infection.	The advantages of a "pre-vaccination screening" strategy is that risk associated with vaccinating seronegatives can be minimized, while maximizing benefit by targeting seropositives only. The public health impact of the "pre-vaccination screening" strategy depends on test sensitivity. High sensitivity ensures that eligible persons

[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.

						receive the vaccine. Low sensitivity would mean that the population level benefit will be lower. Another advantage is that this strategy may also be considered in low to moderate transmission settings. The seroprevalence criteria strategy can only be considered in areas with high seroprevalence, thus excluding many subnational areas that may not meet the seroprevalence threshold.
	Harms of the intervention Are the undesirable anticipated effects small?	*No* ☐	*Un-certain* ☐	*Yes* ☐	*Varies* ☒	Intervention: No screening will be completely specific. Some truly seronegative individuals will be vaccinated based on a false positive test result. Using a screening test with 80% specificity for a pre-vaccination screening strategy, 4% of the population in a seroprevalence setting of 80% would be at a potential increased risk of severe disease; using a screening test with 98% specificity would result in 0.4% at such risk. The risk as a result of a false positive screening test would be higher in lower	The extent of co-circulation of other flaviviruses and population use of flavivirus vaccines such as yellow fever or Japanese encephalitis vaccines will influence the test specificity due to cross-reactivity of all serological assays between the flaviviruses. High test specificity ensures that the risk to seronegative persons is minimized. Therefore, the potential “harm”

			seroprevalence settings. Comparator: Mass vaccination in high seroprevalence settings (as determined by population level seroprevalence studies): the harm will depend on the seroprevalence criteria chosen. If a seroprevalence of 80% is chosen, then potentially 20% of the vaccinated population are at increased short-term risk of severe dengue, although in the long-term this risk will decline. The risk depends on the annual incidence of dengue as it changes over time. Dengue transmission maps indicate that not many subnational areas at administrative level 1 (=administrative boundaries at the first subnational level), even in high dengue endemic countries, have areas with seroprevalence above 80% at age 9 years and even fewer would have >90% seroprevalence in 9 year olds.	of the pre-vaccination strategy varies by test specificity combined with the seroprevalence in any given country. High specificity is more important in lower transmission settings. In a high transmission area with high seroprevalence, although high specificity is always desirable, the proportion of misclassified seronegative persons will be small even with suboptimal specificity.
	Balance between benefits and harms	*Favours inter-vention*: ☒ *Favours com-parison*: ☐ *Favours both*: ☐ *Favours neither*: ☐ Unclear: ☐	Intervention: A pre-vaccination screening strategy would allow for only vaccinating those individuals who are tested as seropositive. This reduces the harm to seronegative individuals. The public health impact of the screen and vaccinate strategy depends on test	With a pre-vaccination screening strategy, public communication regarding the rationale for pre-vaccination blood taking would also be complex. Some truly seronegative individuals will be vaccinated based on a false

			sensitivity. High sensitivity ensures that eligible persons receive the vaccine. Low sensitivity would mean that the population level benefit will be lower. Another advantage is that this strategy may also be considered in low to moderate transmission settings. Comparator: The benefit-risk ratio is more favorable at higher seroprevalence rates. For example, from a population perspective, if 1 000 000 children were vaccinated in settings of 80% seroprevalence in the vaccinated group, in the five years after vaccination, 11 000 hospitalized dengue cases might be averted (12 000 averted in seropositives, 1 000 excess cases in seronegatives) and 2 800 severe dengue cases might be averted (3 200 averted in seropositives, 460 excess cases in seronegatives). Estimates on subnational areas with seroprevalence rates >80% by the age of 9 years show that only few countries have such high levels at the administrative level 1 (=administrative boundaries at the first subnational level).[3]	positive test result as no test will be absolutely specific. Therefore transparent communication is needed for both strategies to inform vaccinees that they may still be at risk of dengue and the need for adherence to other disease preventive measures, even if vaccinated. A seroprevalence threshold-driven vaccine introduction needs to take into account public confidence in national vaccination programmes. Communication would have to ensure full disclosure of potential risks and benefits of vaccinating persons of unknown serostatus. Public acceptance of the risk of severe dengue in seronegative individuals may be low. Although in a mass vaccination programme in areas of high seroprevalence, most vaccinated individuals might be expected to ultimately benefit from the vaccination, nevertheless, some cases of

				severe dengue will occur (either in seropositive persons as the vaccine is not 100% effective or in seronegative persons primed by the vaccine) thus potentially damaging the reputation of the vaccine programme which may also have adverse consequences on other vaccines.
	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 ☐ Moderate ☐ High	Published evidence on the effectiveness of pre-vaccination screening versus population seroprevalence criteria is not available at present. For general aspects of dengue vaccine safety please refer to table 1.	
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	Qualitative studies, key informant interviews and stakeholder analyses have not been completed, hence no definitive conclusions can be drawn on the values or preferences for the two strategies.	
	Values and preferences of the target	*No* / *Probably No* / *Uncertain* / *Probably Yes* / *Yes* / *Varies*	No qualitative studies have been conducted to conclusively determine the values and preferences of the target	

	population: Are the desirable effects large relative to undesirable effects?	☐	☐	☒	☐	☐	☐			population with regards to the level of acceptance of an individual risk versus a population level benefit.	
RESOURCE USE	Are the resources required small?	*No*	*Un-certain*	*Yes*	*Varies*					<u>Intervention:</u> The resources required beyond the cost of the vaccine itself include the costs of the screening tests, and the costs associated with the logistics of screening. <u>Comparator:</u> The resources required for the comparator include the costs of population serosurveys to identify subnational areas with seroprevalence rates above 80%. WHO`s guidance on designing and implementing cross-sectional serosurveys to estimate age-specific dengue seroprevalence highlights that such seroprevalence studies will require considerable resources and expertise.[4]	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.
		☒	☐	☐	☐						
	Cost-	*No*	*Un-certain*	*Yes*	*Varies*					Cost-effectiveness evaluations with	Cost-effectiveness assessments

[4] WHO. Guidelines on dengue serosurveys. Available at http://www.who.int/immunization/research/development/Dengue_Serosurveys_020617.pdf, accessed April 2018

	effectiveness	☐	☒	☐	☐	consideration of the pre-vaccination screening strategy or seroprevalence criteria have not been completed.	will need to consider the local epidemiology, including country-specific hospitalization rates and costs of program implementation. No data are available on the cost of the vaccine and screening tests at this stage. Both the pre-vaccination screening (intervention) as well as the use of seroprevalence criteria (comparator) (necessitating population serosurveys) require laboratory testing. The pre-test probability of an individual being seropositive would be higher in settings with high endemic transmission and thus a screening strategy would likely have greater cost-effectiveness in such settings.
EQUITY	What would be the impact on health inequities?	*Increa-sed* ☐	*Un-certain* ☒	*Re-duced* ☐	*Varies* ☐	If cost of testing and vaccination are covered by a governmental program, this intervention could decrease inequities, under the assumption that other public health interventions would not be de-prioritized.	

ACCEPTABILITY	Which option is acceptable to key stakeholders (Ministries of Health, Immunization Managers)?	*Inter-vention* ☐	*Com-parison* ☐	*Both* ☐	*Neither* ☐	*Un-clear* ☒	It is currently unclear whether key stakeholders will support further use of CYD-TDV and under which conditions. Either of the two strategies (pre-vaccination screening or seroprevalence criteria) add to the complexities of the implementation and costs for a public immunization program.	Community confidence in vaccine programmes (beyond dengue vaccines) also need to be taken into account
	Which option is acceptable to target group?	*Inter-vention* ☐	*Com-parison* ☐	*Both* ☐	*Neither* ☐	*Un-clear* ☒	There are no studies to determine which strategy would be more acceptable to the target group.	The pre-vaccination screening strategy (intervention) is likely to be more acceptable to the target group.
FEASIBILITY	Is the intervention feasible to implement?	*No* ☐	*Probably No* ☐	*Un-certain* ☒	*Probably Yes* ☐	*Yes* ☐	No feasibility studies have been conducted to compare the two strategies.	It is uncertain whether a vaccination program is feasible based on a pre-vaccination screening strategy (intervention) or seroprevalence criteria above 80% (comparator). Whether either one or both strategies are feasible depends on the epidemiological background, cost of both the vaccine and screening tests, and the implementation logistics.

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)	For countries considering vaccination as part of their dengue control programme, pre-vaccination screening is the recommended strategy. With this strategy, only persons with evidence of a past dengue infection would be vaccinated (based on an antibody test, or on a documented laboratory confirmed dengue infection in the past). If pre-vaccination screening is not feasible, vaccination without individual screening could be considered in areas with recent documentation of seroprevalence rates of at least 80% by age 9 years				

Implementation considerations	Criteria for countries to help decide which strategy would result in maximal public health benefit and minimal individual risk should include deliberations around ethical concerns, the heterogeneity of seroprevalence within populations, the feasibility of population seroprevalence studies and individual pre-vaccination screening, the number of people who could be eligible for vaccination under these scenarios, community acceptance, confidence in vaccination programmes, and communication issues. Decisions about implementing a pre-vaccination screening 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. Decisions about implementing a seroprevalence threshold based mass vaccination need to consider various programmatic challenges. Dengue transmission maps indicate that not many subnational areas, even in high dengue endemic countries, have areas with seroprevalence above 80% at age 9 years even fewer locations have a seroprevalence >90%. 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.
Monitoring and evaluation	Monitoring of immunization coverage and disease epidemiology, including duration of protection in seropositive individuals.
Research priorities	There is an urgent need for the development of RDTs which are highly specific and sensitive, in order to determine dengue serostatus. Research on how best to integrate and implement pre-vaccination screening in an immunization programme is recommended.

[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