SAGE Evidence to Decision Framework

Policy question: ***Should the TAK-003 vaccine be recommended over no vaccination to immunocompetent individuals 6 years and older in dengue-endemic countries to reduce the burden of dengue?***

Population: Immunocompetent individuals (≥6 years of age)
Intervention: Two doses of TAK-003
Comparison(s): No vaccination
Outcomes: Symptomatic (virologically confirmed) 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 the homologous serotype, but susceptibility remains to the other heterologous serotypes. A second infection caused 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 healthcare systems. In the last 50 years, the incidence of dengue has increased several-fold, with outbreaks of increasing frequency and magnitude, and continuing geographic expansion. While enhanced disease following secondary infection is the main risk factor for severe dengue outcomes in children and young healthy adults, recent data indicate that the risk of severe disease is higher among older adults and those with comorbidities compared to younger age groups.

Vector control is an important component of a comprehensive dengue control strategy; however, its effectiveness in reducing the human dengue burden has been difficult to demonstrate as a standalone strategy. There is no specific antiviral therapy to reduce the severity of the disease and prevent death. It is critical that the vaccine should be effective against all four serotypes of dengue viruses, including among those who have not been exposed in the past.

A tetravalent dengue vaccine (CYD-TDV, Dengvaxia™) has received market authorization for use in baseline seropositive individuals 6 years and older. The clinical trials of the vaccine showed higher rates of hospitalized/ severe dengue in baseline seronegative subjects for certain serotypes. Hence, the vaccine is only recommended for use in baseline seropositive individuals, requiring pre-screening to determine serostatus before vaccination.

Takeda's tetravalent dengue vaccine (TAK-003) is a live attenuated vaccine. A live-attenuated dengue serotype 2 virus provides the genetic backbone for all four serotypes. The dengue virus type 2 (DENV 2) strain (TDV-2) is based on an attenuated laboratory-derived virus, DEN-2 PDK-53. The other three vaccine strains (TDV-1, TDV-3, and TDV-4) are chimaeras generated by replacing the envelope (E) and pre-membrane (prM) genes of TDV-2 with those from wild-type dengue virus type 1 (DENV 1), type 3 (DENV 3), and type 4 (DENV 4) strains. This vaccine differs from CYD-TDV in that it used DENV2 as the backbone instead of the attenuated Yellow Fever virus backbone. Hence, it includes the non-structural (NS1) protein of the dengue virus, which is not present in CYD-TDV.

The vaccination schedule for the primary series is 2 doses administered subcutaneously with an interval of 3 months between doses.

The TAK-003 vaccine received market authorization in several countries in 2023 and has been licensed by the European Medicines Agency for use in individuals 4 years and older.

	CRITERIA	JUDGEMENTS				RESEARCH EVIDENCE	ADDITIONAL INFORMATION
PROBLEM	Is the problem a public health priority?	No ☐	Uncertain ☐	Yes ☒	Varies by setting ☐	Dengue poses an increasingly large public health threat, with a 30-fold increase in annual reported cases over the past 50 years and continued geographic expansion in the endemicity of the infection. Recent estimates suggest that 3.8 billion people (95% confidence interval: 3.5 billion – 4.1 billion) live in dengue-endemic areas, most of which are in Asia, Africa, and the Americas. Infections may lead to clinical manifestations ranging from relatively mild febrile illness to severe dengue manifesting as plasma leakage, haemorrhage, organ failure, or shock. The reported fatality in hospitalized cases is 0.1 to 1%.	The first licensed dengue vaccine (Dengvaxia®) is only indicated for those with prior exposure to dengue virus demonstrated by previous lab confirmation or pre-vaccination screening, thus limiting its programmatic use and impact.

BENEFITS & HARMS	**Benefits**: Are the desired anticipated effects large?	No ☐	Uncertain ☐	Yes ☐	Varies ☒	A phase 3 clinical trial in endemic settings demonstrated high overall vaccine efficacy (80.2%, 95% confidence interval 73.3-85.3) against virologically confirmed dengue (VCD) and 95.4% efficacy (95% CI 88.4-98.2) against VCD leading to hospitalization. However, efficacy estimates varied by baseline serostatus and infecting dengue virus serotype, as well as by country and age group. Efficacy against serotypes 3 and 4 in baseline seronegative individuals could not be demonstrated.	Modelling indicates that TAK-003 will have the greatest public health impact in settings with high dengue transmission.
	Harms: Are the undesirable anticipated effects small?	No ☐	Uncertain ☐	Yes ☒	Varies ☐	TAK-003 is generally well-tolerated. There were no non-dengue-related safety concerns. While there was no unambiguous signal for enhanced disease in vaccinated subjects, the negative point estimate of the efficacy of TAK-003 against DENV-3 in baseline seronegative subjects, while statistically non-significant, was of concern. The possibility of enhanced disease due to dengue virus serotypes 3 and 4 in seronegative vaccinated individuals cannot be ruled out.	Modelling suggests that even in seronegative persons in relation to DENV3, at a population level, a net benefit is most likely. However, the possibility of enhanced disease due to DENV3 among seronegative persons cannot be ruled out.

	Balance of benefits and harms	Favours intervention ☒	Favours comparison ☐	Favours both ☐	Favours neither ☐	Unclear ☐	The efficacy data and the non-dengue-related severe adverse events favour the intervention. Mathematical models that estimate the balance of benefits and risks of vaccination indicate that in most simulations, the benefits outweigh potential risks. A few simulations indicated a higher risk of hospitalized dengue serotype 3 disease among baseline seronegative subjects.	
		Effectiveness of the intervention						

	What is the overall certainty of this evidence for the critical outcomes?	No included studies ☐	Very low ☐	Low ☐	Moderate ☒	High ☐	The certainty of evidence on the overall efficacy of the vaccine against VCD and dengue leading to hospitalization is high in baseline seropositive children (4-16 y) and in baseline seronegative children against serotypes 1 and 2 (see GRADE tables). The quality of evidence on the efficacy against VCD and hospitalized dengue due to serotypes 3 and 4 among seronegative children (4-16 y) was low (see GRADE tables) The quality of evidence for efficacy in adults (18-60 y) was low. There were no data available for those above 60 years of age (see GRADE tables).	The trial did not have adequate power to draw inferences on efficacy in the stratified analyses and there were too few cases of DENV3 and DENV4 among baseline seronegative subjects to draw valid conclusions about efficacy against VCD caused by these serotypes.
		Safety of the intervention						
		No included studies ☐	Very low ☐	Low ☐	Moderate ☒	High ☐	The quality of the evidence on the non-dengue-related safety concerns was high in all subjects. The certainty of evidence on the risk of enhanced dengue in baseline seronegative children with serotype 3 or 4 infection was low. The risk of enhanced disease due to DENV3 and DENV4 in baseline seronegative persons cannot be ruled out.	

VALUES AND PREFERENCES	How certain is the relative importance of the desirable and undesirable outcomes?	Important uncertainty/ variability ☐	Possible important uncertainty/ variability ☐	Probably no important uncertainty/ variability ☒	No important uncertainty/ variability ☐	No known undesirable outcomes ☐		There is no uncertainty that the desirable outcomes outweigh any undesirable outcomes among baseline seropositive individuals for all serotypes and among baseline seronegative individuals against DENV1 and DENV2. The risk of undesirable effects among vaccinated seronegative individuals when exposed to DENV3 and DENV4 cannot be ruled out.	Modelling indicates that in the first 10 years after vaccination, TAK-003 is predicted to reduce VCD in vaccinated by approx. 30% to 50%, and hospitalisation by 50% to 75%, assuming no effect of vaccine on transmission. Central estimates of impact over 10y in baseline seronegative vaccinated cohort are small but positive, though predicted impacts on disease from primary infection have credible intervals spanning 0
VALUES AND PREFERENCES	**Values and preferences of the target population**: Are the desirable effects large relative to undesirable effects?	No ☐	Probably no ☐	Uncertain ☐	Probably yes ☒	Yes ☐	Varies ☐	Modelling suggests that at a population level, a net benefit is most likely in seronegative persons, even in relation to DENV3, in most of the simulations.	
RESOURCE USE	Are resources required small?	No ☐	Uncertain ☒	Yes ☐	Varies ☐			The price of the vaccine for use in national programmes in low- and middle-income countries is currently not known. However, the programmatic costs for delivery of the vaccine are likely to be similar to that of other vaccines in most settings; programmes may benefit from cost savings due to co-administration with other routine vaccinations like HPV.	

<table>
<tr><td></td><td>Is the intervention cost-effective?</td><td colspan="2">No
☐</td><td colspan="2">Uncertain
☐</td><td colspan="2">Yes
☐</td><td colspan="2">Varies
☒</td><td>The threshold cost for a fully vaccinated person (with 80% vaccination coverage) would be < $30 in most scenarios, which would be cost-effective (assuming cost-effectiveness, if $/DALY averted, is < 10K)</td><td>Cost-effectiveness would depend on the vaccine price and the GDP of the country.</td></tr>
<tr><td>EQUITY</td><td>What would be the impact on health inequities?</td><td colspan="2">Increased
☐</td><td colspan="2">Uncertain
☐</td><td colspan="2">Reduced
☒</td><td colspan="2">Varies
☐</td><td>Assuming that vaccination is targeted to the subnational areas with the highest burden of disease and that the implementation of the targeted strategy is successful, the intervention is likely to reduce health inequities.</td><td></td></tr>
<tr><td>ACCEPTABILITY</td><td>Which option is acceptable to key stakeholders (MOH, Immunization Managers)?</td><td>Intervention
☐</td><td colspan="2">Comparison
☐</td><td colspan="2">Both
☐</td><td colspan="2">Neither
☐</td><td>Uncertain
☒</td><td>Acceptability will depend on a combination of various factors including the burden of dengue in a given country, cost-effectiveness, risk assessment, risk management and communication, demand for vaccine programmatic feasibility and vaccine strategy.</td><td></td></tr>
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	Which option is acceptable to target groups?	Intervention ☐	Comparison ☐	Both ☐	Neither ☐	Uncertain ☒		Given the uncertainty about the possible risk of enhanced disease in certain individuals, it is uncertain what the acceptability among target groups would be. Special studies to assess the acceptability of the vaccine and the behavioural and social determinants of vaccine uptake may be required to address this question in different communities. It is most likely that given the substantial burden of dengue in settings with high dengue transmission, parents would accept a vaccine for their children.	
FEASIBILITY	Is the intervention feasible to implement?	No ☐	Probably no ☐	Uncertain ☐	Probably Yes ☒	Yes ☐	Varies ☐	Administering a vaccine in a 2-dose schedule, 3 months apart is feasible in children 6 years and older provided that pre-screening is not a requirement. The vaccine could potentially be administered at the school level, or in conjunction with the administration of other vaccines such as HPV vaccines.	

BALANCE OF CONSEQUENCES	Undesirable consequences clearly outweigh the desirable consequences in most settings. ☐	Undesirable consequences probably outweigh the desirable consequences in most settings. ☐	The desirable and undesirable consequences are closely balanced or uncertain. ☐	The desirable consequences probably outweigh the undesirable consequences in settings with high dengue transmission. ☒	The desirable consequences clearly outweigh the undesirable consequences in most settings. ☐
TYPE OF RECOMMENDATION	We recommend the intervention. ☐	We suggest considering the recommendation of the intervention. ☐ Only in the context of rigorous research ☒ Only with targeted monitoring and evaluation ☒ Only in specific contexts or specific subpopulations.		We recommend the comparator. ☐	We recommend against the intervention and the comparator. ☐

RECOMMENDATION	**REFER TO THE VACCINE POSITION PAPER FOR THE RECOMMENDATIONS**
IMPLEMENTATION CONSIDERATIONS	**REFER TO THE VACCINE POSITION PAPER FOR THE IMPLEMENTATION CONSIDERATIONS**
MONITORING AND EVALUATION	**REFER TO THE VACCINE POSITION PAPER FOR THE MONITORING AND EVALUATION**

RESEARCH	**REFER TO THE VACCINE POSITION PAPER FOR THE RESEARCH RECOMMENDATIONS**