Deliberations of the Strategic Advisory Group of Experts on Immunization on the use of CYD-TDV dengue vaccine

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The Strategic Advisory Group of Experts (SAGE) on Immunization advises WHO on global policies for vaccines. In April, 2016, SAGE issued recommendations on the use of the first licenced dengue vaccine, CYD-TDV. In November, 2017, a retrospective analysis of clinical trial data, stratifying participants according to their dengue serostatus before the first vaccine dose, showed that although in high seroprevalence settings the vaccine provides overall population benefit, there was an excess risk of severe dengue in seronegative vaccinees. SAGE's working group on dengue vaccines met to discuss the new data and mainly considered two vaccination strategies: vaccination of populations with dengue seroprevalence rates above 80% or screening of individuals before vaccination, and vaccinating only seropositive individuals. We report on the deliberations that informed the recommendation of the pre-vaccination screening strategy, in April, 2018. Important research and implementation questions remain for CYD-TDV, including the development of a highly sensitive and specific rapid diagnostic test to determine serostatus, simplified immunisation schedules, and assessment of the need for booster doses.

Lancet Infect Dis 2019; 19: e31–38

Published Online September 5, 2018 http://dx.doi.org/10.1016/S1473-3099(18)30494-8

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Background

One mandate of WHO is to issue guidance on the use of vaccines against diseases of public health concern. Once a vaccine has been licensed by a WHO-endorsed national regulatory authority, WHO provides a policy position on the use of the product in public health programmes. The Strategic Advisory Group of Experts (SAGE) on Immunization advises WHO on global policies and strategies for vaccines and immunisation, ranging from research and development, to delivery of vaccines, and their linkages with other health interventions. SAGE working groups, composed of independent subject matter experts, propose recommendations for consideration by SAGE with respect to specific vaccines or related issues, using the Grading of Recommendations Assessment, Development and Evaluation process to assess the quality of evidence, and The Developing and Evaluating Communication Strategies to Support Informed Decisions and Practice Based on Evidence framework to document the evidence-based process of developing recommendations.[1] These processes were used to develop SAGE recommendations for the world's first licenced dengue vaccine, CYD-TDV (Dengvaxia), developed by Sanofi Pasteur. Following the licensure of CYD-TDV in December, 2015, in April, 2016 SAGE made recommendations to WHO on the use of this vaccine,[2] which led to the WHO's position paper in July, 2016.[3]

In November, 2017, Sanofi Pasteur released new long-term safety data, following additional analyses; the findings revealed an excess risk of severe dengue in the vaccinated seronegative trial subpopulation.[4] Due to the new evidence on these serious adverse effects, the SAGE working group on dengue vaccines was reconvened in December, 2017 to review the previous recommendations.[5] Here we report on the deliberations of the SAGE working group between December, 2017 and April, 2018 that were reviewed by SAGE in April, 2018, and led to the revised recommendations.[6]

Dengue is the most rapidly spreading mosquito-borne virus disease. It has wide geographical distribution[7,8] and increasingly affects travellers.[9–11] Effective, scalable, and sustainable vector control measures remain elusive,[12] and compliance with personal protective measures is difficult.[13] Hence, there is an urgent need for additional control measures. CYD-TDV is a live attenuated tetravalent dengue vaccine, now licensed on a three-dose schedule in 20 countries in Asia, Latin America, and Australia, typically for use in people aged 9–45 years.[14] The first public vaccination programme with CYD-TDV was launched in the Philippines in April, 2016, with the aim to vaccinate almost 1 million school children in four highly dengue-endemic regions.[14] The first public dengue vaccination programme in the Americas was also launched in 2016, in dengue-endemic parts of Paraná State in Brazil, deploying about 500 000 vaccine doses. Additionally, people living in Brazil, Mexico, El Salvador, the Philippines, Costa Rica, Indonesia, Peru, Paraguay, Guatemala, Thailand, and Singapore can access CYD-TDV through the private market. In other countries (Argentina, Australia, Bolivia, Cambodia, Honduras, Malaysia, Myanmar, and Venezuela), the vaccine has been licensed but not yet launched.[14]

Licensure of the vaccine followed the results from two large placebo-controlled phase 3 trials, involving over 30 000 participants aged 2–16 years, in ten highly dengue-endemic countries, in Asia and Latin America,[15,16] and from a phase 2b trial in Thailand.[17] Post-hoc analyses, pooled across the trials, indicated that vaccine efficacy against symptomatic virologically confirmed dengue was higher in those aged 9–16 years at first vaccination (efficacy=65·6%, 95% CI 60·7 to 69·9) than in those aged 2–8 years (44·6%, 31·6 to 55·0) over the 25-month period after the first dose.[18] In the older age group, over the same follow-up period, vaccination reduced severe dengue by 93·2% (77·3 to 98·0) and dengue

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hospitalisations (ie, dengue requiring admission to hospital) by 80·8% (70·1 to 87·7).[18]

At the time of licensure, an increased risk of hospitalised and severe dengue was noted in the third year after first vaccination, among those aged 2–5 years. This safety signal was not observed in those vaccinated at the age of 6 years or older. Because of the safety signal in those aged 2–5 years, which was not apparent in other age groups, the company sought licensure for the age group of 9 years or older. It was unknown whether the safety signal was attributable to younger age per se, or to the higher prevalence of participants who were dengue-naive (dengue seronegative) in the 2–5 year age group, or a combination of both factors. Pre-vaccination serum samples, to determine baseline dengue serostatus, were obtained from only a sample of trial participants (approximately 4000 children). In this subset, cumulatively over the available observation time of about 4 years, no increased risk of hospitalised dengue was seen among seronegative children aged 9–16 years (1·8% in the vaccine group *vs* 2·0% in the control group), whereas in seronegative children aged 2–8 years, the corresponding rates were 5·2% in the vaccine group and 2·9% in the control group.[19] From year 3 onwards, in those trial participants younger than 9 years, 4·6% of the vaccinated and 1·8% of the controls had hospitalisations due to dengue, whereas in those older than 9 years, there was little difference: 1·9% of vaccinated *vs* 1·5% of control participants. Although the small numbers in the immune subset were insufficient to address conclusively the role of dengue serostatus at vaccination for those older than 9 years, they suggested differential vaccine effects by age.

SAGE recommendations in April, 2016

From 2015 to 2016, WHO convened eight modelling groups to predict the effects of the vaccine in various transmission settings, based on available data. All models assumed that the main determinant of the safety signal in 2–5 year olds was serostatus.[20,21] It was also assumed that the vaccine acts like an asymptomatic dengue infection, without an associated risk of disease. In dengue-seronegative individuals, a first infection with a wild-type dengue virus following vaccination would behave as a secondary-like infection, which would be associated with an increased risk of severe dengue, as seen in natural secondary infections, whereas in seropositive individuals a subsequent natural infection following vaccination would act as a tertiary-like infection, which is associated with a low risk of severe disease.[22,23] In high transmission settings, individuals are expected to experience multiple natural infections, so that unvaccinated seronegative individuals would still probably experience a second natural infection, with associated increased risk of severe dengue. Consequently, the temporary increased risk in seronegative vaccinees would be compensated by a reduced risk of severe dengue at later periods, when compared with unvaccinated seronegative individuals. Thus, in the longer term, in high transmission settings, there would be no net increase in severe dengue in seronegative vaccinees.[21] For a specific level of transmission, there is an optimal age of vaccination that decreases as transmission intensity increases.[24] The modelling results suggested that the public health benefits of vaccination would be greatest if dengue seropositivity in the age group targeted for vaccination was high—ie, in high seroprevalence settings, 70%, by the age of 9 years.[20,21]

SAGE's 2016 recommendations, which limited the use of the vaccine to high seroprevalence settings, balanced the substantial overall reduction in severe dengue through vaccination in those settings against the theoretical enhanced risk of severe disease in a subset of those vaccinated. This risk was not apparent in the empirical safety data, at that time, for the age group for which the vaccine was licensed.[25] The subsequent WHO position on the use of CYD-TDV, in July, 2016, was: "Countries should consider introduction of the dengue vaccine CYD-TDV only in geographic settings where epidemiological data indicate a high burden of disease. Seroprevalence should be approximately 70% or greater in order to maximise public health impact, and the vaccine is not recommended when seroprevalence is below 50% in the age group targeted for vaccination".[26]

When a vaccine is licensed, it is expected that some questions about vaccine safety and efficacy remain, particularly for subpopulations, as well as questions about rare adverse events and duration of protection. Hence, a crucial need for post-licensure studies exists. Regulatory authorities require manufacturers to do such studies under a risk management plan, and countries introducing new vaccines are advised to carefully monitor vaccine performance. WHO's guidance to regulatory authorities, stating that long-term safety assessment should be monitored post-licensure, follows this rationale and practice.[27] Although no safety signal was evident by April, 2016, in the licenced age group (9 years or older), SAGE noted the limited safety data in seronegative individuals in that age group.[2] Since the sample from the vaccine trials was of insufficient size to address the role of pre-vaccination serostatus conclusively for those aged 9 years or older, WHO stressed the importance of obtaining more data on safety in seronegative vaccinees. It was not expected that this issue could be addressed with data from the phase 3 trials because blood samples had not been taken from all trial participants before vaccination. It was anticipated that long-term prospective studies of individuals who were seronegative at the time of vaccination would be required to address the possibility of enhanced risk in these individuals. Therefore, WHO hosted a consultation on how such studies could be done.[28]

Long-term safety data stratified by baseline serostatus

In November, 2017, Sanofi Pasteur announced the results of new analyses to assess the benefit–risk of vaccination in seronegative individuals. These analyses were made possible through the application of a newly developed serological assay, the NS1 IgG ELISA assay,[29] which the company applied to blood samples taken from all trial participants 1 month after the third vaccine dose, and which enabled investigators to infer, retrospectively, the dengue serostatus before receiving the first vaccination. Since CYD-TDV encodes yellow fever vaccine's non-structural proteins, including NS1, which are not found after natural dengue infection, the NS1 antibody ELISA was able to identify individuals exposed to dengue before vaccination with CYD-TDV, with an estimated sensitivity of 95·3% and specificity of 68·6%.[30] Furthermore, imputation methods were employed to infer baseline serostatus.

The new analyses indicated that, overall, the risk of dengue and severe dengue was substantially reduced in those vaccinated, but also highlighted that the vaccine performed differently depending on pre-vaccination serostatus.[30] In brief, vaccine efficacy against virologically confirmed symptomatic dengue was 76% (95% CI 63·9 to 84·0) among inferred baseline seropositive participants aged 9 years or older, in the 2 years following the first vaccine dose, but vaccine efficacy was only 38·8% (–0·9 to 62·9%) among inferred baseline seronegative participants. The long-term follow-up, until 60 months, showed that although the vaccine remained efficacious and safe in seropositive vaccinees, there was an increased risk of severe dengue in seronegative vaccinees from year 3 onwards, after the first dose. Among seronegative participants aged 9–16 years, the cumulative incidence of severe dengue over 5 years was 0·40% among vaccine recipients and 0·17% among controls. The hazard ratio (HR) of severe dengue was 2·44 (0·47 to 12·56) in seronegative vaccinated, compared with seronegative unvaccinated, trial participants.[30] The risk and clinical manifestations of severe dengue in vaccinated seronegative individuals aged 9–16 years were similar to those in unvaccinated seropositive individuals, consistent with the hypothesis that the vaccine acts as an asymptomatic infection. By contrast, there was sustained protection against severe disease in seropositive vaccine recipients throughout the 60 months. The HR of severe dengue was 0·16 (0·07 to 0·37) in seropositive vaccinated, compared with seropositive unvaccinated, trial participants, throughout the 5 years.[30]

Revised SAGE recommendations April, 2018

During the SAGE deliberations in 2016, the possibility of an increased risk of severe dengue in a subset of those in the age group for which the vaccine was licensed was hypothetical, but that risk was not apparent in the clinical trial data available at the time. The new analyses identified an increased risk of severe dengue in seronegative individuals, which necessitated revision of the 2016 SAGE recommendations. SAGE's working group on dengue vaccines met between December, 2017, and April, 2018, to reconsider the benefit–risk assessment for the public health use of CYD-TDV, in light of the new data.[5] Based on the new results from the trials, in a vaccinated group with 70% dengue seroprevalence (the group for which vaccination was recommended by SAGE in 2016), over a 5-year follow-up from the first vaccine dose, for every one excess case of dengue-related hospitalisations in seronegative vaccinees, seven hospitalisation cases were prevented in seropositive vaccinees; and one excess severe dengue case occurred in seronegative vaccinees, compared to four cases prevented in seropositive vaccinees. The benefit–risk ratio is higher in areas with higher seroprevalence. For example, in areas with 80% dengue seroprevalence, for every one excess case of dengue-related hospitalisations in seronegative vaccinees, within a 5-year period, there would be 13 cases prevented in seropositive vaccinees; and for every one excess case of severe dengue in seronegative vaccinees, there would be seven severe cases prevented in seropositive vaccinees. From a population perspective, if 1 million children were vaccinated in settings of 80% seroprevalence, in the vaccinated group about 11 000 dengue-related hospitalisation cases would be averted (12 000 averted in seropositive vaccinees, 1000 excess cases in seronegative vaccinees) within 5 years after vaccination. In the same setting, within the same time period, about 2800 severe dengue cases would be averted (3200 prevented in seropositive vaccinees, 460 excess cases in seronegative vaccinees). Thus, in high transmission settings, the vaccine provides overall population benefit, but excess cases of severe dengue will occur in seronegative individuals.

Considerations with regards to two potential use scenarios

SAGE's working group recognised that although the risk to those dengue seronegative would be avoided if the vaccine was not used at all, not vaccinating at all would deprive those who are seropositive of a vaccine with reasonably high efficacy. In high prevalence settings, this latter group would comprise the majority. After reviewing possible strategies to use the vaccine, the working group primarily considered two possible vaccination strategies.

The first was mass vaccination in areas with documented seroprevalence rates above 80%. The rationale for this strategy is that vaccination based on high seroprevalence criteria would result in a substantially larger prevention of severe and hospitalised dengue cases than the number of excess cases resulting from vaccinating seronegative individuals.

The second strategy considered was pre-vaccination screening. The rationale for this strategy is that screening and vaccinating only those who tested seropositive retains the benefits of vaccinating seropositive individuals, while eliminating, or greatly reducing, the risks to seronegative individuals (depending on the specificity of the screening test).

In the discussion of these two strategies, the working group addressed various questions. What are the ethical considerations to balance population level benefit against individual risk? Which strategy would lead to the highest vaccine uptake? How feasible would be the implementation of serosurvey studies and individual pre-vaccination screening? Which strategy would be more acceptable by communities and ensure continued confidence in dengue vaccine programmes and vaccination in general? And what would be the communication challenges?

Ethical considerations of population benefit vs individual risk

In settings with high seroprevalence, the number of cases of hospitalised and severe dengue prevented in seropositive individuals is substantially greater than the number precipitated in seronegative individuals. Therefore, a trade-off exists between the population benefit conferred by vaccination, and the enhanced risk to the subset of seronegative vaccine recipients. In high transmission settings, the great majority of people have at least two natural dengue infections in their lifetime, and thus experience the enhanced risk of more severe dengue associated with the second natural infection. Therefore, under the assumptions used in the mathematical modelling,[21] in seronegative individuals, vaccination advances the risk period for severe dengue, but it does not increase the lifetime risk of severe dengue, except in transmission settings in which not everyone is likely to experience two natural dengue infections in their lifetime. However, it should be emphasised that these assumptions are based on a model of vaccine action, which cannot be confirmed or refuted by the available trial data. Furthermore, even if the model is correct, advancing (in time) a potentially fatal disease has ethical implications.

The ethical tension between personal and population benefit in vaccination programmes is not new. Vaccines are given to healthy individuals to prevent illness, and so the population's tolerance for vaccine adverse events is very low. Routine vaccines, like all medical products, are associated with some individual risk that is usually extremely low, and greatly outweighed by the benefits to both individuals and communities. The relative magnitude of societal benefits and individual risks is an important consideration when evaluating the acceptability of added risk, together with other key considerations, such as public acceptance. For example, it is known that rotavirus vaccination is associated with a very small risk of inducing intussusception, but this risk is greatly outweighed by the protective effect of the vaccine against severe rotavirus disease.[31] However, an important difference between CYD-TDV and rotavirus vaccines is that, in the latter case, it is not possible to predict which vaccinated children will develop intussusception, but with respect to CYD-TDV, the subgroup (seronegative individuals) at increased risk of severe dengue is technically identifiable. The ethical duty to do no harm might, arguably, require the identification of such individuals and the withholding of vaccination from them.

Testing and vaccinating only seropositive individuals is also not without ethical tensions. This strategy would avoid risk of harm to seronegative individuals and promote population health. However, challenges associated with developing a cost-effective, sensitive, and specific rapid diagnostic test (RDT) might mean that the vaccine cannot be used in large-scale vaccination programmes for several years. Thus, there would be a cost in terms of forgone benefits for seropositive individuals, and population health more generally, in high transmission settings, if vaccination was delayed. Furthermore, unless the test had 100% specificity, some truly seronegative individuals would be incorrectly vaccinated and still be at enhanced risk.

Some ethicists have drawn a distinction between harm resulting from acts, such as that resulting from vaccinating someone (ie, harm to seronegatives vaccinees), and harm resulting from omission, such as that resulting from not vaccinating someone (ie, harm to seropositive individuals by not offering them a vaccine with proven efficacy). The so-called trolleyology analogy, in the accompanying editorial to the publication of the new analyses from the trials, portrays this dilemma.[32] Although the goal to prevent substantial harm that might result from omission sometimes justifies actively causing smaller harms,[33] there is no consensus on how trade-offs should be made between the two kinds of harm (ie, how many cases must be prevented for every case induced). Thus, the choice of the appropriate strategy for the public use of CYD-TDV should also depend on acceptability by communities, what is feasible for vaccination programmes, and cost-effectiveness.

Implementation issues

If the first strategy was to be adopted, a population serosurvey would be done to identify population groups with high enough seroprevalence levels, to ensure substantial public health impact, followed by implementation of mass vaccination in those groups. Given the now proven harm in seronegative individuals, opting for seroprevalence thresholds higher than 70% would be warranted, which makes the seroprevalence criteria hard to implement. For example, opting for seroprevalence thresholds above 80% at age 9 years is associated with several implementation challenges. Dengue transmission maps estimate that not many subnational areas at administrative level 1 (ie, the largest subnational administrative unit of a country) have seroprevalence above 80% at age 9 years, even in high dengue-endemic countries.[34] Even fewer locations have seroprevalence above 90% in 9-year-olds. In the trial regions for phase 3 efficacy studies, selected for their high dengue incidence, the seroprevalence rates for the age group 9–12 years were 75·7% and 76·4%, in Asia and Latin America, respectively.[35] Furthermore, there is evidence of high spatial and temporal heterogeneity of dengue transmission, even in small geographical areas.[36,37] The spatiotemporal heterogeneity of dengue transmission, combined with the need for high seroprevalence thresholds, would necessitate multiple serosurveys to identify suitable areas at microscale, possibly down to district or subdistrict level, thus adding complexity and cost to any public vaccination programme. 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.[38] Lastly, given the limited administrative level 1 areas with seroprevalence rates above 80% at age 9 years, national vaccine coverage rates could be low and, hence, the overall public health impact would be small.

An advantage of a pre-vaccination screening strategy over mass vaccination based on population seroprevalence criteria is that screening could be considered in moderate-transmission settings. Since individuals who have had only one dengue infection would be the target group that would benefit the most from CYD-TDV, the optimal age for vaccine introduction will depend on dengue transmission intensity, and can be informed by country specific data on the age at which dengue-related hospitalisations peak.[14]

Despite the advantages of pre-vaccination screening, major challenges still need to be addressed. Although dengue IgG ELISA assays are readily available in most dengue-endemic countries, they do not provide instant information on an individual's serostatus, which would hamper vaccination campaigns.[39] For large-scale vaccination programmes, screening tests would need to be deliverable at point-of-care as RDTs. However, to date, no RDTs have been validated and licensed for the indication of screening for past dengue infection. Screening tests would need to be highly specific to avoid vaccinating truly seronegative people, and would need to have high sensitivity to ensure that a high proportion of seropositive individuals were vaccinated. However, specificity is unlikely to be 100% due to cross-reactivity with other flaviviruses and flavivirus vaccines.[39] The acceptability of the level of specificity can also differ depending on seroprevalence settings. In lower transmission settings, a test with very high specificity would be required to ensure a low risk of inadvertently vaccinating seronegative individuals. The pre-test probability of an individual being seropositive would be increased in settings with high endemic transmission and, thus, a screening strategy would probably be more cost-effective in such settings. Furthermore, pre-vaccination screening can pose substantial logistic hurdles in large-scale vaccination programmes, including costs (of the test itself and logistics of testing),[40] the need to take a blood sample before vaccination, and community acceptance of the vaccination strategy.

Communication and public confidence in vaccine programmes

A mass vaccination strategy, based on a seroprevalence threshold, could affect public confidence in national vaccination programmes. Communication would have to ensure full disclosure of potential risks and benefits of vaccinating people of unknown serostatus. The inability of vaccinees to know their own serostatus could lead to increased vaccine hesitancy. Since the at-risk sub-population is technically identifiable, public acceptance of a potentially avoidable risk might be low. Although in a mass vaccination programme in areas of high sero-prevalence, most vaccinated individuals might ultimately benefit from the vaccination (according to the mathematical modelling), some cases of severe dengue will occur (either in seropositive individuals since the vaccine is not completely efficacious, or in those seronegatives individuals primed by the vaccine). These cases could potentially damage the reputation of the vaccine programme and have adverse consequences on public acceptance of other vaccines. Local, recent, age-stratified seroprevalence studies would have to be used to guide decision making and introduction at subnational levels. However, introducing mass vaccination programmes in some settings but not others (because not all areas would qualify) would result in complex communication issues to the public.

The communication to the public regarding the rationale for a pre-vaccination screening strategy, including blood taking, would also be complex. The idea that vaccination is only appropriate for those with a past dengue infection might be counterintuitive to the lay public, given their experience with other vaccines, and could also lead to confusion among health-care providers. Furthermore, some truly seronegative individuals will be unintentionally vaccinated if the screening test is less than 100% specific. In addition, although the efficacy against dengue infections in seropositive individuals is high, it is still not complete. Therefore, transparent communication is needed to inform vaccinees that they are still at risk of dengue and should adhere to other disease preventive measures.

Conclusions

The working group concluded that both "mass vaccination based on population seroprevalence criteria"[41] and "pre-vaccination screening"[41] are difficult to implement in vaccination programmes, and neither can achieve high population protection from dengue. The working group summarised the advantages and disadvantages of each strategy (table). It was the combination of implementation issues, vaccine coverage achievement, and ethical and communication considerations that led the working group to clearly favour the pre-vaccination screening

	Population seroprevalence criteria without screening	Pre-vaccination screening
Benefits and harm	Overall substantial population benefit in areas with predicted high transmission. An identifiable subset of the population will be put at increased risk of severe dengue, at least in the short to medium term.	Maximising the benefit (high efficacy and good safety) in seropositive individuals, while avoiding harm in correctly identified seronegative individuals. Some seronegative individuals will be put at increased risk of severe dengue if vaccinated, due to a false positive screening test result.
Proportion of vaccinated population that will be put at increased risk of severe dengue	Dependant on seroprevalence criteria chosen: if vaccine is introduced in a setting with 80% seroprevalence, 20% of the vaccinated population will be put at risk.	Dependant on the specificity of the screening test. The requirements for specificity depend on background seroprevalence. In a setting with lower seroprevalence, the test specificity will need to be higher; in a setting with a higher seroprevalence, a test with lower specificity might be acceptable—eg, in a setting with 80% seroprevalence and a test with 80% specificity, 20% of true seronegatives will be unintentionally vaccinated. That is, 4% of the total population would be unintentionally vaccinated. In a setting with 80% seroprevalence and a test with 98% specificity, 0·4% of the population would be unintentionally vaccinated. However, the aim is to develop a test with a high specificity, to minimise harm to seronegative individuals.
Population eligible for vaccination	Subnational areas with seroprevalence >80% in 9-year-olds are predicted, by modelling, to be rare; those with seroprevalence >90% by age 9 years, very rare.	Coverage will be higher on a population basis compared with the seroprevalence criteria strategy, since all seropositive people in the population are eligible. Strategy can be used in both high and moderate transmission settings, although pre-vaccination probability of seropositivity will be higher in high transmission settings.
Negative consequences	Loss in vaccine confidence (dengue vaccines and possibly other vaccines). Inability of vaccinees to know own serostatus might lead to increased vaccine hesitancy.	Risk of false positive test in truly seronegative individuals, resulting in vaccination of these individuals.
Challenges for implementation	Dengue transmission exhibits a high spatiotemporal heterogeneity. To identify subnational areas with seroprevalence above 80% by age 9 years, multiple small-scale, age stratified, seroprevalence studies need to be done. Limitations of available tests require additional validation work to estimate seroprevalence. Providing appropriate information to those eligible for vaccination of the potential risks and benefits will be more challenging than for other vaccines.	Pre-vaccination blood sampling could lead to decreased acceptance of the vaccination programme. No rapid diagnostic test has been validated or licensed for the indication of screening for past dengue infection. Tests with high sensitivity are needed to ensure that a large proportion of seropositive individuals will benefit from CYD-TDV.
Age	Seroprevalence threshold in target age group increases for higher target ages. So, whereas 80% seroprevalence is required for a target age of 9 years, a threshold of 90% or more is required if 16-year-olds are targeted.	Seropositive individuals of any age, as indicated in the label, can be targeted. Since seropositive individuals are the target group that would benefit most from CYD-TDV, the optimal age for vaccine introduction will depend on dengue transmission intensity, and can be informed by the age at which dengue hospitalisations due to severe dengue peak.
Cost-effectiveness	Cost-effectiveness studies not done for scenarios of >80% seroprevalence. Cost-effectiveness studies were done in 2016 for a seroprevalence threshold of 70%.[21] Cost-effectiveness studies need to consider the costs required to conduct population serosurveys to identify subnational areas with seroprevalence above 80%.	No cost-effectiveness studies have been conducted to date. Cost-effectiveness studies need to consider costs associated with identifying seropositives.

***Table*: Comparison population seroprevalence criteria *vs* individual pre-vaccination screening strategies**

strategy over the seroprevalence threshold mass vaccination strategy. The proposed recommendations from the working group on the public health use of CYD-TDV were presented to, and adopted by SAGE on April 18, 2018, as follows: for countries considering CYD-TDV vaccination as part of their dengue control programme, a pre-vaccination screening strategy, in which only dengue-seropositive persons are vaccinated, is the preferred strategy. 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.[41]

Important research and implementation questions remain for CYD-TDV, in particular the urgent development of validated, sensitive, and specific RDTs to determine serostatus; simplified immunisation schedules; and assessment of the need for a booster dose. Furthermore, locally applicable cost-effectiveness studies are essential to underpin policy decisions to introduce the vaccine. These studies would need to consider the local epidemiology, hospitalisation rates due to dengue and associated health-care costs, the cost of the vaccine, and the cost of pre-vaccination screening (programmatic issues and the costs of the RDTs). Lastly, implementation strategies need to be tested to evaluate how best to roll-out nationally acceptable test-and-vaccinate approaches.

On the basis of the SAGE recommendations, WHO is developing a revised dengue vaccine position paper that will be released in WHO's *Weekly Epidemiological Record*, on Sept 7, 2018. This recommendation will be specific to CYD-TDV, and will be revised when more dengue vaccines,[42,43] currently in late stage clinical development, become available.

Many lessons can be learned from the CYD-TDV experience, including the need for assays that can differentiate between type-specific immune response to dengue viruses and cross-reactive responses to determine whether the vaccine is likely to offer protection against all four dengue virus serotypes.[44]

Immune correlates for both risk and protection are urgently needed.[45] Given the strong evidence for the major impact of serostatus on the performance of CYD-TDV, WHO guidance specifies that for trials of new dengue vaccines, not only should there be long-term follow-up for those vaccinated, but pre-vaccination blood samples should also be taken from all trial participants, and analysis plans should include stratification of results by serostatus.[46]

A dengue vaccine remains a public health priority, and all efforts should be taken to ensure the best use of the currently available dengue vaccine, and development of second-generation vaccines.

Contributors

TMN and JF are the co-chairs of the SAGE working group on dengue vaccines. JH and AW-S led WHO's secretarial support during 2017–18. JH and KV led WHO's secretarial support to the SAGE working group during 2015–16. AC is the chair of SAGE. TMN and KO'B are members of SAGE. AB, EF, KO'B, SF, MG, HMN, L-CN, PGS, and PT are members of the SAGE working group. I-KY is an ad-hoc expert invited to the SAGE working group. MS articulated the ethical considerations, NF made major contributions to modelling the new data and dengue transmission maps. AW-S wrote the first manuscript draft, and all authors contributed to the final version.

Declaration of interests

SAGE working group members and their conflict of interest declarations are listed in: http://www.who.int/immunization/policy/sage/sage_wg_dengue_reconvened_dec2017/en/. AB, AC, AW-S, EF, KO'B, SF, JH, MG, HMN, NF, MS, L-CN, KV, TMN, JF, and PT declared no conflict of interest related to dengue vaccines. PGS is a member of the independent data monitoring committee for trials of the Sanofi Pasteur dengue vaccine. I-KY's institution received unrestricted grants from Sanofi Pasteur related to dengue vaccines.

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