Deliberations of the SAGE working group on the use of CYD-tetravalent dengue vaccine: revised recommendations April 2018

Wilder-Smith A[1], Hombach J[1], Ferguson N[2], Selgelid M[3], O`Brien K[4], Vannice K[1], Barrett A[5], Ferdinand E[6], Flasche S[7], Guzman M[8], Novaes HM[9], Ng LC[10], Smith PG[7], Tharmaphornpilas P[11], Yoon IK[12], Cravioto A[13], Farrar J[14], Nolan TM[15]

*Annelies Wilder-Smith MD, Professor. Initiative for Vaccine Research, World Health Organization, Geneva, Switzerland

Joachim Hombach PhD, Initiative for Vaccine Research, World Health Organization, Geneva, Switzerland

Neil Ferguson PhD, Professor, Department of Infectious Disease Epidemiology, Imperial College, London, United Kingdom.

Michael Selgelid PhD, Professor, Monash Bioethics Centre, World Health Organization Collaborating Centre for Bioethics, Monash University, Melbourne, Australia

Kate O`Brien MD, Professor, International Vaccine Access Center, Johns Hopkins Bloomberg School of Public Health, Baltimore, United States

Kirsten Vannice PhD, Initiative for Vaccine Research, World Health Organization, Geneva, Switzerland

Alan Barrett PhD, University of Texas Medical Branch, Galveston, Texas, United States

Elizabeth Ferdinand MD, Faculty of Medical Sciences, University of the West Indies, Bridgetown, Barbados

Stefan Flasche PhD, Associate Professor, Department of Infectious Diseases Epidemiology, London School of Hygiene & Tropical Medicine, London, United Kingdom

Maria Guzman PhD, Professor, Pedro Kouri Tropical Medicine Institute, Havannah, Cuba

Hillegonde Maria Novaes MD, Professor, Faculty of Medical Sciences, Universidade de São Paulo, Brazil

Lee-Ching Ng PhD, Environmental Health Institute National Environmental Agency, Singapore, Singapore

Peter G Smith DSc, Professor, MRC Tropical Epidemiology Group, London School of Hygiene & Tropical Medicine, London, United Kingdom

Piyanit Tharmaphornpilas MD, Ministry of Public Health, Bangkok, Thailand

In-Kyu Yoon MD, International Vaccine Institute, Seoul, South Korea

Alejandro Cravioto MD, Professor, Facultad de Medicina, Universidad Nacional Autónoma de México, Ciudad de México, Mexico

Jeremy Farrar MD, Wellcome Trust, London, United Kingdom

Terry M Nolan MD, Professor, School of Population and Global Health, University of Melbourne, Melbourne, Australia

*Corresponding author: Professor Annelies Wilder-Smith MD. Initiative for Vaccine Research, World Health Organization, Geneva, Switzerland.
Email: wildersmitha@who.int or anneliesws@gmail.com

Abstract:

The Strategic Advisory Group of Experts on Immunization (SAGE) advises WHO on global policies for vaccines. In April 2016, SAGE issued recommendations on the use of the first licensed dengue vaccine, CYD-TDV (Dengvaxia®). In November 2017, data from a retrospective analysis of clinical trial data, stratifying participants according to their dengue serostatus before the first vaccine dose, revealed that, although in high seroprevalence settings the vaccine provides overall population benefit, there was an excess risk of severe dengue in seronegative vaccine recipients. The SAGE working group on dengue vaccines was re-convened to consider the new data. In their deliberations, two vaccination strategies were mainly considered. The first was to use the vaccine only in populations with high dengue seroprevalence rates, above 80%, and the second was to screen individuals prior to vaccination and to vaccinate only those with serological evidence of previous dengue infection. Issues considered included: the feasibility of population seroprevalence studies and of individual pre-vaccination serological screening; the numbers of people who would be eligible for vaccination under these scenarios; possible effects on public confidence in vaccination programmes; ethical concerns; and communication challenges. Here we report on these deliberations that informed the revised SAGE recommendations in April 2018, that for countries considering CYD-TDV vaccination as part of their dengue control programme, a pre-vaccination screening strategy was preferred, such that only dengue-seropositive persons should be vaccinated. SAGE highlighted that important research and implementation questions remain for CYD-TDV, including the development of a highly sensitive and specific rapid diagnostic test to determine dengue-seropositivity, simplified immunization schedules, and assessment of the need for booster doses.

A mandate of the World Health Organization (WHO) is to issue guidance on the use of vaccines against diseases of public health concern. Once a vaccine has been licensed by a functional national regulatory authority (NRA), WHO provides a policy position on the use of the product in public health programmes. The Strategic Advisory Group of Experts on Immunization (SAGE) advises WHO on global policies and strategies for vaccines and immunization, ranging from research and development to delivery of vaccines and their linkages with other health interventions. SAGE working groups (WGs), composed of independent subject matter experts with geographic diversity, propose recommendations for consideration by SAGE with respect to specific vaccines or related issues, using the GRADE process to assess the quality of evidence and the DECIDE framework to document the evidence-based process of developing recommendations.[1] These were used to develop SAGE recommendations for the world`s first licensed 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 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 sub-population.[4] The SAGE WG on dengue vaccines was re-convened in December 2017[5] to review the previous SAGE recommendations in light of the new evidence of these serious adverse effects. Here we report on the deliberations of the SAGE WG between December 2017 and April 2018 that were reviewed by SAGE in April 2018 and led to the revised recommendations.[6]

Background:

Dengue is the most rapidly spreading mosquito-borne virus disease with wide geographic distribution[7,8], also increasingly affecting travellers.[9,10,11] Effective scalable and sustainable vector control measures remain elusive[12], and compliance with personal protective measures is difficult.[13] Hence additional control measures are urgently needed. CYD-TDV is a live attenuated tetravalent dengue vaccine, now licensed on a 3-dose schedule in 20 countries in Asia, Latin America and Australia, typically for use in persons 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. In addition, 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 the other countries, the vaccine has been licensed, but not yet been launched (Argentina, Australia, Bolivia, Cambodia, Honduras, Malaysia, Myanmar,

Venezuela).[14]

Licensure of the vaccine followed the results from two large placebo-controlled Phase 3 trials involving over 30,000 participants aged 2 to 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 (VE) against symptomatic virologically confirmed dengue (VCD), over the 25-month period from the first dose, was higher in those aged 9-16 years at first vaccination (VE = 65.6%, 95% CI, 60.7 to 69.9) than in those aged 2-8 years (VE = 44.6%, 95% CI, 31.6 to 55.0).[18]   In the older age group, over the same follow-up period, vaccination reduced severe dengue by 93.2% (95% CI, 77.3 to 98.0) and dengue hospitalizations by 80.8% (95% CI, 70.1 to 87.7).[18]

At the time of licensure, an increased risk of hospitalized 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 age 6 years and above. 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 and above. It was unknown whether the safety signal in the 2-5 year age group, but not the older children, might be attributable to younger age *per se* or to the higher prevalence of participants who were dengue-naïve (dengue seronegative) in this age group, or a combination of both. 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 hospitalized dengue was seen among seronegative children aged 9-16 years (1.8% in the vaccine group versus 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 aged <9 years, 4.6% of the vaccinated and 1.8% of the controls had hospitalizations due to dengue, whilst in those aged ≥9 years, there was little difference: 1.9% of those vaccinated and 1.5% control had hospitalizations due to dengue. While 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:

During 2015 to 2016, WHO convened 8 modelling groups to model the effects of the vaccine in various transmission settings based on data then available. 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 naturally.[22,23] In high transmission settings, seronegative individuals would experience multiple natural infections, such that even if CYD-TDV did prime those seronegative for a "secondary-like" infection associated with more severe disease, unvaccinated seronegative individuals would very likely 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 time periods when compared to 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, i.e. 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 such settings against the theoretical enhanced risk of severe disease in a subset of those vaccinated, which was not apparent in the empiric 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 formulated as: "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 maximize 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, particularly for subpopulations, and rare adverse events as well as duration of protection, remain. Hence, the critical need for post-licensure studies. Regulatory authorities require manufacturers to conduct 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 licensed age group of 9 years and above, SAGE noted the limited safety data in seronegative individuals in that age group.[2] As the sample from the vaccine

trials was of insufficient size to conclusively address the role of pre-vaccination serostatus 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 prior to vaccination. It was anticipated that long-term prospective studies would be required, of individuals who were seronegative at the time of vaccination, to address the possibility of enhanced risk in seronegative vaccinees, and 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 one month after the third vaccine dose and which enabled dengue serostatus prior to receiving the first vaccination to be inferred retrospectively. As CYD-TDV encodes yellow fever vaccine non-structural proteins, including NS1, not found after natural dengue infection, the NS1 antibody ELISA was able to distinguish previous dengue exposure from non-exposure before vaccination with CYD-TDV, with sensitivity estimated to be 95.3% and specificity 68.6%.[30] Using these results, 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, VE against virologically confirmed symptomatic dengue in the two years following the first vaccine dose among inferred baseline seropositive participants ≥9 years of age was 76% (95% CI: 63.9, to 84.0), but only 38.8% (95% CI: –0.9 to 62.9%) among inferred baseline seronegative participants. The long-term follow-up, to 60 months, showed that while 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 to 16 years, the cumulative incidence of severe dengue over 5 years was 0.40% among vaccine recipients and 0.17% among controls, a hazard ratio of 2.44 (95% CI: 0.47 to 12.56).[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 above-mentioned hypothesis that the vaccine acts as an asymptomatic infection. In contrast, there was sustained protection against severe disease in seropositive vaccine recipients throughout the 60 months. The hazard ratio of severe dengue

was 0.16 (95% CI: 0.07-0.37) in seropositive vaccinated compared to 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 a theoretical possibility, but such a 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 in the age range for which the vaccine was licenced, which necessitated revision of the 2016 SAGE recommendations. The SAGE WG on dengue vaccines was reconvened in December 2017, 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 1 excess case of hospitalized dengue in seronegative vaccinees there would be about 7 hospitalized cases prevented in seropositive vaccinees, and 1 excess severe dengue in seronegative vaccinees compared to about 4 severe 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 1 excess case within a 5- year period of hospitalized dengue in seronegative vaccinees there would be about 13 cases prevented in seropositive vaccinees, and for every 1 excess case of severe dengue in seronegative vaccinees there would be about 7 severe cases prevented in seropositive vaccinees. From a population perspective, if 1,000,000 children were vaccinated in settings of 80% seroprevalence in the vaccinated group, about 11,000 hospitalized dengue cases would be averted (12,000 averted in seropositive vaccinees, 1,000 excess cases in seronegative vaccinees) within 5 years after vaccination: about 2,800 severe dengue cases would be averted (3,200 averted in seropositive vaccinees, 460 excess cases in seronegative vaccinees) within 5 years after vaccination. 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

The SAGE WG recognized that although the risk to those dengue seronegative would be avoided if the vaccine was not used at all, this 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 WG primarily considered two possible vaccination strategies.

<u>Strategy 1:</u> *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 number of severe and hospitalized dengue cases prevented in vaccinated seropositive individuals than the number of excess cases as a result of vaccinating seronegative individuals.

<u>Strategy 2</u>: *Pre-vaccination screening*. The rationale for this strategy is that screening and vaccinating only those tested seropositive retains the benefits of vaccination 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 WG 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 versus 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. A trade-off exists, therefore, 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. Thus, under the assumptions used in the mathematical modelling[21], in seronegative individuals, vaccination brings forward the risk period for severe dengue but does not increase the lifetime risk of severe dengue except in transmission settings where not everyone is likely to experience two natural dengue infections in their lifetime. However, it should be emphasised that this is 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, bringing forward 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 thus the 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 effective effect of the vaccine against severe rotavirus disease.[31] However, an important difference between CYD-TDV and rotavirus vaccines is that in the case of the latter it is not possible to predict which vaccinated children will develop intussusception, but with respect to CYD-TDV, the subgroup at increased risk of severe dengue, namely the seronegative individuals, are technically identifiable. The ethical duty to "do no harm" might, arguably, thus require identifying such individuals and withholding 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 test may 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 might be incorrectly vaccinated, and still be placed at enhanced risk

Some ethicists have drawn a distinction between harms resulting from acts, such as the harms resulting from vaccinating someone (i.e. the harms to seronegatives vaccinees), and those resulting from omission, such as the harms resulting from not vaccinating someone (i.e. the harms to those seropositive by not offering a vaccine with proven efficacy). The "trolleyology" analogy, in the accompanying editorial to the publication of the new analyses from the trials, aptly portrays this dilemma.[32] Though the goal to prevent significant 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 (i.e. how many cases must be prevented for every case induced). Thus, the choice of the appropriate strategy for the public health use of CYD-TDV should also depend on acceptability to communities, what is feasible for vaccination programmes, and cost-effectiveness.

Implementation issues
If strategy 1 were to be adopted, first a population serosurvey would be undertaken to identify population groups among whom seroprevalence levels are high enough 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 harder to implement. For example, opting for seroprevalence thresholds above 80% at the age of 9 years is associated with several implementation challenges. Dengue transmission maps estimate that not many subnational areas at administrative level 1, even in high dengue endemic countries, have areas with seroprevalence above 80% at age 9 years.[34] Very few locations have seroprevalence > 80% in 9 year olds, and even fewer have locations with seroprevalence >90% in 9 year olds. In the trial sites for Phase 3 efficacy studies, selected for their high dengue incidence, the seroprevalence rates for the age group 9-12 years were 75.7% in the Asian trial and 76.4% in the Latin American trial.[35] Furthermore, there is evidence of high spatial and temporal heterogeneity of dengue transmission, even in small geographic 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 micro scale, possibly down to district or sub-district 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 the age of 9 years, national vaccine coverage rates could be low and hence the overall public health impact would be relatively small.

An advantage of pre-vaccination screening strategy over mass vaccination based on population seroprevalence criteria is that screening may be considered in moderate transmission settings. As individuals who have had only one dengue infection would be the target group that will benefit 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 hospitalizations attributed to dengue peak.[14]

Despite the advantages of pre-vaccination screening, major challenges still need to be addressed. Although dengue IgG ELISA 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 rapid diagnostic tests (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 persons and would need to have high sensitivity to ensure that a high proportion of seropositive persons are 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 may also differ dependent upon seroprevalence settings. Using a screening test with 80% specificity for a pre-vaccination screening strategy, 4% of the population in a seroprevalence setting of 80% would incorrectly be classified as seropositive and be at a potential increased risk of severe disease. Using a screening test with 98% specificity would result in 0.4% of the population at such risk. In lower transmission settings, a test with very high specificity would be required to ensure that the risk of inadvertently vaccinating seronegative individuals was low. 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 be more cost-effective in such settings. Furthermore, pre-vaccination screening may pose significant logistic hurdles in large-scale vaccination programmes, including costs (of the test per se and logistics of testing)[40], the need to take a blood sample prior to vaccination, and community acceptance of such a vaccination strategy.

Communication and public confidence in vaccine programmes

A mass vaccination strategy, based on a seroprevalence threshold, may affect public confidence in national vaccination programmes. Communication would have to ensure full disclosure of potential risks and benefits of vaccinating persons of unknown serostatus. The inability of vaccinees to know their own serostatus may lead to increased vaccine hesitancy. As the at-risk subpopulation is technically identifiable, public acceptance of a potentially avoidable risk may be low. Although in a mass vaccination programme in areas of high seroprevalence, most vaccinated individuals may ultimately benefit from the vaccination based on the mathematical modelling, nevertheless, some cases of severe dengue will occur (either in seropositive individuals as the vaccine is not completely efficacious, or in those seronegatives primed by the vaccine) thus potentially damaging the reputation of the vaccine programme, which may also 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; and 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.

With a pre-vaccination screening strategy, the communication to the public regarding the rationale for pre-vaccination screening, including blood taking, would also be complex. That vaccination is only appropriate for those with a past dengue infection may be counterintuitive to the lay public, given their experience with other vaccines, and could also lead to confusion amongst 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 and SAGE recommendations April 2018

The WG concluded that both "mass vaccination based on population seroprevalence criteria" and "pre-vaccination screening" are difficult to implement in vaccination programmes and neither may achieve high population protection from dengue. The WG summarized the advantages and disadvantages of each strategy (Table 1). It was the combination of implementation issues, vaccine coverage achieved, ethical and communication considerations that led the WG to clearly favour the pre-vaccination screening strategy over the seroprevalence threshold mass vaccination strategy. The proposed recommendations from the WG on the public health use of CYD-TDV were presented to, and adopted by, SAGE on 18 April 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 immunization 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. Cost-effectiveness studies would need to consider the local epidemiology, hospitalization 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 per se). Lastly, implementation strategies need to be tested to evaluate how best to roll out nationally acceptable "test and vaccinate" approaches.

Based on the SAGE recommendations, WHO is developing a revised dengue vaccine position paper that will be released in the Weekly Epidemiological Record on 7 September 2018. This recommendation will be specific to CYD-TDV, and will be revised when further 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 versus cross-

reactive responses to determine whether the vaccine is likely to offer protection against all 4 dengue viruses.[44] Immune correlates for both risk and protection are urgently needed.[45] Given the now 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 those vaccinated, but blood samples should be taken from all trial participants prior to vaccination, 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 dengue vaccines.

Table 1. Comparison of the two strategies: population seroprevalence criteria versus individual pre-vaccination screening

	Population Seroprevalence Criteria without Screening	Pre-Vaccination Screening
Benefits and harm	Overall substantial population benefit in areas with high transmission predicted.	Maximizing the benefit (high efficacy and good safety) in seropositive individuals while avoiding harm in correctly identified those seronegative.
	An identifiable subset of the population will be put at increased risk of severe dengue, at least in the short to medium term.	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	Dependent on seroprevalence criteria chosen: if vaccine is introduced in a setting with 80% seroprevalence, 20% of the vaccinated population will be put at risk.	Dependent on the specificity of the screening test. 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. The requirements for specificity depends 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 may be acceptable. However, the aim is to develop a test with a high specificity to minimize 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 the age of 9 years very rare.	Coverage will be higher on a population basis compared to the seroprevalence criteria strategy, as all seropositive persons in the population are eligible. Strategy can be used in both high and moderate transmission settings, although pre-test 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 may lead to increased vaccine hesitancy.	Risk of false positive test in truly seronegative individuals resulting in vaccination of truly seronegative 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 conducted. 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 may lead to decreased acceptance of the vaccination programme No RDT 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	Seropositive individuals of any age as indicated

	Population Seroprevalence Criteria without Screening	Pre-Vaccination Screening
	increases for higher target ages. So, while 80% seroprevalence required for a target age of 9 years, a seroprevalence threshold of 90% or more is required if 16-year olds are targeted.	in the label can be targeted. As monotypic seropositive individuals would be the target group that will 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 peaks.
Cost effectiveness	Cost effectiveness studies not done for scenarios of >80% seroprevalence. Cost effectiveness studies done in 2016 for seroprevalence threshold at 70% can be found in[21] Cost-effectiveness studies need to consider the costs required to conduct population serosurveys to identify sub-national areas with seroprevalence above 80%.	No cost-effectiveness studies have been conducted to date. Cost-effectiveness studies need to take into account costs associated with identifying seropositives.

Author contributions:

TN and JF are the co-chairs of the SAGE working group on dengue vaccines. JH and AWS led the WHO secretarial support during 2017-2018; JH and KV led the WHO Secretarial support to the SAGE working group during 2015-2016. AC is the chair of SAGE. AB, EF, KOB, SF, MG, MN, LCN, PGS, TP, IKY are members of the SAGE working group.
MS articulated the ethical considerations, NF made major contributions to modelling the new data and dengue transmission maps. AWS wrote the first draft, and all authors contributed to the final manuscript.

Conflict of interest declarations:

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, AWS, EF, KOB, SF, JH, MG, MN, NMF, MS, LCN, and TP 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. IKY`s institution received unrestricted grants from Sanofi Pasteur related to dengue vaccines.

References:

1. Duclos P, Durrheim DN, Reingold AL, Bhutta ZA, Vannice K, Rees H. Developing evidence-based immunization recommendations and GRADE. *Vaccine.* 2012;31(1):12-19.
2. Meeting of the Strategic Advisory Group of Experts on immunization, April 2016 - conclusions and recommendations. *Wkly Epidemiol Rec.* 2016;91(21):266-284.
3. http://www.who.int/wer/2016/wer9130.pdf?ua=1. *WHO position paper on dengue vaccines July 2016.*
4. http://mediaroom.sanofi.com/sanofi-updates-information-on-dengue-vaccine/. *Media Release Sanofi Pasteur 29 November 2017.*
5.
   http://www.who.int/immunization/policy/sage/sage_wg_dengue _reconvened_dec2017/en/). *Re-convened SAGE working group on dengue vaccines.* 2017.
6. *SAGE meeting report April 2018.* Geneva: World Health Organization.
7. Bhatt S, Gething PW, Brady OJ, et al. The global distribution and burden of dengue. *Nature.* 2013;496(7446):504-507.
8. Jentes ES, Lash RR, Johansson MA, et al. Evidence-based risk assessment and communication: a new global dengue-risk map for travellers and clinicians. *J Travel Med.* 2016;23(6).
9. Riddell A, Babiker ZO. Imported dengue fever in East London: a 6-year retrospective observational study. *J Travel Med.* 2017;24(3).
10. Ferguson RW, Henderson SJ, Lee EA, Jung P. Dengue in Peace Corps Volunteers, 2000-14. *J Travel Med.* 2016;23(3).
11. Neuberger A, Turgeman A, Lustig Y, Schwartz E. Dengue fever among Israeli expatriates in Delhi, 2015: implications for dengue incidence in Delhi, India. *J Travel Med.* 2016;23(3).
12. Wilder-Smith A, Gubler DJ, Weaver SC, Monath TP, Heymann DL, Scott TW. Epidemic arboviral diseases: priorities for research and public health. *Lancet Infect Dis.* 2016.

13.   Lalani T, Yun H, Tribble D, et al. A comparison of compliance rates with anti-vectorial protective measures during travel to regions with dengue or chikungunya activity, and regions endemic for Plasmodium falciparum malaria. *J Travel Med.* 2016;23(5).

14.   http://cdrwww.who.int/immunization/sage/meetings/2018/april/2_DengueBackgrPaper_SAGE_Apr2018.pdf. *Background paper on dengue vaccines.* 2018.

15.   Capeding MR, Tran NH, Hadinegoro SR, et al. Clinical efficacy and safety of a novel tetravalent dengue vaccine in healthy children in Asia: a phase 3, randomised, observer-masked, placebo-controlled trial. *Lancet.* 2014;384(9951):1358-1365.

16.   Villar L, Dayan GH, Arredondo-Garcia JL, et al. Efficacy of a tetravalent dengue vaccine in children in Latin America. *N Engl J Med.* 2015;372(2):113-123.

17.   Sabchareon A, Wallace D, Sirivichayakul C, et al. Protective efficacy of the recombinant, live-attenuated, CYD tetravalent dengue vaccine in Thai schoolchildren: a randomised, controlled phase 2b trial. *Lancet.* 2012;380(9853):1559-1567.

18.   Hadinegoro SR, Arredondo-Garcia JL, Capeding MR, et al. Efficacy and Long-Term Safety of a Dengue Vaccine in Regions of Endemic Disease. *N Engl J Med.* 2015;373(13):1195-1206.

19.   http://www.who.int/immunization/sage/meetings/2016/april/1_Background_Paper_Dengue_Vaccines_2016_03_17.pdf. *Background paper on the use CYD-TDV.* 2016.

20.   Ferguson NM, Rodriguez-Barraquer I, Dorigatti I, Mier YT-RL, Laydon DJ, Cummings DA. Benefits and risks of the Sanofi-Pasteur dengue vaccine: Modeling optimal deployment. *Science.* 2016;353(6303):1033-1036.

21.   Flasche S, Jit M, Rodriguez-Barraquer I, et al. The Long-Term Safety, Public Health Impact, and Cost-Effectiveness of Routine Vaccination with a Recombinant, Live-Attenuated Dengue Vaccine (Dengvaxia): A Model Comparison Study. *PLoS Med.* 2016;13(11):e1002181.

22.   Katzelnick LC, Gresh L, Halloran ME, et al. Antibody-dependent enhancement of severe dengue disease in humans. *Science.* 2017;358(6365):929-932.

23.   Alvarez M, Rodriguez-Roche R, Bernardo L, et al. Dengue hemorrhagic Fever caused by sequential dengue 1-3 virus infections over a long time interval: Havana epidemic, 2001-2002. *Am J Trop Med Hyg.* 2006;75(6):1113-1117.

24.   Imai N, Dorigatti I, Cauchemez S, Ferguson NM. Estimating dengue transmission intensity from sero-prevalence surveys in multiple countries. *PLoS Negl Trop Dis.* 2015;9(4):e0003719.

25.   Wilder-Smith A, Vannice KS, Hombach J, Farrar J, Nolan T. Population Perspectives and World Health Organization Recommendations for CYD-TDV Dengue Vaccine. *J Infect Dis.* 2016;214(12):1796-1799.

26.   Dengue vaccine: WHO position paper - July 2016. *Wkly Epidemiol Rec.* 2016;91(30):349-364.

27.   http://www.who.int/biologicals/areas/vaccines/TRS_979_Annex_2.pdf?ua=1.

28.   Wichmann O, Vannice K, Asturias EJ, et al. Live-attenuated tetravalent dengue vaccines: The needs and challenges of post-licensure evaluation of vaccine safety and effectiveness. *Vaccine.* 2017;35(42):5535-5542.

29.   Nascimento EJM, Huleatt JW, Cordeiro MT, et al. Development of antibody biomarkers of long term and recent dengue virus infections. *J Virol Methods.* 2018;257:62-68.

30.   Sridhar S, Luedtke A, Langevin E, et al. Effect of Dengue Serostatus on Dengue Vaccine Safety and Efficacy. *N Engl J Med.* 2018.

31.   Glass RI, Parashar UD. The promise of new rotavirus vaccines. *N Engl J Med.* 2006;354(1):75-77.

32.   Rosenbaum L. Trolleyology and the Dengue Vaccine Dilemma. *N Engl J Med.* 2018.

33.   Selgelid MJ. A Moderate Pluralist Approach to Public Health Policy and Ethics. *Public health ethics.* 2009;2(2):195-205.

34.   https://mrcdata.dide.ic.ac.uk/_dengue/dengue.php. Dengue transmission maps.

35.   L'Azou M, Moureau A, Sarti E, et al. Symptomatic Dengue in Children in 10 Asian and Latin American Countries. *N Engl J Med.* 2016;374(12):1155-1166.

36.   Imai N, Dorigatti I, Cauchemez S, Ferguson NM. Estimating Dengue Transmission Intensity from Case-Notification Data from Multiple Countries. *PLoS Negl Trop Dis.* 2016;10(7):e0004833.

37.   Vongpunsawad S, Intharasongkroh D, Thongmee T, Poovorawan Y. Seroprevalence of antibodies to dengue and chikungunya viruses in Thailand. *PLoS One.* 2017;12(6):e0180560.

38.   http://www.who.int/immunization/research/development/Dengue_Serosurveys_020617.pdf. WHO guidelines on dengue serosurveys.

39.   Arien KK, Wilder-Smith A. Dengue vaccine: reliably determining previous exposure. *The Lancet Global health.* 2018.

40.   Turner HC, Wills BA, Rahman M, et al. Projected costs associated with school-based screening to inform deployment of Dengvaxia: Vietnam as a case study. *Trans R Soc Trop Med Hyg.* 2018.

41.   http://www.who.int/immunization/sage/meetings/2018/april/sage_meeting_summary_apr2018.pdf?ua=1. *SAGE meeting report April 2018.*

42.   Osorio JE, Partidos CD, Wallace D, Stinchcomb DT. Development of a recombinant, chimeric tetravalent dengue vaccine candidate. *Vaccine.* 2015;33(50):7112-7120.

43.   Whitehead SS. Development of TV003/TV005, a single dose, highly immunogenic live attenuated dengue vaccine; what makes this vaccine different from the Sanofi-Pasteur CYD vaccine? *Expert Rev Vaccines.* 2016;15(4):509-517.

44. Anderson KB, Endy TP, Thomas SJ. The dynamic role of dengue cross-reactive immunity: changing the approach to defining vaccine safety and efficacy. *Lancet Infect Dis.* 2018.
45. Katzelnick LC, Harris E, Participants in the Summit on Dengue Immune Correlates of P. Immune correlates of protection for dengue: State of the art and research agenda. *Vaccine.* 2017;35(36):4659-4669.
46. Vannice KS, Wilder-Smith A, Barrett ADT, et al. Clinical development and regulatory points for consideration for second-generation live attenuated dengue vaccines. *Vaccine.* 2018;36(24):3411-3417.