Geneva, 19 April 2018 - WHO published the recommendations of the Strategic Advisory Group of Experts on Immunization (SAGE) on the use of Dengvaxia® on 27 May 2016, and subsequently a WHO position paper on dengue vaccine on 29 July 2016.

Following the disclosure of new data on Dengvaxia® by its manufacturer, Sanofi Pasteur, on 29 November 2017 (as described in more detail below), WHO`s Global Advisory Committee on Vaccine Safety (GACVS) and the WHO Secretariat published interim statements on December 7, 20171, and December 22, 20172, respectively. WHO initiated a process engaging independent external experts to review the data in detail, and reconvened the SAGE working group on dengue vaccines. This process has led to revised recommendations from SAGE on 18 April 2018. An updated WHO position paper on dengue vaccine will be published in September 2018.

The purpose of this document is to supplement the WHO ”Question and Answer” document from December December 22, 20172.

Dengue is the most frequent and rapidly spreading mosquito-borne virus. The first dengue vaccine, CYD-TDV (Dengvaxia®) is currently licensed in twenty countries. The key findings from two large Phase 3 trials involving over 30,000 participants aged 2 to 16 years included:

- Vaccine efficacy against virologically confirmed dengue, over a 25-month period from the first dose of a three-dose immunization regimen among 9-16 year olds was 65.6% and in this age-group, vaccination reduced severe dengue by 93% and dengue hospitalizations by 82%.

- An increased risk of hospitalized dengue was seen in the 2 to 5-year age group in Year 3 of follow-up.
- At the time of SAGE April 2016 meeting, this increased risk was not observed in those aged 9 years and above.

Because of the higher efficacy of the vaccine against dengue and the absence of an observed increased risk of hospitalized dengue observed in older children, licensure of the vaccine was sought in 2015 with an indication of 9 years and above. Mathematical modelling suggested that the public health benefits of vaccination could be maximized if dengue seropositivity in the age group targeted for vaccination was high.

WHO issued its position on the use of CYD-TDV in July 2016 based on recommendations provided by SAGE in April 2016, principally, that countries interested in introducing the vaccine consider its use only in those aged 9 years and above, and in areas with a seroprevalence of

≥70%, and not in areas below 50%. SAGE noted that the evidence of the absence of a safety issue in seronegative individuals aged 9 and above was based on the limited data set of 10%-20% of the trial population, and highlighted the urgent need to better describe the long-term benefit-risk ratio of CYD-TDV in seronegative individuals.

On 29 November 2017, Sanofi Pasteur announced the results of additional studies to better describe the benefit-risk in seronegative individuals. This was made possible through the use of a newly developed NS1-based antibody assay applied to blood samples taken 13 months after vaccination to retrospectively infer dengue serostatus at time of first vaccination.

The new analyses from the long-term safety follow-up indicated that:

- Overall population level benefit of vaccination remains favorable, but the vaccine performs differently in seropositive versus seronegative individuals.
- Vaccine efficacy (VE) against virologically confirmed symptomatic dengue was high among inferred baseline seropositive participants ≥9 years of age: 76% (95%CI: 63.9, to 84.0), but much lower among baseline seronegative participants: 38.8% (95%CI: –0.9 to 62.9%) in the first 25 months after the first dose of vaccine.
- There is an increased risk of hospitalized and severe dengue in seronegative individuals starting about 30 months after the first dose.
- In areas of 70% dengue seroprevalence, over a 5-year follow-up, for every 4 severe cases prevented in seropositive, there would be one excess severe case in seronegative per 1,000 vaccinees; for every 13 hospitalizations prevented in seropositive vaccinees, there would be 1 excess hospitalization in seronegative vaccinees per 1,000 vaccinees.

In light of the new evidence on the long-term safety issue in seronegative individuals, balanced against the documented efficacy and safety in seropositive individuals, SAGE carefully considered two strategies: population seroprevalence criteria versus pre-vaccination screening. SAGE weighed up the feasibility of population seroprevalence studies and individual pre-vaccination screening, heterogeneity of seroprevalence between and within countries, potential vaccine coverage rates, public confidence in national vaccination programmes, perceptions of ethical considerations with regard to population level benefit versus individual level risk, and communication issues.

SAGE acknowledged that currently both “population seroprevalence criteria” and “pre-vaccination screening” are programmatically difficult approaches for achieving high population protection from dengue.

Updated SAGE recommendations on the use of CYD-TDV (Dengvaxia®)

For countries considering vaccination as part of their dengue control program, a “pre-vaccination screening strategy” would be the preferred option, in which only

dengue-seropositive persons are vaccinated.

Conventional serological testing for dengue virus IgG (e.g. dengue IgG ELISA) could be used to identify persons who have had previous dengue infections. Sensitivity and specificity of dengue IgG ELISA should be assessed in a local context, and will depend on the prevalence of other flaviviruses, and past use of flavivirus vaccines (such as Japanese encephalitis and yellow fever vaccines).

Currently available rapid diagnostic tests - despite their lower sensitivity and specificity to detect past dengue infection compared with conventional dengue IgG ELISA - could be considered in high transmission settings until better tests are available. In settings with high dengue transmission (high numbers of seropositives), a test with lower specificity might be acceptable.

The pre-test probability of an individual being seropositive will be higher in settings with high transmission. However, a pre-vaccination screening strategy may also be considered in low to moderate transmission settings. In settings with low transmission (high numbers of seronegatives) a test with high specificity is needed.

Given that no assay will be 100% specific, some truly seronegative individuals may be vaccinated due to a false positive test result. Furthermore, although the efficacy against dengue infections in seropositive individuals is high, it is still not complete. Hence, the limitations of CYD-TDV will need to be clearly communicated to populations offered vaccination.

There is a continued need to adhere to other disease preventive measures and to seek prompt medical care in the event of dengue-like symptoms, regardless of whether vaccinated or not. 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 for all patients with dengue.

Decisions about implementing a “pre-vaccination screening” strategy with the currently available tests will require careful assessment at the country level, including consideration of the sensitivity and specificity of available tests and of local priorities, dengue epidemiology, country-specific dengue hospitalization rates, and affordability of both CYD-TDV and screening tests.

Age

Whether there are age-specific effects, independent of serostatus, is the subject of ongoing research. Currently, the vaccine should be used within the indicated age range, which is typically 9 to 45 years of age. The age to target for vaccination depends on the dengue transmission intensity in a given country, and will be lower in countries with high transmission, and higher in countries with low transmission. The optimal age group to be targeted is the age at which severe dengue disease incidence is highest, and this can be ascertained from national and subnational routine hospital surveillance data.

Schedule

In the absence of data on vaccine efficacy and safety with fewer than three doses, CYD-TDV is recommended as a three dose series given 6 months apart. Should a vaccine dose be delayed for any reason, it is not necessary to restart the course and the next dose in the series should be administered.

Booster

There are currently no data on the use of booster doses. Additional studies to determine the utility of a booster dose and its best timing are under way. Accordingly, there is no current recommendation for a booster dose.

Research priorities

Development of a highly sensitive and specific rapid diagnostic test to determine serostatus, and assessment of simplified immunization schedules and booster needs should be prioritized.

The full report of the SAGE April 2018 meeting will be published in the WHO Weekly Epidemiological Record on Friday, 8 June 2018.

More information on the Strategic Advisory Group of Experts (SAGE)

The Strategic Advisory Group of Experts (SAGE) on Immunization was established by the Director-General of the World Health Organization in 1999 to provide guidance on the work of WHO. SAGE is the principal advisory group to WHO for vaccines and immunization. It is charged with advising WHO on overall global policies and strategies, ranging from vaccines and technology, research and development, to delivery of immunization and its linkages with other health interventions. SAGE is concerned not just with childhood vaccines and immunization, but all vaccine-preventable diseases.