Dengue vaccines: WHO position September 2018

The September 2018 position paper replaces the 2016 WHO position paper concerning the first licensed dengue vaccine, CYD-TDV. It presents new evidence that became available in November 2017. A retrospective analysis of data from clinical trials, using a new serological assay classified trial participants according to their dengue serostatus prior to receipt of the first vaccine dose. The analysis revealed a differential performance of CYD-TDV in trial participants who were seropositive before vaccination compared to those who were seronegative. In view of these findings, SAGE provided revised recommendations in April 2018, on which this position paper is based. Evidence presented at the April 2018 SAGE meeting can be accessed at: http://www.who.int/immunization/sage/previous/en/index.html.

Background:

About 3.9 billion people, in more than 125 countries, are at risk of dengue infection, with approximately 390 million dengue infections occurring annually. About 500 000 persons require hospitalization due to dengue, and about 20,000 deaths occur due to severe dengue every year.

The first licensed dengue vaccine, CYD-TDV (Dengvaxia®), is a live attenuated, recombinant tetravalent vaccine employing the attenuated YF virus 17D vaccine strain as the replication backbone. The vaccination schedule consists of 3 injections of 0.5 mL, given subcutaneously, administered at 6-month intervals. CYD-TDV is licensed in several dengue-endemic countries, with an age indication of 9–45 years in most of those countries. Licensure of CYD-TDV was based on two parallel Phase 3 clinical trials, known as CYD14 and CYD15, involving more than 30 000 children in 10 dengue-endemic countries in Asia and Latin America. In 2017, additional analyses using a novel anti-dengue NS1 IgG ELISA in blood samples taken from all trial participants at month 13 of the trial were conducted to further characterize the risk-benefit profile in subpopulations by serostatus. These data confirmed long-term protection in seropositive individuals but also revealed an excess risk of hospitalized and severe dengue in seronegative vaccine recipients compared to seronegative non-vaccinated individuals.

1 See No. 30, 2016, pp. 349–364.
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CYD-TDV has been shown in clinical trials to be efficacious and safe in persons who have had a dengue virus infection in the past (seropositive individuals), but increases the risk of severe dengue in those who experience their first natural dengue infection after vaccination (seronegative individuals). Therefore, countries should consider introduction of the dengue vaccine CYD-TDV only if the vaccination of seronegative individuals can be avoided.

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

Screening tests would need to be highly specific to avoid vaccinating truly seronegative persons, and need to be highly sensitive to ensure that a high proportion of seropositive persons are vaccinated. No screening test is likely to be completely specific due to potential cross-reactivity with other flaviviruses.

Given the limitations regarding specificity, some seronegative individuals may be vaccinated because of a false positive test result. Furthermore, as vaccine-induced protection against dengue in seropositive individuals is high but not complete, breakthrough disease will occur in some seropositive vaccinees. These limitations will need to be communicated to populations offered vaccination.

Decisions about implementing a pre-vaccination screening strategy 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.

Vaccination should be considered as part of an integrated dengue prevention and control strategy. There is an ongoing need to adhere to other disease preventive
measures such as well-executed and sustained vector control. Individuals, whether vaccinated or not, should seek prompt medical care if dengue-like symptoms occur.

Research priorities
There is an urgent need for the development of highly specific and sensitive RDTs for determination of dengue serostatus. Research is also needed to evaluate vaccine schedules with fewer doses, and to assess the need for booster doses. Locally applicable cost-effectiveness studies are needed to support policy decisions. Research on how best to implement and integrate pre-vaccination screening in an immunization programme is recommended. The development of safe, effective, and affordable dengue vaccines for use irrespective of serostatus remains a high priority.