Summary of the WHO Position Paper on Vaccines against Dengue

This is the first WHO position paper on a dengue vaccine. It focuses primarily on the available evidence concerning the only dengue vaccine to have received regulatory approval, which has been issued by several regulatory authorities since December 2015.

Background

Dengue viruses (DENs) are members of the genus Flavivirus, within the family Flaviviridae. There are 4 serotypes (termed DEN-1 to DEN-4). Dengue viruses are primarily maintained in a human-to-mosquito-to-human cycle. Based on mathematical modelling, the global annual incidence has been estimated at about 50 million – 100 million symptomatic cases in recent years, predominantly in Asia, followed by Latin America and Africa. Factors such as population growth, globalization and travel, and climate change facilitate increased transmission of dengue viruses. Until the recent vaccine licensure, the only method to control or prevent the transmission of dengue virus was through environmental management and vector control. There is no specific anti-viral treatment for dengue illness, and clinical management is based on supportive therapy, primarily judicious monitoring of intravascular volume replacement. Improvements in case management have reduced the case fatality rate of hospitalized dengue illness to less than 1%, whereas historically it was as high as 20%.

In December 2015, the first dengue vaccine (CYD-TDV, or Dengvaxia®) was registered and is now licensed in several countries. CYD-TDV is a prophylactic, tetravalent, live attenuated (recombinant) viral vaccine. The vaccination schedule consists of 3 injections of 0.5 mL administered at 6-month intervals. The vaccine is indicated for individuals 9–45 years or 9–60 years of age (depending on the license), living in dengue endemic areas. Based on two Phase 3 trials, the pooled estimate for vaccine efficacy against virologically-confirmed dengue illness of any serotype in the 25 months post-dose 1 (ITT) was 60.3% (95% CI 55.7%–64.5%). Vaccine efficacy varied by infecting serotype, previous exposure to dengue, age (which is correlated with previous exposure), and severity.

Local and systemic adverse reactions following CYD-TDV are comparable to those recorded for other live attenuated vaccines. During the course of the hospital-based surveillance, a signal emerged from the youngest age group (2–5 years, not included in the indicated age range), for which there was an increased risk of hospitalised dengue in the third year after the first dose (RR of 7.5 (95% CI 1.2–313.8)). During year 4 and year 5, the RRs diminished. The reason for this increased risk in the youngest clinical trial participants is unknown, although hypotheses have been suggested.

WHO Position

Countries should consider introduction of the dengue vaccine CYD-TDV only in geographic settings (national or subnational) where epidemiological data indicate a high burden of disease.

In defining populations to be targeted for vaccination, prior infection with dengue virus of any serotype, as measured by seroprevalence, should be approximately 70% or greater in the age group targeted for vaccination in order to maximize public health impact and cost-effectiveness. Vaccination of populations for which seroprevalence is between 50% and 70% is acceptable but the impact of the vaccination programme may be lower. The vaccine is not recommended when seroprevalence is below 50% in the age group targeted for vaccination. While age-stratified serosurveys are currently the best method for selecting populations suitable for vaccination, subnational,
age-stratified surveillance data may be used to help guide vaccine decision-making. Preferably a combination of seroprevalence, surveillance data, and programmatic factors should define the target population. Any deployment of the vaccine in the context of an outbreak should only be done in areas that meet the recommended seroprevalence criteria for introduction of dengue vaccine in routine programmes.

Dengue vaccine introduction should be a part of a comprehensive dengue control strategy, including well-executed and sustained vector control, evidence-based best practices for clinical care for all patients with dengue illness, and strong dengue surveillance. If CYD-TDV is introduced, it should be administered as a 3-dose series given on a 0/6/12 month schedule. Because of the association of CYD-TDV with increased risk of hospitalized and severe dengue illness in the 2–5 year age group, CYD-TDV is not recommended for use in children under 9 years of age, consistent with current labelling. The target age for routine vaccination should be defined by each country, based on maximizing vaccination impact and programmatic feasibility of targeting specific age groups.

At the time of introduction, countries are encouraged to have a functional pharmacovigilance system with at least minimal capacity to monitor and manage adverse events following immunization. Countries considering vaccination should also have a dengue surveillance system able to detect and report hospitalized and severe dengue cases consistently over time. Dengue surveillance globally should be strengthened, particularly in the context of emerging infections with clinical similarities to dengue and in areas of the world for which data are scarce or absent.

Important research and implementation questions remain for CYD-TDV. Research on reduced or shorter interval dosing schedules and safety in pregnant women are high priorities. An approach to evaluate epidemiologic data based on high-quality age-stratified surveillance is needed to infer likely seroprevalence by age in order to target vaccination efforts where seroprevalence data are not available. As the vaccine is introduced in endemic countries, vaccine effectiveness by dose and duration of protection and long-term impact of vaccine programmes are research priorities. Special studies should be conducted to monitor the occurrence over time of severe dengue illness in vaccinated persons, particularly among vaccinated seronegative persons.