Background

- Number of dengue cases reported annually to WHO has increased from 0.4 to 1.3 million between 1996-2005, reaching 2.2 million in 2010 and 3.2 million in 2015.

- Mathematical modelling estimates that the global annual incidence of symptomatic cases is about 50 million – 100 million.

- In 2013, dengue was estimated to be responsible for approximately 3.2 million severe cases and 9000 deaths with the majority occurring in lower middle income countries and for 1.1 million disability-adjusted life years globally.

- Dengue viruses are primarily maintained in a human-to-mosquito-to-human cycle.
  - Primary vector is *Aedes aegypti* mosquito, which is highly adapted to human habitants.
  - Substantial subnational and local variability in transmission.
There are 4 dengue virus serotypes (DEN-1, DEN-2, DEN-3, and DEN-4) that circulate globally with the most endemic countries reporting circulation of all 4 serotypes in recent years.

Majority of dengue virus infections are asymptomatic.

Individuals infected multiple times with different dengue virus serotypes may experience multiple clinical episodes.
  - Severe illness is more likely to occur with a second dengue virus infection than with the first dengue virus infection

For clinical management, WHO classifies dengue illness as (i) dengue with or without warning signs for progressions towards severe dengue and (ii) severe dengue
Diagnosis, Treatment and Prevention

- Laboratory confirmation of dengue virus infection is usually done by serology or by molecular methods.

- There is no specific anti-viral treatment for dengue illness. Clinical management is based on supportive therapy.

- Until the recent vaccine licensure, the only approach to control or prevent the transmission of dengue virus was through interventions targeting the vector.
One dengue vaccine has been registered in several countries.

- CYD-TDV (Dengvaxia®)
  - Live attenuated (recombinant) tetravalent vaccine.
  - Active substances for serotypes 1, 2, 3, and 4.
  - Licensed for individuals 9-45 years or 9-60 years of age (depending on license).

Several other dengue vaccines are in clinical development.
Vaccine efficacy and safety

- 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.

- Safety signal of increased risk of hospitalization due to dengue illness in the youngest age group included in clinical trial (2–5 years) in the third year after the first dose (RR of 7.5 (95% CI 1.2–313.8)).
WHO Position

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

- To maximize public health impact and cost effectiveness, age groups targeted for vaccination should have 70% or greater seroprevalence.

- Vaccine is not recommended when seroprevalence is below 50% in targeted age group.
WHO Position

- Countries considering vaccination should have a dengue surveillance system to detect and report hospitalized and severe dengue cases consistently over time.

- Serosurveys are currently the best method for selecting populations suitable for vaccination.
  - Sub-national, age-stratified surveillance data may also be used to help guide vaccine decision.

- When defining the target population a combination of seroprevalence, surveillance data, and programmatic factors is preferred.
WHO Position

- Dengue vaccine introduction should be 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;
  - Strong dengue surveillance.

- Decisions about introduction requires careful assessment at the country level including:
  - Consideration of local priorities;
  - National and sub-national dengue epidemiology;
  - Predicted impact and cost-effectiveness with country specific inputs;
  - Affordability and budget impact.

- At 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.
WHO Position

- CYD-TDV should be administered as a 3-dose series given on a 0/6/12 month schedule.

- If a vaccine dose is delayed, the vaccine course should be resumed (not restarted) maintaining a 6-month interval between subsequent doses.

- Countries should have systems in place to track vaccination.
WHO Position

- CYD-TDV is not recommended for use in children under 9 years of age, consistent with current labelling.

- Target age for routine vaccination should be defined by each country based on maximizing vaccination impact and programmatic feasibility of targeting specific age groups.

- Catch-up campaigns targeting those above 9 years of age may be considered if more than a 10%-30% reduction in symptomatic and hospitalized dengue illness over 30 years is desired and the additional cost can be met.
WHAT Position

- Co-administration is permissible with other live and non-live attenuated vaccines.

- Deployment of vaccine during an outbreak should only be done in areas that meet recommended seroprevalence criteria for introduction of vaccine in routine programmes.

- There is no recommendation concerning pregnant and lactating women due to lack of sufficient data in the population.

- Women of child bearing age targeted for vaccination do not need to be tested for pregnancy.
WHO Position

- Until data becomes available from forthcoming studies in HIV-infected individuals or other persons with immune deficiency, there is no recommendation concerning the use of CYD-TDV in HIV-infected or immunocompromised individuals.

- There is no recommendation for vaccination of travellers or health-care workers at this time.
WHO position

- Dengue surveillance 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.

- Use of standardized case definitions is encouraged to enhance data sharing and comparability across regions.

- With the increase in false-positive results from serological testing of CYD-TDV vaccinated individuals, diagnostic testing should move to virological confirmation whenever possible.
Research priorities

- 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.
For more information on the WHO position paper on Vaccination against Dengue please visit the WHO website:

www.who.int/immunization/documents/positionpapers