

Proposed Recommendations

CYD-TDV *Denvaxia*[®], Dengue Vaccine

Terry Nolan

SAGE, Co-Chair Dengue Vaccine WG

WG Considerations

A number of dimensions:

- Population benefit versus individual risk
- Ethical considerations
- Risk perceptions and communication
- Screening tests versus serosurveys
- Programmatic issues
- Vaccine coverage estimates

Came down to an evaluation of:

*Population Seroprevalence Criteria
without Screening*

Pre-Vaccination Screening

1. Benefits and Harm

Population Seroprevalence Criteria without Screening

BENEFIT

Overall substantial population benefit in areas with high seroprevalence predicted.

HARM

An identifiable subset of the population will be put at increased risk of severe dengue, at least in the short to medium term.

Pre-Vaccination Screening

BENEFIT

Maximizing the benefit (high efficacy and good safety) in seropositive while avoiding harm in correctly identified seronegatives.

HARM

Some seronegative individuals will be put at increased risk of severe dengue if vaccinated due to a false positive screening test result.

2. % vaccinated at increased risk of severe dengue

Population Seroprevalence Criteria without Screening

- 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.

Pre-Vaccination Screening

- 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.

3. Population eligible for vaccination

Population Seroprevalence Criteria without Screening

- Subnational areas with seroprevalence >80% in 9 year olds are predicted by modelling to be rare, those with seroprevalence >90% by the age of 9y very rare.

Pre-Vaccination Screening

- Modelling predicts vaccine eligibility 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 will be higher in high transmission settings.

4. Risk perception

Population Seroprevalence Criteria without Screening

- Loss in vaccine confidence (dengue vaccines and possibly other vaccines).
- Inability of vaccinees to know own serostatus may lead to increased vaccine hesitancy.

Pre-Vaccination Screening

- Risk of false positive test: seronegative individuals will be misclassified as seropositive and unintentionally vaccinated as no test will be 100% specific.

5. Implementation challenges

Population Seroprevalence Criteria without Screening

- 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 Screening

- Pre-vaccination blood sampling may lead to decreased acceptance of the vaccination programme
- No rapid diagnostic test (RDT) has been validated or licensed for the indication of screening for past dengue infection.
- Unlikely that any test will have a 100% specificity, thereby still putting some truly seronegatives at risk.
- Tests with high sensitivity are needed to ensure that a large proportion of seropositives will benefit from CYD-TDV.

6. Population impact

Population Seroprevalence Criteria without Screening

Given that areas with seroprevalence above 80% by age 9y are predicted to be rare, population impact is likely to be low.

Pre-Vaccination Screening

Population impact on reduction of hospitalized dengue modelled at approximately 20% over 30 years.

7. Age

Population Seroprevalence Criteria without Screening

- Seroprevalence threshold in target age group increases for higher ages. 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.

Pre-Vaccination Screening

- Seropositive individuals of any age as indicated in the label can be targeted.
- As monotypic seropositives 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.

8. Cost effectiveness

Population Seroprevalence Criteria without Screening

- Cost effectiveness studies not done for seroprevalence >80%. Cost effectiveness studies done in 2016 for 70% seroprevalence.
- Cost-effectiveness studies need to take into account costs required to conduct population serosurveys to identify sub-national areas with seroprevalence above 80%.

Pre-Vaccination Screening

- No cost-effectiveness studies have been conducted to date.
- Cost-effectiveness studies need to take into account costs associated with identifying seropositives.

Recommendation

Pre-Vaccination Screening

- 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 (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 other flavivirus vaccines (Japanese encephalitis and yellow fever).

Currently available dengue rapid diagnostic tests (RDTs)

- Currently available RDTs, 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 numbers of seropositives and relatively low numbers of seronegatives, even an imperfect test with low 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 lower transmission (higher numbers of seronegatives), a test with higher specificity is recommended.

Need to explain limitations of RDTs and vaccine efficacy

- 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 100%
- Hence, the limitations of CYD-TDV will need to be clearly communicated to populations offered vaccination.

Maintain Dengue Control Measures

- 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.

Countries need to consider local factors

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**
- **local priorities**
- **dengue epidemiology**
- **country-specific dengue hospitalization rates**
- **affordability of both CYD-TDV and screening tests.**

Other issues

(covered in the Background document)

- Age of vaccination
- Schedule
- Booster
- Research priorities
- Outbreak response
- Pregnancy
- Immunocompromised
- Travellers
- Surveillance