Dengue pre-vaccination screening and positive predictive values

Although Sanofi Pasteur’s dengue vaccine CYD-TV (Dengvaxia) is already licensed in 20 countries, WHO only recommends its use in individuals from endemic settings with serological confirmation of past dengue virus infection. This pre-vaccination screening recommendation followed an announcement in November, 2017, and a paper published in 2018 that showed that, in the long-term follow-up of phase 3 clinical trials, vaccine recipients who had not been infected by dengue before vaccination (ie, seronegative individuals) had a higher risk of having severe dengue disease and dengue-related hospitalisation than did seronegative individuals who received placebo. Because current evidence suggests that the vaccine confers good protection against symptomatic and severe disease in individuals seropositive to dengue virus, WHO has recommended screening potential vaccine recipients to minimise harm to seronegative individuals while maximising benefits to seropositive people. As noted by Annelies Wilder-Smith and colleagues, many challenges to the implementation of this recommendation exist. Screening tests would need to be highly sensitive and specific, and deliverable at the point of care. High sensitivity is desirable to ensure that the largest number of (seropositive) individuals get access to the vaccine, and high specificity is needed to prevent people who have not been infected from being vaccinated. Unfortunately, to date, no such test has been validated or licensed, nor is it clear what the target sensitivity or specificity of these assays should be.

If a key goal of pre-vaccination screening is to minimise harm to seronegative individuals, sensitivity and specificity might not be the most useful target metrics for assay development. Tests with a given sensitivity and specificity are more likely to misclassify truly seronegative individuals in low transmission settings (where seroprevalence is low) than in high transmission settings, simply because their pre-test probabilities are lower. Focusing on the positive predictive value (PPV) makes more sense, as this value directly quantifies the probability that a person who tests positive is truly seropositive, or the probability that they have been misclassified (1 – PPV).

Therefore, rather than uniformly fixing the desired sensitivity and specificity of the test, it might be more reasonable to decide what an acceptable level of misclassification is, and to find the minimum sensitivity and specificity for different transmission settings that would achieve this level of misclassification or lower.

We calculated the expected PPVs for tests with varying sensitivity and specificity, and across a range of transmission intensities, represented by different levels of seroprevalence (figure; appendix). In high-transmission settings, where the true dengue seroprevalence is more than 70%, it is possible to achieve a PPV of more than 90% with screening tests across a range of sensitivities and specificities. This PPV would mean that less than 10% (1 – PPV) of individuals who test seropositive will be misclassified and erroneously vaccinated. By contrast, in settings with moderate or low transmission, higher sensitivity and specificity are required to achieve a PPV of 90%; where seroprevalence is 50%, the sensitivity and specificity of the assay must be greater than 90%; and where seroprevalence is less than 30%, tests with near perfect specificity (>98%) would be needed. Furthermore, in populations where the expected seroprevalence is very low (<5%), such as among travellers from non-endemic areas, even tests with very high specificity (95%) will misclassify more than half of those who test positive.

Developing a test that ensures acceptable levels of misclassification might be more feasible for endemic regions with high transmission, and it is in these settings that models predict the vaccine could have the largest benefits with regard to protecting individuals from symptomatic and severe disease. Developing screening assays that are specific enough for settings with moderate or low transmission will be more challenging and might not be possible, particularly where individuals might have been exposed to other flaviviruses (either by vaccination or natural infection) such as yellow fever virus, Japanese encephalitis virus, or Zika virus, all of which are known to serologically cross-react with dengue virus in most available immunological assays. Non-dengue flavivirus-derived immunity provides additional challenges to the vaccine: the biological effect of this immunity on vaccine performance, which has not been assessed in trials, is unclear.

Candidate pre-vaccination screening tests must be evaluated and approved, keeping in mind that a key objective of the current WHO recommendation is to minimise risk to individuals. In high-transmission settings, less than perfect tests might, nevertheless, provide some benefit. However, unless a test with near-perfect specificity is developed, marketing of this vaccine in non-endemic areas of continental USA and Europe (which could happen soon given the positive recommendations by regulatory agencies) would most likely result in most vaccinations being inappropriately given to seronegative people.

We declare no competing interests. *Isabel Rodriguez-Barracuer, Henrik Saige, Derek AT Cummings

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**Figure:** Effect of assay specificity and seroprevalence on probability of misclassification. Minimum specificity that would be required in an assay (with sensitivity of 90%) to ensure a probability of misclassification (1 – PPV) of a given value (or less), for a range of transmission settings, represented by different levels of seroprevalence among children aged 9 years (SP). PPV=positive predictive value. See appendix for an expanded figure.
(A) Contingency tables illustrating how a screening test with a given sensitivity and specificity will yield different PPVs and NPVs depending on the underlying seroprevalence (in this example 5% seroprevalence [low transmission] or 80% seroprevalence [high transmission]). (B) Graphs showing the probability of being truly seronegative for individuals who test positive (1–PPV) for tests with varying sensitivities and specificities. Three transmission settings are considered, represented as the seropositivity among children aged 9 years (SP9): 5% seroprevalence (low transmission), 50% seroprevalence (moderate transmission), and 80% seroprevalence (high transmission). Coloured symbols indicate the specific scenarios shown in the contingency tables. The red shaded area indicates where PPVs would be less than 0.5, or where more individuals would be misclassified rather than correctly classified. (C) Graph showing the minimum specificity that would be required in an assay (with sensitivity of 90%) to ensure a probability of misclassification (1–PPV) of a given value (or less), for a range of transmission settings, represented by different levels of SP9. NPV=negative predictive value. PPV=positive predictive value.

Sens=sensitivity. Spec=specificity. SP9=seroprevalence among children aged 9 years.

The code to reproduce these calculations is available at https://github.com/isabelrodbar/dengue_screening_ppv.