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Low anti-rubella antibody levels in public facilities staff in Tokyo

As of Oct 22, 2018, the US Centers for Disease Control and Prevention warned pregnant women to refrain from travelling to Japan, especially to the Kantō region, if not fully protected from rubella, raising its alert level to 2 ("practice enhanced precautions").[1] According to the National Institute of Infectious Diseases (Tokyo, Japan), 2586 cases of rubella were diagnosed between Jan 1 and Dec 12, 2018.[2] The greater Tokyo metropolitan area in Japan is facing a huge outbreak of rubella this year, for which the Ministry of Health, Labour, and Welfare issued an alert[3] on Aug 14, 2018.

Congenital rubella syndrome can be prevented by keeping the anti-rubella antibody at a high concentration by vaccination. Among various methods of screening for immunity against rubella, the haemagglutination inhibition assay is a commonly chosen method by the municipal government to investigate the seroprotective status of the population in Japan. An antibody titre of 1/16 or less measured by this assay is considered by Japanese authorities to be an inadequate level of protection. At the Eijudo Clinic in east-central Tokyo, we conducted rubella screening during the previous rubella outbreak[4] in Japan in 2013. Seven (41%) of 17 staff members at the clinic had antibody titres of 1/16 or less based on the haemagglutination-inhibition assay. In the same year, 14 344 cases of confirmed rubella and 32 cases of congenital rubella syndrome were reported in Japan.[5] Since then, the local medical association has been successful in promoting rubella titre screening for faculty members at all public schools within the ward, but, so far, has been unable to convince the population naive to rubella exposure to be vaccinated. In 2018, before the outbreak became apparent, we carried out the same screening on 39 faculty members of an elementary school close to Eijudo Clinic in Tokyo, and found that 15 participants (39%) had antibody titres of 1/16 or less.

Despite the 5 years that have passed since the last outbreak, the alerts issued, and the strong continuous recommendations from the government to complete rubella vaccination, the proportion of seroprotected individuals in the population remains low, allowing unvaccinated and under-vaccinated individuals to be infected. The settings for the aforementioned screenings, a clinic and an elementary school, are similar in that they are both potential public sources of rubella exposure for pregnant women. We speculate that the low antibody titres seen among these probe populations in the Tokyo area might reflect the situation throughout Japan, based on common and average Japanese attitudes towards vaccines, outbreak response, and public health interest. We are concerned about this risk for pregnant women in or travelling to the greater Tokyo metropolitan area, and to the surrounding Kantō region. As well as alerting people in these populations, we strongly suggest screening and (where necessary) vaccination of staff members in settings where pregnant women are likely to visit.

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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[1] in November, 2017, and a paper[2] 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.[3]

As noted by Annelies Wilder-Smith and colleagues, many challenges to the implementation of this recommendation exist.[4] 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.[4] 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.[5] 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.

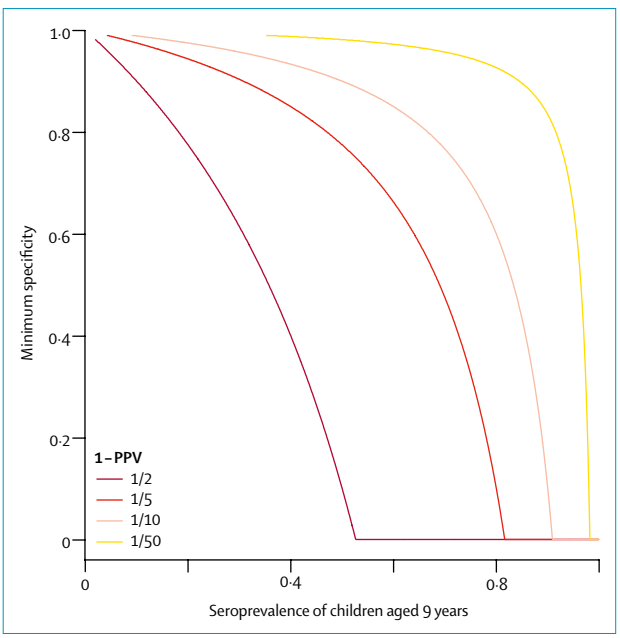

Figure: **Effect of assay specificity and seroprevalence on probability of misclassification**
Minimum specificity that would be required in an assay (with sensitivity of 90%) to ensure a probability of misclassification (1–PPV) of a given value (or less), for a range of transmission settings, represented by different levels of seroprevalence among children aged 9 years (SP_9). PPV=positive predictive value. See appendix for an expanded figure.

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)[6,7] would most likely result in most vaccinations being inappropriately given to seronegative people.

See Online for appendix

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Multidrug-resistant tuberculosis outbreak in South Africa

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We note with concern the Article by Ndivhuho Makhado and colleagues[1] that described the high frequency of Ile491Phe mutations in the *rpoB* gene among a small subset of highly selected isolates of *Mycobacterium tuberculosis* from South Africa. In a letter to *The Lancet Infectious Diseases*,[2] we previously refuted the likelihood of this mutation being widespread; therefore, we are disappointed that the mutation is now being claimed as the cause of an outbreak of multidrug-resistant tuberculosis and used to challenge current diagnostic methodologies that are the bedrock of national tuberculosis programmes.

A population-representative tuberculosis drug-resistance survey using whole-genome sequencing,[3] done at the same time as the study by Makhado and colleagues,[1] showed the true prevalence of the Ile491Phe mutation to be less than 0·1% (one in 1535) among patients with tuberculosis from two provinces neighbouring eSwatini.[3] The single isolate was rifampicin monoresistant in both phenotype and genotype. Furthermore, none of the 140 isoniazid-monoresistant tuberculosis strains with available sequencing data from the survey, including representation from North West and Mpumalanga provinces, had the mutation.[4] By contrast, Makhado and colleagues[1] used convenience sampling of available culture isolates from a single laboratory serving a small area, and the study was, thus, unsuitable for prevalence estimation. The starting point was culture isolates, a practice that is routinely indicated by the national algorithm only when the results of initial Xpert MTB/RIF testing are negative, or when treatment has failed.[5] This selection bias towards drug-resistant isolates is evidenced by the unusually low treatment success rates for patients with and without the mutation. Therefore, Makhado and colleagues' assertion that their findings are generalisable and that the mutation is responsible for a "substantial number of MDR tuberculosis cases" in South Africa[1] is unfounded.

The study[1] had a number of methodological flaws, including the inappropriate description of the findings as evidence of an outbreak; the absence of a description of duplicate sample management; and the lack of adequate explanations for the sample size selection of 277 of the 1823 isoniazid-resistant rifampicin-sensitive strains, or for whole-genome sequencing being done on only 14 of 37 samples identified by Sanger sequencing as harbouring Ile491Phe. Furthermore, epidemiological data pertaining to patients from whom strains originated, including the exact place of residence, country of origin (eg, eSwatini), and occupation, were not provided. It is not possible, therefore, to ascertain the presence of clustering, nor epidemiological linkage—a necessary criterion in declaring an outbreak. On the basis of the evidence provided, all that can be said is that these isolates are genotypically related, which is expected in endemic settings, but recent transmission cannot be inferred.[6,7] It is also unusual to find isolates with no differences in single-nucleotide polymorphisms when transmission networks span several years: a situation that could be explained by laboratory cross-contamination. The hypothesis that these cases are associated with bedaquiline introduction is also not justified because previous treatment history and contact history are not provided. Furthermore, the geographical location of these cases was far from the initial treatment site for the bedaquiline clinical access programme in the province.[8]

Makhado and colleagues recommend that South Africa adopt an assay used in their study, but three of the authors have declared commercial interests in the company that manufactures it. Although no test can be perfect, the WHO-endorsed technologies in use (GenoType MTBDRplus and Xpert MTB/RIF) are validated, detecting at least 95% of cases of rifampicin resistance.[9] Furthermore, the current algorithm in South Africa requires sputum culture and susceptibility testing when patients fail treatment, and whole-genome sequencing is available and used by the reference laboratory in appropriate circumstances. Until meaningful data become available, we believe this approach is appropriate to safeguard current treatment regimens against development of rifampicin resistance.