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a nine-fold increase in neutralising antibody titres from baseline.<sup>5</sup> In the same study, seroresponse persisted 180 days after vaccination in 84.2% (95% CI 74.4–90.7) of individuals who seroresponded after 28 days. By contrast, the cellular response after a natural infection appears much higher than after vaccination. Another study in Guinea,<sup>6</sup> which compared immune responses between ten rVSV-ZEBOV vaccinees and 25 survivors, found high and equivalent antibody titres 6 months after vaccination or natural infection. Overall, these studies of vaccine immunogenicity implemented in operational conditions are consistent with the results generated by early vaccine trials done in healthy adults in the USA, Canada, and Spain.<sup>7,8</sup>

The report by Thom and colleagues also provides useful information regarding the immune responses in contacts of Ebola virus disease cases. Although no distinction between asymptomatic and paucisymptomatic presentations of the infection can be made, both neutralising antibodies and cellular responses were identified in six (9%) of the 66 contacts. This figure compares well with the seropositivity observed in asymptomatic and paucisymptomatic contacts in Guinea (3.3% vs 8.3%) and Sierra Leone (2.6% vs 12.0%).<sup>9,10</sup>

In summary, on the one hand, we have accumulated sufficient clinical and immunological data from survivors of the 2013–16 west African Ebola epidemic in favour of acquired immunity to Ebola virus lasting at least a few years after a natural infection. On the other hand, studies of correlates of protection for Ebola vaccines that support an induced immunity have, so far, only followed patients for up to 6 months. Natural acquired immunity could

provide protection to people who have been exposed to and infected with Ebola virus for at least a few years, even if antibody concentrations decrease with time, owing to backup memory B cells and cellular immunity.

I declare no competing interests.

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## Optimising dengue pre-vaccination screening



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As the world is grappling with the global COVID-19 pandemic, dengue epidemics continue to rage relentlessly in the tropics and subtropics.<sup>1</sup> About 100 million dengue cases are reported every year, often overwhelming already fragile health-care systems, with the highest burden in southeast Asia followed by Latin America.<sup>2</sup> Dengue and COVID-19 have in common that epidemic transmission is driven by population densities, and both are rapidly spread via travellers.<sup>3</sup> The difference between the two diseases is the mode of transmission. The four dengue virus serotypes are transmitted by *Aedes* spp mosquitoes,

which mainly proliferate in the climatic conditions of the tropics and subtropics,<sup>4</sup> whereas severe acute respiratory syndrome coronavirus 2 is transmitted via respiratory droplets ubiquitously.

While the scientific community is racing towards developing a vaccine against COVID-19, we already have a vaccine at hand against dengue. First licensed in 2015, the tetravalent live attenuated dengue vaccine developed by Sanofi Pasteur (CYD-TDV, with the trade name of Dengvaxia) was evaluated in more than 30 000 children in ten countries in Asia and Latin

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America, with now more than 5 years of observation time since administration of the first dose.<sup>5</sup> The combined phase 3 trials showed a moderate–high efficacy, with increasing efficacy with age, serotype 4, and in settings with higher seroprevalence. Further post-hoc analyses with retrospective stratification into baseline serostatus (presence or absence of previous dengue infection at the time of administration of the first dose) revealed that vaccine performance was strongly driven by serostatus: seropositive individuals benefitted from high efficacy, whereas seronegative individuals experienced no statistically significant efficacy but an increase in hospitalised dengue from year 3 onwards after administration of the first dose.<sup>5</sup> Subsequently, WHO recommended that CYD-TDV should only be given to seropositive individuals. Hence screening for dengue serostatus before vaccination is needed.<sup>6</sup>

In *The Lancet Infectious Diseases*, Carlos DiazGranados and colleagues evaluated five commercially available immunoassays—two IgG-based ELISAs (EUROIMMUN and Panbio) and three rapid diagnostic tests (RDTs; TELL ME FAST, SD BIOLINE, and OnSite)—for their potential to classify baseline dengue serostatus, using baseline samples from more than 3000 participants in the immunogenicity subsets of the phase 3 CYD14 and CYD15 efficacy trials.<sup>7</sup> All immunoassays exhibited high specificity (>98% for all immunoassays apart from SD BIOLINE RDT), but variable sensitivities, with higher sensitivities observed for the ELISAs (EUROIMMUN 89.2% [95% CI 87.9–90.3] and Panbio 92.5 [91.4 to 93.5]) than the RDTs (TELL ME FAST 52.5% [50.6 to 54.4], SD BIOLINE 71.1% [69.3 to 72.8], and OnSite 47.6% [45.7 to 49.5]).<sup>7</sup> These results are encouraging, and consistent with an earlier evaluation of various ELISA against RDTs, in which sensitivities for RDTs were found to generally be lower than those of the ELISAs ( $\geq 90\%$ ).<sup>8,9</sup> Those studies also found that sensitivity for the assays evaluated by DiazGranados and colleagues appeared similar in samples from individuals with recent (<13 months) versus remote (3–4 years) virologically confirmed dengue.<sup>8</sup> Additionally, cross-reactivity to other flaviviruses was low with RDTs ( $\leq 7\%$ ), but more significant with ELISAs (up to 51% for West Nile and 34% for Zika).<sup>8</sup>

DiazGranados and colleagues also re-evaluated CYD-TDV vaccine efficacy in participants identified as dengue

seropositive by the five immunoassays.<sup>7</sup> Vaccine efficacy against symptomatic virologically confirmed dengue in immunoassay-positive participants was high across all five immunoassays (from 82.8% [95% CI 66.9–91.1] by SD BIOLINE RDT to 89.7% [64.6–97.0] by OnSite RDT), as was vaccine efficacy against hospitalised virologically confirmed dengue (from 72.8% [38.9–87.9] by EUROIMMUN ELISA to 92.4% [37.8–99.1] by TELL ME FAST RDT), underpinning the public health usefulness of the first licensed dengue vaccine. Vaccine efficacy against severe virologically confirmed dengue was similarly high, but lacked precision owing to very few severe virologically confirmed dengue cases over the follow-up.

DiazGranados and colleagues' findings suggest that current commercially available immunoassays and RDTs could be used for pre-vaccination screening for CYD-TDV. Although a more sensitive or convenient test would improve the performance and efficiency of pre-vaccination screening programmes, countries can start to choose from existing screening tests for their vaccination programmes. The key considerations for selection are accuracy, ease of use, and affordability. Ideally, a screening test should be both highly sensitive and specific to minimise false positives and negatives to yield maximal population level benefit and minimise harm by correctly screening for seropositive individuals only.<sup>6</sup> It should also be affordable, simple to use, and provide a rapid result so that vaccination can be given immediately after serostatus is confirmed. RDTs fulfil these ease-of-use requirements as they can use finger-pricked blood samples and the test can be done outside of laboratory settings with results available in 15–20 min.

While ELISAs are highly sensitive, they can only be done with serum or plasma and the blood samples have to be sent to a laboratory for testing. This requires phlebotomy and delays for obtaining the results. However, phlebotomies during school programmes for the purpose of school-based implementation combined with screening for other diseases could enhance the uptake and acceptance by schools and communities. In private clinics and travel medicine settings,<sup>10</sup> blood is often taken before hepatitis B vaccination to check for hepatitis B serostatus, and thus there is precedence for pre-vaccination screening. Similar approaches can be taken for CYD-TDV.

As vaccine safety is a top priority, perhaps the most important consideration for test selection is test

specificity. A test with high specificity would lead to few false-positive results, thus reducing possible harm from vaccinating a person who is dengue naive. As the number of false-positive results is affected by both test specificity and seroprevalence of dengue in the population, countries need to estimate the positive and negative predictive values of a screening test for each use setting, in addition to considerations of affordability. An additional consideration might be the use of a two-test algorithm: for instance, people are screened first with a RDT and, for those who are negative, a venous blood sample is collected for ELISA, or in areas where other flaviviruses are co-circulating, ELISA-positive results are confirmed with a more specific RDT.

During the COVID-19 pandemic, we cannot neglect the rapidly increasing dengue burden. The study by DiazGranados and colleagues has shown that we have the tools needed to maximise the public health impact of a dengue vaccine.

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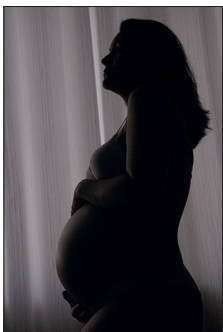
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## Desideratum: a developmentalist view of Zika virus infection



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Zika virus was first isolated from the blood of a rhesus macaque during a study on yellow fever transmission in the Zika forest in Uganda in the late 1940s.<sup>1</sup> In the following years, the virus, transmitted through *Aedes* mosquitoes, remained, besides reports on local case series, almost unrecognised until the 2007 outbreak in the Federated States of Micronesia. It was another 8 years later that the 2015–16 epidemic in Brazil suddenly brought Zika virus into the spotlight because of unexpected severe neurological complications.<sup>2</sup> Most alarming was a dramatic increase of newborn babies with brain anomalies such as calcifications, ventriculomegaly, and particularly microcephaly<sup>3</sup> (congenital Zika syndrome<sup>4</sup>) indicating vertical transmission from the pregnant woman to her fetus. Since then, a large body of research has shown that Zika virus can cross the placental barrier by inducing vascular damage, apoptosis of trophoblasts, and hyperplasia of placental macrophages,<sup>5</sup> which conveys the virus to the fetal compartment, particularly to the fetal brain. Targeting of neural progenitor and microglial cells by

the virus leads to downregulation of neurogenesis and upregulation of apoptosis, which in turn result in stunted growth or even death of developing neurons.<sup>6</sup> The consequence is a marked reduction in brain size. But how often is this the case?

In their Article in *The Lancet Infectious Diseases*, A E Ades and colleagues<sup>7</sup> provided rates of vertical transmission and adverse outcomes, based on Bayesian latent class analysis of data from seven prospective studies done in different settings in the Americas, as well as in travellers and immigrants to Spain from the Americas. Although the diagnostic sensitivity of markers of congenital Zika virus infection is estimated to be lowest in the first trimester of pregnancy,<sup>7</sup> the susceptibility of the developing nervous system seems to be the highest in the first trimester. With an estimated average vertical transmission rate of 47% (95% credible interval 26–76), around 130 per 1000 pregnancies have an adverse outcome when maternal infection happens during the first trimester compared with 30 per 1000 when maternal infection occurs during the second trimester,

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