Predicting the efficacy of new coronavirus vaccines — Are neutralising antibodies enough?

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Identifying an immunological correlate of protection (CoP) is a key objective in vaccine development allowing licensure of new vaccines without direct evidence of efficacy. Having a CoP for COVID-19 vaccines is particularly important as establishing efficacy for new vaccine platforms in placebo-controlled trials is becoming ethically problematic with the growing availability of first generation vaccines with proven efficacy.

Khoury et al. attempted to generate a CoP across different COVID-19 vaccine platforms by comparing efficacy estimates from Phase 3 trials of seven vaccines with their neutralising antibody (Nab) responses in Phase 1/2 trials.[1] They demonstrated a correlation between the mean Nab titre (expressed as a multiple of the mean titre in human convalescent sera reported in the same Phase1/2 study) and efficacy against symptomatic SARS-CoV-2 infection across the seven vaccines. Based on the correlation, the authors derived an equation to predict the efficacy of a new vaccine using the Nab titre ratio between vaccinated and naturally infected individuals.

In this edition of *eBioMedicine*, a "real world" test of the validity of the equation derived by Khoury et al.[1] is reported by Muena et al.[2] The authors measured the ratio between Nab titres in those receiving an inactivated whole virion vaccine (CoronaVac) or the mRNA spike-based vaccine BNT162b2 during the vaccination campaign in Chile and titres in naturally infected individuals; the efficacies predicted from these ratios using the Khoury et al. equation[1] were then compared with effectiveness data for both vaccines generated during the campaign.[3] The ratio was 0.2 for CoronaVac and 5.2 for BNT162b2 giving predicted effectiveness of around 50% and 97% respectively, compared with the observed effectiveness in the Chilean population of 65.9% for CoronaVac and 92.6% for BNT162b2.[3] The data from -Muena et al.,[2] together with published results of Phase 3 trials in Indonesia[4] and Turkey[5] suggest that the Khoury et al. equation underestimates the efficacy of CoronaVac.

Muena et al[2] found robust Nab responses after two CoronaVac doses in previously infected individuals, reaching similar levels to those seen in convalescent sera. It would have been interesting to measure the Nab responseto SARS-CoV-2 variants in CoronaVac recipients with previous infection to assess whether, as reported for third doses of CoronaVac, Nabs to Alpha, Beta and Delta variants as well as the ancestral Wuhan strain are generated.[6] Nab responses to the more antigenically distinct Omicron variant are relatively poor after a third dose of CoronaVac though robust after heterologous boosting with mRNA or adenovirus vectored vaccines.[7]

While Muena et al[2] found strong responses to the SARS-CoV-2 nucleocapsid antigen in naturally infected individuals there was little response after two doses of CoronaVac even in those previously infected. Despite the inclusion of the whole virion in CoronaVac the nucleocapsid component appears to be a poor B-cell antigen though it may contribute to T cell responses along with other non-spike structural proteins.[8] T cell responses, which likely play a role in protection especially against severe disease,[9] were found to be greater after CoronaVac than BNT162b2 in a head-to-head study,[8] and may, as postulated by Muena *et al*,[2] help explain the lower predicted efficacy of CoronaVac based on Nab responses than observed in the Chilean population.

As acknowledged by Muena et al.[2] the main limitation of their study is the small sample size, particularly for recipients of the BNT162b2 vaccine, and the use of a convenience rather than a random sample to recruit participants. Nevertheless they were able to identify obesity as a risk factor for poor response to CoronaVac, consistent with findings by others for the more extensively studied BNT162b2 vaccine.

More comparative immunogenicity and effectiveness studies of different vaccines in the same population of the type conducted by Muena et al.[2] are needed. This is particularly important to validate the predicted clinical benefit of booster doses against variants of concern based on Nab responses[10] and the potential benefit of developing new vaccines incorporating viral antigens from such variants based on the Khoury et al. model.[1]

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Declaration of interests

The author has no conflicts of interest

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