infections is shown by the outcome that includes any nucleic acid amplification test-positive cases. However, there is still value in directly estimating the efficacy against asymptomatic infections. As estimated in table 1 of the Article,[1] this parameter is calculated using the rate ratio that compares asymptomatic infections between the vaccinated and control groups. However, we argue that the rate of asymptomatic infections in the control group is not the appropriate comparator because it requires the implausible assumption that all prevented symptomatic cases were completely averted, rather than converted to asymptomatic infections. If it is instead assumed that all symptomatic infections prevented by the vaccine would become asymptomatic, the appropriate counterfactual would be the rate of asymptomatic infections in the control group plus the rate of symptomatic cases that was averted by vaccine.

Using data presented in table 1 of the Article,[1] we calculated expected efficacy on the basis of this alternative counterfactual comparison to estimate an upper bound on the true efficacy against asymptomatic infections. We estimate efficacy against asymptomatic COVID-19 cases to be 61·9% (appendix), which is much higher than the reported estimate of 22·2%. This analysis provides further confidence that the ChAdOx1 nCoV-19 vaccine (AZD1222) provides substantial protection against asymptomatic infections.

See Online for appendix

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1 Voysey M, Costa Clemens SA, Madhi SA, et al. Single-dose administration and the influence of the timing of the booster dose on immunogenicity and efficacy of ChAdOx1 nCoV-19 (AZD1222) vaccine: a pooled analysis of four randomised trials. *Lancet* 2021; **397:** 881–91.

Authors' reply

It is well established that randomised controlled trials are the gold standard for estimating the effect of interventions. In such studies, outcomes in participants randomised to receive the new intervention are compared with those randomised to the control product, to produce unbiased estimates of the effect of the intervention.

Elizabeth McQuade and James Platts-Mills show a new analysis of published data from our randomised controlled trial[1] of the ChAdOx1 nCoV-19 (AZD1222) vaccine to further explore the effect of vaccination on prevention of asymptomatic infections. McQuade and Platts-Mills propose a counterfactual that is the combination of symptomatic cases prevented and asymptomatic cases observed, to represent the hypothetical situation that might occur if a vaccine solely had effect on symptomatic infections and had no ability to prevent asymptomatic infection. In this situation, an excess of asymptomatic cases in the vaccine group would be observed, which McQuade and Platts-Mills attempt to quantify.

Although the underlying assumptions might be too stringent to be realistic, the results they showed are interesting and highlight the difficulties of estimating true vaccine efficacy against asymptomatic infections. We showed efficacy against all cases—that is, the combination of symptomatic or asymptomatic cases.[1] The analysis of any nucleic acid amplification test-positive outcomes maintains the benefits of the randomisation within the trial while incorporating the people that might have otherwise been symptomatic were it not for vaccination. The highly significant efficacy seen for this endpoint shows the overall benefit of the vaccine in preventing opportunity for transmission of SARS-CoV-2.[1]

Oxford University has entered into a partnership with AstraZeneca for further development of ChAdOx1 nCoV-19. AJP is Chair of the UK Department of Health and Social Care's Joint Committee on Vaccination & Immunisation, but does not participate in discussions on COVID-19 vaccines, is a member of WHO's Strategic Advisory Group of Experts, and a UK National Institute for Health Research (NIHR) Senior Investigator. MV declares no competing interests. This research is funded by NIHR, UK Research and Innovation, the Bill & Melinda Gates Foundation, the Lemann Foundation, Rede D'Or, the Brava and Telles Foundation, and the South African Medical Research Council. We are grateful to the NIHR infrastructure provided through the NIHR Biomedical Research Centres and the NIHR Clinical Research Network at the UK study sites. The views expressed in this Correspondence are those of the authors and not necessarily those of the NIHR or the UK Department of Health and Social Care.

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1 Voysey M, Costa Clemens SA, Madhi SA, et al. Single-dose administration and the influence of the timing of the booster dose on immunogenicity and efficacy of ChAdOx1 nCoV-19 (AZD1222) vaccine: a pooled analysis of four randomised trials. *Lancet* 2021; **397:** 881–91.

COVID-19 vaccine efficacy data: solid enough to delay second dose?

Sharon Amit and colleagues[1] suggest that after a first dose of BNT162b2 vaccine, there was an adjusted rate reduction of COVID-19 disease of 85% (71–92) for days 15–28 in vaccinated compared with unvaccinated healthcare workers (HCWs).[1] We think this Correspondence has fundamental flaws and address them here.

First, HCWs have been shown to have higher risks for SARS-CoV-2 viral infection, which result in asymptomatic, pre-symptomatic (at time of study initiation), or symptomatic infection.[2,3]

Second, individuals documented to have had a SARS-CoV-2 viral infection have a substantially greater response to the first dose of vaccine (up to over a thousand times the neutralising antibodies before the first vaccine dose), which is much greater than the