Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

the excess mortality and stress on health-care systems that were observed in the early phases of the pandemic. The observation that ChAdOx1 nCoV-19 remains more than 80% effective at preventing moderate-to-severe COVID-19 following breakthrough infection with the delta variant reinforces the ongoing utility and importance of this widely distributed vaccine.

Importantly, Thiruvengadam and colleagues pair these epidemiological analyses with immunological data. In a group of ChAdOx1 nCoV-19 vaccine recipients, the authors assessed neutralising antibody titres and CD4 and CD8 T-cell responses against both wild-type (ancestral) and delta viruses, in an effort to understand the immunological responses that might moderate disease severity in the event of breakthrough infection. Neutralising antibody titres, which are strong predictors of vaccine efficacy,[7] were markedly lower in ChAdOx1 nCoV-19 vaccine recipients when measured against the delta variant virus than when measured against wild-type SARS-CoV-2. Loss of neutralisation potency against the delta variant is not unique to the ChAdOx1 nCoV-19 vaccine; indeed, similar reductions have been reported using serum derived from cohorts vaccinated with mRNA vaccines.[8,9] By contrast with antibody responses, the high frequency of spike-specific CD4 and CD8 T cells elicited by ChAdOx1 nCoV-19 vaccination maintained recognition of both wild-type and delta variant spike peptides. In a comprehensive analysis, Thiruvengadam and colleagues showed that both T-cell cytokine secretion and activation were comparable following stimulation with either wild-type or delta spike peptide pools.[2]

Considering the reduced antibody neutralisation but preserved T-cell recognition of the delta variant, these data raise the intriguing question of whether even low levels of neutralising antibodies are sufficient to prevent severe disease, or whether cellular immunity is a key factor in mitigating the risk of hospital admission. Ultimately, such questions will be difficult to answer in the absence of prospective cohort studies or early immune profiling of breakthrough infections. Such data would, however, crucially inform strategies for booster vaccination and the design of next-generation vaccine candidates.

We declare no competing interests.

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1 Tao K, Tzou PL, Nouhin J, et al. The biological and clinical significance of emerging SARS-CoV-2 variants. *Nat Rev Genet* 2021; published online July 28. https://doi.org/10.1038/s41576-021-00408-x.
2 Thiruvengadam R, Awasthi A, Medigeshi G, et al. Effectiveness of ChAdOx1 nCoV-19 vaccine against SARS-CoV-2 infection during the delta (B.1.617.2) variant surge in India: a test-negative, case-control study and a mechanistic study of post-vaccination immune responses. *Lancet Infect Dis* 2021; published online Nov 25. https://doi.org/10.1016/S1473-3099(21)00680-0.
3 Lopez Bernal J, Andrews N, Gower C, et al. Effectiveness of Covid-19 vaccines against the B.1.617.2 (delta) variant. *N Engl J Med* 2021; **385:** 585–94.
4 Sheikh A, McMenamin J, Taylor B, Robertson C. SARS-CoV-2 delta VOC in Scotland: demographics, risk of hospital admission, and vaccine effectiveness. *Lancet* 2021; **397:** 2461–62.
5 Veldhoen M, Simas JP. Endemic SARS-CoV-2 will maintain post-pandemic immunity. *Nat Rev Immunol* 2021; **21:** 131–32.
6 Telenti A, Arvin A, Corey L, et al. After the pandemic: perspectives on the future trajectory of COVID-19. *Nature* 2021; **596:** 495–504.
7 Khoury DS, Cromer D, Reynaldi A, et al. Neutralizing antibody levels are highly predictive of immune protection from symptomatic SARS-CoV-2 infection. *Nat Med* 2021; **27:** 1205–11.
8 Planas D, Veyer D, Baidaliuk A, et al. Reduced sensitivity of SARS-CoV-2 variant delta to antibody neutralization. *Nature* 2021; **596:** 276–80.
9 Mlcochova P, Kemp SA, Dhar MS, et al. SARS-CoV-2 B.1.617.2 delta variant replication and immune evasion. *Nature* 2021; published online Sept 6. https://doi.org/10.1038/s41586-021-03944-y.

Booster doses for inactivated COVID-19 vaccines: if, when, and for whom

Published **Online** December 7, 2021 https://doi.org/10.1016/S1473-3099(21)00696-4

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Dealing with vaccine equity and at the same time ensuring adequate protection for the most vulnerable is essential to reduce the burden of COVID-19. New questions have been challenging the scientific community and policy makers after the initial rollout of mass vaccination campaigns, particularly surrounding the potential waning of vaccine effectiveness. It is still unknown whether supplemental doses are needed, and researchers are working to determine if, when, and for whom booster doses would be helpful for the prevention of COVID-19 illness and pandemic control.

As of the time of writing, the inactivated whole-virus vaccine CoronaVac is the most widely offered COVID-19 vaccine in the world.[1] In *The Lancet Infectious Diseases*,

Gang Zeng and colleagues report a randomised controlled trial embedded in a phase 2 trial to evaluate a third dose of CoronaVac after the two-dose schedule in healthy adults.[2] When a third dose was administered 8 months after the second dose, there was a three-fold to five-fold increase in neutralising antibody (NAb) titres against the original virus of SARS-CoV-2 compared with the NAb after the second dose. Notably, the authors also reported that a homologous third dose had a favourable safety profile. The high concentrations of NAb in adults of all ages after a third dose show that CoronaVac was able to generate immune memory, bringing hope that more people around the world who received, or will receive, inactivated vaccines against COVID-19 will be protected.

Variants of concern (VOCs) have been a source of increased case rates of breakthrough COVID-19 infections among the vaccinated population. A main limitation of Zeng and colleagues' study[2] is that the concentrations of NAbs against different VOCs were not evaluated. Yue and colleagues[3] evaluated 53 volunteers who received the two-dose schedule of CoronaVac and a booster dose 8 months later. The level of NAb against the original variant was similar to that reported by Zeng and colleagues, but there was a 4·2-fold reduction in neutralising antibody titres against the delta (B.1.617.2) variant compared with the original variant.[3] The same reduction of neutralising antibodies against the delta variant was found in a subgroup of volunteers 28 days after the second dose.[3] Vacharathit and colleagues[4] evaluated CoronaVac's immunogenicity after the second dose, finding that NAb titres against the delta variant were lower than NAb titres against the original virus and other variants. Therefore, it is expected that the results of Zeng and colleagues' study would be different if the authors had tested NAb titres against the delta variant or other VOCs after the booster dose. Although NAb titre is not an exclusive determinant of clinical protection, it is correlated with vaccine efficacy against symptomatic disease.[5]

The reduction in NAb titres after 6 months of the first two-dose scheme of CoronaVac was remarkable. NAb titres against the original variant declined to near or below the seropositive cutoff of 8 UI/mL,[2] as previously shown for the gamma (P.1) variant.[6] On this topic, Zeng and colleagues add evidence on how to optimise the timing of the booster dose. The NAb titres in participants receiving a third dose after 8 months were higher than those in participants receiving a third dose 2 months after the second dose.[2] Further studies should systematically evaluate and model when to administer a booster dose, but based on existing evidence, it seems a larger interval than 2 months is needed. A point to consider when making decisions about the intervals between doses is whether booster doses are going to be used in a mass immunisation campaign to prevent outbreaks of VOCs, when long-term effectiveness might not be the primary objective.

Currently, no data are available on effectiveness of a booster dose for inactivated whole-virus COVID-19 vaccines. Only one study using an mRNA vaccine shows preliminary results: a 95·6% efficacy of mRNA vaccine booster after 5 months.[7] Because of the pronounced decrease of NAbs titres[2,6,8] and reduced effectiveness in the older population,[9] WHO's Strategic Advisory Group of Experts on Immunization recommend a third dose of inactivated virus vaccines or a heterologous booster for people aged 60 years and older who already have received the two-dose scheme.[10]

Effectiveness and cost-effectiveness studies to evaluate the protection from, and waning immunity of, third doses of inactivated virus vaccines are needed to generate robust recommendations, especially in the context of VOCs. Key research questions include whether homologous or heterologous booster vaccines should be used, which scheme should be administered for those with an inadequate response to the primary vaccination schedule, and whether to use new vaccines specifically designed to work against VOCs. Importantly, on the basis of current knowledge, it is expected that protection against severe outcomes is maintained for the healthy, non-vulnerable population, who therefore will not necessarily need a booster dose.

JC reports having received grants from NIH, Sanofi, and Merck and personal fees from the Pan American Health Organization. OTR declares no competing interests.

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1 Mallapaty S. China's COVID vaccines have been crucial—now immunity is waning. *Nature* 2021; **598:** 398–99.

2 Zeng G, Wu Q, Pan H, et al. Immunogenicity and safety of a third dose of CoronaVac vaccine, and immune persistence of a two-dose schedule, in healthy adults: interim results from two single-centre, double-blind, randomised, placebo-controlled phase 2 clinical trials . *Lancet Infect Dis* 2021; published online Dec 7. https://doi.org/10.1016/S1473-3099(21)00681-2.

3 Yue L, Zhou J, Zhou Y, et al. Antibody response elicited by a third boost dose of inactivated SARS-CoV-2 vaccine can neutralize SARS-CoV-2 variants of concern. *Emerg Microbes Infect* 2021; published online Oct 19. https://doi.org/10.1080/22221751.2021.1996210.

4 Vacharathit V, Aiewsakun P, Manopwisedjaroen S, et al. CoronaVac induces lower neutralising activity against variants of concern than natural infection. *Lancet Infect Dis* 2021; **21:** 1352–54.

5 Khoury DS, Cromer D, Reynaldi A, et al. Neutralizing antibody levels are highly predictive of immune protection from symptomatic SARS-CoV-2 infection. *Nat Med* 2021; **27:** 1205–11.

6 Souza WM, Amorim MR, Sesti-Costa R, et al. Neutralisation of SARS-CoV-2 lineage P.1 by antibodies elicited through natural SARS-CoV-2 infection or vaccination with an inactivated SARS-CoV-2 vaccine: an immunological study. *Lancet Microbe* 2021; **2:** e527–35.

7 Pfizer. Pfizer and BioNTech announce phase 3 trial data showing high efficacy of a booster dose of their COVID-19 vaccine. Oct 21, 2021. https://www.pfizer.com/news/press-release/press-release-detail/pfizer-and-biontech-announce-phase-3-trial-data-showing (accessed Oct 22, 2021).

8 Sauré D, O'Ryan M, Torres JP, Zuniga M, Santelices E, Basso LJ. Dynamic IgG seropositivity after rollout of CoronaVac and BNT162b2 COVID-19 vaccines in Chile: a sentinel surveillance study. *Lancet Infect Dis* 2021; published online Sept 9. https://doi.org/10.1016/S1473-3099(21)00479-5.

9 Ranzani OT, Hitchings MDT, Dorion M, et al. Effectiveness of the CoronaVac vaccine in older adults during a gamma variant associated epidemic of COVID-19 in Brazil: test negative case-control study. *BMJ* 2021; **374:** n2015.

10 SAGE. Highlights from the meeting of the Strategic Advisory Group of Experts (SAGE) on Immunization. Oct 11, 2021. https://cdn.who.int/media/docs/default-source/immunization/sage/2021/october/sage_oct2021_meetinghighlights.pdf?sfvrsn=3dcae610_15 (accessed Oct 22, 2021).

The potential perils of a drug protection framework in tuberculosis

Published **Online** November 12, 2021 https://doi.org/10.1016/S1473-3099(21)00563-6

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When bedaquiline was approved by stringent regulatory agencies for the treatment of drug-resistant tuberculosis in 2012, it was as the first novel agent for the treatment of tuberculosis to be developed in almost 50 years.[1] Given the gruelling therapeutic regimens being used for drug-resistant tuberculosis at the time—with success rates hovering at a dismal 50% globally—it would seem this novel medication would be embraced as a breakthrough and rapidly rolled out.[2] However, data on bedaquiline use painted a different picture, with fewer than 20% of those in need of the medication actually receiving it by 2016.[3] Although multiple reasons were given for this low uptake of bedaquiline—including costs, safety concerns, and limited practical experience with its use—one often cited reason for denying people access to bedaquiline was fear of generating resistance to the medication.[4] "We have to protect the drug" was a common mantra among those working in the field. In fact, so invested was the tuberculosis community in this framework of drug protection that early WHO recommendations on the use of bedaquiline specified it should only be given to people who had limited treatment options, either because of resistance or intolerance to other second-line medications[5]—a population vastly different from those included in the clinical trials that led to the purported evidence-based recommendations regarding how bedaquiline should be used.

Fortunately, the innovative drug-resistant tuberculosis treatment programme in South Africa adopted a different approach to the use of bedaquiline.[6] Recognising the limitations of the existing treatment approaches, the country decided to roll out bedaquiline through a clinical access programme, which would offer people living with the disease this novel therapeutic option and allow the country to collect data on the real-world performance of the medication. This visionary approach to the introduction of therapeutic innovation radically altered the drug-resistant tuberculosis treatment landscape and ultimately supported bedaquiline being recommended for most people living with the disease around the world.[7] The approach also allowed for the lessons learned in South Africa to be shared and applied more broadly.

In *The Lancet Infectious Diseases*, Nazir Ahmed Ismail and colleagues[8] present another seminal piece of work to come from the country and its early adoption of bedaquiline. The authors used cross-sectional and longitudinal approaches to analyse information on the presence of mutations in *Mycobacterium tuberculosis* that lead to bedaquiline resistance and assess the effect of these mutations on treatment outcomes. In South Africa, patients receiving bedaquiline had samples submitted at baseline, month 2, and month 6 of treatment. Ismail and colleagues included patients who were aged 12 years or older with a positive culture sample at baseline or, if the sample was invalid or negative, a sample within 30 days of the baseline sample submitted for bedaquiline drug susceptibility testing.