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.

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Longer intervals and extra doses of ChAdOx1 nCoV-19 vaccine

As the COVID-19 pandemic evolves, public health authorities continue to make unprecedented decisions about the deployment of limited supplies of vaccines against COVID-19. One strategy to maximise the number of people immunised is to delay the second dose of vaccine, as was implemented in the UK and elsewhere, including for the Oxford–AstraZeneca ChAdOx1 nCoV-19 (AZD1222) vaccine.[1] This decision was supported by the original phase 1–3 trials (COV001, COV002, COV003, and COV005) that showed increased binding antibody responses and vaccine efficacy with an extended prime-boost interval (≥12 weeks *vs* <6 weeks).[2] Because the trial protocols were amended during the enrolment periods of these trials, subcohorts received the second dose at varying intervals. In *The Lancet*, Amy Flaxman and colleagues[3] used these differences in COV001 and COV002 to investigate the persistence of immunogenicity after a single dose of ChAdOx1 nCoV-19 in 480 individuals, the immunity after an extended interval (44–45 weeks) between the first and second doses in 30 individuals, and the antibody immune response to a third dose as a booster given 28–38 weeks after the second dose in 75 individuals. All participants included were aged 18–55 years, the majority were White (>90%), and approximately half were female.

The encouraging results support a strategy of delayed second dosing because antibody titres were substantially higher after the second dose among individuals with almost a year between doses than among individuals who had an 8–12 week interval (median total IgG titres 923 ELISA units [EUs; IQR 525–1764] with an 8–12 week interval *vs* 3738 EUs [1824–6625] with a 44–45 week interval).[3] However, the total public health impact of the extended prime-boost interval is unclear given the trade-off between a longer period at the lower level of protection afforded by a single dose and the higher level of protection obtained after a delayed second dose. Although antibody titres remained elevated, at about 70 EUs, approximately 44–45 weeks after the first dose, titres waned over that period, suggesting that the risk of infection might increase between doses as the interval extends.

Flaxman and colleagues also assessed the effect of a third dose 6–9 months after the second dose among individuals who received the first two doses 2–4 months apart. A third dose is being given to immunosuppressed individuals in France and Israel,[4,5] and there is interest in broader use of a third dose in response to the rapid spread of the delta (B.1.617.2) SARS-CoV-2 variant. Flaxman and colleagues found that a third dose was well tolerated and successfully boosted antibody titres compared with a second dose (median total IgG titre of 1792 EUs [IQR 899–4634] at 28 days after the second dose *vs* 3746 EUs [2047–6420] at 28 days after the third dose) and that neutralising


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antibody titres to SARS-CoV-2 variants of concern and T-cell responses to the Victoria strain were higher after the third dose than the second dose. Because first and second doses are still urgently needed globally and two doses remain effective against severe disease, experts do not currently recommend a third dose.[6] However, these data importantly assuage concerns about the potential for impaired responses after repeated use of a replication deficient simian adenoviral vector and suggest that a third dose of the ChAdOx1 nCoV-19 vaccine could be successful if necessary.

These results are timely and informative for critical decisions about vaccine implementation, but they are not without limitations. Importantly, although the data were collected in randomised trials, the specific comparisons reported were not made between randomised groups, which introduces the potential for biases that are encountered in non-randomised settings, including confounding[7] and selection bias.[8] Instead, variation in prime-boost intervals occurred in a non-randomised fashion on the basis of the relative timing between enrolment and protocol amendments. Because average age and risk level changed over the enrolment period,[9] individuals with longer prime-boost intervals were younger and at potentially lower risk than individuals with shorter intervals, which could confound effects on immunogenicity. Furthermore, individuals who were infected with SARS-CoV-2 between doses were excluded. Because the risk of infection is affected by vaccine response and the duration of the higher-risk period between doses, the study might have oversampled individuals who had better vaccine responses in the extended interval prime-boost group because these individuals would be less likely to become infected and be excluded. The magnitude of these potential biases is unknown.

To address these limitations, a useful framework is to design the observational study specifically to emulate a randomised trial.[10] There are several approaches that can be used, including the clone-censor-weight design[11] and parametric g-computation.[12] The clone-censor-weight design has been used to estimate the effects of rotavirus vaccine protocols,[13] and, using data like those from the current study, could potentially be applied to COVID-19 vaccine protocols as well. Briefly, the data are copied twice with one copy assigned to each vaccine schedule (eg, standard or late second dose), and patients are followed up from the time of their first dose until their data are no longer consistent with the assigned schedule. Carefully constructed weights are then applied and if all important covariates are properly accounted for, the resulting data can be analysed as if they arose from a randomised trial. By not excluding participants who were infected before the second dose, the resulting evidence acknowledges the risk–benefit trade-off made when extending prime-boost intervals.

Evidence to inform decisions about COVID-19 vaccine timing and dosing is urgently needed, despite imperfect data. By acknowledging the observational nature of secondary analyses of randomised trials and by carefully designing non-randomised studies to address the inherent biases, we will be best positioned to rapidly incorporate new evidence into the strategy to contain COVID-19.

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To master heart failure, first master congestion

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The GUIDE-HF team[1] should be congratulated on attempting to master congestion, a key driver of symptoms, signs, and progression of heart failure. Controlling congestion is associated with an excellent prognosis,[2] a key consideration for a new universal definition of heart failure.[3] Symptoms and signs are late, subjective, and insensitive measures of congestion compared with blood biomarkers, ultrasound, and haemodynamics.[3,4] Raised (>15 mm Hg) pulmonary artery diastolic pressure, reflecting left atrial pressure, indicates haemodynamic congestion, although not necessarily congestion in tissues (ie, oedema).[3] In the GUIDE-HF trial, reported by JoAnn Lindenfeld and colleagues in *The Lancet*,[1] pulmonary artery pressure was measured using a transvenously implanted, wireless chip, powered externally by radio-frequency energy, enabling daily transmission of snapshot recordings to remote health-care providers, avoiding in-person visits and facilitating home telemonitoring.[5,6] 375 (38%) of 1000 patients in the trial were women. Participant race was distributed as follows: 808 (81%) of 1000 patients were White, 180 (18%) participants were Black, one (<1%) participant was Asian, four (<1%) participants were Native Americans or Alaska Natives, and nine (1%) patients were classified as other.

Previous research suggests that pulmonary artery pressure monitoring might reduce hospitalisations for heart failure.[7–10] Setting out to confirm this, the GUIDE-HF trial was simple in concept but complex to implement. Patients were masked to their assigned group, but all were contacted regularly. Research staff at the same centre could be masked or not masked depending on their role.[1] This design was suitable for testing a technology, but less suitable for a whole system of care. All participants had devices implanted before random allocation to their study group; 98% of device implantation attempts were successful. Complications were rare and patient adherence to data transmission was good, whether assigned to disclosure or concealment of pulmonary artery pressures. Targets were 15–35 mm Hg for systolic pulmonary artery pressure, 10–25 mm Hg for mean artery pressure, and 8–20 mm Hg for diastolic pulmonary artery pressure. Disappointingly, only mean pulmonary artery pressures have been reported so far.[1]

Around 20% of the 1000 randomly allocated patients were aged 80 years or older, left ventricular ejection fraction was greater than 40% in 469 (47%) patients (for whom guidelines provide few therapeutic recommendations), 557 (56%) patients were hospitalised in the previous year, and baseline pulmonary artery diastolic pressure was already in the target range for around 50% of patients. Plasma concentrations of natriuretic peptides were grossly elevated, possibly because most patients (591 [59%]) had a history of atrial fibrillation. Clinical signs of congestion were not reported. Most patients with a left ventricular ejection fraction of 40% or less received loop diuretics and β blockers and had defibrillators or cardiac resynchronisation devices, but many were not prescribed other guideline-recommended therapies. In the control group, 44 (4%) patients withdrew from the trial or were lost to follow-up compared with 25 (3%) in the monitoring group.

Overall, the trial was neutral for its primary endpoint, recurrent heart failure events (admissions to hospital or emergency hospital visits) or all-cause mortality at 12 months, although women, older patients, Black patients, and those with milder symptoms might have benefited. Pulmonary artery pressure monitoring was not associated with improvements in exercise capacity or quality of life and therefore, by inference, symptoms. Cardiovascular mortality was 5% at 12 months, which was low considering participant ages and multimorbidity. Fewer events than planned occurred in the control