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.

difference in global self-rating of how well patients felt had largely disappeared by day 28 and the time to alleviation of all symptoms was not different between groups, yet the difference in the WHO-5 Well-Being Index, a subjective psychological wellbeing scale, was still present at 28 days. Longer-term follow-up clarifying the effects on the trajectory of illness, especially on persistent morbidity after COVID-19, would be useful.

On the basis of the PRINCIPLE trial data, it seems reasonable to consider inhaled corticosteroid use in early COVID-19 in patients similar to the trial population group (people with ongoing symptoms from COVID-19 aged ≥65 years or ≥50 years with specific comorbidities) who are interested in using them (80% of participants in the inhaled budesonide group in PRINCIPLE used the inhaled corticosteroids for at least a week). Various subgroup analyses in PRINCIPLE do not provide any pointers to which particular patient or illness characteristics in the included population might be more likely to predict benefit. These trial data do not support use in younger populations who are at lower risk of complications (<65 years with no comorbidities or anyone <50 years). Because vaccination was uncommon in trial participants, an important question is whether and what effect would be seen in the fully vaccinated population who have a different illness severity and trajectory.

We see through two recent pragmatic COVID-19 treatment trial platforms an important shift in approach: trials funded by governments and not industry, answering the crucial questions driven by immediate clinician need and not product marketing, and providing data in the spaces of clinical equipoise—this importance should not be underestimated or lost.

We declare no competing interests.

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Optimising SARS-CoV-2 vaccination schedules

The objective of any vaccination strategy is to achieve long-term protection against infection and also to reduce the mortality and morbidity associated with the eventual development of disease. This dual perspective usually requires repeated immunisations. Several factors affect the immunological outcome of repeated immunisations, such as the antigen selected, the time between doses, and the type of vector.[1] Once the initial vaccination schedules have been approved, trials must be designed to optimise immunological outcomes by adjusting these parameters and others.

In *The Lancet*, Xinxue Liu and colleagues[2] present results for four of the eight intervention groups of the Com-COV clinical trial, showing that the immunological response of double-dose ChAdOx1 nCoV-19 (AstraZeneca; hereafter referred to as ChAd) is statistically lower than any other schedule including BNT162b2 (Pfizer–BioNTech, hereafter referred to as BNT) and ChAd at 28 days post boost dose, with a 28-day prime–boost interval. In addition, their findings support previous published data from an academic study done by the Instituto de Salud Carlos III, of which I was an investigator and author,[3] suggesting


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that a heterologous schedule based on the sequential administration of ChAd and BNT could be highly immunogenic, and perhaps more immunogenic than homologous schedules based on ChAd. In addition, Liu and colleagues show that double-dose BNT is more potent in inducing a humoral response than the BNT–ChAd permutation.

The SARS-CoV-2 humoral immune response has been used in early clinical trials as a surrogate marker of protection.[4-6] However, the minimum titre of SARS-CoV-2 protein S neutralising antibodies to induce protection is unknown. We do not even know if this minimum titre exists in clinical practice. In this regard, Liu and colleagues appropriately contextualise their immunological findings with the evidence of protection against hospitalisation and severe disease from phase 3 trials using homologous schedules.[7] The clinical and epidemiological relevance of these immunological differences will be inferred when information about morbidity induced by re-exposure to SARS-CoV-2 in vaccinated populations becomes available.

The authors observed no differences in safety between the four study groups, although reactivity was higher in the heterologous schedules.[8] In this respect, the comparative safety and reactogenicity between the four groups deserve special consideration because the study was designed as a non-inferiority trial. Non-inferiority trials are randomised studies in which authors focus on whether an experimental arm is not clinically and statistically inferior to an active control group.[9] Therefore, when an experimental scheme meets with the non-inferiority criteria for efficacy, the differences in safety between the compared schemes should guide the clinical impact analysis. Additionally, authors included a preplanned definition of superiority that allowed for a switch from non-inferiority to superiority. From a statistical perspective, this demonstration is valid on its own, as long as safety profiles of the compared schedules are similar. If the safety profiles were different, the authors would need to estimate the size effect to assess whether it is sufficient to outweigh the adverse effects. In the Com-COV trial, safety is similar between groups but reactogenicity was higher in the heterologous schedules.[8] It is clear that reactogenicity, although more intense in this study, is of little clinical relevance and could be modulated by modifying the time between doses.[4] Therefore, vaccination policy makers should estimate the size effect of the immunological humoral response to assess whether it is sufficient to compensate for the reactogenicity events.

The Com-COV trial, like the CombiVacS trial,[3] was not able to identify very low-frequency adverse events. Of course, no phase 2 study is able to do so. However, some phase 3 clinical trials have not been sufficiently powered to identify very low-frequency events, such as those that have provoked the controversy over the use of ChAd.[10] Therefore, any approach to identify this type of event must be oriented towards a good use of pharmacovigilance programmes or phase 4 clinical trials. Liu and colleagues reported similar types, frequency, and intensity of events to those detected with the individual use of each of the vaccines.

In summary, the question to be answered is whether the data published by Liu and colleagues, in combination with those previously published by Borobia and colleagues,[3] are enough evidence to initiate the modification of vaccination schedules. Alternatively, large academic phase 3 clinical trials could explore the protection against severe disease, intensive care unit admission, and SARS-CoV-2 mortality using heterologous schedules, but the time and effort that this work would entail should be carefully balanced against the potential benefits.

I am the study chair of the CombiVacS clinical trial and the deputy general manager of the Instituto de Salud Carlos III.

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In-country data will illuminate under-5 mortality disparities

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In *The Lancet*, Nicholas Kassebaum and colleagues present all-cause and cause-specific mortality findings from the Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) to illustrate global, regional, and national progress toward Sustainable Development Goal 3.2 for neonatal and child health.[1] Their analysis provides a comprehensive assessment of under-5 and neonatal mortality across 203 countries, including a focus on preventable mortality and projections to 2030. The authors' meta-level look at death rates and cause-specific mortality, grouped by country level and sociodemographic indices, also looks at the effect of COVID-19 on future projections.

The strength of the GBD lies in its enormous volume of data and sophisticated analytical processes that allow for complex modelling and future projections. The GBD has contributed to a fundamental shift in how we think about measuring progress in global health indicators. However, an important limitation is that aggregate, country-level mortality data obfuscate within-country and subgroup variability. Previous research shows that within-country variability accounts for a greater proportion of under-5 mortality than country-level variability, and under-5 mortality rates vary by a factor of 10 within most countries in sub-Saharan Africa.[2] Such in-country variability raises questions of whether GBD data at the country level are best suited for modelling under-5 deaths,[3] as well as how individual country leaders ought to respond to GBD findings. The authors have tried to address country-level data limitations in part by creating a Socio-demographic Index that stratifies countries on the basis of income per capita, educational attainment, and fertility rates. Yet we know that disparities within countries are often much greater than those between countries.[4]

This analysis also focuses on single, biomedical causes of neonatal and under-5 death. Causes of death are often multifactorial, and many do not lend themselves to a simple clinical diagnosis. For example, for every child who dies from diarrhoea, how many cases can be attributed to overcrowded living situations with poor sanitation, poor education regarding oral rehydration therapy, or inadequate access to vaccinations, each of which requires a different intervention? Relying on the simplified treatment of the cause of death in the GBD is likely to over-emphasise clinical and biomedical solutions, and could fall short if the true goal is to improve programme planning and implementation and have a lasting, scalable effect on outcomes. To that end, another challenge is that, in isolating newborn baby

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