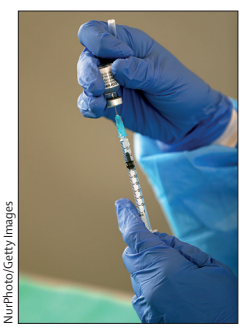
Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Heterologous vaccine regimens against COVID-19



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The rapid development of vaccines against COVID-19 is the biggest achievement of science in the fight against the pandemic. Although the efficacy and safety of all approved vaccines have been demonstrated in large clinical trials, recent safety signals have been reported,[1,2] highlighting the importance of post-marketing surveillance with study populations larger than those of the trials, and representative of populations receiving vaccines as part of routine clinical practice. Safety concerns regarding the ChAdOx1-S vaccine have led some European countries (eg, Denmark) to minimise its use, with other countries recommending the switch from the trial-tested homologous booster to a heterologous booster, such as with BNT162b2.[3] This recommendation has come as a surprise to some, because abundant data on more than 9 million people suggested a much reduced risk of thrombotic events with the second dose of ChAdOx1-S.[4] In contrast, the evidence for the effectiveness and safety of heterologous vaccination regimens remains limited, and based on small phase 2 trials and cohort studies including fewer than 500 participants.[5,6]

In *The Lancet*, Alberto Borobia and colleagues[7] report the first results of a phase 2 trial in five university hospitals across Spain assessing the immunogenicity and reactogenicity of the BNT162b2 vaccine administered as second dose in people primed with ChAdOx1-S. The study included 676 adults aged 18–60 years (mean age 44 years [SD 9]; 382 [57%] women and 294 [43%] men) followed up for 14 days, and showed that BNT162b2, given as a second dose 8–12 weeks after a first dose of ChAdOx1-S, induced a robust immune response and mild reactogenicity. This trial compared this heterologous vaccine regimen to no booster vaccination, and the lack of a homologous vaccination comparator is a limitation of the study,[8] because it does not allow for a direct comparison of the vaccination schedules used in current clinical practice. As in most phase 2 trials, the study has limited representativeness with strict eligibility criteria, including the exclusion of vulnerable and elderly people. This decision is in discord with the global prioritisation of these groups for vaccination.

The high immunogenicity reported by Borobia and colleagues is promising, with 100% of participants exhibiting neutralising antibodies 14 days after BNT162b2 administration. Heterologous schedules are of interest for numerous reasons, including logistical considerations and clinical efficacy. The approval of heterologous vaccination will be an opportunity to make vaccination programmes more flexible in response to fluctuations in supply, which is of particular importance for countries with scarce vaccine access and in countries where different vaccines might become available at different times.[9] Heterologous regimens also have the potential to produce a stronger response,[10] therefore leading to higher efficacy. Finally, it is predicted that mixing vaccines will be necessary with the appearance of new SARS-CoV-2 variants.

Beyond efficacy, safety has been stated to be a key motivator for the use of heterologous vaccination regimens in people primed with ChAdOx1S. However, most of the adverse events listed by regulatory agencies in safety surveillance of COVID-19 vaccines are extremely rare.[11] These events can only be detected in ongoing studies including hundreds of thousands, or millions, of people. The small sample size and short follow-up of the study by Borobia and colleagues did not allow for a full assessment of the safety of the proposed heterologous vaccination regimens.

Additionally, the reported reactogenicity in the study by Borobia and colleagues is not in line with a previous active comparator, randomised controlled trial, where 114 participants who were randomly assigned to the proposed heterologous vaccination regimen had many more, and more intense, short-term adverse events than the participants who received the homologous regimen.[11] More research is needed on the correlation between reactogenicity and severe (albeit extremely rare) adverse effects, and the reasons these two trials show such different results.

In conclusion, heterologous vaccination regimens against COVID-19 provide an opportunity to speed up vaccination campaigns worldwide, maximising their impact on the control of the pandemic. This study is the first report of a randomised controlled trial testing heterologous vaccination, and should be the basis for future studies. Large phase 3 trials including homologous vaccination as a comparator and further

observational studies are urgently needed to inform the clinical effectiveness and safety of heterologous regimens in the target populations and settings.

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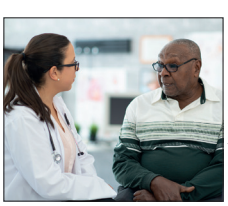
Tirzepatide and the new era of twincretins for diabetes

Type 2 diabetes and obesity are responsible for a large global burden of morbidity and mortality in the form of cardiovascular disease, kidney disease, and retinopathy. Analogues of the incretin GLP-1 have helped to transform the face of type 2 diabetes treatment, combining effective reductions in glycaemia with clinically useful weight loss. More importantly, GLP-1 analogues are proven to reduce mortality, the risk of cardiovascular events, and progression of diabetic kidney disease.[1] However, the achievable doses and efficacy of GLP-1 analogues can be limited by their adverse effects, mainly gastrointestinal in nature, such as nausea, vomiting, gastro-oesophageal reflux, and alterations in bowel habit.[2] In the search for the next step beyond GLP-1, researchers have explored suitable companion treatments to obtain enhanced efficacy.[3] The other incretin, glucose-dependent insulinotropic polypeptide (GIP), is, on first look, a natural partner to GLP-1 and is the more dominant insulinotropic hormone in normal physiology.[4] Tirzepatide, a unimolecular dual agonist of GLP-1 and GIP receptors, was developed with this so-called twincretin concept in mind.[5]

In *The Lancet*, Julio Rosenstock and colleagues[6] report on the first in a series of global registration phase 3 trials for tirzepatide, SURPASS-1. In this double-blind, randomised controlled trial recruiting people with type 2 diabetes naive to injected diabetes treatments and who had not been using oral hypoglycaemic agents for at least 3 months, 478 participants (mean age 54·1 years [SD 11·9], 231 [48%] women) were randomly assigned (1:1:1:1) to once a week tirzepatide (5, 10, or 15 mg) or a placebo injection delivered with similar single-dose devices for a duration of 40 weeks. Baseline characteristics were well balanced between groups. All participants given tirzepatide started at 2·5 mg per week with dose escalation at a fixed rate of 2·5 mg every 4 weeks until they reached their assigned maintenance dose, meaning that it took up to 20 weeks to reach the 15 mg dose. All doses of tirzepatide were superior to placebo with marked reductions in glycated haemoglobin (HbA_{1c}). The estimated mean treatment differences (ETDs) versus placebo were –1·91% (–21 mmol/mol) with tirzepatide 5 mg, –1·93% (–21 mmol/mol) with tirzepatide 10 mg, and –2·11%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