
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.

inspiratory hose, exhaled gases from ICU ventilators are vented into the direct surroundings. Although lower concentrations are generally recommended for sedation of critically ill patients than for patients undergoing surgery, a need for higher doses has been described for patients with specific conditions (eg, acute respiratory distress syndrome).[8] Hence, methods for residual scavenging of exhaled gas are required considering the increased concentrations of the volatile anaesthetic on the ICU. Last but not least, acquiring inhaled sedation in the ICU is associated with substantial costs (besides the costs of purchasing necessary equipment) that are determined by the drugs used and the disposable administration device, which is for single-patient use and should be exchanged daily.

Use of volatile anaesthetics in the operating room and has been reduced in recent years due to ecological concerns. In the ICU, a trend in the opposite direction seems to have evolved over the past few years, with an increasing use of volatile anaesthetics.[9,10] Although isoflurane consumption seems extremely low (3·5 mL/h), especially for an assumed open ventilator system, attention remains to be paid to environmental aspects, particularly with regard to the processing of the scavenged isoflurane.

The effects of an extended duration of use of volatile anaesthetics, and the potential pulmonary protective effects in acute respiratory distress syndrome warrant further investigation. Finally, the cost-effectiveness of volatile anaesthetics will need to be determined and the protection and safety of both ICU staff and the environment assured before a large-scale switch can be made to inhaled sedatives in the ICU setting.

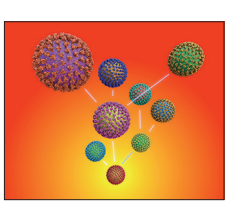
*Marcus J Schultz, Frederique Paulus, Markus W Hollmann
**marcus.j.schultz@gmail.com**

Mahidol Oxford Tropical Medicine Research Unit (MORU), Mahidol University, Bangkok, Thailand (MJS); Center of Expertise Urban Vitality, Amsterdam University of Applied Sciences, Amsterdam, Netherlands (FP); Department of Anaesthesiology, Amsterdam UMC, location AMC, Amsterdam, Netherlands (MWH)

1 Meiser A, Volk T, Wallenborn J, et al. Inhaled isoflurane via the anaesthetic conserving device versus propofol for sedation of invasively ventilated patients in intensive care units in Germany and Slovenia: an open-label, phase 3, randomised controlled, non-inferiority trial. *Lancet Respir Med* 2021; published online Aug 26. https://doi.org/10.1016/S2213-2600(21)00323-4.
2 Kingery WS, Agashe GS, Guo TZ, et al. Isoflurane and nociception: spinal alpha2A adrenoceptors mediate antinociception while supraspinal alpha1 adrenoceptors mediate pronociception. *Anesthesiology* 2002; **96:** 367–74.
3 Qiu Q, Choi SW, Wong SS, Irwin MG, Cheung CW. Effects of intra-operative maintenance of general anaesthesia with propofol on postoperative pain outcomes—a systematic review and meta-analysis. *Anaesthesia* 2016; **71:** 1222–33.
4 Cheng SS, Yeh J, Flood P. Anesthesia matters: patients anesthetized with propofol have less postoperative pain than those anesthetized with isoflurane. *Anesth Analg* 2008; **106:** 264–69.
5 Jiao Y, He B, Tong X, Xia R, Zhang C, Shi X. Intraoperative monitoring of nociception for opioid administration: a meta-analysis of randomized controlled trials. *Minerva Anestesiol* 2019; **85:** 522–30.
6 Cabibel R, Gerard L, Maiter D, Collin V, Hantson P. Complete nephrogenic diabetes insipidus after prolonged sevoflurane sedation: a case report of 3 cases. *A A Pract* 2019; **12:** 155–59.
7 Schuster F, Moegele S, Johannsen S, Roewer N. Malignant hyperthermia in the intensive care setting. *Crit Care* 2014; **18:** 411.
8 Kermad A, Speltz J, Danziger G, et al. Comparison of isoflurane and propofol sedation in critically ill COVID-19 patients-a retrospective chart review. *J Anesth* 2021; published online June 25. https://doi.org/10.1007/s00540-021-02960-6.
9 Sherman J, Le C, Lamers V, Eckelman M. Life cycle greenhouse gas emissions of anesthetic drugs. *Anesth Analg* 2012; **114:** 1086–90.
10 Watts N, Amann M, Arnell N, et al. The 2020 report of The Lancet Countdown on health and climate change: responding to converging crises. *Lancet* 2021; **397:** 129–70.

# Heterologous ChAdOx1-nCoV19–BNT162b2 vaccination provides superior immunogenicity against COVID-19

At the height of the COVID-19 vaccination campaign, supply and local availability issues for the approved vaccines—together with worries about rare side-effects (thrombotic thrombocytopenia)—necessitated the switch to heterologous vaccination schedules, commonly known as mixing vaccines. Several studies have now been completed addressing the efficacy and safety of this practice during the battle for immunisation against SARS-CoV-2 and its variants. In *The Lancet Respiratory Medicine*, David Hillus and colleagues report the interim results of a study from the Charité—Universitätsmedizin in Berlin, Germany, on the safety, reactogenicity, and immunogenicity of homologous and heterologous prime-boost immunisation with the non-replicating chimpanzee adenovirus vaccine ChAdOx1-nCoV19 (AstraZeneca, Cambridge, UK) and mRNA vaccine BNT162b2 (Pfizer-BioNtech, Mainz, Germany).[1] For this prospective observational study, the authors enrolled health-care workers in Berlin who received either homologous ChAdOx1-nCoV19 or heterologous



Tim Vernon/SPL

Published **Online** August 12, 2021 https://doi.org/10.1016/S2213-2600(21)00366-0

See **Articles** page 1255

ChAdOx1-nCoV19–BNT162b2 vaccination with a 10–12-week vaccine interval or homologous BNT162b2 vaccination with a 3-week vaccine interval.

The study enrolled 380 participants, with 174 receiving homologous BNT162b2, 38 receiving homologous ChAdOx1-nCoV19, and 104 receiving ChAdOx1-nCoV19–BNT162b2 vaccination. Heterologous ChAdOx1-nCoV19–BNT162b2 vaccination was well tolerated, and its reactogenicity was similar to that of homologous vaccination. Antibodies against spike S1 subunit, receptor binding domain (RBD), and nucleocapsid antigens were quantitated by enzyme-linked antigen-printed microarrays. The nucleocapsid antibodies discriminated between individuals who were vaccinated and those who had viral infection, who were excluded. In subsequent analyses, Hillus and colleagues assessed neutralising antibodies from serum samples of participants using HRP-conjugated recombinant RBD (representing a surrogate SARS-CoV-2), which binds to the ACE2 receptor. This surrogate virus was pre-incubated with diluted serum and then incubated with ACE-2-coated plates (medac, Wedel, Germany). Alternatively, the authors did pseudovirus neutralisation tests (pNT) with HIV-1 pseudotypes containing the spike protein genes of alpha (B.1.1.7) and beta (B.1.351) SARS-CoV-2 variants. Reciprocals of values for diluted neutralising antibodies that inhibited infection of ACE2-293 cells by 50% were called the 50% inhibitory dose ($ID_{50}$). Additionally, the authors characterised IgG avidity by incubating a 1:100 dilution of serum (in the presence or absence of urea) with subunit S1-coated ELISA plates for 10 min. Bound IgG in the presence or absence of urea was used to calculate the avidity index. Finally, spike protein-specific T-cell responses were measured with an ELISA designed to detect interferon-γ (IFN-γ) released from S1 peptide stimulated T-cells.

Most of the findings were straightforward. Spike-binding IgG responses were similar among participants vaccinated with ChAdOx1-nCoV19–BNT162b2, homologous ChAdOx1-nCoV19, or homologous BNT162b2. However, the median relative avidity index was higher after heterologous ChAdOx1-nCoV19–BNT162b2 prime-boost (93·6%, IQR 91·9–95·5) compared with both homologous ChAdOx1-nCoV19 (71·7%, 64·8–77·4, p=0·0026), and homologous BNT162b2 prime-boosts (73·9%, 63·0–81·6, p=0·014). Inhibition of surrogate virus neutralisation was found to be lower after homologous ChAdOx1-nCoV19 immunisation (median 92·4%, IQR 86·4–96·4) compared with homologous BNT162b2 (96·6%, 95·5–97·2, p=0·034) and ChAdOx1-nCoV19–BNT162b2 (97·1%, 96·9–97·3, p<0·0001). Antibody neutralisation assays directed against alpha and beta pseudoviruses showed that ChAdOx1-nCoV19–BNT162b2 prime-boost inhibited at an $ID_{50}$ of 956·6 (95% CI 835·6–1095·0) for the alpha variant and 417·1 (349·3–498·2) for the beta variant. Serum samples from participants who received homologous BNT162b2 inhibited the pseudovirus variants, with $ID_{50}$ of 369·2 (310·7–438·6) for alpha and 72·4 (60·5–86·5) for beta. Serum samples from participants who received homologous ChAdOx1-nCoV19 also inhibited the alpha ($ID_{50}$ 212·5, 131·2–344·4) and beta (48·5, 28·4–82·8) variants. Clearly, the alpha variant was more susceptible than the beta variant to neutralising antibodies. T-cell reactivity measured by IFN-γ release from S1-stimulated lymphocytes was greatest after ChAdOx1-nCoV19–BNT162b2 vaccination, followed by homologous BNT162b2 vaccination and homologous ChAdOx1-nCoV19 vaccination.

We noted that the difference in time interval between two doses of BNT162b2 vaccine (homologous BNT162b2, received 3 weeks apart) and between the ChAdOx1-nCoV19–BNT162b2 and homologous ChAdOx1-nCoV19 regimens (10–12 weeks apart) could reduce antibody production and T-cell reactivity in the homologous BNT162b2 vaccine group. The order of inoculation of the prime-boost in the heterologous schedule should also have been tested (ie, BNT162b2–ChAdOx1-nCoV19) because another study[2] has shown that this can reduce immunogenicity. Another aspect of slight concern was the smaller number of participants (38 individuals) in the homologous ChAdOx1-nCoV19 group. It also remains to be shown whether the Moderna vaccine (elasomeran, Moderna, Cambridge, MA, USA) behaves in a similar manner as BNT162b2 in the context of heterologous vaccination. It would also be interesting to test the neutralising antibodies against the delta variant. Finally, the duration and degree of protection over time will also be of interest. Overall, Hillus and colleagues' study appears to be well conceived and carefully executed.

Small pilot studies describing heterologous vaccination against COVID-19 have previously been reported in the literature.[3-5] An investigation in mice[5] established groundwork for human cohort studies

that used mixed ChAdOx1-nCoV19–mRNA vaccine regimens.[2,6–10] Another study used flow cytometry to show that levels of stimulated $CD4^+$ helper and $CD8^+$ cytotoxic T lymphocytes producing key cytokines were elevated after ChAdOx1-nCoV19–BNT162b2 and homologous BNT162b2 vaccination compared with those after homologous ChAdOx1-nCoV19 vaccination.[6] Two other studies have also shown increased levels of spike-specific $CD4^+$ and $CD8^+$ lymphocytes and neutralising activity against alpha and beta variants after ChAdOx1-nCoV19–BNT162b2 and homologous BNT162b2 vaccination.[9,10] Finally, a very recent study has suggested that the order of immunising agents (ChAdOx1-nCoV19–BNT162b2 *vs* BNT162b2–ChAdOx1-nCoV19) and the time interval between primary and secondary inoculation might have to be optimised to 10–12 weeks to deliver its full benefits.[2] Clearly, heterologous vaccination in conjunction with mRNA vaccines has emerged as a key weapon in the arsenal against COVID-19.

I declare no competing interests.

*Christopher D Richardson*
**chris.richardson@dal.ca**

Department of Microbiology & Immunology/Pediatrics, Canadian Center of Vaccinology, Dalhousie University, Halifax, Nova Scotia B3K 6R8, Canada

1 Hillus D, Schwarz T, Tober-Lau P, et al. Safety, reactogenicity, and immunogenicity of homologous and heterologous prime-boost immunisation with ChAdOx1 nCoV-19 and BNT162b2: a prospective cohort study. *Lancet Respir Med* 2021; published online Aug 12. https://doi.org/10.1016/S2213-2600(21)00357-X.

2 Ostadgavahi AT, Booth R, Sisson G, et al. Heterologous immunization with Covishield and Pfizer vaccines against SARS-CoV-2 elicits a robust humoral immune response. *J Infect Dev Ctries* 2021; **15:** 653–56.

3 He Q, Mao Q, An C, et al. Heterologous prime-boost: breaking the protective immune response bottleneck of COVID-19 vaccine candidates. *Emerg Microbes Infect* 2021; **10:** 629–37.

4 Spencer AJ, McKay PF, Belij-Rammerstorfer S, et al. Heterologous vaccination regimens with self-amplifying RNA and Adenoviral COVID vaccines induce robust immune responses in mice. *Nat Commun* 2021; **12:** 2893.

5 Schmidt T, Klemis V, Schub D, et al. Immunogenicity and reactogenicity of heterologous ChAdOx1 nCoV-19/mRNA vaccination. *Nat Med* 2021; published online July 26. https://doi.org/10.1038/s41591-021-01464-w.

6 Borobia AM, Carcas AJ, Pérez-Olmeda M, et al. Immunogenicity and reactogenicity of BNT162b2 booster in ChAdOx1-S-primed participants (CombiVacS): a multicentre, open-label, randomised, controlled, phase 2 trial. *Lancet* 2021; **398:** 121–30.

7 Normark J, Vikström L, Gwon YD, et al. Heterologous ChAdOx1 nCoV-19 and mRNA-1273 vaccination. *New Engl J Med* 2021; published online July 14. https://doi.org/10.1056/NEJMc2110716.

8 Barros-Martins J, Hammerschmidt SI, Cossmann A, et al. Immune responses against SARS-CoV-2 variants after heterologous and homologous ChAdOx nCoV-19/BNT162b2 vaccination. *Nat Med* 2021; published online July 14. https://doi.org/10.1038/s41591-021-01449-9.

9 Groß R, Zanonia M, Seidela A, et al. Heterologous ChAdOx1 nCoV-19 and BNT162b2 prime-boost vaccination elicits potent neutralizing antibody responses and T cell reactivity. *medRxiv* 2021; published online July 15. https://doi.org/10.1101/2021.05.30.21257971 (preprint).

10 Liu X, Shaw RH, Stuart ASV, et al. Safety and immunogenicity report from the Com-COV study—a single-1 blind randomised non-inferiority trial comparing heterologous and homologous prime-boost schedules with an adenoviral vectored and mRNA COVID-19 vaccine. *Lancet* 2021; published online Aug 6. https://doi.org/10.1016/S0140-6736(21)01694-9.

# Inhaled trepostinil for severe fibrotic interstitial lung disease: grounds for cautious optimism?

To reverse the irreversible is the dream of every physician. In pulmonary medicine, emphysema and chronic fibrosis are examples of anatomical lesions that do not regress with existing therapies and, to date, complete prevention of progression has not been achieved. Trial endpoints have not indicated the regeneration of normal tissue or the restoration of pulmonary function in fibrotic lung disease. In idiopathic pulmonary fibrosis, nintedanib and pirfenidone attenuate, but do not prevent, disease progression. To our knowledge, neither therapy has, in any study, resulted in a treatment effect suggesting partial regression of disease.

The INCREASE study was a multicentre, randomised, double-blind, placebo-controlled, 16-week, parallel-group study of patients with interstitial lung disease and pulmonary hypertension, documented by right heart catheterisation.[1] Patients received inhaled treprostinil up to 12 breaths (72 µg) four times daily or placebo. The study met its primary endpoint (change in 6-min walk distance) and secondary endpoints, including change in N-terminal pro-brain natriuretic peptide and time to clinical worsening. INCREASE is the first randomised controlled trial to show a positive effect of a vasoactive drug used for group 1 pulmonary arterial hypertension in patients with interstitial lung disease and associated pulmonary hypertension.

Serial pulmonary function tests to evaluate safety were subjected to post-hoc analyses, reported by Steven Nathan and colleagues in *The Lancet Respiratory Medicine*.[2] The findings are surprising and provocative. Overall, inhaled treprostinil was associated with a placebo-corrected improvement in forced vital capacity (FVC) of 28·5 mL


Dr Neil Overy/SPL

Published **Online**
June 29, 2021
https://doi.org/10.1016/S2213-2600(21)00264-2

See **Articles** page 1266