2   Vaccines and Related Biological Products Advisory Committee meeting. December 10, 2020. FDA briefing document. Pfizer-BioNTech COVID-19 vaccine. https://www.fda.gov/media/144245/download (accessed May 15, 2021).

3   Vaccines and Related Biological Products Advisory Committee meeting. December 17, 2020. FDA briefing document. Moderna COVID-19 vaccine. https://www.fda.gov/media/144434/download (accessed May 15, 2021).

4   Soeiro T, Salvo F, Pariente A, Grandvuillemin A, Jonville-Béra AP, Micallef J. Type I interferons as the potential mechanism linking mRNA COVID-19 vaccines to Bell's palsy. *Therapie* 2021; published online April 2. https://doi.org/10.1016/j.therap.2021.03.005.

Heterologous prime–boost vaccination with ChAdOx1 nCoV-19 and BNT162b2

The Oxford-AstraZeneca COVID-19 vaccine ChAdOx1 nCoV-19 is associated with a risk for vaccine-induced immune thrombosis with thrombocytopenia syndrome in the range of one to two cases per 100 000 vaccinations, with younger women showing the highest risk.[1,2] Additional cases have been reported for the Johnson & Johnson adenoviral vector-based Ad26.CoV2.S COVID-19 vaccine.[3] Vaccine-induced antibodies against platelet factor 4 have been implicated in the pathogenesis.[1,2] These antibodies might be amplified by booster vaccination with an adenoviral vector, which prompted recommendations to boost with an mRNA-based vaccine instead, although data on safety and efficacy of heterologous prime–boost regimens are sparse.[4]

We quantified the vaccine-induced antibody response in vaccinees in Germany who received a heterologous COVID-19 vaccination scheme using ChAdOx1 nCoV-19 as prime and BNT162b2 mRNA (BioNTech-Pfizer) as boost vaccination. The results were compared with those of cohorts of health-care workers or volunteers who received homologous BNT162b2 or ChAdOx1 nCoV-19 vaccination

regimens, respectively. Demographic data of the cohorts are presented in the appendix (pp 2–3).

To assess protective antibody responses, a surrogate neutralisation assay (NAb assay; Yhlo, Shenzen, China) based on the competition of serum antibodies with recombinant angiotensin-converting enzyme 2 for binding to the SARS-CoV-2 spike protein receptor-binding domain was used in two certified, university-based diagnostic laboratories in Munich and Erlangen, Germany. The surrogate neutralisation activity correlated closely with that in a cell culture-based SARS-CoV-2 infection-inhibition assay (appendix p 4).

A striking increase of vaccine-induced SARS-CoV-2 surrogate neutralisation activity was observed in 229 of 232 vaccinees who received a BNT162b2 boost vaccination 9–12 weeks after ChAdOx1 nCoV-19 prime vaccination. Sera were analysed on the day of BNT162b2 boost vaccination and 2 weeks after (appendix p 5). The single non-responder reported chronic lymphatic leukaemia. High antibody levels observed in two individuals after ChAdOx1 nCoV-19 prime vaccination most likely reflected previous, undetected SARS-CoV-2 infection.

The figure shows the comparison of surrogate neutralisation activity observed 2 weeks after two doses of BNT162b2, two doses of ChAdOx1 nCoV-19, or one dose of ChAdOx1 nCoV-19 followed by one dose of BNT162b2. The heterologous vaccination regimen induced significantly higher surrogate neutralisation activity than homologous ChAdOx1 nCoV-19 or homologous BNT162b2 vaccination.

Our results, in accordance with a recently published analysis[4] and several studies available on public servers, indicate that a single dose of COVID-19 mRNA vaccine after a ChAdOx1 nCoV-19 prime vaccination is sufficient to achieve high serum neutralisation activity, predicting protection
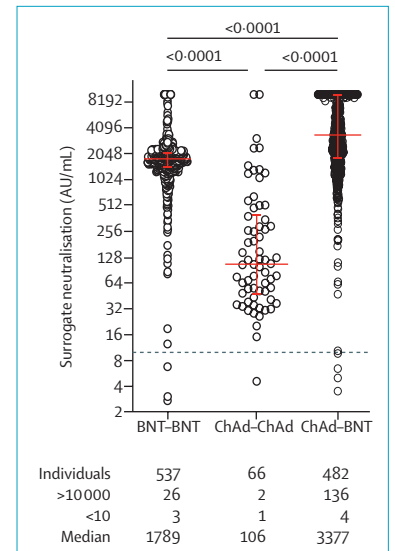
Figure: **Comparison of surrogate neutralisation activity induced by homologous and heterologous COVID-19 vaccine regimens**
Dots represent the results from individual vaccinees analysed by the two study laboratories (appendix pp 2–3). p values from a Dunn's test for multiple comparisons are shown above the graph. Median and interquartile ranges are indicated by red horizontal lines. Below the graph, the total numbers of individual participants, the numbers below the lower (<10) and above the upper (>10 000) cutoff of the surrogate neutralisation assay, and median values of each group are shown.

from SARS-CoV-2 infection.[5] The heterologous vaccination regimen provided the highest surrogate neutralisation activity in our study. However, the shorter interval between the two mRNA vaccinations than between ChAdOx1 nCoV-19-prime and BNT162b2-boost vaccination might have contributed to the higher immunogenicity of the heterologous regimen.

Although we report a non-blinded and non-randomised study, the results obtained in more than 480 individuals who were primed with an adenoviral vector-based and boosted with an mRNA COVID-19 vaccine indicate increased efficacy of a heterologous prime–boost vaccination. This vaccination scheme is an interesting option if the thrombosis risk posed by adenoviral vector-based vaccines is a concern, and it increases flexibility in a setting of vaccine shortage. However, further

studies need to address the safety and clinical efficacy of heterologous vaccination regimens.

*Matthias Tenbusch†,
Sofie Schumacher†, Emanuel Vogel,
Alina Priller, Jürgen Held,
Philipp Steininger, Stephanie Beileke,
Pascal Irrgang, Ronja Brockhoff,
Jon Salmanton-García,
Kathrin Tinnefeld, Hrvoje Mijocevic,
Kilian Schober, Christian Bogdan,
Sarah Yazici, Percy Knolle,
Oliver A Cornely‡, Klaus Überla‡,
*Ulrike Protzer,‡ for the DZIF-
VACCELERATE-CoVaKo study team§*
protzer@tum.de

†Contributed equally
‡Contributed equally
§Team members are listed in the appendix

Institute of Clinical and Molecular Virology, University Hospital Erlangen (MT, PS, PI, KÜ), and Mikrobiologisches Institut—Klinische Mikrobiologie, Immunologie und Hygiene (JH, KS, CB), Universitätsklinikum Erlangen Friedrich-Alexander-Universität Erlangen-Nürnberg, Erlangen, Germany; University Hospital of Cologne, Faculty of Medicine, Department I of Internal Medicine, Cologne, Germany (SS, RB, JS-G, OAC); University of Cologne, Translational Research, Cologne Excellence Cluster on Cellular Stress Responses in Aging-Associated Diseases, Cologne, Germany (SS, RB, JS-G, OAC); Institute of Virology, School of Medicine, Technical University of Munich/Helmholtz Zentrum München, 81675 Munich, Germany (EV, KT, HM, UP); Institute of Molecular Immunology and Experimental Oncology, School of Medicine, University Hospital rechts der Isar, Technical University of Munich, Munich, Germany (AP, SY, PK); DZIF, partner sites Munich and Cologne/Bonn, Germany (PK, OHC, UP)

1 Greinacher A, Thiele T, Warkentin TE, Weisser K, Kyrle PA, Eichinger S. Thrombotic thrombocytopenia after ChAdOx1 nCov-19 vaccination. *N Engl J Med* 2021; **384:** 2092–101.

2 Scully M, Singh D, Lown R, et al. Pathologic antibodies to platelet factor 4 after ChAdOx1 nCoV-19 vaccination. *N Engl J Med* 2021; **384:** 2202–11.

3 MacNeil JR, Su JR, Broder KR, et al. Updated recommendations from the Advisory Committee on Immunization Practices for use of the Janssen (Johnson & Johnson) COVID-19 vaccine after reports of thrombosis with thrombocytopenia syndrome among vaccine recipients—United States, April 2021. *MMWR Morb Mortal Wkly Rep* 2021; **70:** 651–56.

4 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.

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; published online May 17. https://doi.org/10.1038/s41591-021-01377-8.

The SARS-CoV-2 B.1.1.7 variant and increased clinical severity—the jury is out

Dan Frampton and colleagues[1] demonstrated increased viral load but not severity of disease or 28-day mortality in hospitalised patients infected by the B.1.1.7 variant of SARS-CoV-2. By contrast, we found slightly different results when assessing the risk of morbidity and mortality in a matched case-control study in 60 hospitalised patients—30 with the B.1.1.7 variant and 30 with non-B.1.1.7 variants. Cases were matched for admission period and age band. Clinical severity scores, requirement for ventilation, treatments received, and 28-day mortality were compared between groups using anonymised, retrospectively collected data and Wilcoxon rank-sum and χ^2 or Fisher's exact tests.

Our findings (table) show consistent and rational evidence that patients infected with the B.1.1.7 variant developed more serious disease: they had greater clinical severity (eg, higher National Early Warning Score value, lower respiratory rate oxygenation index) and greater requirement for supplemental oxygen and mechanical ventilation, they more often received approved treatments for SARS-CoV-2 infection (eg, dexamethasone, remdesivir, and tocilizumab), and they had more serious clinical outcomes (ie, higher 28-day mortality, WHO clinical progression scale score). Although our results show a tendency towards severe disease with B.1.1.7 infection, it is likely that our study was underpowered as statistical significance was seen only for patients requiring dexamethasone. Nevertheless, our data echo the findings of other, larger studies. For example, Challen and colleagues,[2] who studied a younger population than described here or studied by Frampton and colleagues, with likely less comorbidity, found a 64% increase in 28-day mortality following community infection with the B.1.1.7 variant (control group, 0·26%; B.1.1.7 variant group, 0·41%). Similarly, Davies and colleagues[3] concluded that infections with the B.1.1.7 variant were associated with a hazard of death of 61% (95% CI 42–82) higher than with pre-existing variants.

We believe that the identification of any increased morbidity and mortality risks in patients infected by SARS-CoV-2 variants of concern requires adequately powered studies that use a combination of community and hospital PCR swabs, examine disease severity using more detailed clinical severity scores (such as the WHO clinical progression ordinal scale used by Frampton and colleagues) with physiological measures, and assess the impact of viral load, novel