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.

against different variants decreases at similar decay rates. Although neutralising activity does not equal protection from infection, our findings suggest that previous observations on waning humoral immunity can guide subsequent booster vaccination strategies in the older population.

KV, HG, and FKl are listed as inventors on patent applications regarding SARS-CoV-2-neutralising antibodies filed by the University of Cologne. All other authors declare no competing interests. KV, PT-L, and HG contributed equally. FKu, LES, and FKl contributed equally. Acknowledgments are listed in the appendix (p 7).

*Kanika Vanshylla, Pinkus Tober-Lau, Henning Gruell, Friederike Münn, Ralf Eggeling, Nico Pfeifer, N Han Le, Irmgard Landgraf, Florian Kurth, Leif E Sander, *Florian Klein*
florian.klein@uk-koeln.de

Laboratory of Experimental Immunology, Institute of Virology, Faculty of Medicine and University Hospital Cologne (KV, HG, FKl) and Center for Molecular Medicine Cologne (FKl), University of Cologne, Cologne 50931, Germany; Department of Infectious Diseases and Respiratory Medicine, Charité-Universitätsmedizin Berlin, Freie Universität Berlin and Humboldt-Universität zu Berlin, Berlin, Germany (PT-L, FM, NHL, FKu, LES); Methods in Medical Informatics, Department of Computer Science (RE, NP) and Faculty of Medicine (NP), University of Tübingen, Tübingen, Germany; German Center for Infection Research, Partner Site Tübingen, Tübingen, Germany (NP); Hausarztpraxis am Agaplesion Bethanien Sophienhaus, Berlin, Germany (IL); Department of Tropical Medicine, Bernhard Nocht Institute for Tropical Medicine and Department of Medicine I, University Medical Center Hamburg-Eppendorf, Hamburg, Germany (FKu); German Center for Infection Research, Partner Site Bonn-Cologne, Cologne, Germany (FKl)

1 Levin EG, Lustig Y, Cohen C, et al. Waning immune humoral response to BNT162b2 COVID-19 vaccine over 6 months. *N Engl J Med* 2021; **385:** e84.
2 Cele S, Jackson L, Khoury DS, et al. Omicron extensively but incompletely escapes Pfizer BNT162b2 neutralization. *Nature* 2021; published online Dec 23. https://doi.org/10.1038/s41586-021-04387-1.
3 Schmidt F, Muecksch F, Weisblum Y, et al. Plasma neutralization of the SARS-CoV-2 omicron variant. *N Engl J Med* 2021; **386:** 599–601.
4 Tober-Lau P, Schwarz T, Vanshylla K, et al. Long-term immunogenicity of BNT162b2 vaccination in older people and younger health-care workers. *Lancet Respir Med* 2021; **9:** e104–05.
5 Barda N, Dagan N, Cohen C, et al. Effectiveness of a third dose of the BNT162b2 mRNA COVID-19 vaccine for preventing severe outcomes in Israel: an observational study. *Lancet* 2021; **398:** 2093–100.

Effectiveness of ChAdOx1 nCoV-19 vaccine during the delta (B.1.617.2) variant surge in India

We read with interest the study by Ramachandran Thiruvengadam and colleagues.[1] However, we feel there are some aspects of the study that require further input from the authors.

The mean age of cases is reported to be 35 years and of controls to be 32 years.[1] In India, vaccination of the general population in the 18–45 years age group began in early May, 2021; in this age group, only frontline workers were vaccinated from mid-January to late April, 2021. Considering the quoted duration of the study (April 1 to May 31, 2021), most fully vaccinated individuals would have been frontline workers, and predominantly health workers. However, the unvaccinated group would be representative of the general population. Therefore, the two groups had different levels of exposure to SARS-CoV-2, making comparison and estimates of vaccine efficacy difficult.

The controls were selected on the basis of RT-PCR negativity in a defined time period. However, some of them might have been affected during the first wave of COVID-19 with mild or asymptomatic disease and might have been partially immune to reinfection during the study period, which would be an unknown variable in the study modifying reinfection rate or severity. Measurement of serum neutralising antibody titres against spike or nucleocapsid proteins at baseline could have been used to eliminate this group from the study.

Compared with the total study population, the number of people analysed for T-cell response was small (48 [1·1%] of 4360). Furthermore, the T-cell responses to spike peptide pools of wild-type SARS-CoV-2 and delta (B.1.617.2) SARS-CoV-2 were only studied in a healthy vaccinated group. An unvaccinated group could have been included to check whether cross-reactive T cells primed by endemic coronaviruses can also respond to wild-type SARS-CoV-2 or the delta variant. The concept of cross-immunity has been expanded in the context of COVID-19, both theoretically and experimentally.[2,3] Additionally, these data would have helped us to understand the intensity of the T-cell immune response in the vaccinated population compared with the unvaccinated population. Even those positive for antibodies against SARS-CoV-2 nucleocapsid at baseline could have been included in this testing to investigate how previous infection affects T-cell responses. Such an investigation becomes more relevant in a real-world study when breakthrough infections are known to be quite common.

Finally, an important prerequisite for test-negative case-control studies is matching of cases and controls for disease severity and confounders.[4] Information on such potential confounders and symptom characterisation (especially disease severity) in the control group should be provided. Furthermore, the test-negative design can control for selection and information bias but is not effective in blocking bias due to health-seeking behaviour, which differs between vaccinated and unvaccinated individuals and is affected by the severity of COVID-19.[4]

We declare no competing interests.

**Sasanka Chakrabarti, Sankha Shubhra Chakrabarti, Gourav Chandan, Upinder Kaur, Bimal Kumar Agrawal*
profschakrabarti95@gmail.com

Department of Biochemistry and Central Research Cell (SC, GC) and Department of Medicine (BKA), Maharishi Markandeshwar University, Mullana, Haryana, India; Department of Geriatric Medicine, Institute of Medical Sciences, Banaras Hindu University, Varanasi, UP, India (SSC); Department of Pharmacology, Institute of Medical Sciences, Banaras Hindu University, Varanasi, UP, India (UK)

1 Thiruvengadam R, Awasthi A, Medigeshi G, et al. Effectiveness of ChAdOx1 nCoV-19 vaccine against SARS-CoV-2 infection during the delta (B.1.617.2) variant surge in India: a test-negative, case-control study and a mechanistic study of post-vaccination immune responses. *Lancet Infect Dis* 2022; published online Nov 25. https://doi.org/10.1016/S1473-3099(21)00680-0

2 Chakrabarti SS, Kaur U, Singh A, et al. Of cross-immunity, herd immunity and country-specific plans: experiences from COVID-19 in India. *Aging Dis* 2020; **11:** 1339–44.
3 Sette A, Crotty S. Pre-existing immunity to SARS-CoV-2: the knowns and unknowns. *Nat Rev Immunol* 2020; **20:** 457–58.
4 Chua H, Feng S, Lewnard JA, et al. The use of test-negative controls to monitor vaccine effectiveness: a systematic review of methodology. *Epidemiology* 2020; **31:** 43–64.

Authors' reply

We thank Sasanka Chakrabarti and colleagues for their interest in our Article[1] and would like to clarify some issues. Their concern is that younger vaccinated participants were probably heath-care workers with a higher exposure risk than the controls in our study, making estimation of vaccine effectiveness difficult. However, we did clarify in the appendix of our Article that we accounted for this potential higher risk of exposure by adjusting for the confounding factors of age, sex, and exposure.

The possibility of previous asymptomatic or mildly symptomatic infections remains similar in both the groups and is not confined to controls. Serology for nucleocapsid antibodies could have been useful for diagnosing asymptomatic infections but vaccine effectiveness studies have generally focused on symptomatic infections. Estimates of vaccine effectiveness that consider asymptomatic infections can be quite imprecise. Furthermore, considering the large sample size, collecting samples and performing serological testing would have been prohibitively time consuming and would have defeated the purpose of generating estimates of vaccine effectiveness in a timely manner during the SARS-CoV-2 delta (B.1.617.2) variant surge in India.

Regarding the number of participants tested for cellular responses, the chosen sample size for T-cell assays was one of the largest to date to show that the T-cell responses were conserved between the ancestral virus and the delta variant of SARS-CoV-2, as has been confirmed by recent reports as well.[2] Studying a larger sample size would have been challenging because of sample availability, resources, and the time required. Most vaccine effectiveness studies have tested around 10% of the vaccinated population for cellular responses.[3]

Studying the T-cell responses against endogenous coronaviruses in unvaccinated individuals was beyond our study objectives, and we would welcome such a study. Nonetheless, published literature indicates that the magnitude of T-cell responses in unexposed individuals is considerably lower than in COVID-19 convalescent and vaccinated individuals.[4] It is possible, although speculative, that the cross-reactivity of T cells against endogenous coronaviruses might provide some protection against SARS-CoV-2 and its variants.

The test-negative case-control design is a WHO-recommended and well established design for assessing real-world vaccine effectiveness—eg, for influenza, rotavirus, and SARS-CoV-2 vaccines.[5] This design balances risk profile, health-care seeking behaviour, and access to care among vaccinated and non-vaccinated people. We considered the severity of COVID-19 as a secondary outcome and not as a confounder, and therefore it was not included in the multivariable model.

We declare no competing interests.

*Ramachandran Thiruvengadam, Amit Awasthi, Shinjini Bhatnagar, *Pramod Kumar Garg, on behalf of DBT Consortium for COVID-19 Research*
pgarg@thsti.res.in

Translational Health Science and Technology Institute, Faridabad 121001, India

1 Thiruvengadam R, Awasthi A, Medigeshi G, et al. Effectiveness of ChAdOx1 nCoV-19 vaccine against SARS-CoV-2 infection during the delta (B.1.617.2) variant surge in India: a test-negative, case-control study and a mechanistic study of post-vaccination immune responses. *Lancet Infect Dis* 2022; published online Nov 25. https://doi.org/10.1016/S1473-3099(21)00680-0.
2 Jordan SC, Shin B-H, Gadsden TM, et al. T cell immune responses to SARS-CoV-2 and variants of concern (alpha and delta) in infected and vaccinated individuals. *Cell Mol Immunol* 2021; **18:** 2554–56.
3 Ramasamy MN, Minassian AM, Ewer KJ, et al. Safety and immunogenicity of ChAdOx1 nCoV-19 vaccine administered in a prime–boost regimen in young and old adults (COV002): a single-blind, randomised, controlled, phase 2/3 trial. *Lancet* 2021; **396:** 1979–93.
4 Grifoni A, Weiskopf D, Ramirez SI, et al. Targets of T cell responses to SARS-CoV-2 coronavirus in humans with COVID-19 disease and unexposed individuals. *Cell* 2020; **181:** 1489–501.
5 WHO. Evaluation of COVID-19 vaccine effectiveness. Geneva: World Health Organization, 2021. https://www.who.int/publications-detail-redirect/WHO-2019-nCoV-vaccine_effectiveness-measurement-2021.1 (accessed June 11, 2021).

Evaluating the risk compensation of HIV/AIDS prevention measures

Yang Zheng and colleagues[1] assessed the global disease burden and trends of five sexually transmitted infections (STIs) over the past three decades. An interesting finding was that, contrary to the overall stable trend of the incidence rate, the incidence of syphilis increased in adolescents after 2010, especially in high-income countries.[1] Zheng and colleagues suggested that this increase might be due to condom fatigue, complacency about HIV, and optimism about HIV treatments caused by the success of HIV/AIDS prevention and control measures among high-risk populations.[1] The increasing use of medical protection against HIV might lead to more risky sexual practices and increase the transmission of other STIs, also known as risk compensation.

In 2019, Chow and colleagues[2] described the changes in STI epidemics among men who have sex with men (MSM) under the present context of HIV control. In the USA and European countries, notified syphilis cases among MSM showed the most dramatic increase among several STIs during the 2010s when pre-exposure prophylaxis (PrEP) was introduced and promoted.[2] Coincidentally, Zheng and colleagues' study showed a similar trend on a