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.

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Simon J Bowman, Thomas Dorner, Xavier Mariette, Wen-Lin Luo, Wolfgang Hueber
simon.bowman@uhb.nhs.uk

Rheumatology Department, University Hospitals Birmingham NHS Foundation Trust, Birmingham B15 2TH, UK (SJB); Institute of Inflammation and Ageing, College of Medical and Dental Sciences and National Institute for Health Research Birmingham Biomedical Research Centre, University of Birmingham, Birmingham, UK (SJB); Rheumatology Department, Milton Keynes University Hospital, Milton Keynes, UK (SJB); Department of Medicine, Rheumatology and Clinical Immunology, Charité Universitätsmedizin and Deutsches Rheumaforschungszentrum, Berlin, Germany (TD); Université Paris Saclay, Assistance Publique-Hôpitaux de Paris, Hôpital Bicêtre, INSERM U1184, Le Kremlin Bicêtre, France (XM); Novartis Pharmaceuticals, East Hanover, NJ, USA (W-LL); Novartis Pharma, Basel, Switzerland (WH)

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Misclassification bias in estimating clinical severity of SARS-CoV-2 variants

Tommy Nyberg and colleagues[1] use an unvaccinated cohort to show differences between the intrinsic severity of the omicron (B.1.1.529) and delta (B.1.617.2) variants of SARS-CoV-2 without confounding by pre-existing immunity. They report an 80% reduction in the severity of the omicron compared with the delta variant, suggesting the possibility of living through the COVID-19 pandemic without social and economic disruptions. However, reliance on SARS-CoV-2 test positivity to identify cases of COVID-19 and on all-cause hospitalisations and deaths as outcomes could have introduced misclassification bias and residual confounding.

Up to one in three SARS-CoV-2 infections are asymptomatic,[2] and this proportion was even greater during the omicron wave.[3] Studies that exclusively use test positivity as the case definition might report inflated hospitalisation and case-fatality rates. Misclassification is exacerbated by the higher prevalence of infection due to more transmissible variants and by the increased ratios of non-severe to severe cases, potentially attenuating the differences in severity between variants. In the appendix, we show the potential effects of three SARS-CoV-2 case phenotypes on apparent hospitalisation and case-fatality rates of SARS-CoV-2 infection with the delta and omicron variants. Misclassification could also differ by age, vaccination status, and comorbidities that influence susceptibility to infection and disease.[4,5]

The use of other data streams might help to populate large datasets when clinical data are scarce or absent. For example, administrative coding could be used to identify reasons for hospital admission that are likely to be related (eg, pneumonia) or unrelated (eg, trauma) to COVID-19,[4] and to identify comorbid conditions for inclusion as covariates in comparative analyses.[4,5] The delivery of therapeutics used specifically or most commonly for COVID-19 (eg, remdesivir and dexamethasone) could enrich for those hospitalised with the disease. Ultimately, applying a probabilistic approach to case definition might allow for estimates of confidence when identifying cases and associating outcomes.

After correcting for misclassification bias, the intrinsic severity of the omicron variant of SARS-CoV-2 might be even lower than that suggested by Nyberg and colleagues.

We declare no competing interests.

*Christina Yek, Sarah Warner, Alex Mancera, *Sameer S Kadri*
sameer.kadri@nih.gov

Critical Care Medicine Department, NIH Clinical Center, Bethesda, MD 20892, USA

1 Nyberg T, Ferguson NM, Nash SG, et al. Comparative analysis of the risks of hospitalisation and death associated with SARS-CoV-2 omicron (B.1.1.529) and delta (B.1.617.2) variants in England: a cohort study. *Lancet* 2022; **399:** 1303–12.
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See **Online** for appendix

Authors' reply

We thank Christina Yek and colleagues for their Correspondence regarding our Article.[1] They note that people who test positive for SARS-CoV-2 generally have more severe disease than those who are infected but not tested. This finding could lead to the overestimation of absolute risks, but relative risks are not necessarily biased unless the

proportion of detected severe cases differs systematically between variants. Citing modelling results that indicated a declining infection detection rate in the USA during the transition period between the dominance of the delta (B.1.617.2) and omicron (B.1.1.529) variants, possibly driven by increasing proportions of undetected infections in people with non-severe disease, Yek and colleagues hypothesise a mechanism for differential detection rates: the omicron cases for which a positive test result was recorded might have included a relatively higher proportion of infected people who were prone to severe disease than the analogous delta cases—for example, because a higher proportion of people infected with the omicron variant who sought testing had comorbidity.

However, available data do not suggest a change in the proportion of infections being detected in England by community PCR testing during the study period (although the extent of community testing was reduced later[2]). We believe that the UK is unique in having conducted large-scale, population-based COVID-19 prevalence surveys,[3] alongside its mass testing programmes. To assess the hypothesis of Yek and colleagues, we compared estimates of infection prevalence in the population with estimates of the corresponding prevalence of infections detected through community testing (appendix pp 1–4). Contrary to the hypothesis, we found that community testing detected similar proportions of people infected with the virus during the delta-dominant and omicron-dominant periods in England (appendix pp 2–3).

See Online for appendix

Yek and colleagues further argue that the relative risks of all-cause outcomes might be closer to the null than those of COVID-19-specific outcomes. They suggest that in the absence of direct measurement of COVID-19-specific outcomes, other data could indirectly discriminate probable COVID-19-related and COVID-19-unrelated events. In principle, we agree that cause-specific event data are desirable. However, assuming a constant background rate of unrelated hospitalisations and deaths, differential misclassification of outcome events by variant is unlikely, and non-differential misclassification is more likely to result in bias towards than away from the null. Further, we note that, during the study period, all individuals admitted to hospital in England were tested for COVID-19 at admission, so missed hospitalisation events in individuals with undetected COVID-19 is unlikely. Several studies that reported relative risks of COVID-19-specific hospitalisation have estimated relative risks consistent with those from our study.[4,5]

We acknowledge that our dataset did not include comorbidity data. However, recent studies in other European countries with comorbidity data available reported only minor differences in comorbidity between delta and omicron cases, and provided comorbidity-adjusted relative risks consistent with those from our study.[4–6] One of these studies explored the effect of adjusting versus not adjusting for comorbidity and found only marginal differences.[5]

Taken together, we believe the available data indicate that it is unlikely that the proposed mechanisms have strongly biased the results of our analysis.

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*Tommy Nyberg, Neil M Ferguson, Joshua Blake, Wes Hinsley, Samir Bhatt, Daniela De Angelis, Simon Thelwall, Anne M Presanis
tommy.nyberg@mrc-bsu.cam.ac.uk

MRC Biostatistics Unit, University of Cambridge, Cambridge CB2 0SR, UK (TN, JB, DDA, AMP); NIHR Health Protection Research Unit for Modelling and Health Economics, MRC Centre for Global Infectious Disease Analysis, Jameel Institute, Imperial College London, London, UK (NMF, WH, SB); Statistics, Modelling and Economics Department (DDA), Joint Modelling Team (DDA), and COVID-19 National Epidemiology Cell (ST), UK Health Security Agency, London, UK; NIHR Health Protection Research Unit for Behavioural Science and Evaluation at the University of Bristol, University of the West of England, and University of Cambridge, Bristol, UK (DDA).

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Tesfaye S, Sloan G, Petrie J, et al. Comparison of amitriptyline supplemented with pregabalin, pregabalin supplemented with amitriptyline, and duloxetine supplemented with pregabalin for the treatment of diabetic peripheral neuropathic pain (OPTION-DM): a multicentre, double-blind, randomised crossover trial. Lancet *2022;* ***400:*** *680–90*—In this Article, the spelling of author Steven Julious' name was incorrect. This correction has been made to the online version as of Aug 29, 2022.