Title: The different epidemiological questions on SARS-CoV-2 reinfections

Authors: Simon R. Procter[1], Bronner P. Gonçalves[1]

Affiliations: [1]Department of Infectious Disease Epidemiology, London School of Hygiene & Tropical Medicine, London, UK

Comment

Understanding the changing risk of reinfection with SARS-CoV-2 and the additional disease burden associated with repeated infections has become a research priority, and is now an important question for public health planning. Several studies have estimated lower infection risk after recovery from an initial SARS-CoV-2 infection (e.g. rate ratio 0.19 95% confidence interval [CI] 0.15-0.25 for infection during the second wave in Denmark[1] in individuals with versus without history of prior infection during the first wave) and suggest lower risk of severe presentation during reinfections compared to first infections,[2] providing evidence for naturally acquired protection. As several factors can bias estimations of the effect of previous infections[3] on subsequent infections in an epidemic setting, these studies often accounted for multiple potential confounders, including the temporally varying incidence rate, reason for viral testing, and the infecting variant since the degree of protection might be variant-specific.[4]

In addition to research on natural protective immunity, two different questions were studied in recent epidemiological analyses using large databases with detailed information on timing of infections and vaccination doses: *How is the risk of reinfection with SARS-CoV-2 affected by vaccination?* and *What is the excess disease burden associated with reinfection?* Regarding the former, in Israel,[5] vaccination was shown to further reduce the risk of infection in individuals with a history of previous SARS-CoV-2 infection. In a Danish study,[6] this protective effect was also observed in comparisons performed separately for time periods when different variants were dominant. Furthermore, a national Swedish study[7] showed that the effect of vaccination on reinfection-related hospitalisation (hazard ratio [HR] 0.10 95% CI 0.04-0.22) was even stronger than its effect on reinfection of any severity (HR 0.34 95% CI 0.31-0.39).

The second of these two questions, on the health impact of reinfections, was studied more recently by Bowe and colleague.[8] The authors analysed a comprehensive database from the US Department of Veterans Affairs, comparing clinical outcomes in 40,947 individuals with SARS-CoV-2 reinfection to outcomes in two comparator cohorts, one of individuals who had evidence of a single SARS-CoV-2 infection during the study period and the other of individuals with no evidence of infection. In contrast to studies quantifying the protective effect of an initial infection, where subsequent infection risk is the outcome and the exposure of interest is previous infection versus no infection, in the study by Bowe and colleagues the exposure of interest was reinfection versus no reinfection - thus authors were able to estimate excess disease burden linked to reinfection. The authors accounted for potential confounders and used observed reinfection times in defining follow-up times for the comparator groups to avoid immortal time bias. Mortality was higher in individuals who had reinfection (HR 2.17, 1.93-2.45), as were risks of several acute and post-acute medical

conditions, including fatigue and pulmonary sequelae (HR 2.33, 2.14-2.53, and 3.54, 3.29-3.82, respectively). These associations were also observed in analyses performed by vaccination status, and in individuals with two or more vaccine doses, reinfections were still associated with increased mortality.

Viewed collectively, the earlier and more recent epidemiological studies suggest that (1) previous SARS-CoV-2 infection has a protective effect on the risk of subsequent infections and is associated with reduced severity conditional on infection establishment, (2) vaccination can further reduce the risk of reinfection, and (3) reinfections are associated with excess morbidity and mortality, including amongst vaccinated individuals. However, as discussed by Bowe and colleagues, the population in their study is not representative of the general American population, which might affect the generalisability of their findings. Quantification of the excess morbidity and mortality caused by repeated SARS-CoV-2 infections should thus be performed in additional settings and recruit individuals of all ages. This should also include populations with different symptomatic fractions (see Cohen et al. and discussion therein[9]), since the probability of exposure misclassification might vary and could influence estimates. Together with ongoing monitoring of infections including surveillance of new and existing variants, and assessments of levels of population immunity, a better understanding of the health burden of SARS-CoV-2 reinfections in different settings can help guide future public health interventions.

References

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