Letter to the Editor

Prior SARS-CoV-2 infection is associated with protection against symptomatic reinfection

To the editor,

It has been recently suggested that prior exposure to seasonal coronaviruses might confer cross-protection against SARS-CoV-2.[1] Whether SARS-CoV-2 infection itself confers immunity to reinfection has not been established. Immunity is probable, at least in the short term, because reinfections are infrequently reported, despite over 55 million primary infections occurring worldwide since December 2019.[2] Protection against short term reinfection has been observed in a non-human primate model of SARS-CoV-2.[3] A small clinical study was also suggestive.[4] Immunity to seasonal coronaviruses is maintained for up to 12 months.[5]

The second wave of SARS-CoV-2 transmission provides an opportunity to detect early signals of immunity. We previously defined a large cohort of over 11,000 healthcare workers (HCWs) with documented evidence of previous infection status during the first wave of the SARS-CoV-2 pandemic, from March to April 2020. A second wave of SARS-CoV-2 transmission occurred in our setting from October to November 2020, approximately 7 months later. We undertook a retrospective analysis of HCW testing data during this second wave, to address the question of whether previous SARS-CoV-2 infection was associated with protection.

This study was granted a waiver by the Newcastle and North Tyne Research Ethics Committee. Access to data was granted under Regulation 3(4) of the Health Service Control of Patient Information Regulations 2002 (March 2020) and approved by the Newcastle-upon-Tyne Hospitals (NUTH) NHS Foundation Trust Caldicott Guardian (7566). NUTH is a large tertiary referral centre employing 17,126 staff. SARS-CoV-2 RT-PCR testing has been provided to all HCWs with symptoms of COVID-19 since early March 2020.[6] SARS-CoV-2 PCR testing was undertaken on combined nasopharyngeal and oropharyngeal swabs in viral transport medium, using Public Health England (PHE) approved RT-PCR assays containing two SARS-CoV-2 gene targets. SARS-CoV-2 nucleocapsid IgG antibody testing was undertaken on the Roche Anti-SARS-CoV-2 IgG assay.

We defined two periods for analysis: the first, 10 Mar to 6 July 2020, spanned the first wave of SARS-CoV-2 transmission. The second, 7 July to 20 Nov, included the second wave. Testing data were obtained from a prospectively maintained regional virology diagnostic laboratory internal database. Methods for data collection and cleaning are described separately.[7] In the first period, 481/3338 symptomatic HCWs tested positive for SARS-CoV-2 by PCR, while SARS-CoV-2 IgG was detected in 937/11,103 (8.4%) HCWs. Together, these data allowed us to identify 1038 HCWs with evidence of previous infection (positive PCR and/or Ab) and 10,137 without (negative Ab, without positive PCR).

The primary endpoint for analysis was symptomatic SARS-CoV-2 infection, defined as a positive PCR for SARS-CoV-2 from a combined nasopharyngeal/oropharyngeal swab taken as part of the Trust's symptomatic staff testing programme in the period from 7 Jul 2020 to 20 Nov 2020. Analyses were done using GraphPad Prism version 8.4.3 (GraphPad Software LLC, US). Positivity rates between groups were assessed using contingency tables and Chi[2] (χ^2) hypothesis tests.

We first compared the baseline demographic characteristics of those with or without prior SARS-CoV-2 infection. There were no significant differences in age or gender, but differences in previous positivity rates according to ethnicity and multiple deprivation index were found (Table 1). From 7 Jul until 20 Nov 2020, 2243 HCWs underwent PCR testing for symptoms. 128 had previous confirmed SARS-CoV-2 infection, while 2115 had not. In those previously infected, there was a median of 173 (IQR: 162–229) days from the date of first positive PCR/antibody result to the end of the analysis period. Test positivity rates were 0% (0/128 [95% CI: 0–2.9]) in those with previous infection compared to 13.7% (290/2115 [95% CI: 12.3–15.2]) in those without ($P<0.0001$ χ^2 test). Considering the population as a whole, a positive PCR test was returned in 0/1038 (0% [95% CI: 0–0.4) of those with previous infection, compared to 290/10,137 (2.9% [95% CI: 2.6–3.2]) of those without ($P<0.0001$ χ^2 test).

Fewer HCWs in the previous infection group presented for symptomatic testing. 128/1038 (12.3% [95% CI: 10.5–14.5]) of those with evidence of prior infection had a test due to symptoms in the second period compared to 2115/10,137 (20.8% [95% CI: 20.1–21.6]) in the group without previous infection ($P<0.0001$ χ^2 test). Asymptomatic PCR screening was undertaken on a pilot basis in an additional 481 HCWs, 106 with past infection and 375 without. These HCWs were distinct from the population who underwent symptomatic testing. There were similarly no positive results in the group with previous infection 0/106 (0% [95% CI: 0–3.5]), compared to 22/375 (5.9% [95% CI: 3.9–8.7], $P=0.011$) positive PCR results in the group without previous infection, consistent with results of symptomatic testing.

Few published studies have addressed the question of whether prior SARS-CoV-2 infection leads to immunity.[8] Recent unpublished studies in HCWs reported no evidence of symptomatic reinfection, suggesting that immunity is maintained for at least 6 months.[9,10] In these studies there was a relatively low event rate (123 and 20 symptomatic infections respectively). It is possible that the protective immunity observed may have been explained in part by the relatively low incidence of SARS-CoV-2 infection. Our data confirms and extends these findings. Despite 290 symptomatic infections in 10,137 non-immune HCWs, there were no symptomatic reinfections in over 1000 HCWs with past infection. We conclude that SARS-CoV-2 infection appears to result in protection against symptomatic infection in working age adults, at least in the short

Table 1

Baseline demographic data (where available) and reinfection rates by prior infection category. IMD = index of multiple deprivation. BAME = Black, Asian and Minority Ethnic groups. NS = non-significant (*P* > 0.05).

Factor	Prior infection (*N* = 1038)	No prior infection (*N* = 10,137)	*P* value
Baseline characteristics			
Age median	39.5 (30–49)	40 (30–50)	n.s.
Female	798/967 (82.5%)	7792/9674 (80.5%)	n.s.
BAME	107/949 (11.2%)	796/9497 (8.4%)	0.0025
Lowest quartile IMD	326/958 (34.0%)	2620/9594 (27.3%)	<0.0001
Outcome data			
PCR tested	128/1038 (12.3%)	2115/10,137 (20.8%)	<0.0001
Per test positivity	0/128 (0%)	290/2115 (13.7%)	<0.0001
Proportion PCR positive	0/1038 (0%)	290/10,137 (2.9%)	<0.0001

term. This is consistent with the low rates of reinfection reported in the literature[2] and with the reported ability of vaccines to protect with high efficacy against symptomatic SARS-CoV-2. Whether this is true of asymptomatic infection remains uncertain. It was not possible to investigate a correlation between baseline antibody titre and protection, since no infections occurred in those with detectable IgG.

We acknowledge several limitations to this study. It employed a retrospective design. Individuals were aware of their infection status, which may have influenced testing behaviour, introducing potential ascertainment bias. However, we consider this unlikely to have a major impact on the conclusions, since occupational health advice to HCWs on self-isolation and PCR testing was applied uniformly, without consideration of prior infection status, and similar results were observed in preliminary asymptomatic screening. Investigation of the nature of immunity was beyond the scope of this analysis. Future longitudinal studies will focus on (i) the durability of immunity, (ii) immune correlates of protection, and (iii) the generalisability of these findings to other at-risk populations such as the elderly, those with comorbidities and the immunocompromised.

Funding

Acknowledgement

References

1. Aran D, Beachler DC, Lanes S, Overhage JM. Prior presumed coronavirus infection reduces COVID-19 risk: a cohort study. *J Infect* 2020;81:923–30. doi:10.1016/j.jinf.2020.10.023.

2. Iwasaki A. What reinfections mean for COVID-19. *Lancet Infect Dis* 2020. doi:10.1016/S1473-3099(20)30783-0.

3. Deng W, et al. Primary exposure to SARS-CoV-2 protects against reinfection in rhesus macaques. *Science* 2020;369:818–23. doi:10.1126/science.abc5343.

4. Addetia A, et al. Neutralizing antibodies correlate with protection from SARS-CoV-2 in humans during a fishery vessel outbreak with a high attack rate. *J Clin Microbiol* 2020;58. doi:10.1128/JCM.02107-20.

5. Callow KA, Parry HF, Sergeant M, Tyrrell DA. The time course of the immune response to experimental coronavirus infection of man. *Epidemiol Infect* 1990;105:435–46. doi:10.1017/s0950268800048019.

6. Hunter E, et al. First experience of COVID-19 screening of health-care workers in England. *Lancet* 2020;395:e77–8. doi:10.1016/S0140-6736(20)30970-3.

7. Hanrath AT, et al. SARS-CoV-2 testing of 11,884 healthcare workers at an acute NHS hospital trust in England: a retrospective analysis. *MedRxiv* 2020.

8. Stephens DS, McElrath MJ. COVID-19 and the Path to Immunity. *JAMA* 2020;324:1279–81. doi:10.1001/jama.2020.16656.

9. Lumley SF, et al. Antibodies to SARS-CoV-2 are associated with protection against reinfection. *New Engl J Med* 2020. doi:10.1056/NEJMoa2034545.

10. Wylie D, et al. SARS-CoV-2 responsive T cell numbers are associated with protection from COVID-19: a prospective cohort study in keyworkers. *MedRxiv* 2020.

Aidan T. Hanrath
Translational and Clinical Research Institute, Newcastle University, Newcastle upon Tyne, United Kingdom
National Institute for Health Research (NIHR) Newcastle Biomedical Research Centre, Newcastle University and The Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle upon Tyne, United Kingdom

Brendan A.I. Payne, Christopher J.A. Duncan*
Translational and Clinical Research Institute, Newcastle University, Newcastle upon Tyne, United Kingdom
The Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle upon Tyne, United Kingdom
The Newcastle Hospitals HCW Testing Group[1]

*Corresponding author at: Translational and Clinical Research Institute, Newcastle University, Newcastle upon Tyne, United Kingdom
E-mail address: christopher.duncan@newcastle.ac.uk (C.J.A. Duncan)

[1] **The Newcastle Hospitals HCW Testing Group**
Ina Schim van der Loeff[a,b], Kenneth F. Baker[a,b], David A. Price[c], Peter McDowall[c], Kiera McDowall[c], Sue Cook[c], Peter Towns[c], Ulrich Schwab[c], Adam Evans[c], Jill Dixon[c], Jennifer Collins[c], Shirelle Burton-Fanning[c], David Saunders[c], Jayne Harwood[c], Julie Samuel[c], Matthias L. Schmid[c], Lucia Pareja-Cebrian[c], Ewan Hunter[c], Yusri Taha[c], Elizabeth Murphy[c]