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antibodies to spike will therefore indicate whether there has been a good response, whereas measuring antibodies to nucleocapsid would help identify whether the individual had nonetheless become infected. Measuring the different antibodies might also have prognostic value; a report showed that a predominant humoral response to nucleoprotein is associated with poor outcome in patients admitted to hospital, compared with that of spike.<sup>10</sup> Further investigation is required and the possibility of a one-size-fits-all immunological assay looks less and less likely.

We declare no competing interests.

\*Catherine F Houlihan, Rupert Beale  
c.houlihan@ucl.ac.uk

University College London Hospitals, NHS Foundation Trust, London, UK (CFH); University College London, London, UK (CFH, RB); and The Francis Crick Institute, London, UK (RB)

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## Using serological data to understand unobserved SARS-CoV-2 risk in health-care settings

During past outbreaks of severe acute respiratory syndrome and Middle East respiratory syndrome, many infections occurred within health-care settings.<sup>1</sup> Since the emergence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), growing evidence of nosocomial transmission has been observed, but tracking such outbreaks is challenging because a substantial proportion of infected individuals might exhibit mild or no symptoms.<sup>2</sup> In *The Lancet Infectious Diseases*, Kasper Iversen and colleagues<sup>3</sup> report results from a large seroprevalence survey of almost 30 000 hospital employees in Denmark.<sup>3</sup> The authors found that 1163 (4.04%) of 28 792 staff were seropositive overall, which was slightly higher than the 3.04% (142 of 4672) prevalence observed among local blood donors (risk ratio [RR] 1.33 [95% CI 1.12–1.58]). Seroprevalence was also higher among frontline health-care workers than among staff in other hospital roles (1.38 [1.22–1.56];  $p < 0.001$ ). Staff working in dedicated COVID-19 wards

showed substantially higher rates of seropositivity (1.65 [1.34–2.03];  $p < 0.001$ ) than other frontline health-care workers working in hospitals, reflecting increased risk for this group, a pattern that has also been reported in neighbouring Sweden.<sup>4</sup> Although Iversen and colleagues used a point-of-care lateral flow immunoassay, which is generally considered less conclusive than enzyme-linked immunosorbent assays or similar laboratory-based methods,<sup>5</sup> the authors did a comprehensive pre-study test assessment and estimated a sensitivity of 82.5–90.6% and specificity of 99.2–99.5%. High specificity is essential to minimise high rates of false positives when used in low-prevalence populations, such as the one studied.

The results highlight the risk that SARS-CoV-2 can pose to health-care workers, particularly those in regular contact with patients with COVID-19, and the importance of understanding possible routes of exposure in hospitals. Given the potential for nosocomial transmission to amplify outbreaks,



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Published Online  
August 3, 2020  
[https://doi.org/10.1016/S1473-3099\(20\)30579-X](https://doi.org/10.1016/S1473-3099(20)30579-X)  
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particularly when incidence is otherwise low in the community,<sup>6</sup> serological surveillance is a crucial tool. Serological surveillance can help investigate the dynamics of infections that often go unobserved in the early stages of epidemics or when a large fraction of cases is asymptomatic or with mild symptoms. Among the Danish hospital staff who were seropositive, one in five reported no COVID-19 compatible symptoms at all in the 6 weeks before sample collection.

The study also shows the challenge of identifying a specific and sensitive clinical case definition for COVID-19, with around half of seronegative participants reporting at least one COVID-19-like symptom. This finding suggests that symptoms reported by seropositive individuals were not necessarily all linked to SARS-CoV-2 infection. The analysis found that loss of taste or smell—a symptom that was omitted from many early clinical definitions<sup>7</sup>—was strongly associated with seropositivity (RR 11.38 [95% CI 10.22–12.68]). However, the prevalence of asymptomatic SARS-CoV-2 infections and COVID-19-like symptoms among seronegative staff illustrates the limitations of relying on symptom-based surveillance alone. This finding also shows the importance of developing screening tests that are easily done and sufficiently rapid to enable frequent and accurate detection of acute infection among at-risk staff.

As well as indicating the degree of exposure to SARS-CoV-2, seroprevalence might provide an insight into the possible extent of antibody-mediated immunity. Important questions remain about the precise role of humoral and cellular immunity following SARS-CoV-2 exposure, and whether seropositivity or antibody titres can be considered a proxy measure of protective immunity.<sup>8</sup> If the seroprevalence estimated in the Danish hospital staff does indeed reflect the extent of immunity that would prevent infection, this would be substantially below the level required to generate localised herd immunity that could stop future nosocomial transmission.

Although seroprevalence studies provide a useful indication of existing antibody levels within a population, we still need to know more about the medium-term and long-term persistence of such responses, particularly among individuals who have

had mild or asymptomatic infections. If antibody kinetics against SARS-CoV-2 reflect those against seasonal coronaviruses, as appears increasingly likely,<sup>9</sup> we would anticipate rapid antibody decay and seroreversion (from seropositive to seronegative) within several months to a year.<sup>10</sup> Characterising antibody dynamics and how these vary within and between populations will be crucial for the interpretation of ongoing serological studies and might provide insight into population-level protection and prospects for future vaccine-induced immunity. Faced with the possibility of second epidemic waves, large-scale studies of serological dynamics in at-risk populations, ideally capturing longitudinal trends, will be essential to inform our knowledge of future SARS-CoV-2 transmission dynamics and accompanying COVID-19 risks, and how these risks can be reduced.

We declare no competing interests.

\*Adam J Kucharski, Eric J Nilles  
adam.kucharski@lshtm.ac.uk

Centre for Mathematical Modelling of Infectious Diseases, London School of Hygiene and Tropical Medicine, London, WC1E 7HT, UK (AJK); Brigham and Women's Hospital, Harvard Medical School, Harvard Humanitarian Initiative, Boston, MA, USA

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