SARS-CoV-2 seroprevalence in COVID-19 hotspots

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Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has surprised the world with its range of disease manifestations, from asymptomatic infection to critical illness leading to hospital admission and death.[1,2] Due to the high proportion of asymptomatic or mild infections (approximately 80%), data restricted to laboratory-confirmed cases do not capture the true extent of the spread or burden of the virus, or its infection-fatality ratio.[2] Therefore, serological detection of specific antibodies against SARS-CoV-2 can better estimate the true number of infections. Due to co-circulation of other human coronaviruses, serology for SARS-CoV-2 is not trivial. Antibody cross-reactivity with other human coronaviruses has been largely overcome by using selected viral antigens, and several commercial assays are now available for SARS-CoV-2 serology. However, despite high sensitivity and specificity, a setting with a low pretest probability, such as current population-based seroprevalence studies, warrants careful validation of results.[3] Extensive previous assay validation in well characterised serum samples and confirmation of positive results are thus necessary to prevent false-positive findings from confounding seroprevalence rates.

The first SARS-CoV-2 seroprevalence studies from cohorts representing the general population have become available from COVID-19 hotspots such as China, the USA, Switzerland, and Spain.[4–8] In *The Lancet*, Marina Pollán and colleagues[6] and Silvia Stringhini and colleagues[7] separately report representative population-based seroprevalence data from Spain and Switzerland collected from April to early May this year. Studies were done in both the severely affected urban area of Geneva, Switzerland, and the whole of Spain, capturing both strongly and less affected provinces. Both studies recruited randomly selected participants but excluded institutionalised populations (ie, permanent residents of institutions such as prisons or care homes, as well as hospitalised residents), which is a clear limitation. They relied on IgG as a marker for previous exposure, which was detected by two assays for confirmation of positive results.

The Spanish study,[6] which included more than 60 000 participants, showed a nationwide seroprevalence of 5·0% (95% CI 4·7–5·4; specificity–sensitivity range of 3·7% [both tests positive] to 6·2% [at least one test positive]), with urban areas around Madrid exceeding 10% (eg, seroprevalence by immunoassay in Cuenca of 13·6% [95% CI 10·2–17·8]). These differences in seroprevalence are also reflected in laboratory-confirmed COVID-19 cases, which were much higher in urban areas than in rural areas. Similar numbers were obtained across the 2766 participants in the Swiss study,[7] with seroprevalence data from Geneva reaching 10·8% (8·2–13·9) in early May. The rather low seroprevalence in COVID-19 hotspots in both studies is in line with data from Wuhan, the epicentre and presumed origin of the SARS-CoV-2 pandemic. Surprisingly, the study done in Wuhan approximately 4–8 weeks after the peak of infection reported a low seroprevalence of 3·8% (2·6–5·4) even in highly exposed health-care workers, despite an overwhelmed health-care system.[4] None of the studies reported sex differences, and both the studies from Geneva and Spain reported lower seroprevalence in children than in adults.[6,7] Whether this reflects a lower susceptibility of children to infection in general, or rather that the studies were undertaken while schools and day-care centres were closed, remains to be elucidated.

The key finding from these representative cohorts is that most of the population appears to have remained unexposed to SARS-CoV-2, even in areas with widespread virus circulation. These findings are further supported by the observation that even countries without strict lockdown measures have reported similarly low seroprevalence—eg, Sweden, which reported a prevalence of 7·3% at the end of April—leaving them far from reaching natural herd immunity in the population.[9]

Such seroprevalence studies provide information only about previous exposure, rather than immunity, as no neutralising antibodies are measured. Since no correlate of protection for SARS-CoV-2 has been formally defined, we do not know what titre of neutralising antibodies would protect recovered patients from secondary infection or if non-neutralising antibodies could also contribute to protection. By analogy to common-cold coronaviruses, immunity after SARS-CoV-2 infection is thought to be incomplete and temporary, lasting only several months to a few

years.[10,11] A subset of asymptomatic SARS-CoV-2 cases shows a lower antibody response and titres that wane quickly.[12] It is unknown whether these patients are protected by other immune functions, such as cellular immunity. In summary, such individuals would not be detected by serological assays but might confound the true exposure rate.

In light of these findings, any proposed approach to achieve herd immunity through natural infection is not only highly unethical, but also unachievable. With a large majority of the population being infection naive, virus circulation can quickly return to early pandemic dimensions in a second wave once measures are lifted. In addition, the geographical variability and the dynamic of weekly increasing seroprevalence rates during the early phase of the pandemic highlight that these studies are only snapshots in time and space, and reflect the circumstances of the period in which they were done. As we are still in the midst of an unprecedented global health crisis, such seroprevalence data will continue to be necessary for public health authorities to estimate exposure rates, especially in areas with little testing capacity for acute cases. If and when a vaccine is widely available, ongoing seroprevalence studies will be able to provide information about the extent and duration of vaccine-induced herd immunity.

We declare no competing interests.

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