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## SARS-CoV-2 seroprevalence in Spain

We read with great interest the Article by Marina Pollán and colleagues.<sup>1</sup> It is remarkable that in the Spanish population, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) seroprevalence as of May, 2020, appeared to be the same in men (immunoassay positive 4.6%, 95% CI 4.2–5.0) and women (4.6%, 4.2–5.0). Of note, neither Pollán and colleagues nor Eckerle and Meyer's linked Comment<sup>2</sup> mention the sex distribution throughout different age strata. This is a missed opportunity because Spain, among other countries, showed marked age-specific sex differences among confirmed SARS-CoV-2 cases during the first months of the pandemic.<sup>3</sup>

To depict this difference, we used data provided by governmental health authorities from countries in Europe, as well as the USA and Canada (appendix). In all 12 countries with data available on sex distribution across different ages, the proportion of men with confirmed SARS-CoV-2 was lower than for women in the age group older than 80 years, and was similar to the proportion of older men in the general population. Additionally, some countries also showed sex differences in younger age groups. For example in Spain, as of May 5, 2020, the proportion of men aged 20–39 years with confirmed SARS-CoV-2 was only 36% (women accounted for 64%),<sup>3</sup> which was markedly lower than the proportion of men (50%) aged 20–39 years reported in the general population.<sup>4</sup>

Nationwide seroepidemiological studies such as ENE-COVID<sup>1</sup> should provide details on age-stratified sex distribution to clarify whether sex differences are due to the testing policies or acceptability, or due to exposure differences (ie, more women in high risk groups such as health-care workers). In countries with large sex differences, such as Belgium, the UK,

or Spain, this information might help to elucidate whether SARS-CoV-2 diagnoses have been disproportionately overlooked in specific populations (eg, in young men).

We declare no competing interests.

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- 1 Pollán M, Pérez-Gómez B, Pastor-Barriuso R, et al. Prevalence of SARS-CoV-2 in Spain (ENE-COVID): a nationwide, population-based seroepidemiological study. *Lancet* 2020; **396**: 535–44.
- 2 Eckerle I, Meyer B. SARS-CoV-2 seroprevalence in COVID-19 hotspots. *Lancet* 2020; **396**: 514–15.
- 3 Centro de Coordinación de Alertas y Emergencias Sanitarias. Actualización nº 96. Enfermedad por el coronavirus (COVID-19). May, 2020. [https://www.mscbs.gob.es/profesionales/saludPublica/ccayes/alertasActual/nCov/documentos/Actualizacion\\_96\\_COVID-19.pdf](https://www.mscbs.gob.es/profesionales/saludPublica/ccayes/alertasActual/nCov/documentos/Actualizacion_96_COVID-19.pdf) (accessed July 11, 2020).
- 4 Instituto Nacional de Estadística. <https://www.ine.es/jaxiT3/Tabla.htm?t=9688> (assessed July 11, 2020).

Marina Pollán and colleagues<sup>1</sup> conclude that herd immunity is difficult to achieve because the seroprevalence by point-of-care testing after the first wave of the epidemic was only 5% (95% CI 4.7–5.4).

Antibodies only neutralise the virus in interstitial fluid and the mucosal surface. The intracellular virus that causes illness is countered by cellular immunity mediated by T cells and macrophages. This process is part of a complex pathway and cannot be measured easily, as shown by a report from Sweden.<sup>2</sup> Thus, measuring antibodies and assuming that a population is susceptible lacks a holistic view because Pollán and colleagues failed to take into account the two essential parts of viral immunology. Reinfection with the same strain of SARS-CoV-2 is very rare and protection is offered by cellular immunity and antibodies working in tandem.

Long and colleagues<sup>3</sup> have shown that the antibody response in asymptomatic COVID-19 cases is weak.

Asymptomatic individuals probably have effective cellular immunity that destroys the intracellular virus, even though there is no robust antibody response to neutralise SARS-CoV-2 on the mucosal surface, as the virus enters the respiratory tract or blood stream. A virus has to enter the cell to replicate and cause systemic illness. Cellular immunity is memory-driven, similar to humoral immunity, and might perhaps be more crucial and effective in COVID-19. Pollán and colleagues' findings revealed that relying on SARS-CoV-2 antibodies alone as a test for prevalence and immunity goes against the fundamental tenets of viral immunology.

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- 1 Pollán M, Pérez-Gómez B, Pastor-Barriuso R, et al. Prevalence of SARS-CoV-2 in Spain (ENE-COVID): a nationwide, population-based seroepidemiological study. *Lancet* 2020; **396**: 535–44.
- 2 Sekine T, Perez-Potti A, Rivera-Ballesteros O, et al. Robust T cell immunity in convalescent individuals with asymptomatic or mild COVID-19. *Cell* 2020; **183**: 158–68.e14.
- 3 Long Q-X, Tang X-J, Shi Q-L, et al. Clinical and immunological assessment of asymptomatic SARS-CoV-2 infections. *Nat Med* 2020; **26**: 1200–04.

### Authors' reply

We thank Christian Hoffmann and Eva Wolf for pointing out the contradiction of similar severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) seroprevalence figures between men and women in our nationwide study,<sup>1</sup> compared with the distribution of confirmed COVID-19 cases in the most severely affected countries. Following their suggestion, we provide seroprevalence data stratified by age and sex (appendix) to show that infection rates were similar in men and women during the first epidemic wave in Spain.

According to the consolidated data from the Spanish National Epidemiological Surveillance Network, men account for 43% of COVID-19

See Online for appendix



See Online for appendix

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