Prevalence of SARS-CoV-2 in Spain (ENE-COVID): a nationwide, population-based seroepidemiological study

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Summary

Background Spain is one of the European countries most affected by the COVID-19 pandemic. Serological surveys are a valuable tool to assess the extent of the epidemic, given the existence of asymptomatic cases and little access to diagnostic tests. This nationwide population-based study aims to estimate the seroprevalence of SARS-CoV-2 infection in Spain at national and regional level.

Methods 35 883 households were selected from municipal rolls using two-stage random sampling stratified by province and municipality size, with all residents invited to participate. From April 27 to May 11, 2020, 61 075 participants (75·1% of all contacted individuals within selected households) answered a questionnaire on history of symptoms compatible with COVID-19 and risk factors, received a point-of-care antibody test, and, if agreed, donated a blood sample for additional testing with a chemiluminescent microparticle immunoassay. Prevalences of IgG antibodies were adjusted using sampling weights and post-stratification to allow for differences in non-response rates based on age group, sex, and census-tract income. Using results for both tests, we calculated a seroprevalence range maximising either specificity (positive for both tests) or sensitivity (positive for either test).

Findings Seroprevalence was 5·0% (95% CI 4·7–5·4) by the point-of-care test and 4·6% (4·3–5·0) by immunoassay, with a specificity–sensitivity range of 3·7% (3·3–4·0; both tests positive) to 6·2% (5·8–6·6; either test positive), with no differences by sex and lower seroprevalence in children younger than 10 years (<3·1% by the point-of-care test). There was substantial geographical variability, with higher prevalence around Madrid (>10%) and lower in coastal areas (<3%). Seroprevalence among 195 participants with positive PCR more than 14 days before the study visit ranged from 87·6% (81·1–92·1; both tests positive) to 91·8% (86·3–95·3; either test positive). In 7273 individuals with anosmia or at least three symptoms, seroprevalence ranged from 15·3% (13·8–16·8) to 19·3% (17·7–21·0). Around a third of seropositive participants were asymptomatic, ranging from 21·9% (19·1–24·9) to 35·8% (33·1–38·5). Only 19·5% (16·3–23·2) of symptomatic participants who were seropositive by both the point-of-care test and immunoassay reported a previous PCR test.

Interpretation The majority of the Spanish population is seronegative to SARS-CoV-2 infection, even in hotspot areas. Most PCR-confirmed cases have detectable antibodies, but a substantial proportion of people with symptoms compatible with COVID-19 did not have a PCR test and at least a third of infections determined by serology were asymptomatic. These results emphasise the need for maintaining public health measures to avoid a new epidemic wave.

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Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was identified in December, 2019, as the cause of the illness designated COVID-19.[1] With more than 249 000 confirmed cases and more than 28 000 deaths by July 2, Spain remains one of the European countries most severely affected by the ongoing COVID-19 pandemic.[2,3] However, epidemiological surveillance of confirmed COVID-19 cases captures only a proportion of all infections because the clinical manifestations of infection with SARS-CoV-2 range from severe disease, which can lead to death, to asymptomatic infection.

By contrast, a population-based seroepidemiological survey can quantify the proportion of the population that has antibodies against SARS-CoV-2. A seroepidemiological study provides information on the proportion of the population exposed and, if the antibodies are a marker of total or partial immunity, the proportion of the population that remains susceptible to the virus.

Several serological surveys of SARS-CoV-2 have been done[4–15] and others are ongoing.[16] However, many of them are small or based on non-random sampling of participants (eg, focusing on health-care workers or blood donors) and thus cannot provide precise estimates of seroprevalence by age group in the general population. Additionally, some of these studies have used antibody tests with low sensitivity or specificity or have not reported the characteristics of the test.[16]

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See **Comment** page 514

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See **Online** for appendix

Research in context

Evidence before this study

Spain is one of the European countries most affected by the COVID-19 pandemic so far. Seroepidemiological surveys are a useful tool to track the transmission of epidemics, but few have been done for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). We searched PubMed and its specific hub LitCovid, OpenAIRE, Embase, and medRxiv and bioRxiv preprint servers up to May 25, 2020, for epidemiological studies using the terms "seroprevalence" or "seroepidemiology" and "SARS-CoV-2" without date or language restrictions. Most serological surveys were fairly small or focused on specific population subgroups. Large population-based studies are required to understand the dynamics of the epidemic.

Added value of this study

This is the first nationwide population-based study that presents seroprevalence estimates of antibodies against SARS-CoV-2 at national and regional levels, exploring the landscape of population immunity in Spain. With more than 61 000 participants, this study provides accurate prevalence figures according to sex, age—from babies to nonagenarians—and selected risk factors. Our findings confirm that at least a third of individuals who have developed antibodies against SARS-CoV-2 were asymptomatic. Additionally, our results indicate that children and adolescents have lower seroprevalence than adults and seroprevalence does not vary by sex. Our study confirms that a high-quality point-of-care test could be a good choice for large seroepidemiological studies. The rapid test used here showed good performance compared with a chemiluminescent microparticle immunoassay. Finally, the use of two different assays allowed us to define seroprevalence ranges alternatively favouring specificity (requiring a positive result for both tests) or sensitivity (positive to either test).

Implications of all the available evidence

The relatively low seroprevalence observed in the context of an intense epidemic in Spain might serve as a reference to other countries. At present, herd immunity is difficult to achieve without accepting the collateral damage of many deaths in the susceptible population and overburdening of health systems. Our results, together with previous evidence, suggest that approximately a third of people with SARS-CoV-2 infection remain asymptomatic, which has important public health implications. Regional seroprevalence data offer valuable information to tailor public health policies against this epidemic.

In April, 2020, the Spanish Ministry of Health and the Institute of Health Carlos III, in collaboration with the health services of the Spanish regions (Autonomous Communities), launched ENE-COVID, a nationwide, population-based, longitudinal seroepidemiological study, to quantify the extent of SARS-CoV-2 circulation throughout the country. The study included more than 61 000 individuals from randomly selected households; was designed to be representative by province, age group, and sex; and used two tests for the determination of SARS-CoV-2 antibodies. Here, we describe the study design and the results of the first wave of the study, conducted between April 27 and May 11, 2020.

Methods

Study design and participants

The Seroepidemiological Survey of SARS-CoV-2 Virus Infection in Spain (*Encuesta Seroepidemiológica de la Infección por el Virus SARS-CoV-2 en España*; ENE-COVID) is a nationwide population-based cohort study to investigate seropositivity for SARS-CoV-2 in the non-institutionalised (ie, excluding care-home residents, hospitalised people, people in prisons, nuns and friars in convents, and residents in other collective residences) Spanish population. The study design is described in detail in the appendix (pp 6–10).

Briefly, 35 883 households were selected through a stratified two-stage sampling, with strata formed by cross-classifying the 50 Spanish provinces and the two autonomous cities (appendix p 19) with municipalities grouped by size (<5000, 5000–19 999, 20 000–99 999, and ≥100 000 residents). 1500 census tracts were initially selected with probability proportional to their size, and then 24 households were randomly sampled within each selected census tract by the National Institute of Statistics. All residents in the household were invited to participate in the study, resulting in a selected sample of 102 562 individuals of all ages.

This study involved the coordination and training of 29 laboratories and 4400 health professionals in 1409 health-care centres throughout the Spanish National Health System. A single ad-hoc information system capable of hosting up to 2000 concurrent users was developed and deployed in approximately 2 weeks to allow daily data modification by study staff for 4000 households and 15 000 participants, alongside the coordination and development of uniform, nationwide support for the study procedures.

The study design includes three successive follow-up waves of data collection, with a 1-week break between them. Each wave is scheduled to be completed within 2 weeks. Half of the cohort (12 households per census tract) was randomly assigned to data collection during the first week of each wave and the other half to the second week, so that serum specimens are collected in all participants 2–4 weeks apart. In this Article, we present seroprevalence data from the first wave of the ENE-COVID study, which was conducted from April 27 to May 11, 2020.

Field work was carried out by staff from each of the region's health services under a common protocol developed by the Institute of Health Carlos III, which also coordinated the training of all personnel via a web platform. Individuals residing in the selected households were contacted by telephone and invited to either go to their primary health-care centres or to allow a home visit, where they provided informed consent. Participants answered a questionnaire that included history of symptoms compatible with COVID-19 (ie, fever, chills, severe tiredness, sore throat, cough, shortness of breath, headache, anosmia or ageusia, and nausea, vomiting, or diarrhoea), contact with suspected or confirmed cases, and other risk factors; had a point-of-care rapid test to detect antibodies against SARS-CoV-2; and, optionally, donated a blood sample for subsequent laboratory analysis. The answers to the questionnaire and the result of the point-of-care test were recorded on site in a secure web application, specifically designed for this study by the Ministry of Health. Blood samples were centrifuged, labelled, and stored refrigerated at the primary health-care centres, and sent to the laboratory every 2–3 days. Serum samples were analysed at the National Centre for Microbiology (Institute of Health Carlos III) or in one of 28 selected regional microbiology laboratories.

The Institutional Review Board of the Institute of Health Carlos III approved the study (register number PI 39_2020). The Spanish Data Protection Agency was consulted. Written informed consent was obtained from all study participants. Different forms of informed consent were used for adults, teenagers, parents of participant children, and guardians of mentally disabled participants. Witnesses assisted participants who were not able to read any of the four official languages of Spain.

Detection of SARS-CoV-2 antibodies

Two serological tests were done: a point-of-care rapid test applied directly to fingerprick blood, and a chemiluminescent microparticle immunoassay that requires venepuncture for subsequent analysis in laboratory.

The point-of-care test (Orient Gene Biotech COVID-19 IgG/IgM Rapid Test Cassette; Zhejiang Orient Gene Biotech, Zhejiang, China; reference GCCOV-402a) was a lateral-flow immunochromatographic assay for qualitative differentiation between IgG and IgM against the receptor binding domain of SARS-CoV-2 spike (S) protein,[17] which yields results in 10 min. The manufacturer reported sensitivity of 97·2% for IgG and 87·9% for IgM and specificity of 100% for both IgG and IgM, using RT-PCR as the gold standard. A verification study, done by the National Centre for Microbiology as preparation for ENE-COVID, returned a sensitivity of 82·1% for IgG and 69·6% for IgM in fingerprick blood samples and a specificity of 100% for IgG and 99·0% for IgM (appendix p 11). An independent validation study gave similar results.[18] Due to the lower sensitivity and specificity of IgM, its shorter duration, and the heterogeneity of results observed in initial IgM readings, results for the point-of-care test reported here are based only on IgG.

The second test was a chemiluminescent microparticle immunoassay for qualitative detection of IgG against SARS-CoV-2 nucleoprotein (SARS-CoV-2 IgG for use with ARCHITECT; Abbott Laboratories, Abbott Park, IL, USA; reference 06R8620). We chose this immunoassay test after studying several high-performance serological kits at the National Centre for Microbiology, including ELISA and chemiluminescent immunoassays. The amount of IgG antibodies to SARS-CoV-2 in each sample is determined by comparing its chemiluminescent relative light unit (RLU) to the calibrator RLU (index S/C). Using an index S/C threshold of 1·4, the manufacturer reported a sensitivity of 86·4% after 7 days from symptom onset and 100% after 14 days, and a specificity of 99·6%, using RT-PCR as the gold standard. These

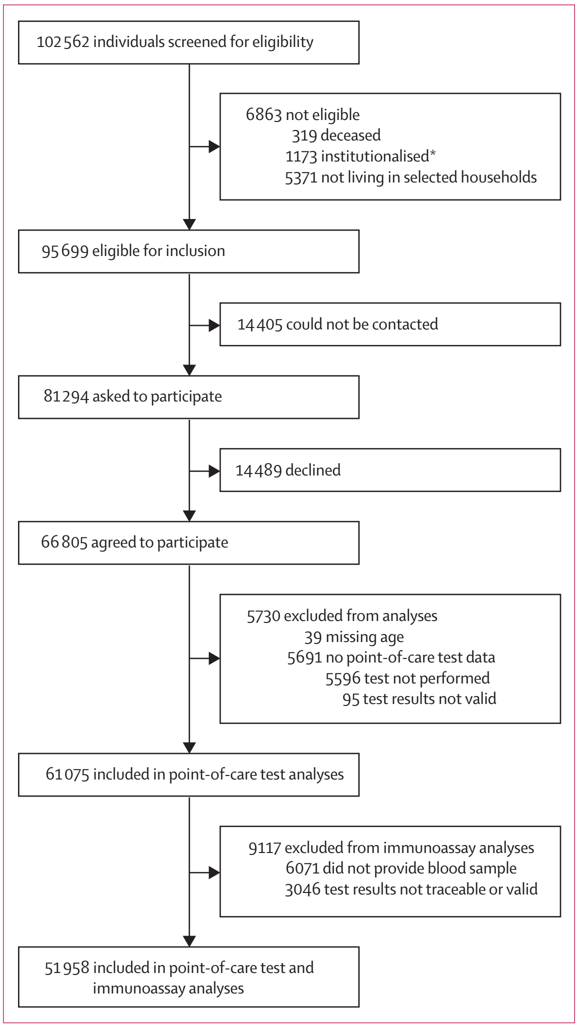

Figure 1: **Flow chart of participants in first wave of the ENE-COVID study**
*Care-home residents, hospitalised people, people in prisons, nuns and friars in convents, and residents in other collective residences.

figures were corroborated by a study in a set of samples from patients positive for SARS-CoV-2 by RT-PCR and in samples obtained in 2018–19, and thus before the epidemic (sensitivity of 100% after 17 days from symptom onset, specificity of 99·9%).[9] Again, a verification study by the National Centre for Microbiology showed a sensitivity of 89·7% in serum samples from RT-PCR-positive patients after 14 days from symptom onset and a specificity of 100% with samples obtained before Dec 8, 2019 (appendix p 12).

	Point-of-care test		Immunoassay	
	Number of participants	Seroprevalence (95% CI)	Number of participants	Seroprevalence (95% CI)
Overall	61 075	5·0% (4·7–5·4)	51 958	4·6% (4·3–5·0)
Sex				
Female	31 726	5·0% (4·7–5·5)	27 141	4·6% (4·2–5·0)
Male	29 349	5·0% (4·6–5·4)	24 817	4·6% (4·2–5·0)
Age, years				
0–19	11 422	3·4% (2·9–3·9)	6527	3·8% (3·2–4·6)
20–34	8469	4·4% (3·7–5·1)	7569	5·0% (4·3–5·8)
35–49	14 532	5·3% (4·7–5·9)	13 354	4·9% (4·3–5·5)
50–64	15 094	5·8% (5·3–6·5)	13 906	4·7% (4·1–5·3)
≥65	11 558	6·0% (5·4–6·8)	10 602	4·5% (3·8–5·3)
Nationality				
Spanish	57 858	5·0% (4·7–5·4)	49 520	4·6% (4·2–4·9)
Other	2643	5·6% (4·3–7·3)	2178	5·7% (4·3–7·5)
Occupation*				
Active worker	25 759	5·8% (5·3–6·3)	23 763	5·3% (4·9–5·9)
Unemployed	4459	3·3% (2·6–4·1)	3981	3·5% (2·7–4·6)
Student	3550	4·6% (3·6–5·8)	3060	4·8% (3·8–6·1)
Retired	11 895	6·0% (5·4–6·8)	10 932	4·5% (3·8–5·3)
Permanent or temporary disability	1476	4·1% (2·9–5·9)	1342	3·6% (2·4–5·5)
House person	3369	4·3% (3·5–5·4)	3033	3·3% (2·5–4·3)
Unpaid social work	49	3·1% (0·7–11·4)	42	4·5% (1·4–13·6)
Other	965	4·2% (2·8–6·2)	839	3·3% (2·1–5·2)
Occupation sector†				
Telecommuting	11 899	6·4% (5·7–7·0)	10 947	5·9% (5·3–6·6)
Retail	1640	4·7% (3·4–6·6)	1515	4·5% (3·1–6·5)
Transport	800	5·9% (3·9–8·7)	731	5·8% (3·6–9·2)
Police, firefighters, or public safety	643	6·2% (4·1–9·2)	589	6·3% (4·0–9·9)
Cleaning	804	4·1% (2·6–6·4)	748	4·5% (2·9–7·1)
Health care	1109	10·2% (7·9–13·0)	1048	10·0% (7·7–12·9)
Nursing home or other social work	1016	7·7% (5·6–10·5)	947	7·9% (5·9–10·6)
Home caregiver	403	6·4% (3·1–12·1)	372	3·7% (1·6–8·3)
Other	7444	4·3% (3·6–5·0)	6865	3·4% (2·8–4·0)
Household size, residents				
1	4863	5·1% (4·3–6·0)	4456	4·0% (3·3–5·0)
2	14 042	5·7% (5·1–6·5)	12 894	5·1% (4·4–5·8)
3–5	38 964	4·8% (4·5–5·3)	32 140	4·6% (4·2–5·1)
≥6	3206	3·8% (2·7–5·3)	2468	3·2% (2·1–4·8)

(Table 1 continues on next page)

Statistical analysis

We estimated seroprevalence as the proportion of individuals who had a positive result in the IgG band of the point-of-care test or, in separate analyses, who had a positive result in the immunoassay. In sensitivity analyses restricted to participants with data on both tests, we estimated seroprevalence as the proportions of individuals who had a positive result in both tests (most specific approach) or in either test (most sensitive approach). We used these analyses to provide a seroprevalence range that either favours specificity (requiring a positive test in both assays) or sensitivity (considering positive results in either test). Using the immunoassay as an alloyed reference, we also estimated the relative sensitivity of the point-of-care test as the proportion of individuals with a positive test among those with a positive result in the immunoassay, as well as the relative specificity as the proportion of individuals with a negative test among those with a negative result in the immunoassay.

Sample size was determined to achieve a minimum precision in the estimation of SARS-CoV-2 seroprevalence in all Spanish provinces, assuming a priori an underlying crude seroprevalence of 5% or higher during the study period, and accounting for non-response and potential clustering of seropositivity by household and census tract. Further details on sample size determination and within-province sampling are provided in the appendix (pp 6–7).

We used sampling weights to adjust the seroprevalence estimates for the different selection probabilities (individuals from less populated provinces were oversampled; appendix pp 8–10) and the distinct non-response rates to the point-of-care test and the immunoassay by sociodemographic characteristics (appendix pp 13, 20). Base design weights were initially calculated as the inverse of the sampling fractions within each province and municipality size stratum, which were further adjusted for non-response by post-stratifying the sample on income (lower or higher than the province-specific median), sex, and age group (<20, 20–34, 35–49, 50–64, or ≥65 years), so that the weighted sum of respondents in each stratum matched the known population total.[19] Different sampling weights were constructed for the point-of-care test and the immunoassay, with trimmed extreme weights (0·2% and 0·6%, respectively) to counter highly influential observations. The weights for the immunoassay were also used for the sensitivity analysis combining both tests.

Due to the complex study design, all statistical analyses accounted for stratification by province and municipality size group, as well as clustering of seropositivity for SARS-CoV-2 by household and census tract, when computing SEs of seroprevalence estimates. Design effects resulted in inflation factors for SEs of the overall seroprevalence estimates with the point-of-care test of 2·00 and of 1·99 for the immunoassay. Finite population corrections were applied because some sampling fractions of census tracts per stratum and households per census tract were not negligible. 95% CIs were calculated using logit-transformed seroprevalence estimates and their SEs, with the usual design-based degrees of freedom equal to the number of first-stage sampling units minus the number of strata, and were back-transformed to the original scale for reporting. Analyses were done using survey commands in Stata (version 16).

Role of the funding source

The funders facilitated data acquisition but had no role in the design, analysis, interpretation, or writing. The first three authors had full access to all the data. The first five authors and the senior author (RY) had final responsibility for the decision to submit for publication.

Results

Of 95 699 eligible individuals, 14 405 could not be contacted and 14 489 declined to participate (figure 1). Of the remaining 66 805 study participants, 61 075 participants received the point-of-care test (63·8% of eligible individuals and 75·1% of 81 294 contacted individuals) and 51 958 the immunoassay (54·3% and 63·9%, respectively; figure 1). The proportion of testing was lower in individuals aged 25–29 years and older than 65 years (and in individuals aged <15 years for the immunoassay), in middle-aged men compared with middle-aged women, and in lower income levels (appendix p 13).

Between April 27 and May 11, 2020, seroprevalence for the entire country was 5·0% (95% CI 4·7–5·4) by the point-of-care test and 4·6% (4·3–5·0) by immunoassay (table 1); the seroprevalence specificity–sensitivity range was 3·7% (3·3–4·0; both tests positive) to 6·2% (5·8–6·6; either test positive). Estimates varied markedly across provinces (figure 2; appendix pp 14–15). In seven provinces in the central part of Spain, including Madrid, seroprevalence was greater than 10% by both the point-of-care test and immunoassay separately (figure 2). In provinces along the coast, seroprevalence was greater than 5% only in Barcelona (appendix pp 14–15). Seroprevalence estimates were similar for both tests. Alternative definitions of seroprevalence (either favouring sensitivity or specificity) did not change the ranking of the provinces (appendix pp 14–15, 21).

According to the point-of-care test, seroprevalence was 1·1% (95% CI 0·3–3·5) in infants younger than 1 year and 3·1% (2·2–4·2) in children aged 5–9 years, increasing with age until plateauing around 6% in people aged 45 years or older (figure 3; appendix p 16). According to the immunoassay, seroprevalence was lower in the oldest age groups (≥85 years) compared with other adults. Seroprevalence with the point-of-care test was similar for females and males, was highest in the largest municipalities (6·4% [95% CI 5·8–7·1] in towns with at least 100 000 residents *vs* 4·2% [3·5–5·1] in those with <5000 residents), and was higher in health-care workers (10·2% [7·9–13·0]) than in other occupational groups; these results were supported by the immunoassay

	Point-of-care test		Immunoassay	
	Number of participants	Seroprevalence (95% CI)	Number of participants	Seroprevalence (95% CI)
(Continued from previous page)				
Census tract income‡				
<5th percentile	2865	5·1% (3·4–7·5)	2382	4·6% (3·1–6·7)
5th to <25th percentile	13 278	5·0% (4·2–5·9)	11 229	4·7% (3·8–5·8)
25th to <50th percentile	15 356	5·0% (4·3–6·0)	13 096	4·6% (3·9–5·6)
50th to <75th percentile	14 074	4·8% (4·1–5·6)	11 804	4·3% (3·6–5·1)
75th to <95th percentile	12 183	5·0% (4·2–5·9)	10 583	4·6% (3·7–5·7)
≥95th percentile	3319	6·2% (4·7–8·0)	2864	5·4% (4·0–7·4)
Municipality size, inhabitants				
≥100 000	18 530	6·4% (5·8–7·1)	15 974	6·0% (5·4–6·7)
20 000–99 999	18 547	4·2% (3·7–4·7)	15 553	3·8% (3·3–4·3)
5000–19 999	12 940	3·7% (3·2–4·4)	10 727	3·2% (2·7–3·9)
<5000	11 058	4·2% (3·5–5·1)	9704	3·8% (3·0–4·9)

SARS-CoV-2=severe acute respiratory syndrome coronavirus 2. *Among participants aged 17 years or older. Active workers are defined as anyone who is working, regardless of whether they had to leave the house to do so. †Among active workers during lockdown. One worker did not provide the sector. ‡Categories based on percentiles from province-specific distributions of census tract average income in 2017.

Table 1: **Seroprevalence of SARS-CoV-2 by general characteristics**

(table 1). Seroprevalence specificity–sensitivity ranges are shown in the appendix (p 17). For health-care workers, the range was 8·3% (6·1–11·2; both tests positive) to 11·7% (9·2–14·7; either test positive). Differences were smaller between categories defined by nationality, household size, and income percentile.

Compared with those without contact with a confirmed COVID-19 case, seroprevalence was greater in those who had a confirmed case in their household (ranging from 31·4% to 37·4% between the two tests), in their workplace (9·9–10·6%), among their non-cohabitating family members and friends (13·2–13·7%), or among their caregivers and cleaning staff (12·4–13·5%) or clients (11·2–11·7%; table 2; appendix p 18).

Among those with a positive test, the proportion of individuals who reported anosmia or three or more symptoms compatible with COVID-19 was 49·1% (95% CI 46·2–51·9) for the point-of-care test and 54·2% (51·0–57·2) for the immunoassay. The proportion of individuals with a positive test who were asymptomatic was 32·7% (30·2–35·4) and 28·5% (25·6–31·6), respectively, with a specificity–sensitivity range of 21·9% (19·1–24·9; both tests positive) to 35·8% (33·1–38·5; either test positive). Based on the overall seroprevalence range of 3·7% to 6·2% and the above proportions of seropositive individuals who were asymptomatic, it was estimated that between 376 000 and 1 042 000 asymptomatic individuals went undetected in the non-institutionalised Spanish population.

For both tests, the seroprevalence was 16·9% in those who reported a history of symptoms compatible with COVID-19 (specificity–sensitivity range 15·3% [95% CI 13·8–16·8] to 19·3% [17·7–21·0]) and 88·6–90·1% in

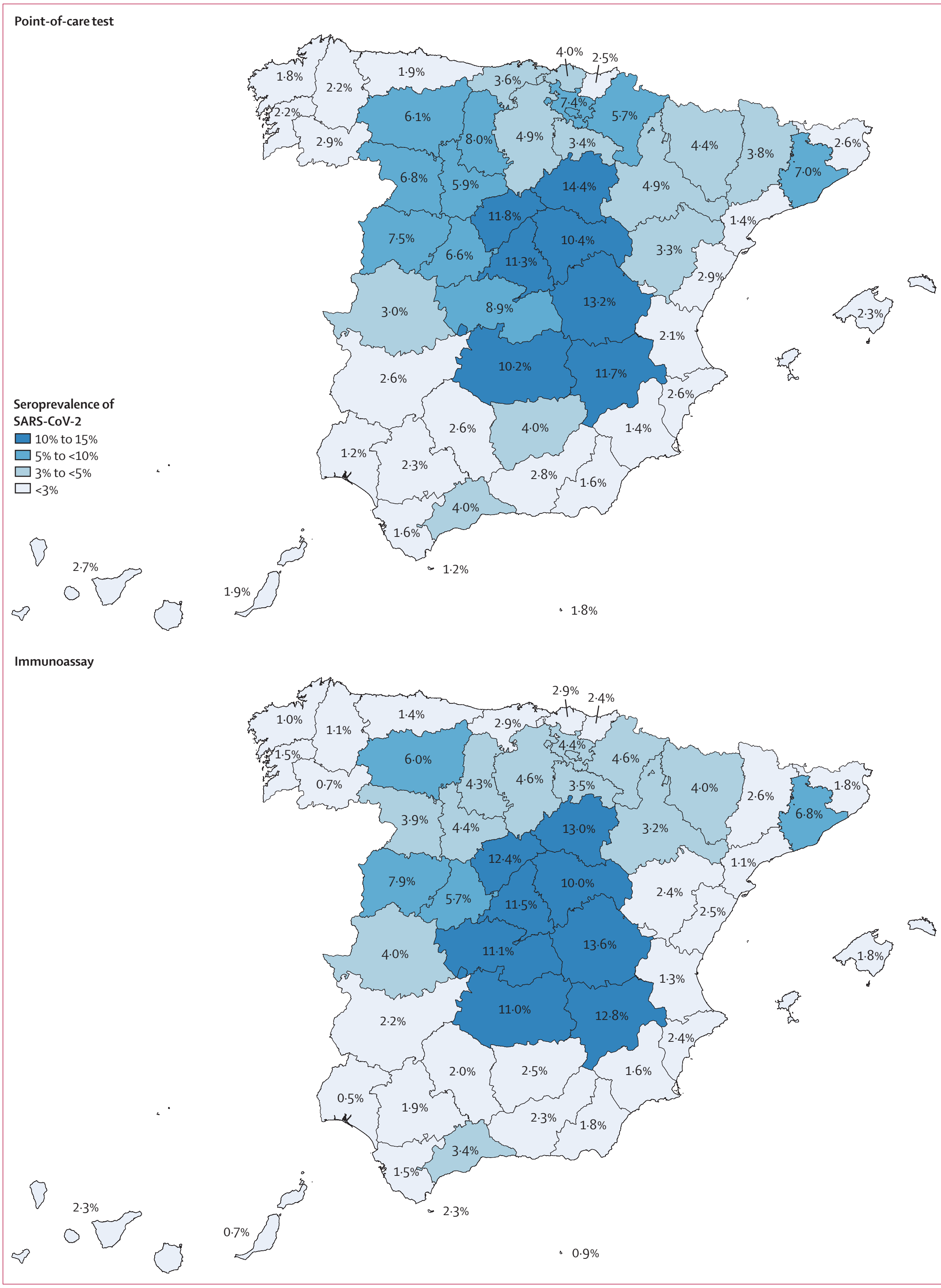

Figure 2: **Seroprevalence of SARS-CoV-2 by province by the point-of-care test and immunoassay**
SARS-CoV-2=severe acute respiratory syndrome coronavirus 2.

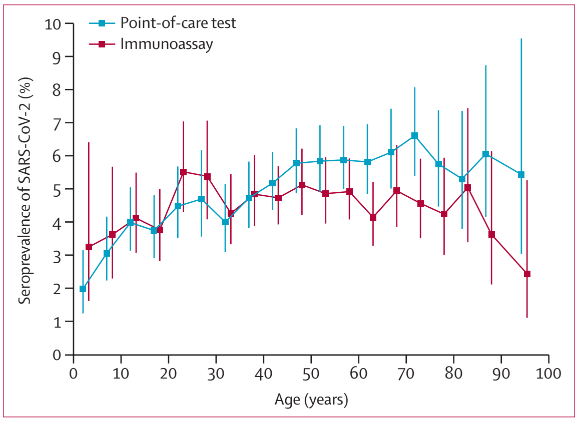

Figure 3: **Seroprevalence of SARS-CoV-2 by age**
Vertical lines represent 95% CIs. SARS-CoV-2=severe acute respiratory syndrome coronavirus 2.

those with a self-reported positive PCR more than 14 days before the test (specificity–sensitivity range 87·6% [81·1–92·1] to 91·8% [86·3–95·3]; table 2; appendix p 18). The immunoassay was positive for 65·8% (41·5–83·9) of individuals who had a positive PCR within 14 days of the test, whereas the point-of-care test was positive for only 45·6% (25·0–67·8; table 2; appendix p 18).

Among those participants with a history of COVID-19-related symptoms who presented antibodies, the proportion of individuals reporting a previous PCR test ranged between 16·4% (95% CI 13·8–19·5; either test positive) and 19·5% (16·3–23·2; both tests positive). Among them, a positive PCR was obtained in 75·1% (66·9–81·8; either test positive) and 78·8% (70·3–85·4; both tests positive), respectively.

When using the immunoassay as an alloyed reference, the relative sensitivity of the point-of-care test was 79·6% (77·1–81·8) overall, ranging from 61·0% (55·8–65·9) in those without COVID-19-related symptoms to 97·2% (91·7–99·1) in those with a positive PCR more than 14 days before (table 3). The relative specificity of the point-of-care test was 98·3% (98·2–98·5) overall, remaining higher than 97% in all subgroups except those with a positive PCR (table 3).

	Point-of-care test		Immunoassay	
	Number of participants	Seroprevalence (95% CI)	Number of participants	Seroprevalence (95% CI)
Symptoms compatible with COVID-19*				
Asymptomatic	40 325	2·5% (2·3–2·8)	34 016	2·0% (1·8–2·3)
Paucisymptomatic	12 399	4·5% (4·0–5·0)	10 669	3·9% (3·4–4·4)
Symptomatic	8351	16·9% (15·5–18·4)	7273	16·9% (15·4–18·5)
≤14 days before study visit	2397	13·9% (11·8–16·4)	2155	14·0% (11·8–16·5)
>14 days before study visit	5954	18·0% (16·4–19·8)	5118	18·0% (16·3–19·9)
PCR status				
Never done	59 568	4·6% (4·3–4·9)	50 594	4·2% (3·8–4·5)
Negative	1249	7·9% (6·0–10·3)	1134	8·0% (6·0–10·6)
Positive (≤14 days before study visit)	35	45·6% (25·0–67·8)	31	65·8% (41·5–83·9)
Positive (>14 days before study visit)	213	88·6% (82·3–92·8)	195	90·1% (84·3–93·9)
Contact with confirmed case				
No contact	55 989	3·9% (3·6–4·2)	47 385	3·4% (3·1–3·7)
Household member	1011	31·4% (26·5–36·8)	860	37·4% (31·8–43·3)
Non-cohabitating family member or friend	1467	13·2% (11·0–15·8)	1284	13·7% (11·2–16·7)
Co-worker	1579	10·6% (8·5–13·1)	1461	9·9% (8·0–12·2)
Cleaning staff, housemaid, or caregiver	83	13·5% (6·3–26·5)	78	12·4% (7·0–21·0)
Client†	940	11·7% (9·1–14·9)	888	11·2% (8·6–14·4)
Contact with symptomatic person				
No contact	50 691	3·2% (3·0–3·5)	42 894	2·7% (2·4–3·0)
Household member	4503	15·1% (13·3–17·0)	3728	15·6% (13·6–17·9)
Non-cohabitating family member or friend	2351	12·7% (10·7–14·9)	2037	12·2% (10·0–14·7)
Co-worker	2382	10·7% (9·0–12·6)	2221	10·1% (8·4–12·1)
Cleaning staff, housemaid, or caregiver	109	8·8% (3·9–18·8)	96	6·1% (2·9–12·3)
Client†	1033	10·0% (7·8–12·8)	980	10·2% (7·8–13·1)

SARS-CoV-2=severe acute respiratory syndrome coronavirus 2. *Asymptomatic (no symptoms), paucisymptomatic (1–2 symptoms without anosmia or ageusia), and symptomatic (anosmia or ageusia, or at least three symptoms among fever; chills; severe tiredness; sore throat; cough; shortness of breath; headache; or nausea, vomiting, or diarrhoea). †Client or patient if health-care worker.

Table 2: **Seroprevalence of SARS-CoV-2 by self-reported clinical characteristics**

Discussion

The findings from this nationwide seroprevalence study for SARS-CoV-2 indicate that the prevalence of IgG antibodies against this coronavirus is around 5% in Spain. Because the study was designed to obtain representative data at both national and provincial level, we were able to observe marked regional differences between the centre of Spain and the outskirts that generally match the surveillance data.[2] The prevalence in hotspot areas such as Madrid is more than five times higher than that observed in low-risk regions such as most provinces along the coasts.

To our knowledge, ENE-COVID is the largest population-based SARS-CoV-2 seroprevalence study in Europe. With more than 61 000 participants, the size of this study surpasses the combined 35 784 individuals described in a recent review of serosurveys.[16] The use of two IgG antibody tests aimed at different SARS-CoV-2 antigens allows us to specify a range of seroprevalence between 3·7% and 6·2%, depending on whether we favour greater specificity (ie, a positive result in both tests), which might be preferred when prevalence is low,[20] or greater sensitivity (ie, a positive result in either test). These estimates confirm the magnitude of seroprevalence suggested by smaller studies.[5,7,8]

We found no differences in seroprevalence between females and males. Similar to what has been reported for other endemic coronaviruses,[21] prevalence increased throughout childhood and adolescence, remained fairly

	Number of participants	Seroprevalence with immunoassay (95% CI)	Point-of-care test	
			Relative sensitivity (95% CI)	Relative specificity (95% CI)
Overall	51958	4·6% (4·3–5·0)	79·6% (77·1–81·8)	98·3% (98·2–98·5)
Sex				
Female	27141	4·6% (4·2–5·0)	80·1% (76·7–83·1)	98·3% (98·1–98·6)
Male	24817	4·6% (4·2–5·0)	79·0% (75·5–82·2)	98·3% (98·1–98·5)
Age, years				
0–19	6527	3·8% (3·2–4·6)	82·4% (75·1–88·0)	98·9% (98·5–99·2)
20–34	7569	5·0% (4·3–5·8)	71·5% (64·1–77·9)	98·9% (98·5–99·2)
35–49	13354	4·9% (4·3–5·5)	78·4% (73·4–82·6)	98·3% (98·0–98·6)
50–64	13906	4·7% (4·1–5·3)	83·4% (79·3–86·8)	98·0% (97·6–98·3)
≥65	10602	4·5% (3·8–5·3)	82·3% (77·1–86·5)	97·6% (97·2–98·0)
Census tract income*				
<5th percentile	2382	4·6% (3·1–6·7)	75·7% (62·4–85·4)	97·9% (96·5–98·8)
5th to <25th percentile	11229	4·7% (3·8–5·8)	82·2% (77·2–86·3)	98·6% (98·3–98·9)
25th to <50th percentile	13096	4·6% (3·9–5·6)	78·3% (73·3–82·5)	98·3% (97·9–98·6)
50th to <75th percentile	11804	4·3% (3·6–5·1)	77·9% (71·4–83·3)	98·3% (97·9–98·6)
75th to <95th percentile	10583	4·6% (3·7–5·7)	79·5% (73·9–84·1)	98·3% (97·9–98·6)
≥95th percentile	2864	5·4% (4·0–7·4)	85·3% (74·7–92·0)	98·1% (97·2–98·6)
Self-reported symptoms†				
Asymptomatic	34016	2·0% (1·8–2·3)	61·0% (55·8–65·9)	98·6% (98·4–98·7)
Paucisymptomatic	10669	3·9% (3·4–4·4)	76·4% (70·0–81·7)	98·3% (97·9–98·6)
Symptomatic				
≤14 days before study visit	2155	14·0% (11·8–16·5)	85·3% (78·7–90·1)	97·3% (96·1–98·2)
>14 days before study visit	5118	18·0% (16·3–19·9)	92·0% (89·1–94·1)	97·0% (96·1–97·7)
Self-reported PCR status				
Never done	50594	4·2% (3·8–4·5)	78·0% (75·3–80·4)	98·3% (98·2–98·5)
Negative	1134	8·0% (6·0–10·6)	82·0% (70·7–89·6)	98·5% (97·5–99·1)
Positive (≤14 days before study visit)	31	65·8% (41·5–83·9)	76·4% (33·2–95·5)	98·3% (87·8–99·8)
Positive (>14 days before study visit)	195	90·1% (84·3–93·9)	97·2% (91·7–99·1)	82·4% (59·7–93·7)

Relative performance is among 51958 participants with both point-of-care test and immunoassay. SARS-CoV-2=severe acute respiratory syndrome coronavirus 2. *Categories based on percentiles from province-specific distributions of census tract average income in 2017. †Asymptomatic (no symptoms), paucisymptomatic (1–2 symptoms without anosmia or ageusia), and symptomatic (anosmia or ageusia, or at least three symptoms among fever; chills; severe tiredness; sore throat; cough; shortness of breath; headache; or nausea, vomiting, or diarrhoea).

Table 3: **Relative performance of point-of-care test compared with immunoassay for detection of IgG antibodies for SARS-CoV-2**

stable at older ages when using the point-of-care test, and, when using the immunoassay only, decreased after age 85 years. The lower prevalence in children might be in part related to lower nasal gene expression of angiotensin-converting enzyme 2.[22]

The first wave of the study was done while Spain was under lockdown. Participants working in essential sectors did not show higher seroprevalence values than the general population, with the exception of health-care workers (specificity–sensitivity range 8·3–11·7%), who have been previously reported to have a greater exposure to SARS-CoV-2.[10,23] In Spain, health-care workers comprise 24% of all confirmed COVID-19 cases—a proportion partly explained by greater access to PCR testing—and 9% of hospitalised cases in their age range.[24,25]

Our results confirm that close contact with people with COVID-19, and particularly those in the same household, increases viral transmission. Appropriate quarantine and separation from other household members can be particularly challenging and not realistic in urban areas and less affluent scenarios. While mass quarantine during the lockdown would reduce the number of potentially infective contacts, it would also increase the transmission of the virus in a confined space, as a recent simulation study has suggested.[26]

Serological surveys are the best tool to determine the spread of an infectious disease, particularly in the presence of asymptomatic cases or incomplete ascertainment of those with symptoms.[27] Both phenomena—asymptomatic cases and partial ascertainment—are relevant here. The proportion of asymptomatic infections reported in different studies varies greatly, ranging from 4% to 41%.[28] Here, asymptomatic cases represent between 21·9% and 35·8% of all SARS-CoV-2 infections, corresponding to between 376000 and 1042000 asymptomatic infections in the entire non-institutionalised Spanish population. This finding reinforces the importance of rapid identification, study, and isolation of people with confirmed SARS-CoV-2 infection and their contacts to prevent the spread of the epidemic.

Regarding incomplete ascertainment, only between 16% and 20% of symptomatic participants with antibodies against SARS-CoV-2 reported a previous PCR, and it was positive in around 75–79% of them. We are relying on participants' retrospectively self-reported symptoms, so a certain amount of misclassification cannot be ruled out. Still, these figures suggest that a substantial number of symptomatic patients with COVID-19 did not undergo PCR testing. However, the fact that only 15·3–19·3% of symptomatic participants had antibodies against SARS-CoV-2 suggests that a sizable proportion of suspected cases might have symptoms not caused by this coronavirus.

Seroprevalence was close to 90% after 14 days since a positive PCR test, which is consistent with a recent study concluding that SARS-CoV-2 IgG antibodies are detected in more than 90% of infected people 2 weeks after symptom onset,[29] and the recently reported 99% of antibody response among confirmed COVID-19 cases.[30] For the few patients who do not develop antibodies against SARS-CoV-2, it is unknown whether they are susceptible to reinfection.[29,31,32] Prevalence in those participants reporting negative PCR was higher than in those without a PCR test, which might be explained by delayed PCR testing that yields a negative result or by imperfect sensitivity of PCR tests.[33]

One of the most practical conclusions from our survey is that, although the immunoassay had better performance features, our rapid point-of-care test yielded comparable epidemiological information while having a greater uptake, lower cost, and easier implementation. Thus, a high-performance point-of-care test could be a suitable option for large seroepidemiological studies. Additionally, as the two tests addressed different viral proteins, they might be providing complementary information. Differences in seroprevalence between our two tests among recently PCR-positive people could be compatible with a later appearance of IgG antibodies against the receptor binding domain of the S protein compared with those against the nucleoprotein.[34] It is important to bear in mind that, in a context of low prevalence figures as those found in this Article, false-positive results might be a relevant issue. Even though the S protein and nucleoprotein show less than 30% similarity with endemic betacoronaviruses, a cross-reaction cannot be ruled out.[35] In this sense, the combination of both tests provides a more conservative estimation of the real figures.

We focused on IgG antibodies, which last longer than IgM or IgA and are associated with viral neutralising activity.[35,36] The point-of-care test also detected IgM antibodies, but the IgM band had lower sensitivity and specificity, might be positive in presence of rheumatoid factor,[37] and was subject to substantial variability in initial IgM readings.

A key strength of our study is the random selection of households from the national municipal register (updated on Jan 1, 2020), which allowed us to contact a representative sample of the non-institutionalised Spanish population. However, this decision has its drawbacks: young adults have proven to be more difficult to find, probably due to their higher mobility, with many of them officially registered at their parents' home but living elsewhere. Also, some potential participants were staying at their second residences, leaving an empty house whose members could not be included. Moreover, household selection excludes care-home residents, who, according to recent estimations,[38] could account for around 6% of Spaniards older than 75 years. Even though care homes have been a hotspot of infection and death in the country, most Spanish elders reside in households and they are adequately represented in our study. The remarkably high participation across the country, even in the venepuncture-based assay, reflects the keen interest that the Spanish population has in knowing its serological status. Participation rates were a bit lower in less affluent areas, but this was compensated by adjustment for median income in the census tract. We could not explore differences by race, as this information was not available. However, most participants were Spaniards, who are mostly white. Our study only detected IgG antibodies, but the extent of the immunity they provide is unknown at this moment. However, cellular immunity, which was not evaluated here, might also play a role in protecting against SARS-CoV-2 reinfection.

ENE-COVID provides seroprevalence data at a regional level to inform national and local public health policies. It offers a picture of SARS-CoV-2 circulation that can be compared with surveillance data to evaluate differences in diagnostic exhaustiveness. In addition, comparative performance among regions with similar prevalence but different burden in terms of deaths and health-care capacity could help to suggest areas of improvement and highlight unattended needs that should be considered to face a future epidemic wave.

In conclusion, our study provides nationwide and regional estimates of SARS-CoV-2 dissemination in Spain, showing remarkable differences between higher and lower prevalence areas. One in three infections seems to be asymptomatic, while a substantial number of symptomatic cases remained untested. Despite the high impact of COVID-19 in Spain, prevalence estimates remain low and are clearly insufficient to provide herd immunity. This cannot be achieved without accepting the collateral damage of many deaths in the susceptible population and overburdening of health systems. In this situation, social distance measures and efforts to identify and isolate new cases and their contacts are imperative for future epidemic control.

Contributors
MP, BP-G, and RP-B were responsible for the conception and design of the study. RY and FB are the executive coordinators of the project and led the relationship with regional health services. JO, MP-O, AF-G, and PM-A are responsible for validation studies to choose the serological tests, the coordination of participant microbiological laboratories, and acquisition of laboratory data. JLS, MMa, JFM-M, and JLP are responsible for the study operation, including the coordination of data acquisition and logistics. IC and MMo developed the operational protocols for field work and were responsible for training the involved administrative and health personnel. MP, BP-G, RP-B, NFdL, FR-C, and MAH were in charge of statistical analyses and table and figure design. All remaining authors in the ENE-COVID group contributed to data acquisition, laboratory analyses, and quality control for their respective regions or at national level. The first draft was written by MP, BP-G, RP-B, MAH, and JO. All authors contributed to data interpretation, critically reviewed the first draft, and approved the final version and agreed to be accountable for the work.

Declaration of interests
We declare no competing interests.

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References
1 Zhu N, Zhang D, Wang W, et al. A novel coronavirus from patients with pneumonia in China, 2019. *N Engl J Med* 2020; **382:** 727–33.

2 Instituto de Salud Carlos III. COVID-19 in Spain. https://cnecovid.isciii.es/covid19 (accessed July 2, 2020).

3 European Centre for Disease Prevention and Control. COVID-19 situation update worldwide, as of 18 June 2020. https://www.ecdc.europa.eu/en/geographical-distribution-2019-ncov-cases (accessed July 2, 2020).

4 Sood N, Simon P, Ebner P, et al. Seroprevalence of SARS-CoV-2-specific antibodies among adults in Los Angeles County, California, on April 10–11, 2020. *JAMA* 2020; published online May 18. https://doi.org/10.1001/jama.2020.8279.

5 Valenti L, Bergna A, Pelusi S, et al. SARS-CoV-2 seroprevalence trends in healthy blood donors during the COVID-19 Milan outbreak. *medRxiv* 2020; published online May 31. https://doi.org/10.1101/2020.05.11.20098442 (preprint).

6 Snoeck CJ, Vaillant M, Abdelrahman T, et al. Prevalence of SARS-CoV-2 infection in the Luxembourgish population: the CON-VINCE study. *medRxiv* 2020; published online May 18. https://doi.org/10.1101/2020.05.11.20092916 (preprint).

7 Salje H, Kiem CT, Lefrancq N, et al. Estimating the burden of SARS-CoV-2 in France. *Science* 2020; published online May 13. https://doi.org/10.1126/science.abc3517.

8 Stringhini S, Wisniak A, Piumatti G, et al. Repeated seroprevalence of anti-SARS-CoV-2 IgG antibodies in a population-based sample from Geneva, Switzerland. *medRxiv* 2020; published online May 6. https://doi.org/10.110/2020.05.02.20088898 (preprint).

9 Bryan A, Pepper G, Wener MH, et al. Performance characteristics of the Abbott Architect SARS-CoV-2 IgG assay and seroprevalence in Boise, Idaho. *J Clin Microbiol* 2020; published online May 7. https://doi.org/10.1128/JCM.00941-20.

10 Garcia-Basteiro AL, Moncunill G, Tortajada M, et al. Seroprevalence of antibodies against SARS-CoV-2 among health care workers in a large Spanish reference hospital. *medRxiv* 2020; published online May 2. https://doi.org/10.1101/2020.04.27.20082289 (preprint).

11 Shakiba M, Nazari SSH, Mehrabian F, Rezvani SM, Ghasempour Z, Heidarzadeh A. Seroprevalence of COVID-19 virus infection in Guilan province, Iran. *medRxiv* 2020; published online May 1. https://doi.org/10.1101/2020.04.26.20079244 (preprint).

12 Doi A, Iwata K, Kuroda H, et al. Estimation of seroprevalence of novel coronavirus disease (COVID-19) using preserved serum at an outpatient setting in Kobe, Japan: a cross-sectional study. *medRxiv* 2020; published online May 1. https://doi.org/10.1101/2020.04.26.20079822 (preprint).

13 Erikstrup C, Hother CE, Pedersen OBV, et al. Estimation of SARS-CoV-2 infection fatality rate by real-time antibody screening of blood donors. *medRxiv* 2020; published online April 28. https://doi.org/10.1101/2020.04.24.20075291 (preprint).

14 Wu X, Fu B, Chen L, Feng Y. Serological tests facilitate identification of asymptomatic SARS-CoV-2 infection in Wuhan, China. *J Med Virol* 2020; published online April 20. https://doi.org/10.1002/jmv.25904.

15 Temperton N. Serological analysis of 1000 Scottish blood donor samples for anti-SARS-CoV-2 antibodies collected in March 2020. FigShare. April 12, 2020. https://doi.org/10.6084/m9.figshare.12116778.v2 (preprint).

16 Bobrovitz N, Arora RK, Yan T, et al. Lessons from a rapid systematic review of early SARS-CoV-2 serosurveys. *medRxiv* 2020; published online May 14. https://doi.org/10.1101/2020.05.10.20097451.

17 Li Z, Yi Y, Luo X, et al. Development and clinical application of a rapid IgM-IgG combined antibody test for SARS-CoV-2 infection diagnosis. *J Med Virol* 2020; published online Feb 27. https://doi.org/10.1002/jmv.25727.

18 Hoffman T, Nissen K, Krambrich J, et al. Evaluation of a COVID-19 IgM and IgG rapid test; an efficient tool for assessment of past exposure to SARS-CoV-2. *Infect Ecol Epidemiol* 2020; **10:** 1754538.

19 Chen TC, Clark J, Riddles MK, Mohadjer LK, Fakhouri THI. National Health and Nutrition Examination Survey, 2015–2018: sample design and estimation procedures. *Vital Health Stat 2* 2020; **184:** 1–26.

20 Bryant JE, Azman AS, Ferrari MJ, et al. Serology for SARS-CoV-2: apprehensions, opportunities, and the path forward. *Sci Immunol* 2020; **5:** eabc6347.

21 Huang AT, Garcia-Carreras B, Hitchings MDT, et al. A systematic review of antibody mediated immunity to coronaviruses: antibody kinetics, correlates of protection, and association of antibody responses with severity of disease. *medRxiv* 2020; published online April 17. https://doi.org/10.1101/2020.04.14.20065771 (preprint).

22 Bunyavanich S, Do A, Vicencio A. Nasal gene expression of angiotensin-converting enzyme 2 in children and adults. *JAMA* 2020; published online May 20. https://doi.org/10.1001/jama.2020.8707.

23 Folgueira MD, Munoz-Ruiperez C, Alonso-Lopez MA, Delgado R. SARS-CoV-2 infection in health care workers in a large public hospital in Madrid, Spain, during March 2020. *medRxiv* 2020; published online April 27. https://doi.org/10.1101/2020.04.07.20055723 (preprint).

24 Centro Nacional de Epidemiología/Red Nacional de Vigilancia Epidemiológica. Análisis de los casos de COVID-19 en personal sanitario notificados a la RENAVE hasta el 10 mayo en España. May 29, 2020. https://www.isciii.es/QueHacemos/Servicios/VigilanciaSaludPublicaRENAVE/EnfermedadesTransmisibles/Paginas/InformesCOVID-19.aspx (accessed June 30, 2020).

25 Centro Nacional de Epidemiología/Red Nacional de Vigilancia Epidemiológica. Análisis de los casos de COVID-19 notificados a la RENAVE hasta el 10 de mayo en España. Informe COVID-19 nº 33. May 29, 2020. https://www.isciii.es/QueHacemos/Servicios/VigilanciaSaludPublicaRENAVE/EnfermedadesTransmisibles/Paginas/InformesCOVID-19.aspx (accessed June 30, 2020).

26 Peak CM, Kahn R, Grad YH, et al. Individual quarantine versus active monitoring of contacts for the mitigation of COVID-19: a modelling study. *Lancet Infect Dis* 2020; published online May 20. https://doi.org/10.1016/S1473-3099(20)30361-3.

27 Metcalf CJE, Farrar J, Cutts FT, et al. Use of serological surveys to generate key insights into the changing global landscape of infectious disease. *Lancet* 2016; **388:** 728–30.

28 Byambasuren O, Cardona M, Bell K, Clark J, McLaws M-L, Glasziou P. Estimating the extent of asymptomatic COVID-19 and its potential for community transmission: systematic review and meta-analysis. *medRxiv* 2020; published online June 4. https://doi.org/10.1101/2020.05.10.20097543 (preprint).

29 Health Information and Quality Authority. Evidence summary of the immune response following infection with SARS-CoV-2 or other human coronaviruses. June 9, 2020. https://www.hiqa.ie/sites/default/files/2020-06/Evidence-summary_SARS-CoV-2-immune-response.pdf (accessed June 17, 2020).

30 Wajnberg A, Mansour M, Leven E, et al. Humoral immune response and prolonged PCR positivity in a cohort of 1343 SARS-CoV 2 patients in the New York City region. *medRxiv* 2020; published online May 5. https://doi.org/10.1101/2020.04.30.20085613 (preprint).

31 Zhao J, Yuan Q, Wang H, et al. Antibody responses to SARS-CoV-2 in patients of novel coronavirus disease 2019. *Clin Infect Dis* 2020; published online March 28. https://doi.org/10.1093/cid/ciaa344.

32 Tay MZ, Poh CM, Rénia L, MacAry PA, Ng LFP. The trinity of COVID-19: immunity, inflammation and intervention. *Nat Rev Immunol* 2020; published online April 28. https://doi.org/10.1038/s41577-020-0311-8.

33 Kim H, Hong H, Yoon SH. Diagnostic performance of CT and reverse transcriptase-polymerase chain reaction for coronavirus disease 2019: a meta-analysis. *Radiology* 2020; published online April 17. https://doi.org/10.1148/radiol.2020201343.

34 Huang J, Mao T, Li S, et al. Long period dynamics of viral load and antibodies for SARS-CoV-2 infection: an observational cohort study. *medRxiv* 2020; published online April 27. https://doi.org/10.1101/2020.04.22.20071258 (preprint).

35 Theel ES, Slev P, Wheeler S, Couturier MR, Wong SJ, Kadkhoda K. The role of antibody testing for SARS-CoV-2: is there one? *J Clin Microbiol* 2020; published online April 29. https://doi.org/10.1128/JCM.00797-20.

36 To KK-W, Tsang OT-Y, Leung W-S, et al. Temporal profiles of viral load in posterior oropharyngeal saliva samples and serum antibody responses during infection by SARS-CoV-2: an observational cohort study. *Lancet Infect Dis* 2020; **5:** 565–74.

37 Wang Q, Du Q, Guo B, et al. A method to prevent SARS-CoV-2 IgM false positives in gold immunochromatography and enzyme-linked immunosorbent assays. *J Clin Microbiol* 2020; published online April 10. https://doi.org/10.1128/JCM.00375-20.

38 Abellan García A, Aceituno Nieto P, Fernández Morales I, Ramiro Fariñas D, Pujol Rodríguez R. Una estimación de la población que vive en residencias de mayores. April 24, 2020. http://envejecimientoenred.es/una-estimacion-de-la-poblacion-que-vive-en-residencias-de-mayores (accessed June 30, 2020).