FAST TRACK

Infection fatality risk for SARS-CoV-2 in community dwelling population of Spain: nationwide seroepidemiological study

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ABSTRACT

OBJECTIVE

To estimate the infection fatality risk for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), based on deaths with confirmed coronavirus disease 2019 (covid-19) and excess deaths from all causes.

DESIGN

Nationwide seroepidemiological study.

SETTING

First wave of covid-19 pandemic in Spain.

PARTICIPANTS

Community dwelling individuals of all ages.

MAIN OUTCOME MEASURES

The main outcome measure was overall, and age and sex specific, infection fatality risk for SARS-CoV-2 (the number of covid-19 deaths and excess deaths divided by the estimated number of SARS-CoV-2 infections) in the community dwelling Spanish population. Deaths with laboratory confirmed covid-19 were obtained from the National Epidemiological Surveillance Network (RENAVE) and excess all cause deaths from the Monitoring Mortality System (MoMo), up to 15 July 2020. SARS-CoV-2 infections in Spain were derived from the estimated seroprevalence by a chemiluminescent microparticle immunoassay for IgG antibodies in 61 098 participants in the ENE-COVID nationwide seroepidemiological survey between 27 April and 22 June 2020.†

RESULTS

The overall infection fatality risk was 0.8% (19 228 of 2.3 million infected individuals, 95% confidence interval 0.8% to 0.9%) for confirmed covid-19 deaths and 1.1% (24 778 of 2.3 million infected individuals, 1.0% to 1.2%) for excess deaths. The infection fatality risk was 1.1% (95% confidence interval 1.0% to 1.2%) to 1.4% (1.3% to 1.5%) in men and 0.6% (0.5% to 0.6%) to 0.8% (0.7% to 0.8%) in women. The infection fatality risk increased sharply after age 50, ranging from 11.6% (8.1% to 16.5%) to 16.4% (11.4% to 23.2%) in men aged 80 or more and from 4.6% (3.4% to 6.3%) to 6.5% (4.7% to 8.8%) in women aged 80 or more.

CONCLUSION

The increase in SARS-CoV-2 infection fatality risk after age 50 appeared to be more noticeable in men than in women. Based on the results of this study, fatality from covid-19 was greater than that reported for other common respiratory diseases, such as seasonal influenza.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Infection fatality risk for SARS-CoV-2 (deaths from all covid-19 infections) is a key indicator for policy decision making because case fatality risk (deaths from individuals with confirmed covid-19) excludes most asymptomatic and mild symptomatic infections

Population based seroepidemiological studies can estimate the total number of infected individuals, regardless of symptoms, and age and sex specific infection fatality risk

Because confirming deaths from covid-19 is often difficult, calculation of the infection fatality risk should be complemented with data on excess all cause mortality

WHAT THIS STUDY ADDS

This study found an infection fatality risk for SARS-CoV-2 of 0.83-1.07% in the community dwelling population of Spain

The risk of death was low in infected individuals aged younger than 50, but increased sharply with age, particularly in men

In the oldest age group (≥80 years), an estimated 12-16% of infected men and 5-6% of infected women died in Spain during the first wave of the covid-19 pandemic

Introduction

The infection fatality risk—the proportion of infected individuals who die from an infection—is a key indicator to design public health policies to control infectious diseases. Because the magnitude of the infection fatality risk for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is still debated,[1 2] lockdowns and other forms of social distancing have been questioned as appropriate responses to the coronavirus disease 2019 (covid-19) pandemic.

An accurate estimation of the infection fatality risk of SARS-CoV-2 is difficult. Even if all symptomatic infections were diagnosed, which has not happened so far in most countries, asymptomatic infections cannot be clinically identified. Therefore, estimating the infection fatality risk relies on population based seroepidemiological surveys that provide an estimate of the proportion of individuals infected, regardless of symptoms.[3] Also, because determining the number of deaths from covid-19 is often difficult, calculation of the infection fatality risk can be complemented with data on excess mortality.

A recent unpublished review of 24 serological reports,[4] several also unpublished, estimated an overall infection fatality risk of 0.68% (95% confidence interval 0.53% to 0.83%). The methodological quality of many of these studies was questionable, however, with some exceptions.[5] Estimates of infection fatality risk were mostly based on surveillance registered deaths, and substantial heterogeneity was seen between studies, with estimates ranging from 0.16% to 1.60%. Also, because the infection fatality risk for SARS-CoV-2 is expected to increase with age and might differ by sex, overall crude estimates of infection fatality risk cannot be directly compared between populations with different age and sex structures (eg, China and western Europe). Accurate and reliable age and sex specific estimates of infection fatality risk are needed.

We report overall, and age and sex specific, estimates of the infection fatality risk for SARS-CoV-2 from the large nationally representative seroepidemiological survey of SARS-CoV-2 virus infection in the community dwelling Spanish population (Encuesta Seroepidemiológica de la Infección por el Virus SARS-CoV-2 en España; ENE-COVID).

Methods

Estimation of SARS-CoV-2 infections

We calculated the prevalence of IgG antibodies against SARS-CoV-2 in the community dwelling Spanish population with data from ENE-COVID, a nationwide population based seroepidemiological survey. The design of the survey has been described previously.[6] Briefly, 1500 census tracts, and up to 24 households within each tract, were randomly selected with a two stage sampling method stratified by province and municipality size. All residents in the 35 885 selected households were invited to participate in the study, resulting in a selected sample of 104 605 individuals of all ages. Serial data from epidemiological questionnaires and serology tests were collected for all study participants in three successive follow-up rounds between 27 April and 22 June 2020.

Each round was completed in two weeks, with a one week break between rounds. Half of the households were randomly assigned to data collection during the first week of each round and the other half to the second week, so that serum specimens were collected in all participants two to four weeks apart. The study used two immunoassays to detect IgG antibodies: a point-of-care test (Orient Gene Biotech covid-19 IgG/IgM Rapid Test Cassette) and a chemiluminescent microparticle immunoassay (CMIA) that required venepuncture (SARS-CoV-2 IgG for use with ARCHITECT; Abbott Laboratories, Abbott Park, IL; reference 06R8620), with better performance characteristics (supplementary methods and supplementary figure 1 show a summary of reported sensitivity and specificity estimates of the CMIA test).[6]

Of 98 891 individuals who were eligible for the ENE-COVID seroepidemiological survey, 10 238 could not be contacted, 14 926 declined to participate, 15 had missing data for age, and 5421 did not have valid results from the point-of-care test. Of the remaining 68 291 study participants, 61 098 received the CMIA test in at least one round (61.8% of eligible individuals and 68.9% of contacted individuals), with 43 212 participants receiving the CMIA test in all three rounds, 11 618 in two rounds, and 6268 in one round (fig 1). Response to the CMIA test was lower in individuals aged younger than 10 (22.3% of eligible individuals) and older than 80 (51.7%), and in men aged 20-59 compared with women (62.6% *v* 70.1%).

We calculated the seroprevalence, overall and in groups defined by age and sex, as the proportion of participants who had detectable IgG antibodies against SARS-CoV-2 in any round by the CMIA test (supplementary table 1). To account for the different sampling selection probabilities by province and to adjust for non-response to the CMIA test based on sex, age, and average income in the census tracts, we assigned sampling weights to each study participant. Design based standard errors for seroprevalence were computed taking into account stratification by province and municipality size and the clustering of seropositivity by household and census tract.[6]

In sensitivity analyses, we corrected the seroprevalence estimates of SARS-CoV-2 for the sensitivity and specificity of the CMIA test, which were estimated as 90.6% (95% confidence interval 88.1% to 92.6%) and 99.3% (99.0% to 99.5%), respectively, from a meta-analysis of 23 diagnostic accuracy studies. In these studies, sensitivity ranged from 75% to 100% in 1494 samples from patients with confirmed covid-19 of different severity, and specificity ranged from 97.5% to 100% in 7696 samples obtained before the pandemic, with moderate between study heterogeneity for sensitivity (I^2=46%) and no heterogeneity for specificity (I^2=0%) (supplementary methods and supplementary figure 1).

We calculated the number of seropositive people in Spain by multiplying the age and sex specific prevalence of IgG antibodies by the size of the corresponding community dwelling Spanish population groups as of 15 July 2020.[7]

Estimation of deaths from covid-19

Given the practical difficulties in reporting and confirming deaths from covid-19 during the pandemic, we estimated the infection fatality risk separately for deaths with confirmed covid-19 and excess all cause deaths.[8] The two sources of information were the Spanish National Epidemiological Surveillance Network (RENAVE) and the Monitoring Mortality System (MoMo).

RENAVE[9 10] provided individual data on the 29 137 deaths with laboratory confirmed covid-19 registered in Spain up to 15 July 2020. Personal data were missing for 249 deaths (0.9%), which were distributed according to the sex and age group distributions of all other deaths. The median interval between onset of symptoms and death in the RENAVE data was 12 days (interquartile range 7-19).

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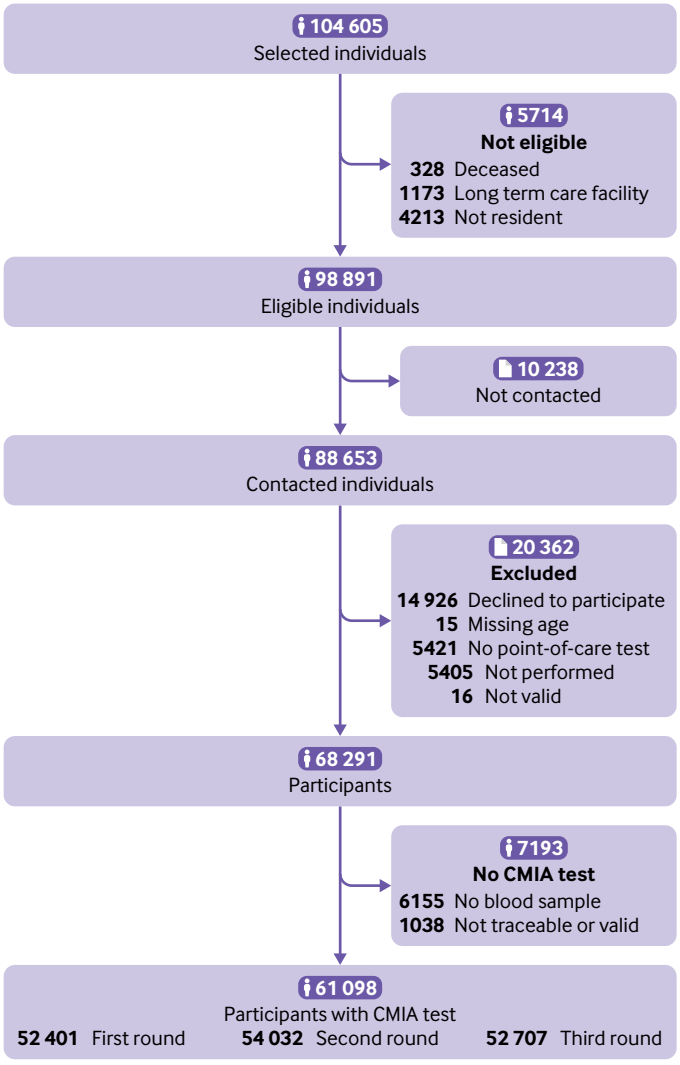

Fig 1 | Flowchart of participants in the seroepidemiological survey of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus infection in the community dwelling Spanish population (ENE-COVID), 27 April-22 June 2020. CMIA=chemiluminescent microparticle immunoassay

MoMo collects information on deaths from 3945 municipal civil registries that cover 93% of the Spanish population.[11] With a model described previously,[12] MoMo data are used to quantify excess deaths for a particular period, as the difference between the observed daily deaths corrected for reporting delay and those expected based on historical seasonal variation (centred seven day moving averages) and a non-linear secular trend (annual median daily deaths) from the past 10 years. Between 1 March and 15 July 2020, 44 459 excess all cause deaths were estimated (mainly for 13 March to 22 May 2020).[11] MoMo estimates are of similar magnitude to those reported with a different method.[13]

RENAVE and MoMo do not distinguish between people living in long term care facilities and the community dwelling population. An estimated 9909 deaths with confirmed covid-19 and 19 681 deaths with suspected covid-19 were reported in long term care facilities, mainly nursing homes, during the same period (supplementary table 2). We subtracted these deaths from those identified by RENAVE and MoMo, respectively, in the population aged 60 and older (supplementary methods).

Estimation of infection fatality risks

The infection fatality risk is the number of deaths from covid-19 divided by the number of individuals with SARS-CoV-2 infection. We obtained separate estimates of the overall infection fatality risk based on covid-19 deaths from RENAVE (lower bound of deaths because of limited confirmation of deaths in the surveillance network) and the excess all cause deaths from MoMo (possible upper bound of deaths because included are deaths that might not result from direct or indirect effects of the pandemic). We then repeated the analyses in each stratum defined by sex and 10 year age groups. We also estimated sex and age standardised infection fatality risk ratios by geographical unit (NUTS1).[14] We calculated 95% confidence intervals based on delta methods that accounted for the binomial variance in the number of deaths and the estimated design based variance in the number of infections. The supplementary methods provide further details on point and interval estimates of infection fatality risks and standardised infection fatality risk ratios. Analyses were carried out with survey commands in Stata, version 16, and survey package in R, version 4.

Patient and public involvement

Patients and members of the public were not directly involved as this study used registered information on national surveillance systems and results from the ENE-COVID nationwide seroepidemiological survey.

Results

The overall SARS-CoV-2 seroprevalence was 4.9% (95% confidence interval 4.6% to 5.3%), which corresponded to 2.3 million (95% confidence interval 2.2 to 2.5 million) community dwelling individuals in Spain with antibodies against SARS-CoV-2 by 22 June 2020 (table 1). Seroprevalence was similar in men and women and increased with age up to 20-29 (5.7-5.8%), with a smooth decline at older ages.

Up to 15 July 2020, 19 228 laboratory confirmed covid-19 deaths and 24 778 excess all cause deaths were estimated in community dwelling individuals in Spain. The distribution by sex and age was similar for both sources of data on deaths: 64% of covid-19 deaths and 62% of excess deaths were in men; 79% of confirmed covid-19 deaths and 83% of excess deaths were in individuals aged 70 or older.

Overall, the infection fatality risk estimate was 0.83% (19 228 of 2.3 million infected individuals, 95% confidence interval 0.78% to 0.89%) for deaths with confirmed covid-19 and 1.07% (24 778 of 2.3 million infected individuals, 1.00% to 1.15%) for excess deaths. The corresponding estimates were 1.11% (95% confidence interval 1.02% to 1.21%) and 1.40% (1.29% to 1.52%) for men, and 0.58% (0.53%

to 0.62%) and 0.77% (0.71% to 0.84%) for women (table 1).

The infection fatality risk estimate varied with age: less than one per 1000 to age 49, with much lower values in younger age groups (<1 per 10 000 to age 29), and increased sharply in older age groups (fig 2). In men aged 80 or older, the infection fatality risk estimate was 11.6% (95% confidence interval 8.1% to 16.5%) for deaths with confirmed covid-19 and 16.4% (11.4% to 23.2%) for excess deaths. In women aged 80 or older, the corresponding estimates were 4.6% (3.4% to 6.3%) and 6.5% (4.7% to 8.8%) (table 1). Standardised infection fatality risk ratios for deaths with confirmed covid-19 were consistent between geographical regions and the whole country (supplementary fig 2).

In sensitivity analyses, the estimates of infection fatality risk corrected for imperfect sensitivity and specificity were slightly higher, with a corrected overall infection fatality risk of 0.88% (19 228 of 2.2 million infected individuals, 95% confidence interval 0.80% to 0.97%) for deaths with confirmed covid-19 and 1.14% (24 778 of 2.2 million infected individuals, 1.03% to 1.25%) for excess deaths (supplementary table 3).

Discussion

We estimated an infection fatality risk for SARS-CoV-2 of 0.83-1.07% in Spain up to 15 July 2020. The infection fatality risk was greater in men than in women and increased with age: 11.6-16.4% in men aged 80 or older and 4.6-6.5% in women aged 80 or older. The higher mortality in elderly people might result from a greater number of comorbidities (cardiovascular disease, type 2 diabetes, lung and chronic kidney diseases)[15] and immunological changes[16] that affect the severity of SARS-CoV-2 infections.[17 18] The higher mortality in men might result from more comorbidities and risk factors (eg, smoking, obesity) than in women, and also differences in cellular immunity between men and women, including poorer T cell activation and an increase in proinflammatory cytokines in men.[19]

Comparison with previous studies

Comparing estimates of infection fatality risk between studies is difficult because of differences in methodology and populations. For example, some studies reported case fatality risks (number of deaths divided by the number of individuals with confirmed covid-19) rather than infection fatality risks, and others estimated infection fatality risks based on modelling assumptions rather than on data from population based seroepidemiological surveys.[4 20] Our overall estimate of infection fatality risk was similar to that found in seroepidemiological surveys with a low risk of bias,[4 5] and our sex and age specific estimates suggest that the heterogeneity in published estimates of infection fatality risk is largely because of the different sex and age structure of the population. Our crude estimates of infection fatality risk, in common with countries with a similar age structure, such as Italy,[8 21] were greater than those for countries with a younger population.[4] Variations in infection fatality risk values might also be related to the local dynamics of the pandemic (eg, surge in number of new infections of covid-19, spread of the virus among vulnerable communities), combined with the capacity of the health system to cope and treat many patients.

Table 1 | Infection fatality risk for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in community dwelling population by sex and age during the first wave of the covid-19 pandemic in Spain 2020

Sex, age (years)	No in population (000s)	SARS-CoV-2 seroprevalence (%; 95% CI)*	Individuals with SARS-CoV-2 antibodies (000s; 95% CI)	No of confirmed covid-19 deaths	No of excess all cause deaths	Infection fatality risk (%; 95% CI)	
						Based on confirmed covid-19 deaths	Based on excess all cause deaths
Overall	46 887.1	4.9 (4.6 to 5.3)	2305.8 (2152.8 to 2469.1)	19 228	24 778	0.83 (0.78 to 0.89)	1.07 (1.00 to 1.15)
Male:	23 006.9	4.8 (4.4 to 5.2)	1105.1 (1016.9 to 1200.6)	12 317	15 480	1.11 (1.02 to 1.21)	1.40 (1.29 to 1.52)
0-9	2205.5	3.2 (1.9 to 5.4)	71.7 (42.5 to 119.7)	3	32	0.00 (0.00 to 0.01)	0.04 (0.02 to 0.08)
10-19	2557.9	3.6 (2.8 to 4.8)	93.3 (71.0 to 122.2)	3	0	0.00 (0.00 to 0.01)	0.00 (0.00 to 0.01)
20-29	2479.1	5.8 (4.7 to 7.1)	142.7 (116.1 to 174.9)	18	0	0.01 (0.01 to 0.02)	0.00 (0.00 to 0.01)
30-39	2978.7	4.7 (3.8 to 5.7)	139.7 (114.0 to 170.9)	48	3	0.03 (0.02 to 0.05)	0.00 (0.00 to 0.01)
40-49	3916.7	5.3 (4.6 to 6.2)	209.0 (180.0 to 242.4)	192	168	0.09 (0.07 to 0.11)	0.08 (0.07 to 0.10)
50-59	3493.8	5.3 (4.5 to 6.1)	184.0 (157.8 to 214.3)	705	601	0.38 (0.32 to 0.45)	0.33 (0.27 to 0.39)
60-69	2598.2	4.9 (4.1 to 5.9)	127.1 (105.3 to 153.2)	1904	2065	1.50 (1.24 to 1.82)	1.62 (1.34 to 1.97)
70-79	1783.7	4.7 (3.7 to 6.0)	83.6 (65.4 to 106.5)	4145	5114	4.96 (3.87 to 6.33)	6.12 (4.78 to 7.80)
≥80	993.3	4.6 (3.2 to 6.5)	45.6 (31.8 to 64.9)	5299	7497	11.6 (8.06 to 16.5)	16.4 (11.4 to 23.2)
Female:	23 880.1	5.0 (4.7 to 5.4)	1200.5 (1110.5 to 1297.4)	6911	9298	0.58 (0.53 to 0.62)	0.77 (0.71 to 0.84)
0-9	2078.3	4.2 (2.7 to 6.7)	88.0 (55.1 to 139.0)	2	11	0.00 (0.00 to 0.01)	0.01 (0.01 to 0.03)
10-19	2396.7	4.4 (3.4 to 5.6)	105.1 (81.7 to 134.7)	3	22	0.00 (0.00 to 0.01)	0.02 (0.01 to 0.03)
20-29	2404.1	5.7 (4.6 to 7.0)	137.4 (111.2 to 169.3)	17	10	0.01 (0.01 to 0.02)	0.01 (0.00 to 0.01)
30-39	3012.4	5.2 (4.4 to 6.2)	156.7 (132.0 to 185.8)	29	71	0.02 (0.01 to 0.03)	0.05 (0.03 to 0.06)
40-49	3877.8	5.3 (4.6 to 6.2)	206.8 (177.9 to 240.0)	103	91	0.05 (0.04 to 0.06)	0.04 (0.03 to 0.06)
50-59	3563.5	5.2 (4.5 to 6.0)	184.4 (158.8 to 213.8)	318	369	0.17 (0.14 to 0.21)	0.20 (0.17 to 0.24)
60-69	2803.4	5.0 (4.2 to 6.0)	140.4 (117.2 to 167.9)	749	875	0.53 (0.44 to 0.65)	0.62 (0.51 to 0.75)
70-79	2138.1	4.6 (3.7 to 5.8)	98.9 (79.0 to 123.4)	1986	2646	2.01 (1.60 to 2.52)	2.68 (2.13 to 3.35)
≥80	1605.8	5.0 (3.7 to 6.8)	80.2 (58.7 to 108.9)	3704	5203	4.62 (3.38 to 6.29)	6.49 (4.74 to 8.82)

*Proportion of participants with detectable IgG antibodies against SARS-CoV-2 in any round of the ENE-COVID nationwide seroepidemiological survey by the chemiluminescent microparticle immunoassay, 27 April-22 June 2020, Spain.

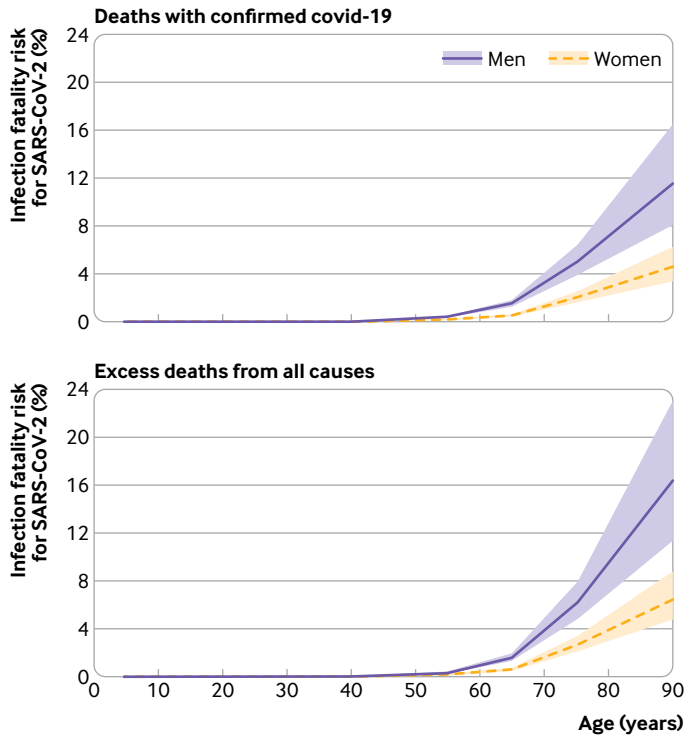

Fig 2 | Infection fatality risk for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by sex and age, based on deaths with confirmed covid-19 (top) and excess deaths from all causes (bottom), for the community dwelling population during the first wave of the covid-19 pandemic in Spain 2020. Shaded regions represent 95% confidence intervals for infection fatality risk

Strengths and limitations of this study

Our study has several strengths. Firstly, we used data from ENE-COVID, a nationwide population based seroepidemiological study.[10] The first round of the study started one month after the peak incidence of covid-19, around 20 March, and the last round ended on 22 June. Thus the study was designed to detect all individuals with antibodies during the first wave of the pandemic because most participants would have been infected one month before their first participation and IgG antibodies are detected two to three weeks after the onset of symptoms in more than 90% of infections.[22] Although IgG antibodies in some infected participants could have decreased over time,[23] particularly in mild infections, a recent study showed that this phenomenon occurs at least three months after infection,[24] so substantial underestimation of the number of infected individuals is unlikely.

Secondly, the test selected to measure antibodies against SARS-CoV-2 had high sensitivity and high specificity, according to our meta-analysis (supplementary fig 1). We used pooled estimates of sensitivity and specificity from the meta-analysis to calculate corrected ENE-COVID values for seroprevalence; the resulting estimates of infection fatality risk were slightly higher but consistent with the primary results (supplementary table 3), showing the robustness of our estimates.

Thirdly, because confirmation of deaths from covid-19 is difficult during a large scale pandemic, we used mortality data from two sources: deaths in individuals with laboratory confirmed covid-19 and excess all cause deaths. The latter included mortality directly because of SARS-CoV-2 infection and net mortality as a result of the societal effects of the pandemic and its control measures, such as delayed care for emergencies[25] and for pre-existing chronic conditions caused by reorganisation of medical care and patients' reluctance to seek attention,[26 27] and reduced traffic injuries and other unintentional injuries.[28] To include potentially delayed covid-19 deaths, we considered all deaths registered up to 15 July (supplementary figure 3 shows the time distribution of individuals with covid-19 and deaths in Spain).

A potential limitation of the study is that the two mortality surveillance systems (RENAVE and MoMo) did not differentiate between deaths in long term care facilities and deaths in the community. Therefore, we calculated deaths with confirmed and suspected covid-19 in nursing homes from reports from the Spanish regional authorities, separated the deaths by sex and age group (as described in the supplementary methods), and subtracted these deaths from the total number of deaths. Because of insufficient diagnostic capacity in regions greatly affected by the first wave of the pandemic, individuals with covid-19 could not be confirmed in many instances whereas deaths in patients with suspected covid-19 living in nursing homes might have been underreported. If this were the case, the infection fatality risk based on excess deaths in the community dwelling population might be overestimated.

Our estimates of infection fatality risk do not apply to people living in nursing homes in Spain (about 334 000 residents; 76% aged 80 or older[29]) where more than 19 000 people died during the study period.[30] Long term care facilities have clusters of vulnerable populations where the virus could spread rapidly,[31] and estimating the infection fatality risk for SARS-CoV-2 in long term care facilities will require a unique approach.[32 33] Because nursing homes had limited access to hospital care during the initial outbreak in Spain,[34] our estimates of infection fatality risk cannot be applied to elderly people in long term care facilities.

Policy implications and conclusions

We estimated the infection fatality risk for SARS-CoV-2 by age and sex from one of the largest seroepidemiological surveys in the world, carried out during the initial covid-19 outbreak. Our overall infection fatality risk estimates (0.83-1.07%) were about 10 times larger than those for seasonal influenza.[35] The high infection fatality risk in the older age groups supports existing measures (eg, social distancing, face masks, and educational campaigns) to shield these groups from infection. But relying exclusively on shielding elderly people might be a high risk strategy for the management of a pandemic. Given the high rate of transmission of the disease and the large proportion of susceptible individuals in the population, even a substantial reduction in

transmission in the elderly population could result in many deaths.

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Contributors: RP-B and BP-G are joint first authors, and AL and MP are joint senior authors. RP-B, BP-G, MAH, and MP were responsible for the conception and design of the study; RY and FB are the executive coordinators of the ENE-COVID study; MP-O, JO-I, and AF-G were responsible for the serological analysis of the ENE-COVID study, coordinating the microbiological laboratories. JLS, IC, MM, JLP, and JFM-M were responsible for the ENE-COVID study logistics; IL-G, PF-N, CD-S, and AL extracted and curated the data from the Spanish National Epidemiological Surveillance Network (RENAVE) and the Monitoring Mortality System (MoMo); RP-B, BP-G, MAH, NFL, and MP were in charge of statistical analyses, and table and figure design; other authors included in the ENE-COVID group contributed to data acquisition, laboratory analyses, and quality control of the ENE-COVID study at their respective regions or at the national level, or both. The first draft was written by RP-B, BP-G, MAH, MP-O, RY, AL, and MP. All authors contributed to data interpretation, substantially reviewed the first draft and approved the final version, and agreed to be accountable for the work. RP-B, BP-G, and MP act as guarantors, accept full responsibility for the work, had access to the data, and controlled the decision to publish. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Ethical approval: The ENE-COVID study was approved by the institutional review board of the Institute of Health Carlos III (register No PI 39_2020); written informed consent was obtained from participants.

Data sharing: The manuscript includes all values needed to replicate the infection fatality risk estimations, and the sources used are indicated. ENE-COVID seroprevalence values are provided here for all sex and age groups. Data on deaths are from the Spanish National Epidemiological Surveillance Network (RENAVE) and the Monitoring Mortality System (MoMo). Anonymised data from these systems are available on request. The specific formulary for this purpose is provided by the Department of Communicable Diseases, National Centre for Epidemiology, Carlos III Institute of Health, Monforte de Lemos 5, 28029 Madrid, Spain (vigilancia.cne@isciii.es and mortalidad@isciii.es). Population figures were provided by the National Institute of Statistics and are publicly available (https://www.ine.es). The code for calculation of the infection fatality risk is available at https://portalcne.isciii.es/enecovid19/.

The lead authors (RP-B, BP-G, and MP) affirm that the manuscript is an honest, accurate, and transparent account of the study being reported, and no important aspects of the study have been omitted.

Dissemination to participants and related patient and public communities: ENE-COVID individual results were provided to participants; a lay summary of the main results of ENECOVID is available at https://portalcne.isciii.es/enecovid19/.

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1 Faust JS, Del Rio C. Assessment of deaths from COVID-19 and from seasonal influenza. *JAMA Intern Med* 2020;180:1045-6. doi:10.1001/jamainternmed.2020.2306

2 Ioannidis J. The infection fatality rate of COVID-19 inferred from seroprevalence data.*medRxiv* 2020;2020.05.13.20101253. doi:10.1101/2020.05.13.20101253

3 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. doi:10.1016/S0140-6736(16)30164-7

4 Meyerowitz-Katz G, Merone L. A systematic review and meta-analysis of published research data on COVID-19 infection fatality rates. *Int J Infect Dis* 2020;101:138-48. doi:10.1016/j.ijid.2020.09.1464

5 Perez-Saez J, Lauer SA, Kaiser L, et al, Serocov-POP Study Group. Serology-informed estimates of SARS-CoV-2 infection fatality risk in Geneva, Switzerland. *Lancet Infect Dis* 2020;S1473-3099(20)30584-3. doi:10.1016/S1473-3099(20)30584-3

6 Pollán M, Pérez-Gómez B, Pastor-Barriuso R, et al, ENE-COVID Study Group. Prevalence of SARS-CoV-2 in Spain (ENE-COVID): a nationwide, population-based seroepidemiological study. *Lancet* 2020;396:535-44. doi:10.1016/S0140-6736(20)31483-5

7 Instituto Nacional de Estadística. Encuesta de Población Activa. Población en viviendas familiares. 2020. https://www.ine.es/jaxiT3/Tabla.htm?t=4028

8 Modi C, Boehm V, Ferraro S, Stein G, Seljak U. How deadly is COVID-19? A rigorous analysis of excess mortality and age-dependent fatality rates in Italy.*medRxiv* 2020;2020.04.15.20067074. doi:10.1101/2020.04.15.20067074

9 Ministerio de Sanidad, Instituto de Salud Carlos III. Estrategia de Detección Precoz, Vigilancia y Control de COVID-19. 2020. https://www.mscbs.gob.es/profesionales/saludPublica/ccayes/alertasActual/nCov/documentos/COVID19_Estrategia_vigilancia_y_control_e_indicadores.pdf

10 Instituto de Salud Carlos III. COVID-19 in Spain. 2020. https://cnecovid.isciii.es/covid19/

11 Instituto de Salud Carlos III. Vigilancia de la mortalidad diaria (MoMo). https://momo.isciii.es/public/momo/dashboard/momo_dashboard.html

12 León-Gómez I, Delgado-Sanz C, Jiménez-Jorge S, et al. [Excess mortality associated with influenza in Spain in winter 2012]. *Gac Sanit* 2015;29:258-65. doi:10.1016/j.gaceta.2015.01.011

13 Kontis V, Bennett JE, Rashid T, et al. Magnitude, demographics and dynamics of the effect of the first wave of the COVID-19 pandemic on all-cause mortality in 21 industrialized countries. *Nat Med* 2020;1-10. doi:10.1038/s41591-020-1112-0

14 Eurostat, European Union. Nomenclature of territorial units for statistics. https://ec.europa.eu/eurostat/web/nuts/background

15 Burn E, Tebe C, Fernandez-Bertolin S, et al. The natural history of symptomatic COVID-19 in Catalonia, Spain: a multi-state model including 109 367 outpatient diagnoses, 18 019 hospitalisations, and 5,585 COVID-19 deaths among 5 627 520 people.*medRxiv* 2020;2020.07.13.20152454. doi:10.1101/2020.07.13.2015245
16 Nikolich-Žugich J. The twilight of immunity: emerging concepts in aging of the immune system [correction in: *Nat Immunol* 2018;19:1146]. *Nat Immunol* 2018;19:10-9. doi:10.1038/s41590-017-0006-x
17 Tay MZ, Poh CM, Rénia L, MacAry PA, Ng LFP. The trinity of COVID-19: immunity, inflammation and intervention. *Nat Rev Immunol* 2020;20:363-74. doi:10.1038/s41577-020-0311-8.
18 Mathew D, Giles JR, Baxter AE, et al, UPenn COVID Processing Unit. Deep immune profiling of COVID-19 patients reveals distinct immunotypes with therapeutic implications. *Science* 2020;369:eabc8511. doi:10.1126/science.abc8511
19 Takahashi T, Ellingson MK, Wong P, et al, Yale IMPACT Research Team. Sex differences in immune responses that underlie COVID-19 disease outcomes. *Nature* 2020. doi:10.1038/s41586-020-2700-3
20 Sorci G, Faivre B, Morand S. Explaining among-country variation in COVID-19 case fatality rate. *Sci Rep* 2020;10:18909. doi:10.1038/s41598-020-75848-2
21 Villa M, Myers JF, Turkheimer F. COVID-19: Recovering estimates of the infected fatality rate during an ongoing pandemic through partial data.*medRxiv* 2020;2020.04. doi:10.1101/2020.04.10.20060764
22 Health Information and Quality Authority. Evidence summary of the immune response following infection with SARS-CoV-2 or other human coronaviruses. 2020. Report V3.0. https://www.hiqa.ie/sites/default/files/2020-08/Evidence-summary_SARS-CoV-2-immune-response.pdf
23 Long Q-X, Tang X-J, Shi Q-L, et al. Clinical and immunological assessment of asymptomatic SARS-CoV-2 infections. *Nat Med* 2020;26:1200-4. doi:10.1038/s41591-020-0965-6
24 Ripperger TJ, Uhrlaub JL, Watanabe M, et al. Orthogonal SARS-CoV-2 serological assays enable surveillance of low-prevalence communities and reveal durable humoral immunity. *Immunity* 2020;53:925-933.e4. doi:10.1016/j.immuni.2020.10.004
25 Rodríguez-Leor O, Cid-Álvarez B, Ojeda S, et al. Impact of the COVID-19 pandemic on interventional cardiology activity in Spain. *RECICE* 2020;4060. doi:10.24875/RECICE.M20000123
26 Condes E, Arribas JR, COVID19 MADRID-S.P.P.M. group. Impact of COVID-19 on Madrid hospital system. *Enferm Infecc Microbiol Clin* 2020;S0213-005X(20)30236-6. doi:10.1016/j.eimc.2020.06.005
27 Moreno R, Alonso JJ, Caballero R, et al. Influence of age and gender on arrival of patients with ST-segment elevation acute myocardial infarction to tertiary centers during COVID-19 pandemic. Experience of Madrid, Spain, STEMI network (Codigo Infarto Madrid). *Am J Emerg Med* 2020;S0735-6757(20)30494-0. doi:10.1016/j.ajem.2020.06.013
28 Instituto Nacional de Estadística. Defunciones según la Causa de Muerte. 2020. https://www.ine.es/jaxiT3/Tabla.htm?t=7947
29 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 – EnR. 2020. http://envejecimientoenred.es/una-estimacion-de-la-poblacion-que-vive-en-residencias-de-mayores/
30 RTVE. Radiografía del coronavirus en residencias de ancianos: más de 19.600 muertos con COVID-19 o síntomas compatibles. 2020. https://www.rtve.es/noticias/20201117/radiografia-del-coronavirus-residencias-ancianos-espana/2011609.shtml
31 Bouza E, Pérez-Granda MJ, Escribano P, et al, Senex-COVID-19 Study Group. Outbreak of COVID-19 in a nursing home in Madrid. *J Infect* 2020;81:647-79. doi:10.1016/j.jinf.2020.06.055
32 McMichael TM, Currie DW, Clark S, et al, Public Health–Seattle and King County, EvergreenHealth, and CDC COVID-19 Investigation Team. Epidemiology of Covid-19 in a long-term care facility in King County, Washington. *N Engl J Med* 2020;382:2005-11. doi:10.1056/NEJMoa2005412.
33 Danis K, Fonteneau L, Georges S, et al, ECDC Public Health Emergency Team. High impact of COVID-19 in long-term care facilities, suggestion for monitoring in the EU/EEA, May 2020. *Euro Surveill* 2020;25. doi:10.2807/1560-7917.ES.2020.25.22.2000956
34 Rada AG. Covid-19: the precarious position of Spain's nursing homes [correction in: *BMJ* 2020;369:m1586]. *BMJ* 2020;369:m1554. doi:10.1136/bmj.m1554
35 Centers for Disease Control and Prevention. Disease burden of influenza. 2020. https://www.cdc.gov/flu/about/burden/index.html

Web appendix: Supplementary material