Assessing the Age Specificity of Infection Fatality Rates for COVID-19: Systematic Review, Meta-Analysis, and Public Policy Implications

Andrew T. Levin, William P. Hanage, Nana Owusu-Boaitey,
Kensington B. Cochran, Seamus P. Walsh, and Gideon Meyerowitz-Katz

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Affiliations: Levin is a professor of economics at Dartmouth College, research associate of the NBER, and international research fellow of the Centre for Economic Policy Research. Hanage is an associate professor of epidemiology at the Harvard T.H. Chan School of Public Health. Meyerowitz-Katz is an epidemiologist at the University of Wollongong and research monitoring and surveillance coordinator at the Western Sydney Local Health District. Owusu-Boaitey has a Ph.D. in immunology and is currently engaged in graduate work in medicine and bioethics at the Case Western Reserve University School of Medicine. Cochran and Walsh are recent graduates of Dartmouth College.

Corresponding Author:

Gideon Meyerowitz-Katz
Research, Monitoring & Surveillance Coordinator
Western Sydney Local Health District
PO Box 792
Seven Hills, NSW 2147 Australia
Phone: +61-2-9881-8878
Email: gideon.meyerowitzkatz@health.nsw.gov.au

Structured Abstract

Objective: Determine age-specific infection fatality rates for COVID-19 to inform public health policies and communications that help protect vulnerable age groups.

Methods: Studies of COVID-19 prevalence were collected by conducting an online search of published articles, preprints, and government reports. A total of 120 studies were reviewed in depth and screened, of which 34 studies satisfied the inclusion criteria and were included in the meta-analysis. Age-specific IFRs were computed using the prevalence data in conjunction with reported fatalities four weeks after the midpoint date of the study, reflecting typical lags in fatalities and reporting. Meta-regression procedures in Stata were used to analyze IFR by age.

Results: Our analysis finds a exponential relationship between age and IFR for COVID-19. The estimated age-specific IFRs are very low for children and younger adults but increase progressively to 0.4% at age 55, 1.4% at age 65, 4.6% at age 75, and 15% at age 85. We find that differences in the age structure of the population and the age-specific prevalence of COVID-19 explain about 90% of the geographical variation in population IFR.

Discussion: These results indicate that COVID-19 is hazardous not only for the elderly but also for middle-aged adults, for whom the infection fatality rate is two orders of magnitude greater than the annualized risk of a fatal automobile accident and far more dangerous than seasonal influenza. Moreover, the overall IFR for COVID-19 should not be viewed as a fixed parameter but as intrinsically linked to the age-specific pattern of infections. Consequently, public health measures to mitigate infections in older adults could substantially decrease total deaths.

Introduction

Since the onset of the COVID-19 pandemic in winter 2020, it has been evident that the severity of the disease varies markedly across infected individuals.[1, 2] Some remain asymptomatic throughout the course of infection or experience only mild symptoms such as headache or ageusia, whereas others experience much more severe illness, hospitalization, or even death. Thus, official case reporting may tend to encompass a high fraction of severe cases but only a small fraction of asymptomatic or mildly symptomatic cases. Moreover, the availability of live virus tests has varied significantly across locations and over time, and the deployment of such tests may differ markedly across demographic groups.

Consequently, assessments of the *case fatality rate (CFR)*, the ratio of deaths to reported cases, are fraught with pitfalls in gauging the severity of COVID-19. For example, early case reports from Wuhan noted a preponderance of older people among hospital admissions and a high CFR. Subsequent studies have documented that children and young adults tend to exhibit fewer and milder symptoms and a far lower CFR. Nonetheless, the link between age and severity of COVID-19 infections has remained unclear for the reasons noted above.

To provide more accurate assessments of the spread of COVID-19, researchers have conducted seroprevalence studies in numerous locations. Such studies analyze samples of serum to detect antibodies in those infected with SARS-CoV-2, the virus that causes COVID-19. Seroprevalence results can be used to estimate the *infection fatality rate (IFR)*, the ratio of fatalities to total infections, thereby facilitating the identification of vulnerable segments of the population and informing key policy decisions aimed at mitigating the consequences of the pandemic.

For example, as shown in Table 1, the New York Department of Health conducted a large-scale seroprevalence study and estimated about 1·6 million SARS-CoV-2 infections among the 8 million residents of New York City.[3] However, only one-tenth of those infections were captured in reported COVID-19 cases, about one-fourth of which required hospitalization, and a substantial fraction of cases had fatal outcomes.[4] All told, COVID-19 fatalities in NYC represented a tenth of reported cases but only one-hundredth of all SARS-CoV-2 infections.

Nonetheless, divergences in study design and reporting have hampered comparisons of seroprevalence and IFRs across locations and demographic groups. For example, a number of studies have analyzed a representative sample of the general population, while other studies have made use of “convenience samples” of residual sera collected for other purposes (such as laboratory tests or blood donations). Some studies have simply reported results for raw prevalence (the fraction of seropositive results), whereas other studies have reported results adjusted for antibody test characteristics (sensitivity and specificity).

While the NYC data indicate an IFR of about 1%, seroprevalence estimates from other locations have yielded a wide array of IFR estimates, ranging from about 0·6% in Geneva to levels exceeding 2% in northern Italy. Such estimates have fueled intense controversy about the

severity of COVID-19 and the appropriate design of public health measures to contain it, which in turn hinges on whether the hazards of this disease are mostly limited to the elderly and infirm. Indeed, a recent meta-analysis noted the high degree of heterogeneity across aggregate estimates of IFR and concluded that research on age-stratified IFR is *"urgently needed to inform policymaking."*[5]

This paper reports on a systematic review and meta-analysis of age-specific IFRs for COVID-19. We specifically consider the hypothesis that the observed variation in IFR across locations may primarily reflect the age specificity of COVID-19 infections and fatalities. Based on these findings, we are able to assess and contextualize the severity of COVID-19 and examine how age-specific prevalence affects the population IFR and the total incidence of fatalities.

Methodology

To perform the present meta-analysis, we collected published papers and preprints on the seroprevalence and/or infection fatality rate of COVID-19 that were publicly disseminated prior to 18 September 2020. As described in Supplementary Appendix B, we systematically performed online searches in MedRxiv, Medline, PubMed, Google Scholar, and EMBASE, and we identified other studies listed in reports by government institutions such as the U.K. Parliament Office.[6] Data was extracted from studies by three authors and verified prior to inclusion.

We restricted our meta-analysis to studies of advanced economies, based on current membership in the Organization for Economic Cooperation and Development (OECD), in light of the distinct challenges of health care provision and reporting of fatalities in developing economies.[7] We also excluded studies aimed at measuring prevalence in specific groups such as health care workers.

Our meta-analysis encompasses two distinct approaches for assessing the prevalence of COVID-19: (1) seroprevalence studies that test for antibodies produced in response to the virus, and (2) comprehensive tracing programs using extensive live-virus testing of everyone who has had contact with a potentially infected individual. Seroprevalence estimates are associated with uncertainty related to the sensitivity and specificity of the test method and the extent to which the sampling frame provides an accurate representation of prevalence in the general population; see Supplementary Appendix C. Prevalence measures from comprehensive tracing programs are associated with uncertainty about the extent of inclusion of infected individuals, especially those who are asymptomatic.

Sampling frame

To assess prevalence in the general population, a study should be specifically designed to utilize a random sample using standard survey procedures such as stratification and weighting by demographic characteristics. Other sampling frames may be useful for specific purposes such as

sentinel surveillance but not well-suited for assessing prevalence due to substantial risk of systemic bias. Consequently, our meta-analysis excludes the following types of studies:

- *Blood Donors*. Only a small fraction of blood donors are ages 60 and above—a fundamental limitation in assessing COVID-19 prevalence and IFRs for older age groups—and the social behavior of blood donors may be systematically different from their peers.[8, 9] These concerns can be directly investigated by comparing alternative seroprevalence surveys of the same geographical location. As of early June, Public Health England (PHE) reported seroprevalence of 8·5% based on specimens from blood donors, whereas the U.K. Office of National Statistics (ONS) reported markedly lower seroprevalence of 5·4% (CI: 4·3–6·5%) based on its monitoring of a representative sample of the English population.[10, 11]

- *Dialysis Centers*. Assessing seroprevalence of dialysis patients using residual sera collected at dialysis centers is crucial for gauging the infection risks faced by these individuals, of which a disproportionately high fraction tend to be underrepresented minorities. Nonetheless, the seroprevalence within this group may be markedly different from that of the general population. For example, a study of U.K. dialysis patients found seroprevalence of about 36%, several times higher than that obtained using a very large random sample of the English population.[12, 13] Similarly, a recent U.S. study found a seropositive rate of 34% for dialysis patients in New York state that was more than twice as high as the seroprevalence in a random sample of New York residents.[3, 14]

- *Hospitals and Urgent Care Clinics.* Estimates of seroprevalence among current medical patients are subject to substantial bias, as evident from a pair of studies conducted in Tokyo, Japan: One study found 41 positive cases among 1071 urgent care clinic patients, whereas the other study found only two confirmed positive results in a random sample of nearly 2000 Tokyo residents (seroprevalence estimates of 3·8% vs. 0·1%).[15, 16]

- *Active Recruitment*. Soliciting participants is particularly problematic in contexts of low prevalence, because seroprevalence can be markedly affected by a few individuals who volunteer due to concerns about prior exposure. For example, a Luxembourg study obtained positive antibody results for 35 out of 1,807 participants, but nearly half of those individuals (15 of 35) had previously had a positive live virus test, were residing in a household with someone who had a confirmed positive test, or had direct contact with someone else who had been infected.[17]

Our critical review has also underscored the pitfalls of seroprevalence studies based on “convenience samples” of residual sera collected for other purposes. For example, two studies assessed seroprevalence of Utah residents during spring 2020. The first study analyzed residual sera from two commercial laboratories and obtained a prevalence estimate of 2·2% (CI: 1·2–3·4%), whereas the second study collected specimens from a representative sample and obtained

a markedly lower prevalence estimate of 0·96% (CI: 0·4–1·8%).[18, 19] In light of these issues, our meta-analysis includes residual serum studies but we flag such studies as having an elevated risk of bias.

Comprehensive Tracing Programs

Our meta-analysis incorporates data on COVID-19 prevalence and fatalities in countries that have consistently maintained comprehensive tracing programs since the early stages of the pandemic. Such a program was only feasible in places where public health officials could conduct repeated tests of potentially infected individuals and trace those whom they had direct contact. We identify such countries using a threshold of 300 for the ratio of cumulative tests to reported cases as of 30 April 2020, based on comparisons of prevalence estimates and reported cases in Czech Republic, Korea, and Iceland; see Supplementary Appendices D and E.[20] Studies of Iceland and Korea found that estimated prevalence was moderately higher than the number of reported cases, especially for younger age groups; hence we make corresponding adjustments for other countries with comprehensive tracing programs, and we identify these estimates as subject to an elevated risk of bias.[21-23]

Measurement of fatalities

Accurately measuring total deaths is a substantial issue in assessing IFR due to time lags from onset of symptoms to death and from death to official reporting. Symptoms typically develop within 6 days after exposure but may develop as early as 2 days or as late as 14 days.[1, 24] More than 95% of symptomatic COVID patients have positive antibody (IgG) titres within 17-19 days of symptom onset, and those antibodies remain elevated over a sustained period.[25-28] The mean time interval from symptom onset to death is 15 days for ages 18–64 and 12 days for ages 65+, with interquartile ranges of 9–24 days and 7–19 days, respectively, while the mean interval from date of death to the reporting of that person's death is about 7 days with an IQR of 2–19 days; thus, the upper bound of the 95% confidence interval between symptom onset and reporting of fatalities is about six weeks (41 days).[29]

Figure 1 illustrates these findings in a hypothetical scenario where the pandemic was curtailed two weeks prior to the date of the seroprevalence study. This figure shows the results of a simulation calibrated to reflect the estimated distribution for time lags between symptom onset, death, and inclusion in official fatality reports. The histogram shows the frequency of deaths and reported fatalities associated with the infections that occurred on the last day prior to full containment. Consistent with the confidence intervals noted above, 95% of cumulative fatalities are reported within roughly four weeks of the date of the seroprevalence study.

As shown in Table 2, the precise timing of the count of cumulative fatalities is relatively innocuous in locations where the outbreak had been contained for more than a month prior to the date of the seroprevalence study. By contrast, in instances where the outbreak had only recently

been contained, the death count continued rising markedly for several more weeks after the midpoint of the seroprevalence study.

Therefore, we construct age-specific IFRs using the seroprevalence data in conjunction with cumulative fatalities four weeks after the midpoint date of each study; see Supplementary Appendix F. We have also conducted sensitivity analysis using cumulative fatalities five weeks after the midpoint date, and we flag studies as having an elevated risk of bias if the change in cumulative fatalities between weeks 4 and 5 exceeds 10%.

By contrast, matching prevalence estimates with subsequent fatalities is not feasible if a seroprevalence study was conducted in the midst of an accelerating outbreak. Therefore, our meta-analysis excludes seroprevalence studies for which the change in cumulative fatalities from week 0 to week 4 exceeds 200%.

Metaregression procedure

To analyze IFR by age, we use meta-regression with random effects, using the *meta regress* procedure in *Stata* v16.[30, 31] We used a random-effects procedures to allow for residual heterogeneity between studies and across age groups by assuming that these divergences are drawn from a Gaussian distribution. Publication bias was assessed using Egger's regression and the trim-and-fill method. See Supplementary Appendix G for further details.

Results

After an initial screening of 1153 studies, we reviewed the full texts of 120 studies, of which 54 studies were excluded due to lack of age-specific data on COVID-19 prevalence or fatalities.[11, 15, 16, 28, 32-81] Seroprevalence estimates for two locations were excluded because the outbreak was still accelerating during the period when the specimens were being collected and from two other locations for which age-specific seroprevalence was not distinguishable from zero.[18, 82-84] Studies of non-representative samples were excluded as follows: 13 studies of blood donors; 5 studies of patients of hospitals, outpatient clinics, and dialysis centers; 4 studies with active recruitment of participants, and 6 narrow sample groups such as elementary schools.[10, 14, 16, 17, 82, 85-107] Supplementary Appendix H lists all excluded studies.

Consequently, our meta-analysis encompasses 34 studies, of which 28 are included in our metaregression and 6 are used for out-of-sample analysis. The metaregression studies can be categorized into three distinct groups:

- *Representative samples* from studies of England, France, Ireland, Italy, Netherlands, Portugal, Spain, Geneva (Switzerland), and four U.S. locations (Atlanta, Indiana, New York, and Salt Lake City).[3, 13, 19, 108-117]

- *Convenience samples* from studies of Belgium, Sweden, Ontario (Canada), and eight U.S. locations (Connecticut, Louisiana, Miami, Minneapolis, Missouri, Philadelphia, San Francisco, and Seattle).[18, 118-120]

- *Comprehensive tracing programs* for Australia, Iceland, Korea, Lithuania, and New Zealand.[121-125]

The metaregression includes results from the very large REACT-2 seroprevalence study of the English population.[13] Thus, to avoid pitfalls of nested or overlapping samples, two other somewhat smaller studies conducted by U.K. Biobank and the U.K. Office of National Statistics are not included in the metaregression but are instead used in out-of-sample analysis of the metaregression results.[11, 126] Similarly, the metaregression includes two large-scale studies involving representative samples from three French provinces and from Salt Lake City, and hence two other studies using convenience samples from laboratories in France and in Utah are used in the out-of-sample analysis along with two other small-scale studies.[18, 19, 127-129]

Data taken from included studies is shown in Supplementary Appendix I. Supplementary Appendix J assesses the risk of bias for each individual study. As indicated in Supplementary Appendix K, no publication bias was found using Egger's test ($p > 0.10$), and the trim-and-fill method produced the same estimate as the metaregression.

We obtain the following metaregression results:

$$\underset{}{log_{10}(IFR)} \quad = \quad \underset{(0.07)}{-3.27} \quad + \quad \underset{(0.0013)}{0.0524 * age}$$

where the standard error for each estimated coefficient is given in parentheses. These estimates are highly significant with t-statistics of -44·5 and 40·4, respectively, and p-values below 0·0001. The residual heterogeneity $\tau^2 = 0{\cdot}071$ (p-value < 0.0001) and $I^2 = 97{\cdot}0$, confirming that the random effects are essential for capturing unexplained variations across studies and age groups. The adjusted R^2 is 94·7%.

As noted above, the validity of this metaregression rests on the condition that the data are consistent with a Gaussian distribution. The validity of that assumption is evident in Figure 3: Nearly all of the observations fall within the 95% prediction interval of the metaregression, and the remainder are moderate outliers.

This specification of the metaregression also assumes that the intercept and slope parameters are stable across the entire age distribution. We have confirmed the validity of that assumption by estimating alternative specifications in which the parameters are allowed to differ between three distinct age categories (ages 0–34, 35–59, and 60+ years). The estimated parameters are similar across all three age categories, and the null hypothesis of parameter constancy is consistent with the metaregression data (see Supplementary Appendix L).

Figure 4 depicts the exponential relationship between age and the level of IFR in percent, and Figure 5 shows the corresponding forest plot. Evidently, the SARS-CoV-2 virus poses a

substantial mortality risk for middle-aged adults and even higher risks for elderly people: The IFR is very low for children and young adults but rises to 0·4% at age 55, 1·4% at age 65, 4·6% at age 75, 15% at age 85, and exceeds 25% for ages 90 and above. These metaregression predictions are well aligned with the out-of-sample IFRs; see Supplementary Appendix M.

As shown in Figure 6, the metaregression explains nearly 90% of the geographical variation in population IFR, which ranges from about 0·5% in Salt Lake City and Geneva to 1·5% in Australia and England and 2·7% in Italy. The metaregression explains this variation in terms of differences in the age structure of the population and age-specific prevalence of COVID-19.

Discussion

The IFR is central to our understanding of the public health impact of the COVID-19 pandemic and the appropriate policies for mitigating those consequences. In the absence of effective therapies or vaccines, such policies will primarily involve non-pharmaceutical interventions (NPIs). NPIs may include relatively mild measures (such as prohibitions on large gatherings) or more draconian restrictions such as shelter-in-place edicts, popularly known as “lockdowns.”

Unfortunately, public debate on these issues has been hampered by diverging assessments of the severity of COVID-19. For example, some early seroprevalence studies (using relatively small and non-representative samples, often in areas of low prevalence) yielded miniscule estimates of population IFR similar to those of seasonal influenza. Such estimates implied that strict NPIs would be completely irrational given the limited benefits and severe economic and social costs. With the dissemination of many more seroprevalence studies over recent months, a wide array of hypotheses have been mooted to explain the diverging implications for IFR, including regional variations in the quality of treatment or the extent of T-cell immunity to other betacoronaviruses.

By contrast, our critical review identifies the key characteristics of seroprevalence studies that can be used to provide reliable assessments of IFR. Indeed, once we focus on this group of studies (which includes nine national seroprevalence studies), our metaregression reveals a remarkably high degree of consistency in the implications for age-specific IFR. Moreover, our results indicate that most of the variation in population IFR across locations reflects differences in the extent to which vulnerable age groups were exposed to the virus.

One key implication of our findings is that the incidence of fatalities from a COVID-19 outbreak depends crucially on the age groups that are infected, which in turn reflects the age structure of that population and the extent to which public health measures limit the incidence of infections among vulnerable age groups. Indeed, even if an outbreak is mainly concentrated among younger people, it may be very difficult to prevent the virus from spreading among older adults.

To illustrate the benefits of age-stratified public health strategies for COVID-19, we have constructed a set of three scenarios for the U.S. trajectory of infections and fatalities (see Supplementary Appendix N). Each scenario assumes that U.S. prevalence rises to a plateau of

around 20% but with different patterns of age-specific prevalence. In particular, if prevalence becomes uniform across age groups, this analysis projects that total U.S. fatalities would exceed 500 thousand and that population IFR would converge to around 0·8%. By contrast, a scenario with relatively low incidence of new infections among vulnerable age groups would be associated with less than half as many deaths and a much lower population IFR of about 0·3%.

A further implication of our results is that the risks of infection to the middle aged cannot be neglected. This is important for pandemic management strategies that aim to avoid large influxes of patients to healthcare. Indeed, it is likely that an unmitigated outbreak among adults over 35 years old could have severe consequences on the healthcare system. Table 3 contextualizes this issue by comparing the age-specific IFRs from our meta-regression analysis to the annualized risks of fatal automobile accidents or other unintentional injuries in England and in the United States.[130, 131] For example, an English person aged 55–64 years who gets infected with SARS-CoV-2 faces a fatality risk that is more than 200 times higher than the annual risk of dying in a fatal car accident. These results also confirm that COVID-19 is far more deadly than seasonal flu, for which the population IFR is about 0·05% (see Supplementary Appendix O). Moreover, seasonal influenza outbreaks are limited by prior immunity, whereas that is not the case for SARS-CoV-2.

Our critical review highlights the benefits of assessing prevalence using large-scale studies of representative samples of the general population rather than convenience samples of blood donors or medical patients. Conducting such studies on an ongoing basis will enable public health officials to monitor changes in prevalence among vulnerable age groups and gauge the efficacy of public policy measures. Moreover, such studies enable researchers to assess the extent to which antibodies to SARS-CoV-2 may gradually diminish over time as well as the extent to which advances in treatment facilitate the reduction of age-specific IFRs.

Our critical review also underscores the importance of methodological issues in assessing IFR. For example, the raw prevalence results reported by a national study of Italy would imply a population IFR of about 2·3%, whereas test-adjusted prevalence implies a substantially higher IFR of 2·7%. Likewise, a few recent studies have excluded all deaths occurring in nursing homes and retirement communities and have obtained estimates of population IFR that are markedly lower than our estimates based on all confirmed COVID-19 fatalities, whereas assessments of IFR based on measures of excess mortality are broadly similar to our estimates.[110, 132-134] See Supplementary Appendix P for further discussion.

Our metaregression results are broadly consistent with the study of Verity et al. (2020), which was completed at a very early stage of the COVID-19 pandemic and characterized an exponential pattern of age-specific IFRs (see Supplementary Appendix Q).[135] Our results are also well-aligned with a more recent meta-analysis of population IFR; indeed, our age-specific analysis explains a very high proportion of the dispersion in population IFRs highlighted by that study.[5] In contrast, our findings are markedly different from those of an earlier review of

population IFR, mostly due to differences in selection criteria.[136] Finally, the exponential pattern of our age-specific IFR estimates is qualitatively similar to that of age-specific CFRs but the magnitudes are systematically different (see Supplementary Appendix R).

A potential concern about measuring IFR based on seroprevalence is that antibody titers may diminish over time, leading to underestimation of true prevalence and corresponding overestimation of IFR, especially for locations where the seroprevalence study was conducted several months after the outbreak had been contained. However, a key feature of our metaregression analysis is that we also utilize age-specific IFR data based on RT-PCR results (*not* seroprevalence) for five countries that have maintained comprehensive tracing programs since the onset of the pandemic, namely, Australia, Iceland, Korea, Lithuania, and New Zealand. As shown in figure 3, the age-specific IFRs for those five countries are well aligned with the metaregression predictions, indicating that these findings do not rely upon any specific method of gauging prevalence.

A substantial limitation of our work is that we have not considered factors apart from age that affect the IFR of COVID-19. For example, a recent U.K. study found that mortality outcomes are strongly linked to specific comorbidities such as diabetes and obesity but did not resolve the question of whether those links reflect differences in prevalence or causal effects on IFR.[137] See Supplementary Appendix S for additional evidence. Likewise, we have not considered the extent to which IFRs may vary with other demographic factors such as race and ethnicity or potential causal interactions between these factors.[32, 61] Further research on these issues is clearly warranted.

It should also be noted that our analysis has focused exclusively on the incidence of fatalities but has not captured the full spectrum of adverse health consequences of COVID-19, some of which may be severe and persistent. Further research is needed to assess age-stratified rates of hospitalization as well as longer-term sequelae attributable to SARS-CoV-2 infections. These factors are likely to be particularly important in quantifying risks to health care.

In summary, our meta-analysis demonstrates that COVID-19 is not only dangerous for the elderly and infirm but also for healthy middle-aged adults. The metaregression explains nearly 90% of the geographical variation in population IFR, indicating that the population IFR is intrinsically linked to the age-specific pattern of infections. Consequently, public health measures to protect vulnerable age groups could substantially reduce the incidence of mortality.

Declaration of Interests

The authors have no financial interests nor any other conflicts of interest related to this study. No funding was received for conducting this study. This study was preprinted at: *https://www.medrxiv.org/content/10.1101/2020.07.23.20160895v3*.

Table 1: COVID-19 Infections in New York City

	Total as of July 15, 2020	Share of Infections
NYC residents	8 million	*NA*
Estimated infections	1·6 million	100%
Symptomatic infections	1·1 million	65%
Reported cases	220 thousand	12%
Hospitalized patients	55 thousand	3%
Fatal outcomes	23 thousand	1%

Note: This table reports on the characteristics of COVID-19 infections in New York City (NYC). Infection prevalence was estimated by the New York Department of Health.[3] The ratio of symptomatic to total infections reflects a recent assessment by the U.S. Center for Disease Control and Prevention.[29] The number of cases, hospitalized patients, and fatal outcomes is reported by the NYC Department of Health.[4]

Table 2*:* Timing of reported fatalities for selected seroprevalence studies

	Cumulative Fatalities			Change (%)	
Location	**Study midpoint**	**4 weeks later**	**5 weeks later**	**Weeks 0 to 4**	**Weeks 4 to 5**
Europe					
Belgium	6,262	8,843	9,150	41	3
Geneva, Switzerland	255	287	291	13	1
Spain	26,834	27,136	28,324	1	4
Sweden	2,586	3,831	3,940	48	3
USA					
Connecticut	2,257	3,637	3,686	61	1
Indiana	932	1,984	2,142	113	8
Louisiana	477	2,012	2,286	322	14
Miami	513	1,160	1,290	126	11
Minneapolis	393	964	1093	145	13
Missouri	218	562	661	158	18
New York	20,212	28,663	29,438	42	3
Philadelphia	456	1509	1754	231	16
San Francisco	265	424	449	60	6
Seattle	536	732	775	37	6
Utah	41	96	98	134	2

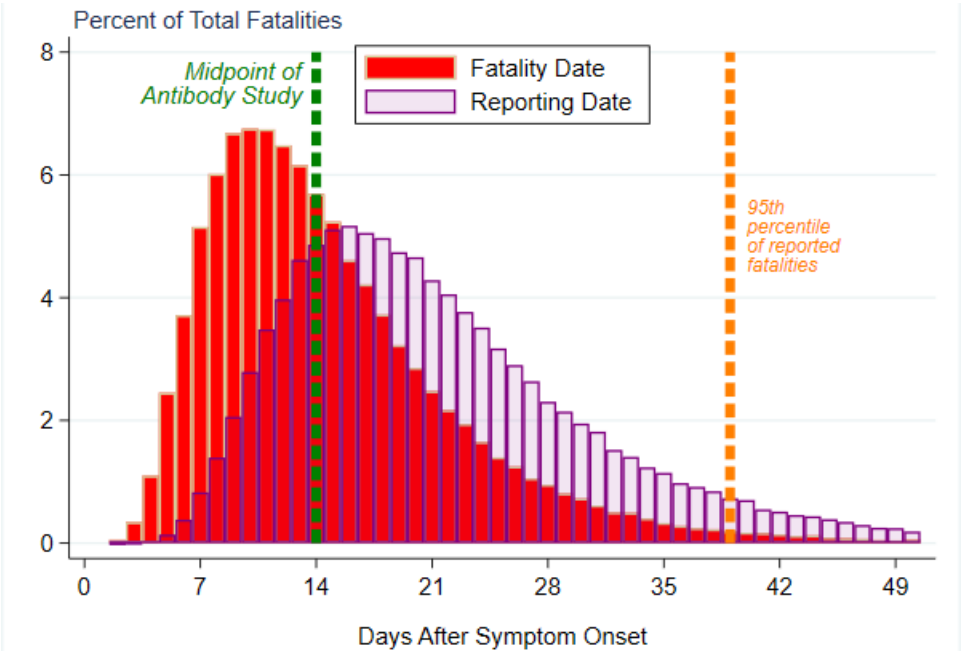
Note: This table shows data on confirmed COVID-19 deaths for 4 European locations and 11 U.S. locations where seroprevalence has been assessed.[18, 114, 119, 138-140] Sources of fatality data are given in Supplementary Appendix F. For each location, the second column shows cumulative fatalities from the onset of the pandemic until the midpoint date of that seroprevalence study, while the next two columns report cumulative deaths 4 and 5 weeks later, respectively. The last two columns show the percent change in cumulative fatalities over each specified time interval (weeks 0 to 4 and weeks 4 to 5, respectively).

Table 3: Age-specific fatality rates for COVID-19 infections vs. accidental deaths (%)

Age Group	COVID-19 IFR (95% CI)	Automobile Fatalities		Other Accidental Fatalities	
		England	USA	England	USA
0 to 34	0·004 (0·003–0·005)	0·002	0·015	0·004	0·032
35 to 44	0·068 (0·058–0·078)	0·002	0·012	0·017	0·043
45 to 54	0·23 (0·20–0·26)	0·002	0·013	0·019	0·043
55 to 64	0·75 (0·66–0·87)	0·003	0·013	0·014	0·043
65 to 74	2·5 (2·1–3·0)	0·003	0·013	0·020	0·040
75 to 84	8·5 (6·9–10·4)	0·005	0·017	0·069	0·094
85+	28·3 (21·8–36·6)	0·007	0·019	0·329	0·349

Note: This table compares IFRs for COVID-19 with the incidence of accidental deaths in England and in the USA. For each age group, the second column shows the metaregression estimate of the age-specific IFR with its 95% confidence interval enclosed in parentheses. The final four columns report the annual incidence of automobile fatalities and other accidental fatalities as a percent of the population of each age group in each country. The accidental fatality data for England as of 2019 is reported by the U.K. Office of National Statistics, while the corresponding U.S. data are reported as of 2018 by the U.S. National Center for Health Statistics.[130, 131]

Figure 1: Time lags in the incidence and reporting of COVID-19 fatalities



Note: This figure illustrates time lags in the incidence and reporting of COVID-19 fatalities using the results of a simulation calibrated to reflect the estimated distribution for time lags between symptom onset, death, and inclusion in official fatality reports.[29] As indicated by the vertical green line, this simulation assumes that the seroprevalence study was conducted two weeks after the pandemic was curtailed. The histogram shows the frequency of deaths and reported fatalities associated with the infections that occurred on the last day prior to full containment. As indicated by the orange vertical line, 95% of cumulative fatalities are reported within about four weeks after the midpoint date of the seroprevalence study.

Figure 2: Study selection (PRISMA flow diagram)

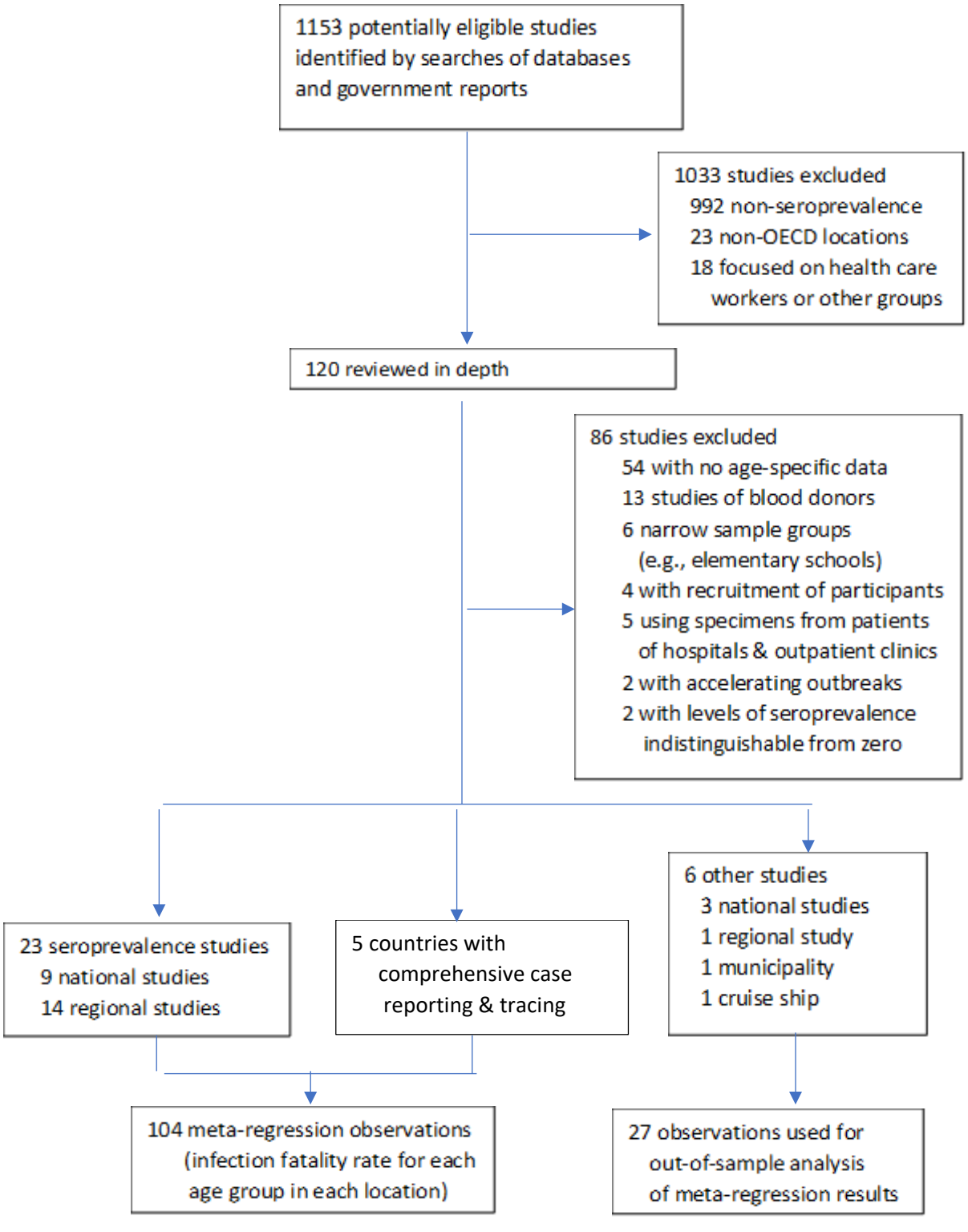
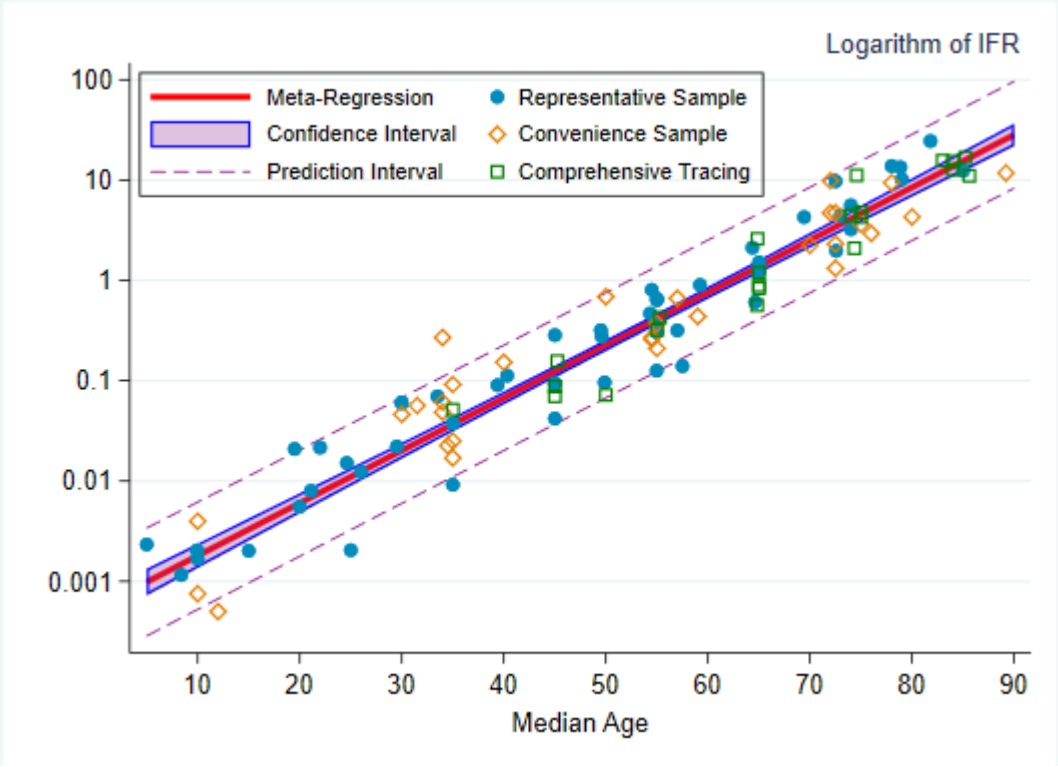
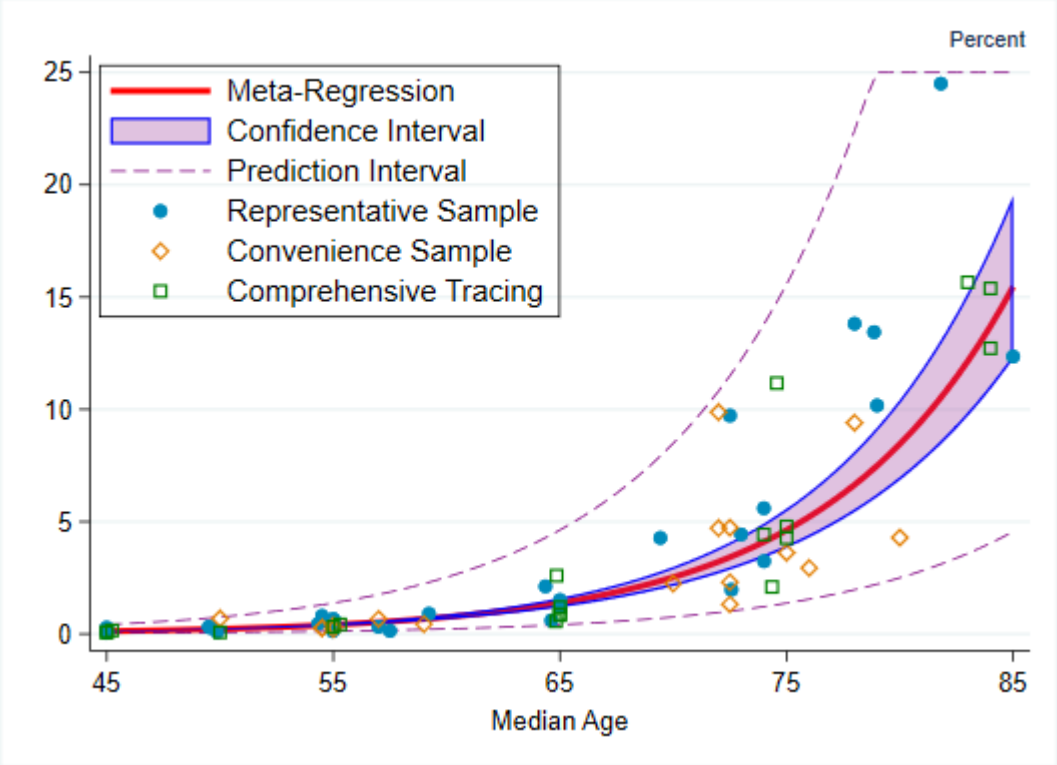


Figure 3: The log-linear relationship between IFR and age



Note: Our metaregression indicates that the infection fatality rate (IFR) increases exponentially with age, and hence this figure uses a base-10 logarithmic scale so that the relationship is evident across all ages from 5 to 95 years. Each marker denotes a specific metaregression observation, that is, the IFR for a particular age group in a particular location. The marker style reflects the type of observation: circles for observations from seroprevalence studies of representative samples, diamonds for seroprevalence studies of convenience samples, and squares for countries with comprehensive tracing programs. The red line denotes the metaregression estimate of IFR as a function of age, the shaded region depicts the 95% confidence interval for that estimate. The dashed lines denote the prediction interval (which includes random variations across studies and age groups), and almost all of the 108 metaregression observations lie within that interval.

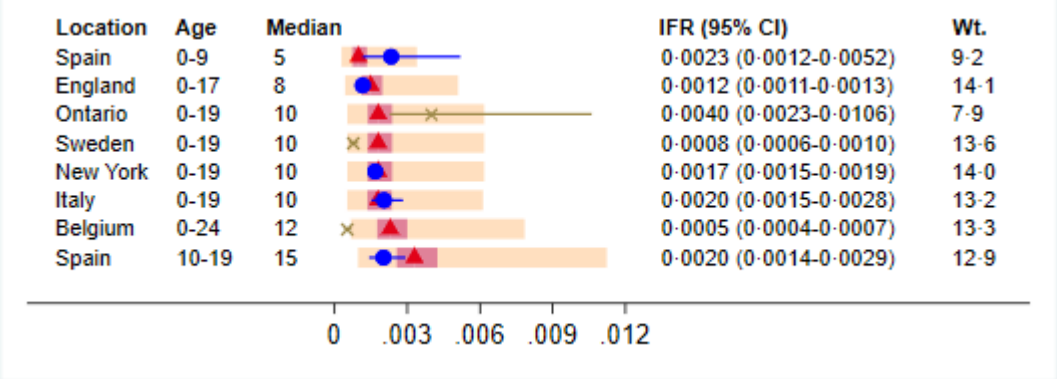
Figure 4: Benchmark analysis of the link between age and IFR



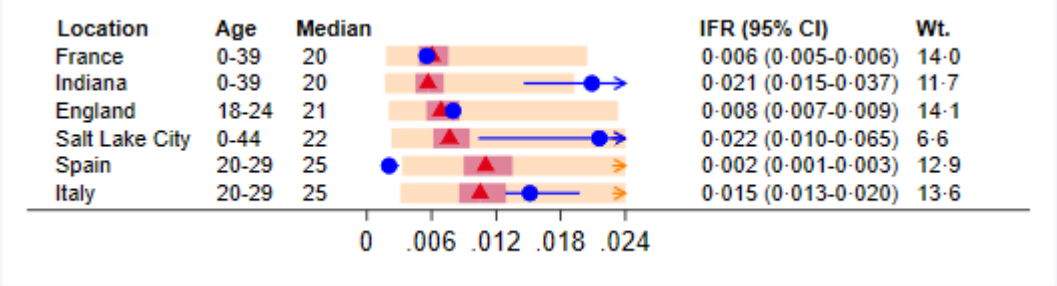
Note: This figure depicts the relationship between the infection fatality rate (IFR) and age, where IFR is shown in percentage terms. Each marker denotes a specific metaregression observation, that is, the IFR for a particular age group in a particular location. The marker style reflects the type of observation: circles for observations from seroprevalence studies of representative samples, diamonds for seroprevalence studies of convenience samples, and squares for countries with comprehensive tracing programs. The red line denotes the metaregression estimate of IFR as a function of age, the shaded region depicts the 95% confidence interval for that estimate. The dashed lines denote the prediction interval (which includes random variations across studies and age groups); almost all of the 104 metaregression observations lie within that interval.

FIgure 5: Forest plot of metaregression data

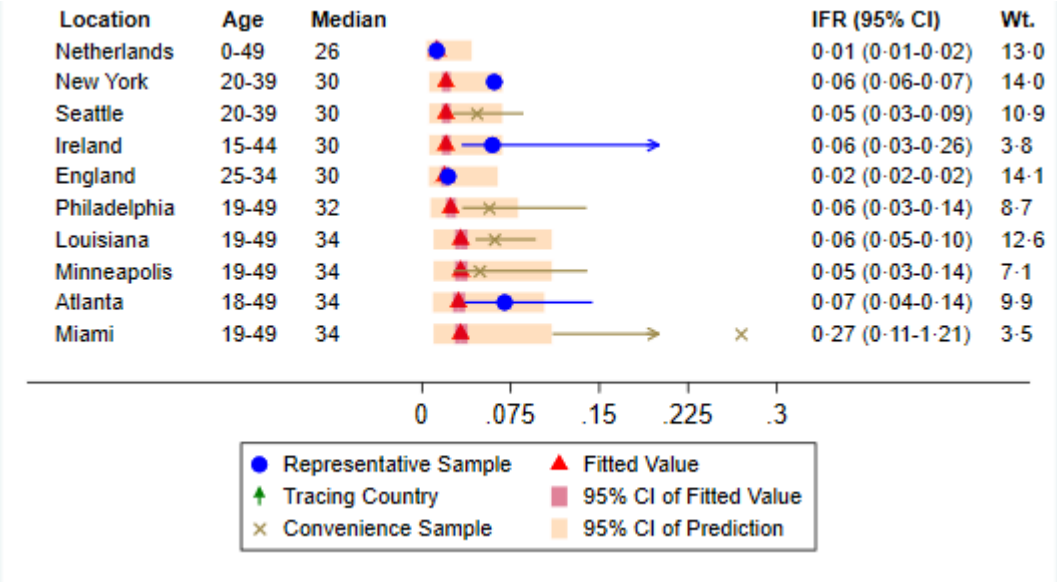
Cohorts with median age of 5-15 years



Cohorts with median age of 16-25 years

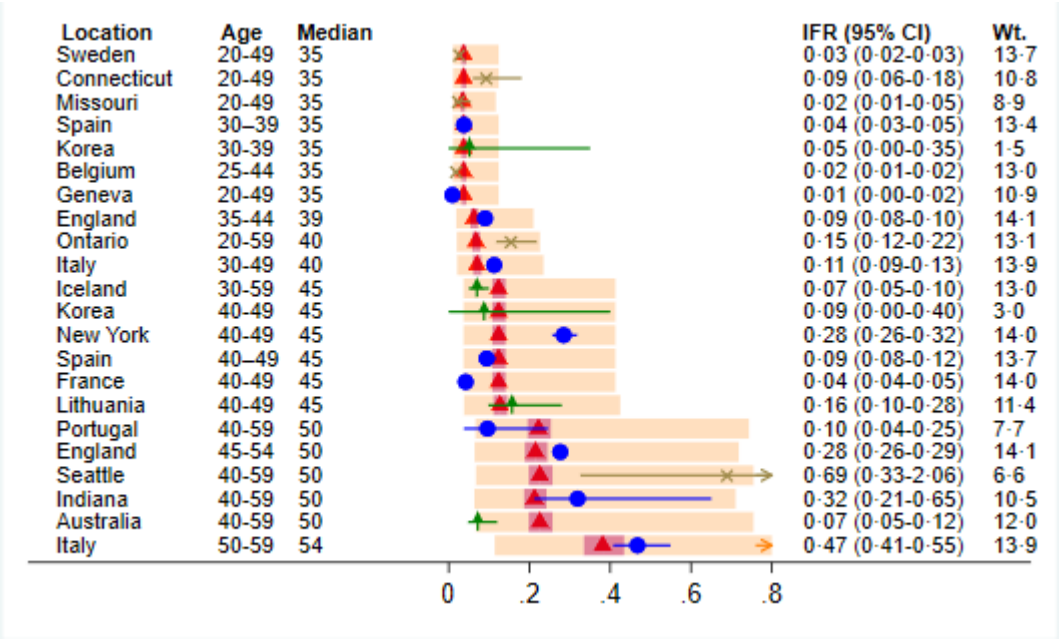


Cohorts with median age of 26-34 years

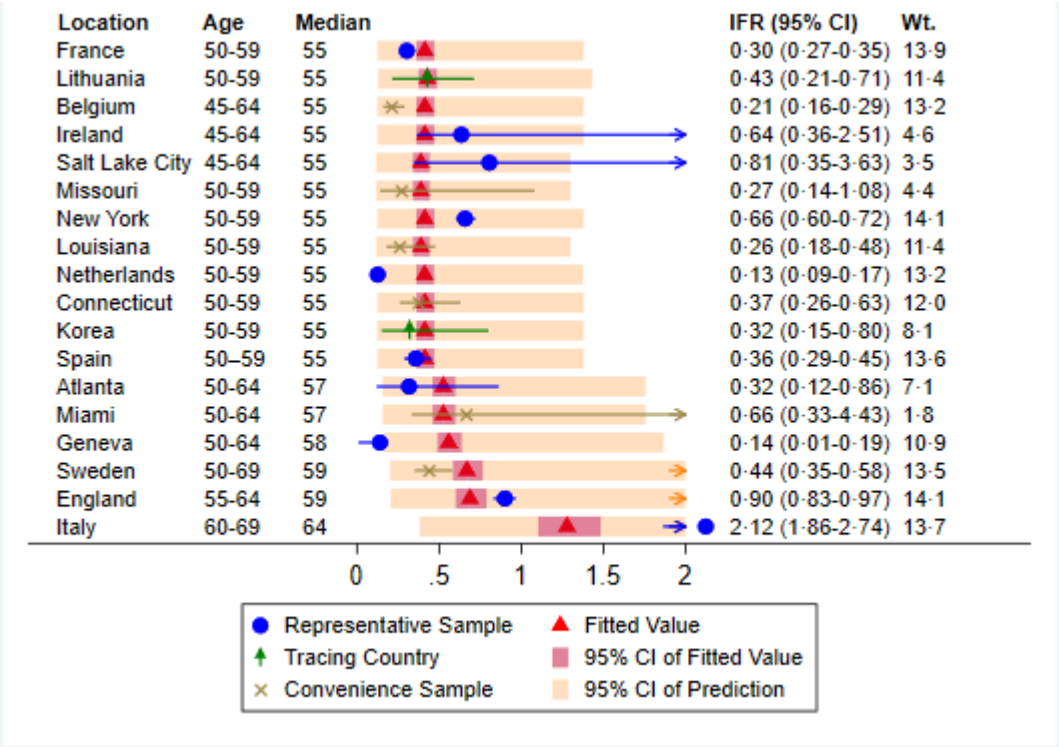


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Cohorts with median age of 35-54 years

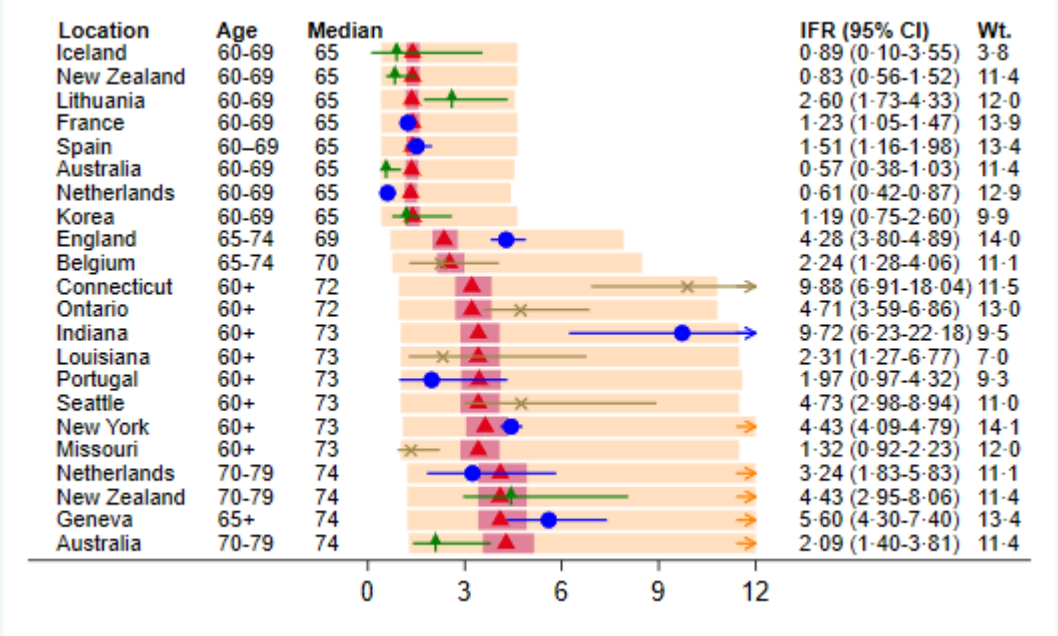


Cohorts with median age of 55-64 years



(Figure 5 continues on next page)

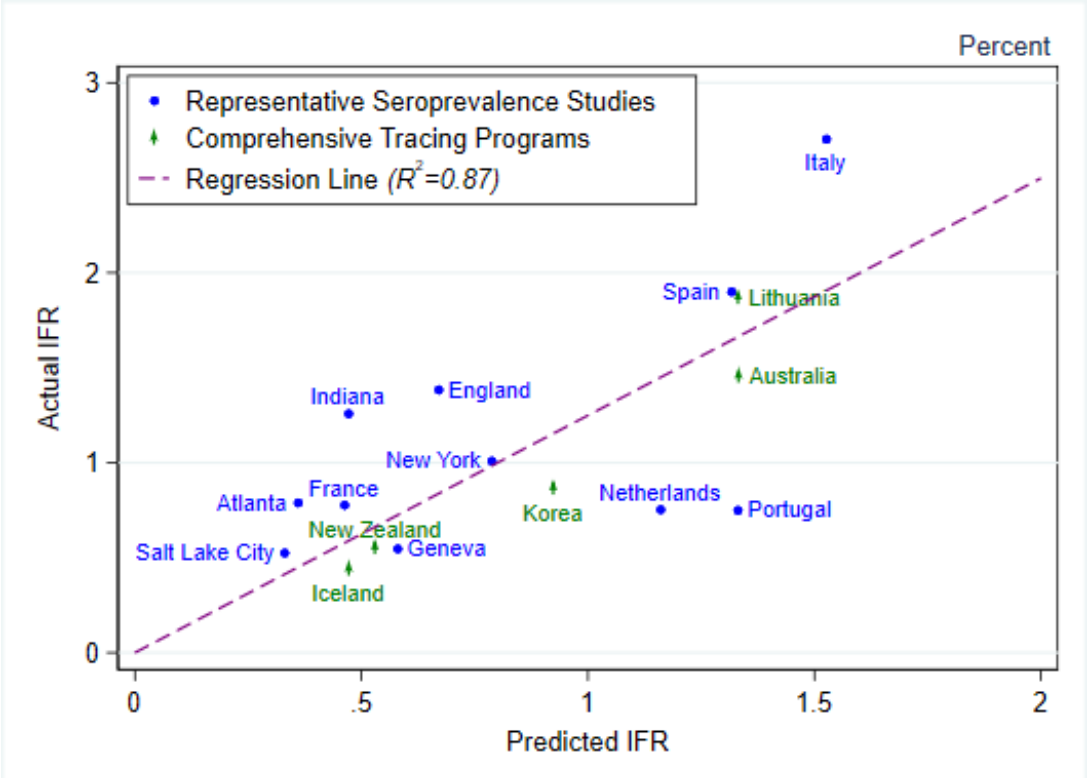
Cohorts with median age of 65-74 years



Cohorts with median age of 75 years and above



Figure 6: Variations in population IFR across geographical locations



Note: This figure depicts the extent to which the metaregression results account for variations in population IFR across geographical locations. The blue circles denote seroprevalence studies of representative samples, and the green diamonds denote countries with comprehensive tracing programs. For each observation, its position on the horizontal axis denotes its predicted IFR obtained by aggregating across the age-specific predictions of the metaregression, and its position on the vertical axis denotes the actual population IFR for that location. The dashed segments denote the estimated line obtained by fitting a regression to these 16 observations. The R^2 of this regression is 0.87, indicating that nearly 90% of the variation in population IFR can be explained by variations in age composition and age-specific prevalence of COVID-19.

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Supplementary Appendix A: PRISMA Checklist[1]

Section/topic	#	Checklist item	Page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Title Page
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Title Page
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	1-2
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	1-2
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	NA
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	2
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	2, App.B
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	App. B
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, included in the meta-analysis).	2-5, App. D
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	2, App. F, H
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	2-5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies and how this information is to be used in any data synthesis.	2-5
Summary measures	13	State principal summary measures.	1-5
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency.	5, App. G
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	5, App. G
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	5, App. G

RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	6, 9-10, App. J
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	7-9, App. F, H
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	App. I
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	14-16
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	11-13
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	App. K
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	App. L
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups.	9-10
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	18
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	17-18
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Title Page

Supplementary Appendix B: Meta-analysis search procedure

To perform the present meta-analysis, we collected published papers and preprints regarding the seroprevalence and/or infection fatality rate of COVID-19. To identify these studies, we systematically performed online searches in MedRxiv, Medline, PubMed, and Google Scholar using the criterion *((“infection fatality rate” or “IFR” or “seroprevalence” or “antibodies”) and (“COVID-19” or “SARS-Cov-2”))*. We also used a search tool created by the University of Zurich for searching EMBASE using the same search criterion.[2] We identified other studies listed in reports by government institutions such as the U.K. Parliament Office.[3] Finally, we confirmed the coverage of our search by referring to two recent meta-analysis studies of the overall IFR for COVID-19, a recent meta-analysis of the ratio of measured seroprevalence to reported cases, and the SeroTracker global dashboard of SARS-CoV-2 seroprevalence studies.[4-7] Our search encompassed studies that were publicly disseminated prior to 25 September 2020. For cases in which a study was identified by the aforementioned search but age-specific seroprevalence was not found, an expanded search was performed to obtain those details using additional keywords (e.g., the location of the study). Data was extracted from studies by three authors and verified prior to inclusion.

Supplementary Appendix C: Seroprevalence adjustments for test characteristics

Studies of COVID-19 seroprevalence have utilized a variety of distinct test procedures. Enzyme-linked immunosorbent assays (ELISA) proceed by tagging antibody-antigen interactions with a reporter protein. Chemiluminescent immunoassays (CLA) work similarly by tagging the antigen-antibody interaction with a fluorescent protein. Lateral Flow Assays (LFA), also known as rapid diagnostic tests (RDT), produce a colored band upon antigen-antibody interaction. Microneutralization tests (MNT), recombinant immunofluorescent assays (RIA), and plaque reduction neutralization tests (PRNT) can be performed in laboratories and provide extremely accurate assessments.

Recognizing that SARS-Cov-2 is both novel and hazardous, public regulatory agencies have issued "emergency use authorizations" (EUA) to facilitate the rapid deployment of test kits. Subsequent studies by independent laboratories have reassessed the characteristics of these test kits, in many cases finding markedly different results than those of the manufacturer. Such differences reflect (a) the extent to which test results may be affected by seemingly trivial differences in its implementation, and (b) the extent to which serological properties may vary across different segments of the population. For example, a significant challenge in producing accurate tests is to distinguish COVID-19 antibodies from those associated with other coronaviruses (including the common cold). Consequently, the assessment of test characteristics may vary with seemingly innocuous factors such as the season of the year in which the blood samples were collected.

The reliability of a seroprevalence test depends on its *sensitivity* (the likelihood that the test correctly detects the virus in an infected person) and *specificity* (the likelihood that the test has a negative result for a uninfected person) as well as the true prevalence of the disease. For example, in a population where the true prevalence is low, a test with sensitivity below 100% will yield a substantial fraction of false positive results.

Some seroprevalence studies have reported results for *raw prevalence*, that is, the ratio P / N, where P denotes the number of positive test results and N denotes the number of individuals who were tested, with confidence intervals that solely reflect sampling uncertainty (i.e., variations associated with drawing a finite sample of N observations). However, such estimates and confidence intervals may be misleading in the absence of adjustments that reflect the sensivity and specificity of the test method (except in the case of "gold standard" methods with 100% specificity and 100% sensitivity). Indeed, a recent systematic review and meta-analysis found very substantial divergences in sensitivity and specificity of COVID-19 serological tests.[8]

If the sensitivity and specificity of the test are assumed to be known with certainty, then the *test-adjusted prevalence* can be computed using the Gladen-Rogan formula[9] as follows:

$$adjusted\ prevalence\ =\ \frac{raw\ prevalence\ +\ specificity\ -\ 1}{sensitivity\ +\ specificity\ -\ 1}$$

Likewise, the test-adjusted confidence interval can be computed by multiplying the raw confidence interval by the factor 1/(*sensitivity* + *specificity* – 1).

Some recent seroprevalence studies have reported test-adjusted results using the Gladen-Rogan formula.[10-15] However, a number of other seroprevalence studies have only reported raw prevalence results.[12, 16-20] To facilitate the consistency of our meta-analysis, we follow the same approach of adjusting those raw prevalence results using the Gladen-Rogan formula, as reported in the table below.

Nonetheless, the sensitivity and specificity of COVID-19 antibody test kits should generally not be treated as parameters known with certainty. Indeed, the U.S. Food and Drug Administration reports 95% confidence intervals for each of these test properties in its information sheet for all EUA test kits.[21] In particular, following the approach of Gelman and Carpenter (2020), we use a Bayesian procedure to compute seroprevalence estimates and confidence intervals that incorporate uncertainty about the sensitivity and specificity of the test kit used in each of these seroprevalence studies.[22, 23] As shown in Table C1, the contrast between the Gladen-Rogan vs. Bayesian results are most striking for study observations obtained using a relatively small sample size in a context of low prevalence. In some cases, the Bayesian confidence interval indicates that the level of seroprevalence cannot be distinguished from zero, and hence those observations are excluded from our metaregression (see Appendix X).

Table C1: Raw vs. test-adjusted measures of seroprevalence

Location	Age Group	Sample (N)	Prevalence (%)			95% Confidence Interval					
						Lower Bound			Upper Bound		
			Raw	Rogan-Gladen	Bayesian	Raw	Rogan-Gladen	Bayesian	Raw	Rogan-Gladen	Bayesian
Belgium[24]	0-24	1263	6.0	6.7	5.7	4.2	4.7	2.0	8.6	9.6	8.4
	25-44	1710	5.9	6.6	5.4	4.2	4.7	1.9	8.3	9.2	8.0
	45-64	1831	6.2	6.9	5.6	4.7	5.2	2.1	8.3	9.2	8.3
	65-74	878	4.1	4.6	3.6	2.3	2.6	0.7	7.2	8.0	6.1
	75-84	816	7.0	7.8	7.0	4.2	4.7	3.4	11.7	13.0	10.1
	85+	809	13.2	14.7	14.2	8.9	9.9	9.8	19.6	21.8	18.7
France[25]	0–39	2262	10.8	12.0	NA	9.6	10.6	NA	12.1	13.5	NA
	40–49	2897	11.5	12.7	NA	10.3	11.4	NA	12.6	14.0	NA
	50–59	3019	5.8	6.5	NA	5.0	5.5	NA	6.7	7.4	NA
	60–69	3272	4.1	4.5	NA	3.4	3.8	NA	4.7	5.3	NA
	70+	3175	3.1	3.4	NA	2.5	2.7	NA	3.7	4.1	NA
Hungary[17]	14-39	3353	0.5	0.1	0.2	0.3	0.0	0.0	0.9	0.5	0.6
	40-64	4735	0.7	0.3	0.3	0.4	0.0	0.0	1.0	0.6	0.7
	65+	2386	0.8	0.4	0.4	0.4	0.0	0.1	1.3	0.9	0.9
Ireland[26]	12–29	519	1·9	1·5	NA	0·7	0·3	NA	3·1	2·7	NA
	30–49	746	1·6	1·2	NA	0·7	0·3	NA	2·5	2·1	NA
	50–69	686	1·6	1·2	NA	0·7	0·3	NA	2·5	2·2	NA
Italy[16]	0-19	9460	2.2	1.8	1.8	1.7	1.3	1.2	2.8	2.4	2.2
	20-29	11302	2.1	1.7	1.7	1.7	1.3	1.1	2.4	2.0	2.1
	30-49	13816	2.4	2.0	2.0	2.1	1.7	1.4	2.8	2.4	2.4
	50-59	10639	3.1	2.7	2.7	2.7	2.3	2.1	3.5	3.1	3.2
	60-69	8324	2.6	2.2	2.2	2.1	1.7	1.6	2.9	2.5	2.7
	70+	11118	2.5	2.1	2.1	2.1	1.7	1.5	2.9	2.5	2.5
Portugal[18]	0-9	404	2.0	2.2	1.8	0.8	0.9	0.1	5.4	6.0	3.9
	10-19	377	2.1	2.4	1.8	0.8	0.9	0.1	5.5	6.1	4.2
	20-39	377	0.8	0.9	0.8	0.1	0.1	0.1	4.8	5.3	2.3
	40-59	479	2.3	2.6	2.0	0.9	1.0	0.2	5.9	6.6	4.2
	60+	664	2.4	2.7	2.0	1.1	1.2	0.2	4.9	5.4	4.0

Table C1: Raw vs. test-adjusted measures of seroprevalence *(contd.)*

Spain[20]	0-9	1590	2.8	2.4	2.4	1.5	1.1	1.5	5.2	4.8	3.4
	10-19	4937	3.3	2.9	2.9	2.4	2.0	2.3	4.5	4.1	3.5
	20-29	4808	3.8	3.4	3.4	2.8	2.4	2.7	5.2	4.8	4.1
	30–39	6445	3.5	3.1	3.0	2.6	2.2	2.4	4.5	4.1	3.6
	40–49	9670	4.0	3.6	3.6	3.1	2.8	3.0	4.9	4.5	4.1
	50–59	9652	4.1	3.7	3.7	3.2	2.8	3.1	5.1	4.7	4.2
	60–69	7564	3.8	3.4	3.4	2.9	2.5	2.8	4.9	4.5	3.9
	70+	7293	3.5	3.1	3.1	2.3	1.9	2.5	5.4	5.0	3.6
Indiana, USA[19]	0-39	1011	1.4	1.0	1.0	0.7	0.3	0.2	2.2	1.8	1.9
	40-59	1301	1.1	0.7	0.7	0.5	0.1	0.1	1.8	1.4	1.4
	60+	1206	0.7	0.3	0.4	0.3	0.0	0.0	1.3	0.9	1.1

Supplementary Appendix D: Countries with comprehensive tracing programs

Country	Cases *(thousands)*	Tests per confirmed case
New Zealand	1·1	1862
Australia	6·7	1054
South Korea	10·8	576
Lithuania	1·4	415
Iceland	1·8	321
Slovakia	1·4	194
Latvia	0·8	191
Austria	15·4	115
Slovenia	1·4	112
Czech Republic	7·6	104
Greece	2·6	95
Denmark	9·0	94
Estonia	1·7	70
Luxembourg	3·8	68
Israel	15·8	57
Norway	7·7	47
Poland	14·0	37
Hungary	2·8	36
Portugal	24·7	35
Belgium	49·9	32
Germany	159·1	31
Finland	4·9	31
Switzerland	29·3	27
Spain	215·2	27
Japan	14·1	25
Italy	203·6	19
Colombia	6·2	16
Canada	51·6	15
Ireland	20·3	13
Turkey	117·6	13
Chile	14·9	13
United Kingdom	167·2	10
Netherlands	38·8	8
United States	1039·9	8
Mexico	17·8	4
France	129·6	NA
Sweden	21·7	NA

Note: This table reports data for all OECD countries as of 30 April except Lithuania (28 April) and Poland (5 May); data on tests per confirmed case was not available for France and Sweden.[27] A national seroprevalence study of the Czech Republic found that infections exceeded confirmed cases by a factor of 5, suggesting that comprehensive tracing requires substantially more than 100 tests per confirmed case. By contrast, a seroprevalence study of Iceland indicates that its tracing program was effective in identifying a high proportion of SARS-CoV-2 infections.[28] For example, the Korea Center for Disease Control analyzed a total of 2995 serum samples collected for the National Health and Nutrition Examination Survey between 21 April and 13 August, and only one of those specimens tested positive for antibodies and neutralizing antibodies.[29] Similarly, a seroprevalence study of 1500 outpatients in Seoul found only one positive result.[30]

Supplementary Appendix E: Prevalence vs reported cases in Iceland

Age Group	Reported Cases	Estimated Infections	*Confidence Interval*		Ratio of Infections to Reported Cases	*Confidence Interval*	
			Lower	*Upper*		*Lower*	*Upper*
30-39	289	469	*469*	*703*	1·6	*1·6*	*2·4*
40-49	357	644	*473*	*859*	1·8	*1·3*	*2·4*
50-59	306	337	*211*	*547*	1·1	*0·7*	*1·8*
60-69	213	225	*188*	*375*	1·1	*0·9*	*1·8*
70-79	63	70	*63*	*304*	1·1	*1·0*	*4·8*
80+	25	26	*13*	*319*	1·0	*0·5*	*12·8*
All 30+	1253	1771	*1415*	*3109*	1·41	*1·13*	*2·48*

Sources: Cases are reported by Iceland Directorate of Health as of 14 June 2020, when Iceland had 1796 recovered cases, 10 fatalities, and 4 individuals in isolation (none hospitalized).[31] Estimated infections and 95% confidence intervals are taken from the prevalence study of Gudbjartsson et al. (2020), which conducted tests of a random sample of the general population on 16–31 March 2020.[32] As of 21 April 2020 (three weeks after the conclusion of that study), there were 1785 reported cases (98·6% of the total reported cases as of 14 June 2020).

Supplementary Appendix F: Age-specific fatality data and source information

F.1: Fatality data for European seroprevalence studies with representative samples

Location and source of fatality data	Study midpoint date in 2020	Fatality reporting date in 2020	Age group, years	Fatalities
Belgium[33]	April 23	May 16	0–24	1
			25–44	30
			45–64	409
			65–74	1061
			75–84	2144
			85+	5087
England[34]	July 1	July 29	0–17	11
			18–24	30
			25–34	131
			35–44	394
			45–54	1348
			55–64	3605
			65–74	7631
			75+	38629
France[35-38]	May 14	May 31	0–39	78
			40–49	167
			50–59	610
			60–69	1494
			70+	15050
Geneva, Switzerland[39]	April 26	June 1	0–19	0
			20–49	2
			50–64	16
			65+	268
Ireland[40]	July 4	August 2	15–44	19
			45–64	98
Italy[34]	July 16	August 13	0–19	4
			20–29	16
			30–49	369
			50–59	1186
			60–69	3433
			70+	29134
Netherlands[34]	April 9	May 7	0–49	40
			50–59	137
			60–69	454
			70–79	1539
			80+	2426
Portugal[34]	June 14	July 12	0–9	0
			10–19	0
			20–39	4
			40–59	75
			60+	1581
Spain[41]	May 25	July 15	0–9	5
			10–19	6
			20–29	35
			30–39	77
			40–49	295
			50–59	1023
			60–69	3049
			70+	24647

Notes: (1) The France seroprevalence study encompassed the regions of Grand Est, Ile de France, and Nouvelle Aquitaine. Total confirmed COVID-19 fatalities (including deaths in hospitals and in other medical and social institutions) were reported by region as of May 31.[35] The age composition of hospital fatalities for each region (published on June 3, May 28, and May 28, respectively) was used to compute total age-specific fatalities as of May 31.[36-38] Fatalities in other medical and social institutions were allocated to the 70+ age group. (2) Spain had 29137 laboratory-confirmed COVID-19 fatalities as of 15 July 2020, including 9909 deaths in nursing homes. Age-specific fatalities outside of nursing homes are reported by Pastor-Barriuso et al. (2020).[41] Abellán et al. (2020) estimated that 4% of Spanish nursing home residents were aged 65-69 while the remaining 96% were aged 70+.[42] We used those proportions to allocate the 9909 nursing home deaths to the corresponding age groups.

F.2: Fatality data for European and Canadian seroprevalence studies with convenience samples

Location and source of fatality data	Study midpoint date in 2020	Fatality reporting date in 2020	Age group, years	Fatalities
France[43, 44]	April 12	May 31	0–9	3
			10–19	3
			20–29	21
			30–39	84
			40–49	231
			50–59	860
			60–69	2204
			70–79	5650
			80+	19746
Ontario[45]	June 17	July 15	0–19	1
			20–59	122
			60+	2600
Sweden[46]	May 10	June 18	0–19	1
			20–49	63
			50–69	504
			70+	4485

Notes: France had a total of 28802 confirmed COVID-19 fatalities as of 31 May 2020, including 18475 deaths in hospitals and 10327 deaths in other medical and social institutions; France does not have real-time reporting of deaths in personal homes.[44] Age-specific COVID-19 fatalities are only reported for hospitals; therefore, age-specific COVID-19 fatalities for other medical and social institutions are allocated proportionally for ages 70–79 and 80+ based on the relative incidence of overall excess mortality during weeks 10 to 22 for those two age groups as reported by Eurostat (which collects that data daily from France Santé Publique).[43]

F.3 Fatality data for U.S. seroprevalence studies

Location and source of fatality data	Study midpoint date in 2020	Fatality reporting date in 2020	Age Group	Fatalities
Atlanta[47]	May 1	May 31	0–17	1
			18–49	20
			50–64	51
			65+	294
Connecticut[48]	April 30	May 28	0–19	2
			20–49	75
			50–59	157
			60+	3633
Indiana[49]	April 27	May 25	0–39	20
			40–59	148
			60+	1864
Louisiana[50]	April 5	May 6	0–18	1
			19–49	85
			50–59	126
			60+	1053
Miami[51]	April 8	May 6	0–18	0
			19–49	61
			50–59	169
			60+	1060
Minneapolis[52]	May 5	June 4	0–18	0
			19–49	18
			50–59	47
			60+	928
Missouri[53]	April 23	May 23	0–19	0
			20–49	18
			50–59	43
			60+	620
New York[54]	April 23	May 21	0–19	12
			20–39	482
			40–49	1026
			50–59	2764
			60+	24376
Philadelphia[55, 56]	April 19	May 17	0–18	1
			19–49	57
			50–59	323
			60+	2639
Salt Lake City[57]	May 22	June 19	0–44	4
			45–64	31
			65+	90
San Francisco[58]	April 25	May 25	0–18	0
			19–49	25
			50–59	66
			60+	333
Seattle[59]	March 27	April 26	0–19	0
			20–39	8
			40–59	69
			60+	700

Note: Some seroprevalence age brackets were adjusted (+/- 5 years) to match the age structure of that location's COVID-19 fatality report. For Pennsylvania and Utah, county-level data as of May 17 is available for total fatalities but not reported by age group; consequently, the statewide age distribution of fatalities was used to allocate county-level fatalities by age for each of those locations.

F.4 Fatality data for comprehensive tracing countries

Location and source of fatality data	Reporting date	Age group, years	Fatalities
Australia[60]	June 12	0–39	0
		40–59	3
		60–69	13
		70–79	31
		80+	55
Iceland[31]	June 14	0–29	0
		30–59	1
		60–69	2
		70–79	3
		80+	4
Korea[61]	July 11	0–29	0
		30–39	2
		40–49	3
		50–59	15
		60–69	41
		70–79	84
		80+	144
Lithuania[62]	June 21	0–39	0
		40–49	1
		50–59	3
		60–69	12
		70–79	23
		80+	37
New Zealand[63]	July 9	0–59	0
		60–69	3
		70–79	7
		80+	12

Note: Age-specific fatality data for Lithuania was published as of 01 June 2020, at which point there was a total of 70 reported fatalities; thus, the six subsequent fatalities through 22 June 2020 were assumed to have the same age distribution as the fatalities through 01 June 2020.

Supplementary Appendix G: Metaregression methodology

To analyze IFR by age, we use meta-regression with random effects, using the *meta regress* procedure in *Stata* v16.[64, 65] We used a random-effects procedures to allow for residual heterogeneity between studies and across age groups by assuming that these divergences are drawn from a Gaussian distribution. The procedure provides reasonable results even if the errors are not strictly normal but may be unsatisfactory if the sample includes large outliers or the distribution of groups is not unimodal. In analytical terms, this framework can be expressed as follows:

$$log(IFR_{ij}) = \alpha + \beta * age_{ij} + \epsilon_{ij} + u_{ij}$$

$$\text{where } u_{ij} \sim N(0, \tau^2) \text{ and } \epsilon_{ij} \sim N(0, \sigma_{ij}^2)$$

In this specification, IFR_{ij} is the estimated IFR in study *i* for age group *j*, age_{ij} denotes the median age of that group, ϵ_{ij} denotes the source of idiosyncratic variations for that particular location and age group, and u_{ij} denotes the random effects that characterize any systematic deviations in outcomes across locations and age groups. Under the maintained assumption that each idiosyncratic term ϵ_{ij} has a normal distribution, the idiosyncratic variance is $\sigma_{ij}^2 = ((U_{ij} - L_{ij})/3.96)^2$, where U_{ij} and L_{ij} denote the upper and lower bounds of the 95% confidence interval for that study-age group. The random effects u_{ij} are assumed to be drawn from a homogeneous distribution with zero mean and variance τ^2. The null hypothesis of $\tau^2 = 0$ characterizes the case in which there are no systematic deviations across studies or age groups. If that null hypothesis is rejected, then the estimated value of τ^2 encapsulates the magnitude of those systematic deviations.

Under our baseline specification, the infection fatality rate increases exponentially with age—a pattern that has been evident in prior studies of age-specific case fatality rates.[66, 67] Consequently, our meta-regression is specified in logarithmic terms, with the slope coefficient β encapsulating the impact of higher age on *log(IFR)*. Consequently, the null hypothesis that IFR is unrelated to age can be evaluated by testing whether the value of β is significantly different from zero. If that null hypothesis is rejected, then the estimated values of α and β characterize the estimated relationship between log(IFR) and age. Consequently, the predicted relationship between IFR and age can be expressed as follows:

$$IFR = e^{\alpha + \beta * age_{ij}}$$

The 95% confidence interval for this prediction can obtained using the delta method. In particular, let IFR_a denote the infection fatality rate for age *a*, and let σ_c denote the standard error of the meta-regression estimate of log(IFR_a). If IFR_a has a non-zero value, then the delta method indicates that its standard error equals σ_c / IFR_a , and this standard error is used to construct the confidence interval for IFR_a at each age *a*. Likewise, the prediction interval for log(IFR_a) is computed using a standard error of $\sigma_c + \tau$ that incorporates the systematic variation in the random effects across studies and age groups, and hence the corresponding prediction interval for IFR_a is computed using a standard error of $(\sigma_c + \tau)/IFR_a$.

In estimating this metaregression, we exclude observations for which the lower bound of the 95% confidence interval for seroprevalence of that particular age group equals zero, and hence the upper bound of that age-specific IFR is not well defined. Similarly, we exclude observations for which the lower bound of the 95% confidence interval for seroprevalence is less than the observed COVID-19 mortality rate for that age group, since such observations would imply an upper bound for the IFR that exceeds 100%. Finally, we exclude observations for which no COVID-19 fatalities were recorded for a given age group and hence the implied value of the infection fatality rate is at its lower bound of zero and the corresponding confidence interval cannot be precisely determined.

Supplementary Appendix H: List of excluded studies

H.1 Studies excluded due to absence of age-specific prevalence or fatality data

Location	Description
Alberta, Canada[68]	On July 30, Alberta's chief medical officer announced the results of a serology study of 9400 blood specimens collected for other purposes and indicated that "less than one percent" were positive. No further details were available as of September 17, 2020.
Ariano Irpino, Italy[69]	This seroprevalence study collected specimens in late May from 13444 individuals (about 75% of municipality residents) and found a raw prevalence of 4·83%. No age-specific results were reported.
Australia[70]	This study analyzed specimens from 2991 individuals undergoing elective surgery during May–June 2020 and found test-adjusted seroprevalence of 0·28% (CI: 0–0·71%). No age-specific seroprevalence results were reported. Although the sample of patients may not be fully representative of the Australian population, these results confirm that prevalence in Australia was indistinguishable from zero at the time of the study, as expected for a comprehensive tracing program (see Supplementary Appendix C).
Austria[71]	Statistik Austria conducted an experimental study in which specimens were collected from 269 individuals ages 16+. The test-adjusted seroprevalence was 4·71% (CI: 1·36–7·97%). No age-specific results were reported.
Bad Feilnbach, Germany[72]	This study collected specimens from a random sample of 2153 adults between 23 June and 4 July 2020 and found raw seroprevalence of 6·0%. No age-specific results were reported as of September 17.
Baton Rouge, Louisiana, USA[73]	This study analyzed specimens from a random sample of 2138 individuals between July 15–31 and found seroprevalence of 3·6%. No age-specific seroprevalence results were reported.
Blaine County, Idaho, USA[74]	This study collected specimens from 972 individuals on May 4-19 and found an IgG prevalence of 22·7% (CI: 20–25·5%). The authors concluded that "the small number of county deaths (*n*=5) makes estimating the infection fatality rate unreliable." No age-specific fatality data is publicly available for this county.
Bolinas, California, USA[75]	This study collected specimens from a random sample of 1312 confirmed residents of Bolinas on April 20-24. The test-adjusted seroprevalence was 0·16% (CI: 0·02–0·46%). No age-specific seroprevalence results were reported.
Bonn, Germany[76]	This study analyzed specimens from 4771 individuals participating in the Rhineland Study, an ongoing community-based prospective cohort study of Bonn residents ages 30 years and older. Specimens were collected between 24 April and 30 June 2020 and analyzed using a combination of ELISA, RIA, and PRNT methods. The ELISA assay found 46 positive results and indicated seroprevalence of 0·97% (CI 0·72–1·30%). By contrast, the PRNT assay found only 17 positive results and indicated a markedly lower seroprevalence of 0·36% (CI: 0·21–0·61%). No age-specific seroprevalence results were reported.
British Columbia, Canada[77]	This study analyzed 885 laboratory specimens from outpatient clinics for the period May 15-27 and found only four positive cases (0·6%). No age-specific seroprevalence was reported.
Burlington, Vermont, USA[78]	This study analyzed specimens from 454 primary care patients at a Level 1 medical center in Burlington on 25–28 June 2020 and found 10 positive results using a two-step serologic assay and found raw prevalence of 2·2 percent (CI: 0·8–3·6%). The median age of individuals with positive vs. negative results were nearly identical (51·9 vs. 51·4 years).
Caldari Ortona, Italy[79]	This study collected specimens from 640 residents on April 18-19 and found raw prevalence of 12%. No age-specific results were reported.
Chelsea, Massachusetts, USA[80]	This study collected specimens from 200 pedestrians and found a raw seroprevalence of 22·5% using an IgG LFA. No age-specific results were reported.

Connecticut, USA[81]	This study analyzed specimens from a random sample of 505 adults residing in non-congregate settings. The sample design reflected the assumption of statewide prevalence of 10% (roughly similar to that of the neighboring state of New York) with the aim of obtaining prevalence estimates with precision of 2% at a confidence level of 90%. However, the study obtained a much lower estimated prevalence of 3·1% (95% CI: 1·1–5·1%). Consequently, the sample size proved to be insufficient to provide reliable age-specific results; the margin of error exceeds the estimated prevalence for all age groups reported in the study.
Czech Republic[82]	The Czech Ministry of Health conducted a large-scale seroprevalence survey on April 23-May 1, collecting specimens from a random sample of 22316 residents and testing for IgG antibodies using the Wantai test kit. Only 107 positive cases were identified (raw prevalence = 0·4%), and hence the test-adjusted confidence intervals include the lower bound of zero prevalence. That result is consistent with the very low number of reported cases in the Czech Republic as of early May; for example, Prague had only 1,638 reported cases for a population of 1·3 million.
Denmark[83]	This study analyzed specimens from a random sample of 2427 individuals in early June and identified 34 positive cases, yielding a test-adjusted prevalence of 1·2% (CI: 0·7–1·7%). Age-specific estimates were not reported as of September 17.
Faroe Islands Denmark[84]	This study analyzed specimens from a random sample of 1075 participants during late April and obtained 6 positive results; the test-adjusted prevalence was 0·7% (CI: 0·3–1·3%). No age-specific results were reported.
Finland[85]	Finland National Institute for Health and Welfare has been conducting an ongoing study of seroprevalence using random sampling of the population. Each specimen is initially screened for antibodies using a rapid test, and all specimens with positive screening results are analyzed using a microneutralization test (MNT) with confirmed specificity of 100%. As of August 8, this process screened 3155 specimens and obtained 8 positive MNT results (0.25%). No age-specific results were reported as of September 17.
Gangelt, Germany[86]	This study analyzed specimens from a random sample of 919 participants from the municipality of Gangelt (population 12,597) on March 31 to April 6 and obtained a test-adjusted prevalence of 15·5% (CI: 12·3–19·0%). Official government reports indicate that Gangelt had 7 COVID-19 fatalities at the time of the study but the death toll rose to 12 by late June, indicating an overall IFR of about 0·6%, similar to the IFR for Geneva. Age-specific fatalities have not been reported for Gangelt.
Greece[87]	This study analyzed residual serum specimens from 6586 individuals collected during March and April and found 24 positive results. The test-adjusted prevalence was 0% (CI: 0–0·23%). Prevalence was reported for four age groups (0–29, 30–49, 50–69, and 70+); each of those confidence intervals included the lower limit of 0%.
Hibino, Japan[88]	This study analyzed specimens from 615 employees of a Japanese company in Tokyo, including 350 individuals who were tested on two separate occasions. Among the 95 individuals with positive IgG results on the first occasion, there were 12 with negative IgG results in their second test. Among the 252 with an initial negative result, 54 had positive IgG results in their second test. No age-specific test results were reported.
Hideaway, Texas USA[89]	This study analyzed specimens from 293 adults and found 7 positive results. Age-specific results were not reported.
Ischgl, Austria[90]	This study analyzed specimens from 184 adults in Ischgl (an Austrian municipality of 1,604 residents) and obtained 85 positive results, i.e., prevalence of 46·2%. The study reported the fraction of positive results for specific age groups (4 out of 11 adults 55-64 years, 2 out of 8 adults 65-74 years, and 1 out of 2 adults ages 75+) but did not report test-adjusted estimates or confidence intervals by age group. Ischgl had only 2 reported COVID-19 fatalities as of July 1.
Israel[91]	Israel Health Ministry initiated a large-scale seroprevalence study in May. Subsequent media reports indicated that initial tests of 70000 Israelis indicated that prevalence varied significantly across regions and health organizations. No age-specific results had been released as of September 17.
Japanese Evacuees[92]	This study performed PCR tests on 565 Japanese citizens expatriated from Wuhan, China. There were eight positive tests, indicating a raw prevalence of 1·4%, but assessment of age-specific prevalence or IFRs is not feasible given the small sample, low prevalence, and lack of data on case outcomes.
Jersey, United Kingdom[93]	This study collected samples from 629 households comprising 1,062 individuals and estimated seroprevalence at 4·2% (CI 2·9 to 5·5%), indicating that about 3,300 Jersey residents have been infected. Jersey has had 30 COVID-19 fatalities (as of July 15), and hence the overall IFR is about 1% (similar to that of NYC). However, the seroprevalence sample is too small to facilitate accurate assessments of age-specific IFRs; for ages 55+, there were 258 samples and 12 positive cases,

Lisbon, Portugal[94]	This study analyzed specimens from 300 hospital patients and healthcare workers, 2500 university staff, and 187 adult volunteers and found that the ability to detect SARS-CoV-2 antibodies remained robust for five months in a large proportion of previously virus-positive screened subjects.
Louisville, Kentucky, USA[95]	This study analyzed specimens from 2237 individuals, including 509 who responded to mailed invitations and 1728 who volunteered after hearing about the study via news or social media, and found raw seroprevalence of 4·1% (CI: 3·2–5·1%). Age-specific results were not reported as of September 17.
Miami-Dade County, Florida, USA[96]	This study analyzed samples from 2,357 individuals in April and obtained 65 positive IgG results; an additional 275 individuals were tested in June with 4 positive results. Test-adjusted seroprevalence estimates and confidence intervals have not been published as of September 17.
New York City, New York, USA[97]	This study analyzed seroprevalence using specimens from four groups of patients (Cardiology, OB/GYN, Oncology, and Surgery) starting in mid-February. For the final week of the study (April 19), positive results were obtained for 47 of 243 patients; that seroprevalence estimate of 19·3% is well-aligned with the results of the New York Department of Health study. However, the sample size of this cohort is too small for assessing age-specific IFRs.
Neustadt-am-Rennsteig, Germany[98]	This study analyzed seroprevalence of 626 residents (71% of the population of this municipality) and estimated seroprevalence of 8·4% (52 positive cases). However, this sample size is too small for assessing age-specific IFRs.
New Orleans, Louisiana, USA[99]	This study analyzed seroprevalence in a random sample of 2,640 participants and obtained a seroprevalence estimate of 6·9% and an IFR of 1·6% (CI 1·5 to 1·7%). The study did not report on age-specific seroprevalence or IFRs.
New York City, New York, USA[100]	This study estimated age-specific infection fatality rates in New York City during spring 2020 using case, mortality, and mobility data. No seroprevalence data was utilized.
Norbotten, Sweden[101]	This study analyzed a randomly-selected sample of 425 adults and obtained 8 positive results; the test-adjusted seroprevalence was 1·9% (CI: 0·8–3·7%). However, only 2 positive results were for ages 30-64 and 2 positive results for ages 65+, so age-specific prevalence and IFRs cannot be reliably estimated.
Norway[102]	Norwegian Institute of Public Health collected 900 residual serum specimens from nine laboratories from various regions of Norway and obtained test-adjusted seroprevalence of 1·0% (CI: 0.1–2·4%). The study found 4 positive results out of 372 specimens for adults ages 25–59 and 2 positive results out of 206 specimens for adults ages 60+. The authors noted that *"these results should be interpreted with caution"* due to the limited size of the sample.
Occitania, France[103]	This study analyzed samples from 613 individuals *"exposed to the virus to varying extents mimicking the general population in Occitania"* and found seroprevalence of 1·3% (CI: 0·6–2·6%). The study did not report any age-specific data.
Oklahoma, USA[104]	The Oklahoma Department of Health publishes weekly data on raw seroprevalence using samples collected from labs within the state, but its reports do not include test-adjusted estimates, confidence intervals, or age-specific results.
Oslo, Norway[105]	As of August 12, this ongoing study had analyzed specimens from 3250 participants in the Norwegian Mother, Father and Child Survey (MoBa) and found seroprevalence of "less than 2 percent." No confidence intervals or age-specific results were reported.
Pima County, Arizona, USA[106]	This study analyzed specimens from 5882 self-recruited members of the local community and found 60 specimens with neutralizing antibodies (1·0%). Age-specific seroprevalence was not reported.
Rhode Island, USA[107]	This study invited 5000 randomly-selected households, collected samples from "roughly 10 to 15 percent" who agreed to participate, and obtained seroprevalence of 2·2% (CI: 1·1–3·9%). No age-specific results have been reported as of September 17.
Riverside County, California, USA[108]	This study tested a randomized sample of 1,726 residents during July and found raw seroprevalence of 5·9%. The press release (issued on July 27) indicated that the results "are still being analyzed"; no test-adjusted seroprevalence results or age-specific findings have been reported as of September 17.
San Francisco Mission District, California[109]	This study analyzed active infections and seroprevalence of 3,953 residents in a densely population majority Latinx neighborhood in downtown San Francisco. Positive seroprevalence in older adults was very low (22 out of 3,953) and hence too small for assessing age-specific IFRs.
San Miguel County, Colorado, USA[110]	The San Miguel County Health Department assessed seroprevalence in March and April using samples from 5,283 participants (66% of county residents). Raw prevalence was very low (0·53%), with only 3 confirmed positive results for adults ages 60 years and above.

Slovenia[111]	Researchers at the University of Ljubljana assessed seroprevalence using an IgG ELISA test for a random sample of 1,318 participants on April 20 to May 3. Test-adjusted prevalence was 0·9% (CI: 0 to 2·1%), indicating that the sample may have included only 10 infected individuals; no age-specific results were reported.
South-East England[112]	This study collected samples from 481 participants of the TwinsUK cohort and obtained 51 positive results (raw prevalence of 12%). No age-specific results were reported.
Stockholm, Sweden[113]	This study did not directly assess prevalence but produced estimates of IFR for two age groups (ages 0-69 and 70+) using a novel methodology linking live virus tests, reported cases, and mortality outcomes. The estimated IFR was 4·3% for ages 70+.
Stockholm Districts, Sweden[114]	This study analyzed samples from 213 randomly selected individuals in two residential areas of Stockholm on June 17–18 and found markedly different seroprevalence rates of 4·1% and 30%, respectively. No age-specific results were reported.
Stockholm Region, Sweden[115]	Stockholm County began offering antibody testing on a free walk-up basis. As of July 20, 166,431 antibody tests had been performed, of which 17·7% were positive. No demographic data or test-adjusted seroprevalence results had been reported as of September 17.
Miyagi, Osaka, and Tokyo, Japan[116]	This study collected samples from randomly-selected residents of three cities on June 1-7 and used two IgG test kits (Abbott and Roche); results were deemed "positive" only if confirmed by both tests Estimated seroprevalence was 0·1% in Tokyo (2 positive results from 1,971 specimens), 0·17% in Osaka (5 positive results from 2,970 specimens), and 0·03% in Miyagi (1 positive result from 3,009 specimens). No age-specific prevalence estimates were reported.
United States[117]	Seroprevalence estimates are reported in the U.S. CDC's weekly COVID-19 surveillance summary using data collected by 85 state and local public health laboratories. These reports include age-specific seroprevalence but no details regarding sample selection, test characteristics, or confidence intervals and hence could not be used in our metaregression.
Utsunomiya, Japan[118]	This study tested a random sample of 742 participants and found 3 confirmed positive results among 463 adults ages 18 to 65 years; the test-adjusted prevalence for that age group was 0·65% (CI: 0·13–1·8%). No positive results were obtained for the sample of 181 adults ages 65+ years.
Virginia, USA[119]	Virginia Department of Health collected specimens from a random sample of 3113 participants ages 16+ during early June and estimated prevalence of 2·4%. No confidence intervals or age-specific results had been released as of September 17.
Vo, Italy[120]	Vo' is a municipality of 3,300 people, nearly all of whom (87%) participated in an infection survey in late February. However, there were only 54 infections among people ages 50+, so assessing age-specific IFRs is not feasible.
Washoe County, Nevada, USA[121]	This study collected samples from 234 individuals on June 9-10 and obtained 5 positive IgG results. No age-specific results were reported.
Winston-Salem, North Carolina, USA[122]	This ongoing study has been collecting specimens from a representative sample of area residents since mid-April, and raw prevalence was characterized as *"about 10%."* On July 28 the researchers reported that the test was not sufficiently sensitive and that a new test would be deployed henceforth.
Zurich, Switzerland[123]	This study analyzed specimens from 578 individuals, including 90 with prior confirmed COVID-19 infections, 177 with positive patient contacts, and 311 who were randomly selected residents of Zurich. Seroprevalence in the randomly-selected group was estimated at 3·9% using the optimized test method.

H.2: Studies excluded due to accelerating outbreak

Location	Date	Cumulative fatalities in thousands		Change (%)
		Study midpoint	4 weeks later	
Los Angeles, California, USA[124]	April 10-11	0·265	1·468	454
New York City, New York, USA[10]	March 23-April 1	1·066	14·261	1238

H.3 Studies excluded due to non-representative samples

H.3.1 Active recruitment of participants

Location	Description
Luxembourg[125]	Of the 35 participants who tested positive, 19 had previously interacted with a person who was known to be infected or had a prior test for SARS-CoV-2.
Boise, Idaho[126]	This study was promoted during a "Crush the Curve" publicity campaign and required participants to sign up for a test.
Santa Clara, California, USA[127]	Participants were recruited via social media and needed to drive to the testing site. Stanford Medicine subsequently released a statement indicating that the study was under review due to concerns about potential biases.[128]
Frankfurt, Germany[129]	This study was conducted at an industrial worksite. Among the 5 seropositive participants, 3 had prior positive tests or direct contact with a known positive case.

H.3.2 Studies of hospitals, urgent care clinics, and dialysis centers

Location	Description
Brooklyn, New York, USA[130]	This study used samples from an outpatient clinic and yielded a much higher infection rate than other seroprevalence studies of the New York metropolitan area.
Kobe, Japan[131]	This study tested for IgG antibodies in 1,000 specimens from an outpatient clinic and found 33 positive cases. However, the study did not screen out samples from patients who were seeking treatment for COVID-related symptoms. Moreover, the study reported raw prevalence and confidence interval but did not report statistics adjusted for test characteristics. The manufacturer (ADS Biotec / Kurabo Japan) has indicated that this test has specificity of 100%, based on a sample of 14 pre-COVID specimens, but that specificity has not been evaluated by any independent study. The authors concluded by noting the selection bias and recommended that *"further serological studies targeting randomly selected people in Kobe City could clarify this potential limitation."*
Tokyo, Japan[132, 133]	The authors of this study specifically cautioned against interpreting their results as representative of the general population. In particular, the sample of 1,071 participants included 175 healthcare workers, 332 individuals who had experienced a fever in the past four months, 45 individuals who had previously taken a PCR test, and 9 people living with a COVID-positive cohabitant. The study obtained a raw infection rate of 3·8%, but the rate is only 0·8% if those subgroups are excluded.
United States[134]	This study analyzed residual plasma of 28503 randomly selected adult patients receiving dialysis in July 2020. Seroprevalence for the tested sample was 8·0% (CI: 7·7–8·4%), However, prevalence of dialysis patients can diverge markedly from that of the general population; for example, this sudy finds a seropositive rate of 34% for patients residing in New York state, nearly three times higher than the 14% seroprevalence rate obtained using a random sample of that state.[11]
Zurich, Switzerland[135]	This study analyzed two distinct set of samples: (i) blood donors and (ii) hospital patients. Nearly all blood donors were ages 20 to 55, so that sample is not useful for assessing age-specific IFRs for older adults. The sample of hospital patients was not screened to eliminate cases directly related to COVID-19, so that sample may not be representative of the broader population, e.g., inhabitants of the city of Zurich constituted a relatively large fraction of seropositive results compared to residents from the rest of the canton of Zurich. The study found an overall IFR of 0·5% similar to that of Geneva.

H.3.3 Studies of blood donors

Location	Description
Apulia, Italy[136]	This study assessed specimens from a sample of 904 healthy blood donors at a transfusion center in southeastern Italy and obtained 9 positive results (0·99%).
Canada[137]	Canadian Blood Services analyzed 37737 specimens from blood donors collected between 9 May and 18 June 2020 and found 275 positive results. Test-adjusted seroprevalence was 0·7% (CI:0·60–0·79%).
Denmark[138]	This study assessed specimens from a sample of 20640 Danish blood donors and calculated a test-adjusted prevalence of 1·9% (CI:0·8–2·3). Unfortunately, the antibody test used in this study was subsequently identified as unreliable, and the Danish government returned all remaining test kits to the manufacturer.[139]
England[140]	Public Health England has conducted ongoing surveillance of seroprevalence using specimens from healthy adult blood donors. For example, in 7694 samples tested during May (weeks 18-21), the test-adjusted prevalence was 8·5% (CI: 6·9–10%).
Germany[141]	This study assessed residue sera from 3186 regular blood donors collected during March 9–June 3 and obtained 29 positive results (raw prevalence 0·9%). The authors stated: *"It should be emphasized that the preselection of blood donors as a study cohort is accompanied by limitations regarding representation of population."*
Lombardy, Italy[142]	This study assessed specimens from 390 blood donors residing in the Lodi red zone collected on April 6 and found a raw seroprevalence rate of 23%.
Milan, Italy[143]	This study assessed specimens from a random sample of 789 blood donors over the period from February 24 (at the start of the outbreak) to April 8.
Netherlands[144]	This study assessed specimens from 7361 adult blood donors collected on April 1-15 and found seroprevalence of 2·7%.
Rhode Island, USA[145]	This study assessed specimens from 2008 blood donors collected during April 27–May 11 and found seroprevalence of 0·6%.
Scotland[146]	This study assessed specimens from 3500 blood donors collected between March 17 and May 19. The authors noted that the resulting estimates of seroprevalence *"are complicated by non-uniform sampling...based on the locations where weekly donations took place...[and] further confounded by the absence of samples from individuals below age 18 and individuals over age 75."*
San Francisco, California, USA[147]	This study assessed specimens from 1000 blood donors that were collected during March and found one positive result (raw prevalence 0·1%).
United States[148]	This study analyzed residual sera from 252882 U.S. blood donors obtained between June 1 and July 31 and found an overall seroprevalence of 1·83%.
United States[149]	This study analyzed residual sera from 953926 U.S. blood donors obtained between June 15 and August 23 and found seropositivity of 1·82% (CI: 1·79–1·84%).

H.3.4 Studies of elementary schools

Location	Description
Oisie, France[150]	This sample of 1,340 participants included elementary school teachers, pupils, and their families. Only two individuals in the sample were ages 65 years and above.
Saxony, Germany[151]	This study analyzed specimen samples from students and teachers at thirteen secondary schools in eastern Saxony and found very low seroprevalence (0·6%).
Southwest Germany[76]	This study analyzed specimens from 2482 children (ages 1–10 years) and one of their parents collected between 22 April and 15 May 2020. Seroprevalence for children was 0·6% (CI: 0·3–1·0%), while the prevalence among their parents was 1·8% (CI: 1·2–2·4%).
Zurich, Switzerland[152]	This study collected samples from 2585 school children ages 6–16 years and found seroprevalence of 2·8% (CI: 1·6–4·1%).

H.3.5 Life insurance applicants

Location	Description
United States[153]	This study analyzed specimens for 50130 consecutive life insurance applicants whose blood samples were collected for insurance underwriting purposes between 12 May and 25 June 2020. The study found 1520 positive results, that is, raw seroprevalence of 3·0%. The study did not find significant differences in prevalence across three age groups (18–40, 41–60, and 61–85 years).

H.3.5 Close contacts of positive cases

Location	Description
Lombardy, Italy[154]	This study used a database of 62881 contacts of COVID-19 cases and conducted RT-PCR tests and antibody screening on 5484 individuals. The study reported that 2824 individuals had positive tests (51·5% of the sample), of which 62 individuals subsequently died with a COVID-19 diagnosis.

H.4 Exclusion of observations with seroprevalence indistinguishable from zero

Note: The metaregression analysis excludes observations for which either (a) the lower bound of the 95% confidence interval equals zero, and hence the upper bound of the IFR is not well defined; or (b) the lower bound of the 95% confidence interval is less than the observed COVID-19 mortality rate for that age group, implying an upper bound for the IFR that exceeds 100%.

H.4.1 Exclusion of observations from European seroprevalence studies

			95% Confidence Interval (%)	
Location	Age Group	Prevalence (%)	Lower Bound	Upper Bound
Hungary[17]	14–39	0·1	0·0	0·5
	40–64	0·3	0·0	0·6
	65+	0·4	0·0	0·9
Portugal[18]	20–39	0·9	0·1	5·3

H.4.2 Exclusion of observations from U.S. seroprevalence studies

			95% Confidence Interval (%)	
Location	**Age Group**	**Prevalence (%)**	**Lower Bound**	**Upper Bound**
Atlanta, Georgia, USA[155]	0–17	0	0	1·0
	65+	0·7	0·1	4·5
Connecticut, USA[10]	0–18	0·8	0	2·9
Louisiana, USA[10]	0–18	2·8	0	11·5
Miami, Florida, USA[10]	0–18	2·4	0	7·8
Minneapolis, Minnesota, USA[10]	0–18	5·8	0	14·3
	50–59	0·7	0	2·8
	60+	1·0	0	3·2
Missouri, USA[10]	0–18	1·4	0	4·1
Oregon, USA[156]	0–17	0	0	10·4
	18–49	0	0	0·7
	50–64	0·1	0	1·0
	65+	1·4	0·1	2·8
Philadelphia, Pennsylvania, USA[10]	0–18	2·2	0	6·9
	50–64	0·8	0	2·8
	65+	1·6	0·3	3·5
Salt Lake City, Utah, USA[14]	65+	0·6	0	1·4
San Francisco, California, USA[10]	0–18	1·7	0	7·7
	19–49	1·1	0	2·6
	50–64	0·7	0	2·4
Seattle, Washington, USA[10]	0–18	0·7	0	2·5

H.5 Exclusion of observations with no observed fatalities

Location	Age Group	Population *(millions)*	Infections *(thousands)*	
			Estimate	95% confidence interval
Geneva	5–19	0·796	7·300	4·300–11·200
Hungary	0–14	1·391	7·795	3·758–11·971
Portugal	0–9	0·841	17·663	6·729–45·418
	10–19	1·015	21·318	8·121–55·834
Australia	0–39	13·533	2·800	4·200–12·600
Iceland	0–29	0·136	0·554	0·407–0·608
Korea	0–29	15·623	15·180	6·939–21·685
Lithuania	0–39	1·198	1·845	0·843–2·635
New Zealand	0–59	3·751	3·726	1·876–5·627

Note: This table shows observations for relatively young age groups in locations where no COVID-19 fatalities were recorded for that age group and hence the implied value of the infection fatality rate is at its lower bound of zero and its confidence interval cannot be precisely determined.

Appendix I: Seroprevalence Rates for Studies Included in Meta-Analysis

I.1 European seroprevalence studies with representative samples

Location	Dates in 2020	Age Group, years	Population, millions	Prevalence (%)	95% Confidence Interval (%)
England[157]	April 16–July 3	0–17	12·023	9·2	6·2–12·2
England[15]	June 20–July 13	18–24	4·747	7·9	7·3–8·5
		25–34	7·609	7·8	7·4–8·3
		35–44	7·147	6·1	5·7–6·6
		45–54	7·623	6·4	6·0–6·9
		55–64	6·782	5·9	5·5–6·4
		65–74	5·576	3·2	2·8–3·6
		75+	4·778	3·3	2·9–3·8
France[25]	May 4–24	0–39	11·669	12·0	10·6–13·5
		40–49	3·124	12·7	11·4–14·0
		50–59	3·097	6·5	5·5–7·4
		60–69	2·691	4·5	3·8–5·3
		70+	3·209	3·4	2·7–4·1
Ireland[26]	June 22–July 16	15–44	1·971	1·5	0·3–2·7
		45–64	1·218	1·2	0·3–2·1
Italy[16]	July 6–27	0–19	10·859	1·8	1·3–2·4
		20–29	6·201	1·7	1·3–2·0
		30–49	16·317	2·0	1·7–2·4
		50–59	9·352	2·7	2·3–3·1
		60–69	7·337	2·2	1·7–2·5
		70+	10·278	2·1	1·7–2·5
Netherlands[158]	April 1–17	0–49	10·053	3·5	2·5–5·2
		50–59	2·524	4·3	3·2–5·8
		60–69	2·130	3·5	2·5–5·0
		70–79	1·592	3·0	1·7–5·3
		80+	0·837	2·8	0·9–7·3
Portugal[18]	May 21–July 8	0–9	0·841	2·2	0·9–6·0
		10–19	1·015	2·4	0·9–6·1
		20–39	2·289	0·9	0·1–5·3
		40–59	3·057	2·6	1·0–6·6
		60+	2·995	2·7	1·2–5·4
Spain[41]	May 18–June 1	0–9	4·284	2·4	1·1–4·8
		10–19	4·955	2·9	2·0–4·1
		20–29	4·883	3·4	2·4–4·8
		30–39	5·902	3·1	2·2–4·1
		40–49	7·938	3·6	2·8–4·5
		50–59	7·046	3·7	2·8–4·7
		60–69	5·340	3·4	2·5–4·5
		70+	6·939	3·1	1·9–5·0
Geneva, Switzerland[39]	April 13–May 8	5–19	0·080	9·2	5·4–14·1
		20–49	0·219	13·1	9·8–17·0
		50–64	0·099	10·5	7·3–14·1
		65+	0·084	6·8	3·8–10·5

I.2 European and Canadian seroprevalence studies with convenience samples

Location	Dates in 2020	Age Group *(years)*	Population *(millions)*	Prevalence (%)	95% Confidence Interval (%)
Belgium[33]	April 20–26	0–24	3·229	6·7	4·7–9·6
		25–44	2·957	6·6	4·7–9·2
		45–64	3·081	6·9	5·2–9·2
		65–74	1·147	4·6	2·6–8·0
		75–84	0·691	7·8	4·7–13·0
		85+	0·327	14·7	9·9–21·8
Ontario[159]	June 5–30	0–19	3·142	0·8	0·3–1·4
		20–59	7·977	1·0	0·7–1·3
		60+	3·448	1·6	1·1–2·1
Sweden[46]	April 27–May 24	0–19	2·321	5·7	4·5–7·0
		20–49	3·861	6·5	5·2–7·8
		50–69	2·390	4·8	3·6–6·0
		70+	1·526	3·1	2·1–4·1

I.3 U.S. seroprevalence studies with representative samples

Location	Dates in 2020	Age Group *(years)*	Population *(millions)*	Prevalence (%)	95% Confidence Interval (%)
Atlanta, USA[155]	April 28–May 3	0–17	0·402	0·0	0·0–1·0
		18–49	0·867	3·3	1·6–6·4
		50–64	0·328	4·9	1·8–12·9
		65+	0·226	0·7	0·1–4·5
Indiana, USA[19]	April 25–29	0–39	3·546	2·7	1·5–3·9
		40–59	1·674	2·8	1·4–4·2
		60+	1·512	1·3	0·6–2·0
New York, USA[11]	April 23	0–19	4·898	14·6	13·1–16·1
		20–39	5·409	14·6	13·1–16·1
		40–49	2·356	15·3	13·7–17·0
		50–59	2·623	16·0	14·6–17·5
		60+	4·544	12·1	11·2–13·1
Salt Lake City, USA[160, 161]	May 4–June 10	0–44	1·544	1·2	0·4–2·5
		45–64	0·427	0·9	0·2–2·1
		65+	0·223	0·6	0·0–1·4

I.4 U.S. Seroprevalence Studies with Convenience Samples

Location	Dates in 2020	Age Group *(years)*	Population *(millions)*	Prevalence (%)	95% Confidence Interval (%)
Connecticut, USA[10]	April 26–May3	0·830	0–19	0·8	0·0–2·9
		1·341	20–49	6·1	3·1–9·3
		0·519	50–59	8·1	4·8–
		0·876	60+	4·2	2·3–6·0
Louisiana, USA[10]	April 1–8	1·146	0–18	2·8	0·0–11·5
		1·879	19–49	7·4	4·7–10·0
		0·587	50–59	8·3	4·5–11·9
		1·037	60+	4·4	1·5–8·0
Miami, USA[10]	April 6–10	1·341	0–19	2·4	0·0–7·8
		2·513	20–49	0·9	0·2–2·2
		1·272	50–59	2·0	0·3–4·0
		1·203	60+	3·0	1·7–4·5
Minneapolis, USA[10]	April 30–May 12	0·966	0–18	5·8	0·0–14·3
		1·610	19–49	2·3	0·8–4·2
		0·513	50–59	0·7	0·0–2·8
		0·809	60+	1·0	0·0–3·2
Missouri, USA[10]	April 20–26	1·527	0–19	1·4	0·0–4·1
		2·348	20–49	3·4	1·4–5·5
		0·796	50–59	2·0	0·5–3·8
		1·466	60+	3·2	1·9–4·6
Philadelphia, USA[10]	April 13–25	0·944	0–18	2·2	0·0–6·9
		1·707	19–49	5·9	2·4–9·8
		1·268	50–59	0·8	0·0–2·8
		0·825	60+	1·6	0·3–3·5
San Francisco, USA[10]	April 23–27	1·649	0–18	1·7	0·0–7·7
		2·960	19–49	1·1	0·0–2·6
		1·262	50–59	0·7	0·0–2·4
		1·023	60+	0·9	0·2–2·5
Seattle, USA[10]	March 23–April 1	1·009	0–19	0·7	0·0–2·5
		1·332	20–39	1·3	0·7–2·3
		1·115	40–59	0·9	0·3–1·9
		0·870	60+	1·7	0·9–2·7

I.5 Prevalence in countries with comprehensive tracing programs

Location	Dates in 2020	Population, millions	Age Group, years	Prevalence (%)	95% Confidence Interval (%)
Australia[60]	February 1–June 12	13·533	0–39	0·06	0·03–0·09
		6·414	40–59	0·06	0·04–0·10
		2·651	60–69	0·09	0·05–0·13
		1·846	70–79	0·08	0·04–0·12
		1·055	80+	0·05	0·03–0·07
Iceland[31]	February 1–June 15	0·136	0–29	0·4	0·3–0·5
		0·132	30–59	1·1	0·8–1·6
		0·038	60–69	0·5	0·3–1·0
		0·023	70–79	0·3	0·27–1·3
		0·013	80+	0·2	0·1–2·5
Korea[61]	February 1–May 17	15·623	0–29	0·11	0·05–0·17
		7·080	30–39	0·08	0·04–0·12
		8·219	40–49	0·06	0·03–0·09
		8·477	50–59	0·07	0·03–0·10
		6·454	60–69	0·05	0·03–0·08
		3·560	70–79	0·05	0·03–0·07
		1·856	80+	0·06	0·03–0·09
Lithuania[62]	February 1–June 18	1·198	0–39	0·15	0·07–0·22
		0·356	40–49	0·18	0·10–0·29
		0·421	50–59	0·17	0·10–0·33
		0·353	60–69	0·13	0·08–0·20
		0·223	70–79	0·09	0·05–0·14
		0·172	80+	0·13	0·07–0·19
New Zealand[63]	February 1–July 9	3·751	0–59	0·10	0·05–0·15
		0·522	60–69	0·07	0·04–0·10
		0·362	70–79	0·04	0·02–0·07
		0·187	80+	0·04	0·02–0·06

I.6 Prevalence estimates of large-scale studies used in out-of-sample analysis

Location	Dates in 2020	Population, millions	Age Group, years	Prevalence (%)	95% Confidence Interval (%)
England (ONS)	April 26–July 26	25·051	15–49	6·1	4·9–7·5
		15·738	50–69	4·8	4.0–5·8
		8·782	70+	3·9	3·0–5·2
France[162]	April 6–12	0-9	7·527	5·9	1·6–10·2
		10-19	7·883	3·5	0·7–6·4
		20-29	7·371	7·0	3·8–10·2
		30-39	8·011	3·4	1·0–5·8
		40-49	8·326	7·7	4·6–10·9
		50-59	8·635	9·7	6·4–13·1
		60-69	7·765	10·0	6·5–13·5
		70–79	5·728	5·9	3·1–8·7
		80+	4·027	7·3	4·2–10·3
Great Britain (U.K. Biobank)	May 27–July 6	23·562	0–29	10·8	9·4–12·3
		8·641	30–39	8·2	7·2–9·3
		8·180	40–49	7·2	6·2–8·4
		8·810	50–59	7·1	6·2–8·0
		6·928	60–69	6·4	5·6–7·2
		8·782	70+	5·4	4·7–6·1
Utah, USA (CDC)	April 20–May 3	1·228	19–44	1·8	0·6–3·5
		0·632	45–64	2·9	0·9–5·2
		0·366	65+	2·7	0·9–5·0

I.7 Prevalence estimates of small-scale studies used in out-of-sample analysis

Location	Dates in 2020	Population,	Age Group, years	Prevalence (%)	95% Confidence Interval (%)
Diamond Princess cruise ship	Feb 1–March 7	**1150**	0–49	8·3	NA
		398	50–59	14·8	NA
		923	60–69	19·2	NA
		1015	70–79	23·1	NA
		216	80+	25·0	NA
Castiglione d'Adda, Italy	May 18–25	**3052**	15–64	19·1	14·9–23·2
		538	65–74	31·3	25·4–37·3
		401	75–84	36·6	28·3–44·9
		149	85+	42·1	31·1–53·1

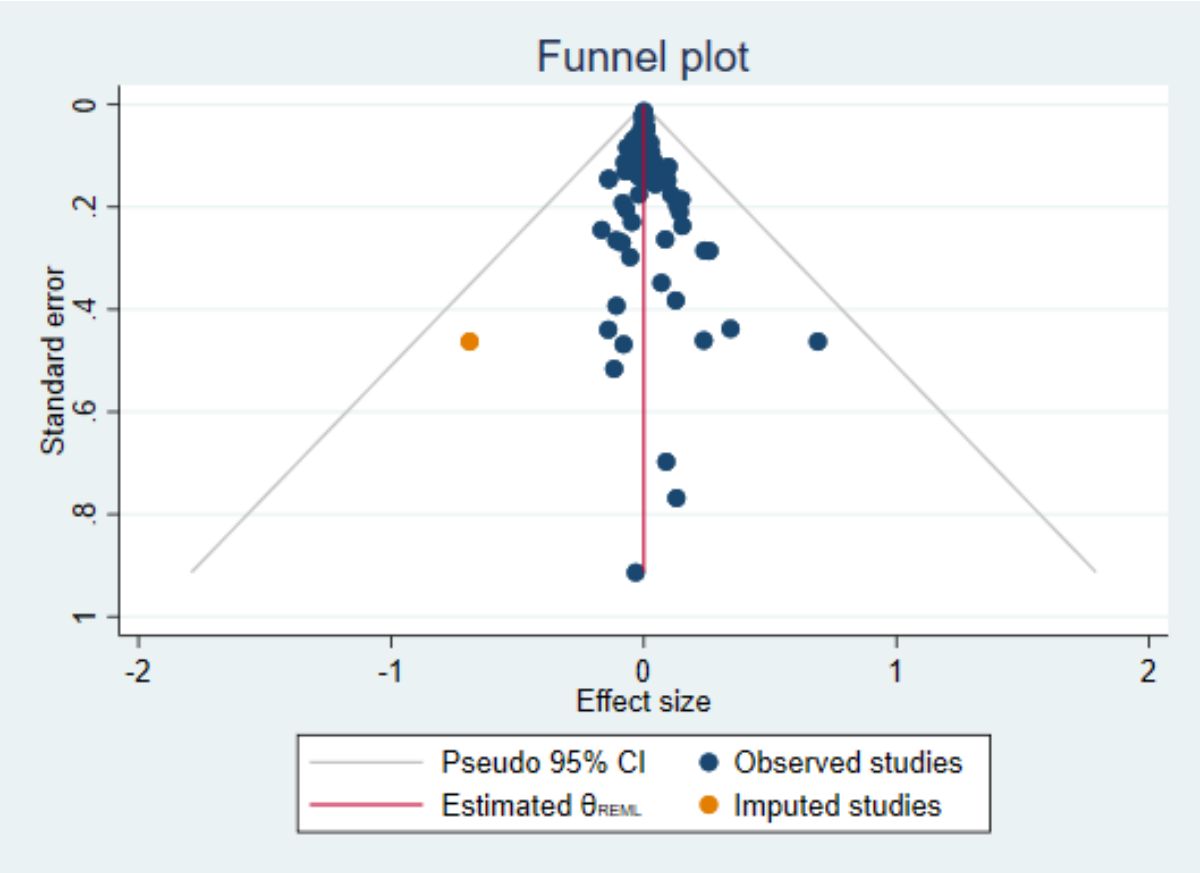
Supplementary Appendix J: Assessment of risk of bias for included studies



Supplementary Appendix K: Assessment of Publication Bias

(1) Regression-based Egger test for small-study effects
Random-effects model estimated using REML
H0: β = 0; no small-study effects
β = 0.04, SE(β) = 0.136,
z = 0.27, Prob > |z| = 0.7882

(2) Nonparametric trim-and-fill analysis of publication bias
Linear estimator, imputing on the right
Number of studies = 105
Model: Random-effects
Method: REML
Observed = 104, Imputed = 1
Effect Size and 95% Confidence Interval
Observed: 0.000 (-0.009, 0.009)
Observed + Imputed: 0.000 (-0.009, 0.009)



Supplementary Appendix L: Stability of metaregression results across age categories

Age Category	# Metaregression Observations	Intercept (95% CI)	Slope Coefficient (95% CI)
Age < 35 Years	**24**	**-3·46 (-3·81, -3·11)**	**0·065 (0·050, 0·080)**
35 ≤ Age ≤ 60 Years	**38**	**-3·13 (-3·69, -2·57)**	**0·048 (0·037, 0·060)**
Age > 60 Years	**41**	**-3·27 (-3·61, -2·93)**	**0·053 (0·038, 0·067)**
All Ages	**104**	**-3·27 (-3·61, -2·93)**	**0·052 (0·038, 0·067)**

Parameter Stability Test:

H_0 = stability of intercept and slope coefficient across all three age categories

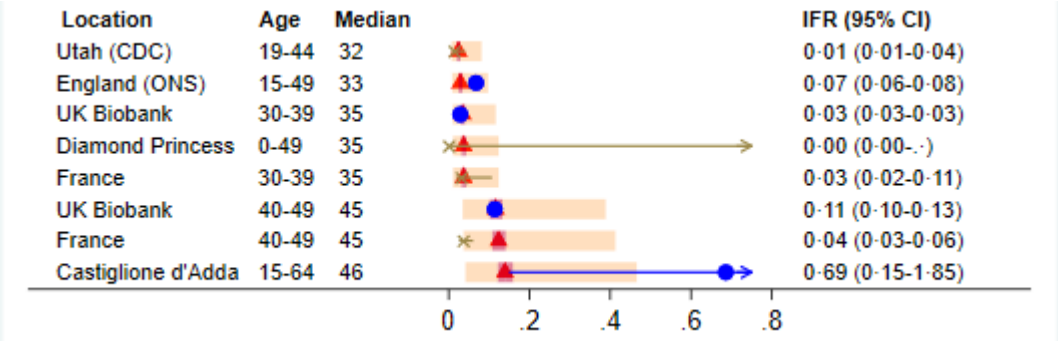
F Statistic (4,102) = 2·13

P-value = 0·083 ***(i.e., H_0 is not rejected at 95% confidence level)***

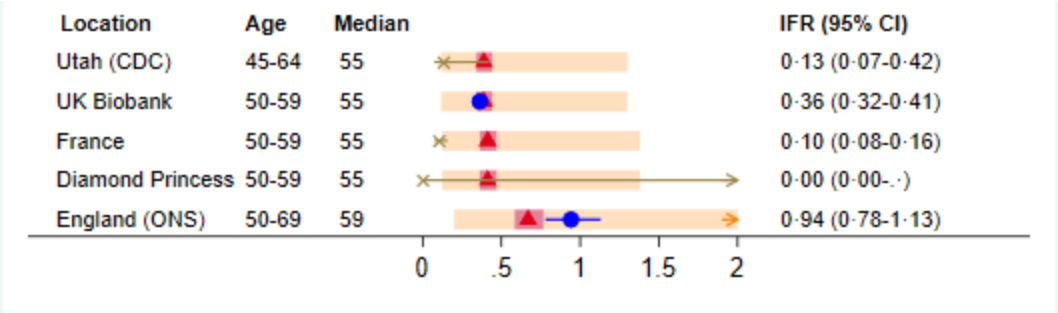
Supplementary Appendix M: Out-of-sample analysis of metaregression results

Study	Description
Castiglione d'Adda, Italy[163]	This study assessed seroprevalence in a random sample of 509 residents of the municipality of Castiglione d'Adda, the location of the first COVID-related fatality in Italy. Specimens were collected on May 18–25. Seroprevalence was estimated at 22·6% (CI: 17·2–29·1%). This study is included in our meta-analysis but not in our metaregression because this municipality is covered by a nationwide seroprevalence study of Italy.[16]
Diamond Princess Cruise Ship[164]	This ship was carrying 3,711 passengers and crew; its demographic composition was not necessarily representative of any specific geographical location. RT-PCR tests indicated that 619 individuals had been infected prior to the ship's debarkation on March 7, and 14 individuals subsequently died due to COVID-related causes. The IFR was 0·5% for ages 60-69, 2·9% for ages 70-79, and 7·9% for ages 80+, broadly consistent with the metaregression results of this study.
France Laboratories[162]	Santé Publique France analyzed 3084 specimens of residual sera from two French laboratories (Cerba and Eurofins Bimnis) obtained during the week of 6–12 April, using the LuLISA-N test developed at the Institut Pasteur. Test-adjusted seroprevalence was 6·73% (CI: 5·36–8·11%). Our metaregression includes a larger study of a representative sample of the French population in three regions (Grand Est, Ile de France, and Nouvelle Aquitaine) that accounted for about two-thirds of COVID-19 cases and fatalities during spring 2020. Consequently, this study is included in our meta-analysis but not in our metaregression to avoid pitfalls of nested or overlapping samples.
U.K. Biobank[165]	This study assessed seroprevalence using specimens collected from a demographically balanced panel of 17,776 participants on May 27 to July 6. Our metaregression includes a much larger seroprevalence study of the English population.[15] Consequently, this study is included in our meta-analysis but not in our metaregression to avoid pitfalls of nested or overlapping samples.
U.K. Office of National Statistics[13]	The U.K. Office for National Statistics (ONS) regularly reports estimates of seroprevalence from specimens provided for routine testing using an IgG ELISA test conducted by research staff at the University of Oxford. On August 18 the ONS reported age-specific results for the cumulative sample of 4840 specimens received from 26 April to 26 July and indicated that these results were broadly consistent with the findings of the UK REACT-2 study (which utilized a much larger sample).
Utah, USA[10]	This study analyzed commercial lab specimens from 1132 individuals collected during April 20–May 3. This study is not included in our meta-analysis because a subsequent study analyzed a much larger randomized sample of 6527 residents of the Salt Lake City metropolitan area during May 4–June 10.[160] As of May, that metro area accounted for nearly 90% of COVID-related fatalities in Utah.

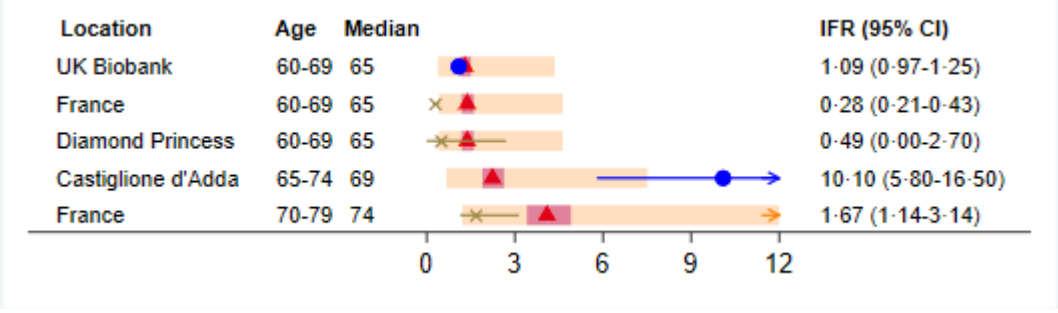
Cohorts with median age of 35-54 years



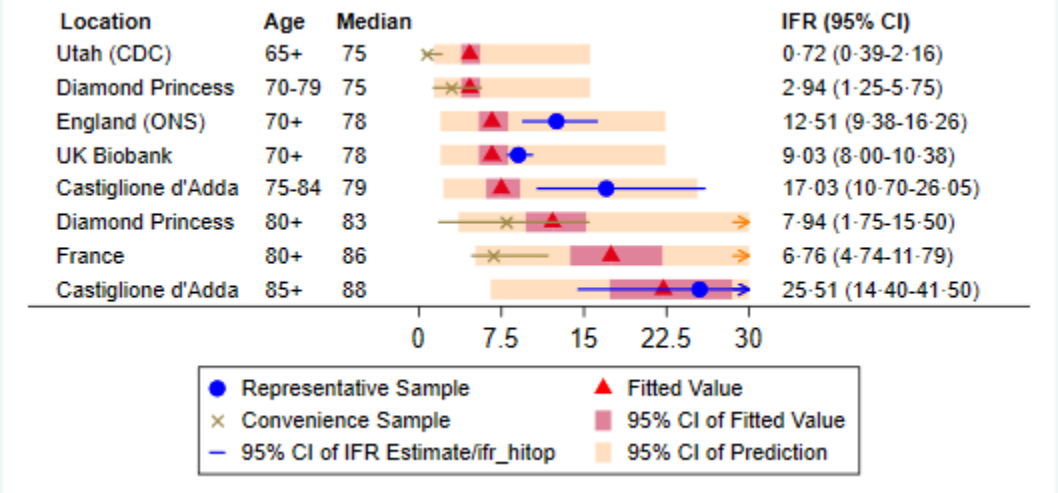
Cohorts with median age of 55-64 years



Cohorts with median age of 65-74 years



Cohorts with median age of 75 years and above



Supplementary Appendix N: U.S. scenario analysis

Scenario	Infection Rate by Age (*percent*) All	0-49	50-64	65+	Deaths *(thousands)*	IFR *(percent)*
Scenario #1: *current pattern of age-specific prevalence*	20	23	16	14	375	0·6
Scenario #2: *uniform prevalence*	20	20	20	20	525	0·8
Scenario #3: *protection of vulnerable age groups*	20	26	10	6	235	0·3

Note: All three alternative scenarios have the same average infection rate of 20% but with distinct patterns of age-specific prevalence. The metaregression IFR estimates are used to project fatalities and population IFR for each scenario.

Supplementary Appendix O: Infection fatality rate for seasonal influenza

The U.S. Center for Disease Control and Prevention provides annual estimates of the U.S. impact of seasonal influenza based on reporting from state and local public health laboratories and other sources. For the winter season of 2018-2019, its preliminary estimate is 35·5 million symptomatic cases and 34 thousand fatalities.[166] A systematic review and meta-analysis of 55 studies found that 25·4% to 61·8% of influenza infections were subclinical, i.e., did not meet the criteria for acute respiratory illness.[167] Using the midpoint of that interval, we estimate that the total U.S. incidence of seasonal influenza during winter 2018-19 was about 63 million and hence that the infection fatality rate was about 0.05%.

Supplementary Appendix P: Excess mortality

In some locations, reported deaths may not fully capture all fatalities resulting from COVID-19 infections, especially when a large fraction of such deaths occurs outside of medical institutions. In the absence of accurate COVID-19 death counts, *excess mortality* can be computed by comparing the number of deaths for a given time period in 2020 to the average number of deaths over the comparable time period in prior calendar years, e.g., 2015 to 2019. This approach has been used to conduct systematic analysis of excess mortality in European countries.[168] For example, the Belgian study used in our metaregression computed age-specific IFRs using seroprevalence findings in conjunction with data on excess mortality in Belgium; the authors noted that Belgian excess mortality over the period from March to May coincided almost exactly with Belgium's tally of reported COVID-19 cases.[33]

Supplementary Appendix Q: Comparison of age-specific IFRs

	Verity et al. (2020)		Metaregression Results	
Age	IFR	95% CI	IFR	95% CI
0-9	0.00161	(0.0002–0.02)	0.001	(0.0007–0.0013)
10-19	0.00695	(0.001–0.05)	0.003	(0.002–0.004)
20-29	0.0309	(0.014–0.092)	0.011	(0.009–0.013)
30-39	0.084	(0.04–0.19)	0.037	(0.031–0.043)
40-49	0.161	(0.08–0.32)	0.123	(0.108–0.141)
50-59	0.595	(0.34–1.28)	0.413	(0.362–0.471)
60-69	1.93	(1.11–3.89)	1.38	(1.19–1.61)
70-79	4.28	(2.45–8.44)	4.62	(3.83–5.57)
80+	7.8	(3.80–13.3)	15.46	(12.2–19.5)

Note: This table compares the estimated age-specific IFRs obtained by Verity et al. (2020)[169] with the metaregression results of this paper.

Supplementary Appendix R: Comparison of age-specific IFRs and CFRs

Age (years)	IFR (%)	CFR (%)	Ratio
0-29	0·003	0·3	100
30-39	0·037	0·5	14·7
40-49	0·12	1·1	9·2
50-59	0·41	3·0	7·5
60-69	1·4	9·5	7·1
70-79	4·6	22·8	5·1
80+	15·5	29·6	2·0

Note: This table compares the estimated age-specific IFRs from our metaregression with the age-specific case fatality rates (CFRs) of Bonanad et al. (2020).[66]

Supplementary Appendix S: Comorbidities and Demographic Factors

While age and fatality risk are closely related, differences in the age structure of the population and age-specific infection rates surely cannot explain all deviations in IFR across regions and populations. Consequently, the role of co-morbidities and other demographic and socioeconomic factors merits further research that carefully distinguishes between infection risk and IFR.

A recent U.K. study has shown that COVID-19 mortality outcomes are strongly linked to comorbidities such as chronic pulmonary disease, diabetes, and obesity.[170] However, that study specifically warns against drawing causal conclusions from those findings, which may reflect a higher incidence of COVID-19 rather than a higher IFR for individuals with those comorbidities. Indeed, as shown in Table S1, a study of hospitalized U.K. COVID-19 patients found that patient age was far more important than any specific comorbidity in determining mortality risk.[67] For example, the COVID-19 fatality risk for an obese 40-year-old hospital patient was found to be moderately higher than for a non-obese individual of the same cohort but only one-tenth the fatality risk for a non-obese 75-year-old hospital patient.

The high prevalence of comorbidities among COVID-19 patients has been well documented but not compared systematically to the prevalence of such comorbidities in the general population. For example, one recent study of hospitalized COVID-19 patients in New York City (NYC) reported that 94% of those patients had at least one chronic health condition.[171] However, as shown in Table S2, that finding is not particularly surprising given the prevalence of comorbidities among middle-aged and elderly NYC residents. For example, nearly 30% of older NYC adults (ages 60+) are diabetic, while 23% have cardiovascular disease (including hypertension), and 8% have chronic pulmonary diseases—practically identical to the incidence of those comorbidities in the sample of hospitalized COVID-19 patients. Indeed, obesity was the *only* comorbidity that was much more prevalent among hospitalized COVID-19 patients than in the general population of older NYC adults. Nonetheless, obesity is also much more prevalent among lower-income groups who are more likely to live in high-density neighborhoods and work in high-exposure jobs, and hence such data clearly cannot be used to distinguish prevalence vs. severity of COVID-19.

Our meta-analysis has not directly considered the extent to which IFRs may vary with other demographic factors, including race and ethnicity. Fortunately, valuable insights can be garnered from other recent studies. In particular, one recent seroprevalence study of residents of two urban locations in Louisiana found no significant difference in IFRs between whites and Blacks.[99]

Nonetheless, the incidence of COVID-19 mortality among people of color is extraordinarily high due to markedly different infection rates that reflect systematic racial and ethnic disparities in housing and employment. For example, a recent infection study of a San Francisco neighborhood found that 80% of positive cases were Latinx – far higher than the proportion of Latinx residents in that neighborhood.[109] That study concluded as follows: *"Risk factors for recent infection were Latinx ethnicity, inability to shelter-in-place and maintain income, frontline service work, unemployment, and household income less than $50,000 per year."*

Other researchers have reached similar conclusions, attributing elevated infection rates among Blacks and Hispanics to dense housing of multi-generational families, increased employment in high-contact service jobs, high incidence of chronic health conditions, and lower quality of health care.[172]

In summary, while our meta-analysis has investigated the effects of age on IFR for COVID-19, further research needs to be done on how infection and fatality rates for this disease are affected by comorbidities as well as demographic and socioeconomic factors.

Table S1: Fatality hazard ratios for hospitalized U.K. COVID-19 patients

Age	Hazard Ratio	Comorbidity	Hazard Ratio
20 to 49	1	Diabetes	1·1
50 to 59	2·7	Malignant Cancer	1·1
60 to 69	5·5	Chronic Cardiac Disease	1·2
70 to 79	9·8	Chronic Pulmonary Disease	1·2
80+	13·5	Chronic Kidney Disease	1·3
		Obesity	1·3
		Liver Disease	1·5

Source: Doherty et al. (2020), Figure 5.

Table S2: Comorbidity prevalence in New York City hospitalized COVID-19 patients vs. general population

Comorbidity	NYC Hospitalized COVID Patients	NYC Population (Ages 50+)	Difference
Cancer	5·6%	6·3%	-0·7%
Cardiovascular Disease			
Hypertension	53·1%	49·2%	3·9%
Coronary artery disease	10·4%	10·5%	-0·1%
Congestive heart failure	6·5%	6·9%	-0·4%
Chronic Respiratory Disease			
Asthma	8·4%	8·6%	-0·2%
Chronic obstructive pulmonary disease	5·0%	7·7%	-2·7%
Obstructive sleep apnea	2·7%	2·8%	-0·1%
Immunosuppression			
HIV	0·8%	2·7%	-2·0%
History of solid organ transplant	1·0%	NA	NA
Kidney Disease			
Chronic	4·7%	13·1%	-8·4%
End-Stage	3·3%	0·6%	2·6%
Liver Disease			
Cirrhosis	0·3%	0·9%	-0·6%
Hepatitis B	0·1%	0·5%	-0·3%
Hepatitis C	0·1%	0·1%	0·0%
Metabolic Disease			
Obesity (BMI>=30)	41·7%	26·9%	14·8%
Diabetes	31·7%	27·6%	4·1%
Ever Smoked	15·6%	43·8%	-28·2%

Note: The following sources were used to gauge the prevalence of comorbidities among NYC residents ages 50 years and above. *Asthma*: U.S. Center for Disease Control & Prevention (2018). *Cancer*: New York State Cancer Registry (2016). *Cardiovascular Diseases*: New York Department of Health (2020). *Diabetes*: New York State Comptroller (2015). *HIV*: New York City Department of Health (2018). *Kidney Disease*: IPRO End-Stage Renal Disease Network of New York (2014). *Liver Disease*: Moon et al. (2019) and Must et al. (1999). *Chronic Pulmonary Disease*: New York Department of Health (2019). *Obesity*: New York City Department of Health (2019).

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