Report 34: COVID-19 Infection Fatality Ratio: Estimates from Seroprevalence

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Summary

The infection fatality ratio (IFR) is a key statistic for estimating the burden of coronavirus disease 2019 (COVID-19) and has been continuously debated throughout the current pandemic. Previous estimates have relied on data early in the epidemic, or have not fully accounted for uncertainty in serological test characteristics and delays from onset of infection to seroconversion, death, and antibody waning. After screening 175 studies, we identified 10 representative antibody surveys to obtain updated estimates of the IFR using a modelling framework that addresses the limitations listed above. We inferred serological test specificity from regional variation within serosurveys, which is critical for correctly estimating the cumulative proportion infected when seroprevalence is still low. We find that age-specific IFRs follow an approximately log-linear pattern, with the risk of death doubling approximately every eight years of age. Using these age-specific estimates, we estimate the overall IFR in a typical low-income country, with a population structure skewed towards younger individuals, to be 0.23% (0.14-0.42 95% prediction interval range). In contrast, in a typical high income country, with a greater concentration of elderly individuals, we estimate the overall IFR to be 1.15% (0.78-1.79 95% prediction interval range). We show that accounting for seroreversion, the waning of antibodies leading to a negative serological result, can slightly reduce the IFR among serosurveys conducted several months after the first wave of the outbreak, such as Italy. In contrast, uncertainty in test false positive rates combined with low seroprevalence in some surveys can reconcile apparently low crude fatality ratios with the IFR in other countries. Unbiased estimates of the IFR continue to be critical to policymakers to inform key response decisions. It will be important to continue to monitor the IFR as new treatments are introduced.

The code for reproducing these results are available as a R Research Compendium on Github: `mrc-ide/reestimate_covidIFR_analysis`.

1. Introduction

One of the most contested statistics during the coronavirus disease 2019 (COVID-19) pandemic has been the infection fatality ratio (IFR): the proportion of those infected who will go on to die from that infection. From a policy perspective it is important to have robust and up-to-date estimates of the IFR throughout the epidemic so that an assessment of the future potential mortality can be made and appropriate public health intervention measures can be enacted to mitigate risk [1,2]. To date, estimates of the overall COVID-19 IFR have ranged from <0.01% - 2.3%, with a review combining estimates across studies reporting an overall estimate of 0.68% (0.53-0.82%) [3–5]. In addition, a recent analysis using pooled data from national serological surveys to estimate age-specific IFRs found that the IFR rose steeply with age, ranging from <0.01% in those aged under 30 to 7.3% in the 80 and older age group [4], broadly consistent with previous estimates [6–8]. It is important to note that neither the overall IFR nor age-specific IFRs are expected to be constant across different populations, as they likely depend on: the age distribution of the population, the distribution of infection across age groups, access to healthcare resources, the prevalence of underlying health conditions in the population, biological sex, and other factors. In particular, the overall population IFR may differ depending on the magnitude of outbreaks in care-home settings, where mortality has often been high [9].

Estimating the IFR requires two key pieces of information: data on deaths and data on the number of infections in the population. Although there are challenges with quantifying and defining COVID-19 deaths, these data are widely reported and one of the more reliable indicators of COVID-19 burden. However, determining the cumulative number of people infected in a population has proved to be far more challenging. Testing capacity is often limited and many infections are asymptomatic [10], which makes laboratory confirmed symptomatic case numbers a poor estimate of infection attack rates. As a result, serological tests (detecting antibodies) have been used to estimate cumulative infections among populations. These tests have several limitations: (1) tests rely on a humoral immune response and will miss infections that do not mount a detectable antibody response or recent infections where antibodies have not yet developed; (2) antibodies naturally wane over time, which can lead to seroreversion (defined in this context as an individual with a confirmed infection and positive serological test later testing negative); (3) tests will produce imperfect results (*i.e.* sensitivity and specificity are less than 100%). Many published studies reporting IFRs did not account for uncertainty in serological test sensitivity and specificity, nor delays from onset to death and onset to seroconversion (although there are exceptions [4,11,12]). Failing to account for these uncertainties can lead to biased estimates of the IFR in directions that are hard to predict.

Here, we develop a flexible statistical framework for estimating the IFR that accounts for uncertainty in serological test sensitivity and specificity, variation in severity and infection rates by age, and delay from onset of infection to seroconversion and/or to death. In addition, we explore the robustness of our IFR estimates in light of waning antibody titres and potential seroreversion. We find that although overall IFR estimates vary substantially, the age-specific IFRs demonstrate similar patterns across all studies. Using these new estimates, we suggest that in high income settings the IFR is slightly greater than previously reported, whilst in low income settings the IFR is likely to be less -- reflecting differences in age demographics.

2. Methods

2.1 Study Identification and Data Extraction

Serological studies were identified using an existing, continuously updated systematic review: the `SeroTracker` dashboard [13]. For IFR estimation we applied additional inclusion and exclusion criteria designed to capture severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) seroprevalence studies representative of the general population (**Supplementary Table 1**). Key inclusion criteria were that the serosurvey was conducted in a defined geographic area for which data on COVID-19 deaths in all age groups were available, and that serological test sensitivity and specificity was reported. Estimates of the sensitivity and specificity of the serological assay were obtained preferentially from validation conducted as part of each serosurvey, rather than external validation (*e.g.* by manufacturers). We excluded studies of health care workers or of patients recruited in clinical settings, since their risk of infection is higher than the general population. In instances where the reported serological age-groups did not directly match with reported cumulative death age-groups, we assumed similar seroprevalence values in contiguous age groups or used the overall average for missing age groups (**Supplementary Materials: Data Extraction and Manipulation**).

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We preferentially obtained data on COVID-19 deaths by age and date of death from Ministries of Health and national public health agencies (**Supplementary Table 2**), and when otherwise not available, used data from the COVID-19 Data Repository by the Center for Systems Science and Engineering at Johns Hopkins University (JHU CSSE COVID-19 Data) up to August 17, 2020 (accessed September 14, 2020) [14,15]. The August 17, 2020 cutoff was selected as one-month after the release of the RECOVERY trial results under the assumption that changes in COVID-19 clinical practice would alter the IFR compared to earlier in the pandemic [16]. Similarly, demographic information was extracted from both governmental and non-governmental websites. Cumulative care home mortality data were used to estimate the IFR with and without care home deaths, where available.

2.2 Crude and Test-Adjusted IFR estimates

The crude IFR was calculated by dividing the number of observed cumulative deaths at the serological study midpoint (numerator) by the cumulative number of infections at the same point (denominator). The number of infections was estimated as the observed seroprevalence multiplied by the population size, plus COVID-19 deaths occurring up to the midpoint of the serosurvey to avoid survival bias. The 95% confidence intervals on the crude IFR were calculated using a Monte Carlo sampling approach, where the uncertainty in the seroprevalence was propagated by drawing 100,000 values of the expected seroprevalence based on the binomial distribution (*i.e.* the number of test-positives given the total tested). For Denmark, Italy, and Sweden where only the seroprevalence and confidence intervals were reported (*i.e.* counts of test-positives and total tested were not available) intervals were logit-transformed and used to calculate variances directly. Test-adjusted IFR estimates were calculated in the same way, but first adjusting the seroprevalence for the sensitivity and specificity of the serological test reported by the study.

2.3 Statistical Modelling

From simulations assuming seroconversion with and without seroreversion, we found that the crude and test-adjusted IFRs could be biased upwards or downwards (**Supplementary Figure 2; Supplementary Materials: Insights from Simulated Data**). However, by accounting for onset-outcome delay distributions and serological test characteristics (*e.g.* sensitivity, specificity, and duration of the serosurvey study period), we were able to obtain unbiased estimates while also appropriately capturing the uncertainty in the IFR estimation (**Figure 1**). As a result, we developed a statistical age-based model that incorporates delays from onset of infection to seroconversion and onset of infection to death, differences in IFR and infection rates by age, and the uncertainty in the serosample collection time and the sensitivity and specificity of serological tests. The mathematical derivation and a further description of the priors and fitting process are available in **Supplementary Materials: Age-Based Statistical Model Derivation**. Briefly, the model assumes that the observed COVID-19 daily deaths are the result of infections at an earlier point in time. This infection curve was fit using an exponentiated natural cubic spline, and projected forwards by an infection-to-death delay distribution and age-specific infection fatality ratio when fitting to death data from each study. The area under the infection curve, equivalent to the cumulative incidence of infections, was then fit to the seroprevalence data at the time of each serosurvey for each study. The model assumes that the temporal profile of the infection incidence curve is the same for all strata (e.g. age-groups) but that its magnitude can vary by

strata (i.e. infection rates can vary by age). The age-based model was fit in a Bayesian context via Metropolis-Coupled Markov Chain Monte Carlo (MC^3) using the *drjacoby* R package [17]. The model code and simulator are available as a stand-alone R-package on Github: `mrc-ide/COVIDCurve`.

Correctly estimating serological test specificity is critical for expressing uncertainty in the IFR, particularly when seroprevalence is low [18]. In large serosurveys where seroprevalence varies across different regions within the survey, serological test specificity can be estimated based on the relationship between seroprevalence and regional COVID-19 mortality. In the simplest case, under the assumption that the IFR is constant in each region, seroprevalence and COVID-19 mortality are expected to have a linear relationship in which the expected seroprevalence at zero deaths (and by implication zero infections) captures the false positive rate of the test. We re-estimated test specificity for serological studies where regional data were available, by fitting a simplified version of the age-based model described above to seroprevalence and cumulative regional deaths at the midpoint of the most recent serosurvey, adjusting for age demographic differences within regions using RStan[19] (**Supplementary Materials: Estimating Specificity: Region-based Statistical Model Description**). These estimates were then used as informative priors for the subsequent IFR analyses of each survey.

Convergence of models was assessed by visualizing the posterior distributions as well as requiring the Gelman-Rubin's convergence diagnostic to be lower than 1.1 [20]. For the age-specific IFR model using MC^3, the metropolis coupling acceptance rate between rungs was also examined.

As a sensitivity analysis, we accounted for seroreversion, here defined as an individual with a confirmed infection and positive serological test later testing negative (due to waning antibodies). We sought to model seroreversion under the most extreme reasonable rate of antibody waning (*i.e.* the lowest sensitivity amongst previously-infected individuals). As a result, we used previously published data on non-hospitalised PCR-confirmed COVID patients tested longitudinally with the Abbott SARS-CoV-2 IgG serological assay to estimate the rate of seroreversion [21] (**Supplementary Materials: Symptom Onset to Seroreversion Parameter Estimation)**. The Abbott assay sensitivity was shown to drop most rapidly over time compared to other serological tests used on the same patients. Although the Abbott assay was only used in the Italian study among our included serosurveys, and seroreversion rates are expected to differ by assay (most of which have not been evaluated for seroreversion to date), using this rapid seroreversion rate provides a higher estimate of the potential number of cumulative infections, and therefore our estimates of the IFR with seroreversion are conservative and offer a contrast to our alternative model of no seroreversion.

Finally, we calculated pooled-IFR estimates using a weighted log-linear regression on the age-specific IFR posterior estimates. Weights were incorporated as the precision from the age-specific 95% credible intervals. Prediction intervals were calculated from the log-normal density function using the mean from the model fit and model variance. Overall pooled-IFR estimates were calculated by standardizing to the demographics of representative countries within the low-income country (LIC), low-middle income country (LMIC), upper-middle income country (UMIC), and high-income country (HIC) bracket, respectively [2] (**Supplementary Materials: Pooled IFR Calculation)**.

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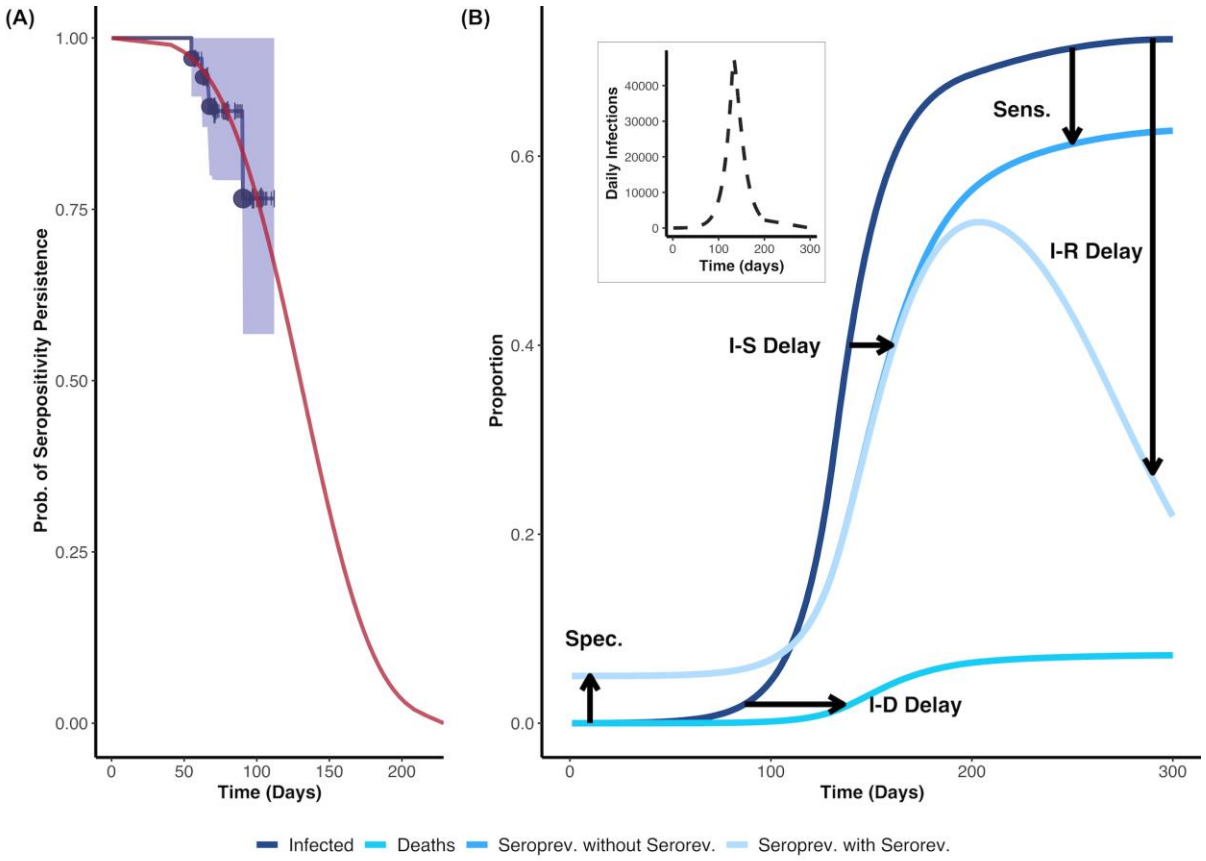

Figure 1 - Factors accounted for in estimating IFR: (**A**) Persistence of seropositive test results among a cohort of 88 COVID-19 patients who did not require hospitalisation and whose serological status was detected with the Abbott assay (re-analyzed from Muecksch *et al.* 2020). The Kaplan-Meier survival curve with 95% confidence intervals (blue) with censored observations (ticks) and seroreversion events (circles) is shown for comparison. Both censoring and seroreversion points are scaled according to the number of events observed on the given day (range 1-6). The fitted Weibull survival function (red) of persistence of a serological positive result is shown in red. The fit was estimated from symptom onset to time of seroreversion, where the time of seroreversion was estimated incorporating interval censoring. The mean time from symptom onset to seroreversion was 129.63 days. (**B**) Schematic showing cumulative infections, deaths and seroprevalence with and without seroreversion over time. We highlight the effects of delays from infection to seroconversion (I-S Delay), to death (I-D Delay), and to seroreversion (I-R Delay) as well as serological test sensitivity (Sens.), serological test specificity (Spec.) on the observed data. The daily infection curve used as input for the simulation is shown as the plot inset. Early in the outbreak, false positives dominate due to low prevalence and imperfect specificity, whilst later the difference between true cumulative incidence and observed seroprevalence is mainly due to low sensitivity and/or seroreversion. The delays show how the cumulative infection curve is lagged behind the observed seroprevalence. Similarly, the contrast of the seroprevalence curve with and without seroreversion reveals the loss of sensitivity over time.

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3. Results

Of the 175 studies screened for inclusion (**Additional File**), we identified 10 serological studies (6 national surveys, 4 subnational surveys) for data extraction and subsequent modeling (**Supplementary Table 2**). The most common reasons for exclusion were lack of information on the serological test performance or participants being recruited in clinical settings (**Additional File**). The overall observed seroprevalence among the studies ranged from approximately 1.6% in Zurich, Switzerland to 12% in New York State, USA, while the overall crude IFR ranged from 0.33% in Denmark to 2.3% in Italy (**Table 2**). Where available, age-disaggregated seroprevalences did not follow a consistent pattern across settings: infection rates were relatively constant in some studies (*e.g.* Brazil) while increasing or decreasing with age in others (*e.g.* Spain and England, respectively; **Supplementary Figure 1**). Seroprevalence was strongly correlated with cumulative mortality when data were stratified by regions within a serological study (**Figure 2A**). However, the slope of the seroprevalence-mortality relationship varied considerably between studies, suggesting differences in one or more of: the serological test performance, deaths reporting, true IFR, or sampling bias. Across the studies considered, higher overall seroprevalence was not associated with a higher IFR (**Table 1**). We similarly observed no relationship between seroprevalence and IFR when national-level surveys were disaggregated by region (**Figure 2B**).

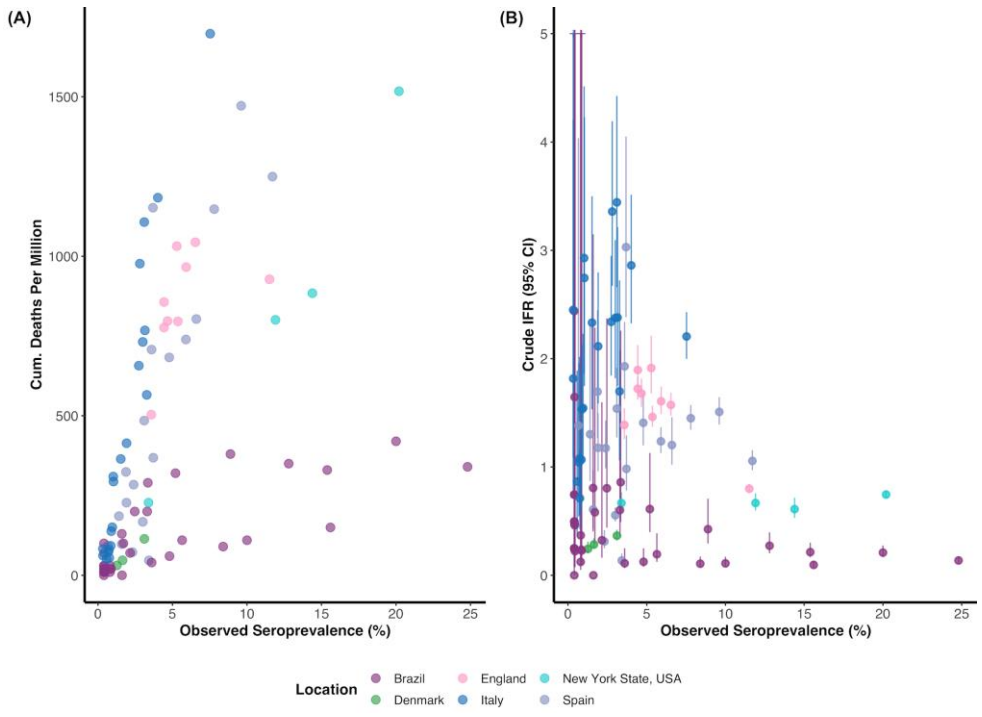

Figure 2- Mortality and the Crude Infection Fatality Ratio versus Observed Seroprevalence: (**A**) Relationship between seroprevalence and COVID-19 mortality per 1,000,000 among surveys which could be broken down by region (6/10 studies). (**B**) The crude infection fatality ratio (IFR) (%) versus the observed seroprevalence among the studies with regional surveys. Overall there was no evidence of higher IFRs in regions with higher seroprevalence (*i.e.* regions that were hit hardest by the pandemic).

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For each study with regional data (Brazil, England, Denmark, Italy, Spain, and New York State), we re-estimated the specificity of the serological assay based on the relationship between seroprevalence and mortality (**Supplementary Figure 10**). We found that the estimated specificity often differed from the reported values (**Supplementary Table 8**). For example, the study in Spain reported 100% specificity (95% CI: 97.7 - 100%) but our estimated value was 98.79% (95% CI: 98.55 - 99.02; **Table 1; Supplementary Figure 10**). At the low overall seroprevalence observed in many studies, similar small changes in specificity can have important implications for IFR estimates; therefore, we used our updated specificity and sensitivity estimates as informative priors in the analysis of the age-specific IFR in each survey.

Using our inference framework that accounts for delays and uncertainty in serological test characteristics, we found that 2/10 studies (Denmark; Sweden) had highly uncertain IFRs. These results were due to low sensitivity or specificity of the serological tests, leading to a large number of false positives or false negatives relative to the observed seroprevalence (**Table 1**). Among the remaining studies where the IFR could be determined with more certainty, the overall IFR ranged from 0.49 - 2.53% (**Table 2**). In a subset of surveys (Switzerland, Netherlands, Spain, and New York), the crude IFRs closely matched the modelled IFRs, consistent with serological studies being conducted after peak infections and deaths (**Supplementary Figures 6-9**). For other surveys, such as that for Italy which was conducted several months after the peak of the epidemic, including seroreversion had some effect on the estimated IFR (declining from 2.53% to 2.23%). Seroreversion had relatively little effect on IFR estimates for other studies, despite the assumption of rapid seroreversion in this sensitivity analysis, which was likely to be faster than the true value in most studies.

We analyzed how deaths in care homes may be affecting IFR estimates. We found that excluding care home deaths substantially reduced the overall modelled IFR (**Table 1**).

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Table 1 - Overall Infection Fatality Ratio Estimates among the Included Studies: The first five columns contain data and parameters used to calculate the crude IFR, the last five columns contain the posterior estimates from the full model. The reported seroprevalence are listed along with the most recent dates for the seroprevalence survey. Cumulative deaths are summed to the mid-date of the most recent seroprevalence survey, and were usually confirmed COVID-19 test-positive patients except in England, which also reported probable COVID-19 deaths (individuals without test results but with COVID-19 on the death certificate). Citations for serological test validation and seroprevalence studies are included in Supplementary Table 1 (T+: test positive, D+: true positives, T-: test negative, D- true negatives). For the six studies with regional data, estimates of specificity and sensitivity were from analysis of regional data: posterior distributions with the median and 95% credible intervals are provided in place of the serological test validation numbers (*). Sensitivity and specificity are indicated for the model with seroreversion, although these parameter estimate posteriors were similar for both models (Supplementary Table 7). Among the ten studies considered, six had data available on care home deaths. IFRs that excluded care home deaths were modelled without seroreversion. Overall IFR estimates were calculated by standardizing the age-specific IFR estimates according to the inferred age-specific attack rate and the population demography with respect to the age-groups used in the model (median, (95% Credible Intervals)). For comparison, the overall IFR estimates calculated by standardizing for solely the demography and assuming the same attack rate in each age-group are provided in Supplementary Table 4.

	Data					***Model Estimates***				
Study Location	**Cumulative COVID-19 Deaths**	**Reported Seroprevalence (dates)**	**Serostudy Sensitivity (%)** (T+/D+ or' 95% CrI)	**Serostudy Specificity (%)** (T-/D- or 95% CrI)	**Crude IFR** (95 CI%)	**Sensitivity (%)** (95% CrI)	**Specificity(%)** (95% CrI)	**IFR without Seroreversion** (95% CrI)	**IFR with Seroreversion$^{\beta}$** (95% CrI)	**IFR: Care Home Deaths Excluded, no seroreversion** (95% CrI)
Brazil*	51,179	2.42% (Jun. 04 - Jun. 07)	85.14 (81.93, 87.97)	99.72 (99.55, 99.85)	0.99 (0.92, 1.06)	85.32 (82.12, 88.15)	99.76 (99.6, 99.86)	1.03 (0.93, 1.17)	0.99 (0.89, 1.13)	
Denmark*	452	2.4% (Apr. 27 - May 03)	82.09 (75.51, 87.58)	99.25 (98.94, 99.56)	0.33 (0.23, 0.48)	82.46 (76.14, 87.77)	99.16 (98.72, 99.46)	0.53 (0.37, 1.01)	0.52 (0.37, 0.99)	0.33 (0.23, 0.61)
England*	47,954	5.94% (Jun. 20 - Jul. 03)	78.4 (65.68, 88.15)	99.44 (99.11, 99.71)	1.41 (1.38, 1.45)	79.89 (67.73, 89.43)	99.59 (99.34, 99.78)	1.18 (0.99, 1.34)	1.04 (0.84, 1.19)	0.73 (0.62, 0.83)
Italy*,$^{\alpha}$	34,610	2.44% (May 25 - Jul. 15)	96.04 (89.84, 99.05)	99.7 (99.59, 99.79)	2.3 (1.94, 2.72)	96.52 (91.04, 99.13)	99.69 (99.57, 99.78)	2.53 (2.31, 2.77)	2.23 (2.03, 2.45)	
Netherlands	5,643	5.5% (May 10 - May 20)	98.28 (171/174)	99.65 (281/282)	0.6 (0.58, 0.63)	98.22 (95.6, 99.5)	99.83 (99.45, 99.98)	0.62 (0.58, 0.68)	0.59 (0.55, 0.66)	
Spain*	29,054	5.27% (Jun. 08 - Jun. 22)	81.84 (75.67, 87.01)	98.79 (98.55, 99.02)	1.12 (1.08, 1.16)	84.73 (83.09, 88.44)	99.04 (98.85, 99.21)	1.14 (1.08, 1.22)	1.07 (1.01, 1.14)	0.75 (0.71, 0.8)
Sweden	5,030	7.1% (Jun. 08 - Jun. 12)	99.36 (156/157)	98.89 (267/270)	0.68 (0.46, 1)	99.3 (97.22, 99.94)	99.16 (98.13, 99.76)	1.03 (0.88, 1.37)	0.99 (0.84, 1.35)	0.55 (0.46, 1.01)
Geneva, Switzerland	262	10.84% (May 03 - May 10)	91.16 (165/181)	100 (176/176)	0.48 (0.42, 0.56)	91.44 (86.93, 94.87)	99.89 (98.73, 100)	0.49 (0.42, 0.59)	0.48 (0.4, 0.58)	0.22 (0.18, 0.27)
Zurich, Switzerland	124	1.59% (May 01 - May 31)	90.74 (49/54)	99.89	0.51 (0.45, 0.58)	91.76 (83.18, 96.89)	99.87 (99.74, 99.95)	0.52 (0.41, 0.67)	0.5 (0.39, 0.64)	
New York State, USA*	17,718	12.1% (Apr. 19 - Apr. 28)	89.39 (85.57, 92.55)	98.73 (98.15, 99.27)	0.75 (0.74, 0.76)	89.69 (85.89, 92.72)	98.69 (98, 99.2)	0.77 (0.72, 0.83)	0.75 (0.7, 0.8)	0.61 (0.57, 0.66)

$^{\alpha}$ Serovalidation data for the Italian serosurvey using the Abbott assay were not validated within the same study; here we used an alternative study testing the same assay.
$^{\beta}$ Assuming an extreme rate of seroreversion for sensitivity analysis based on the Abbott assay. The true seroreversion rates in these studies are unknown, but are likely less extreme, particularly if the Abbott assay was not used (only the Italy study used the Abbott assay).

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Age-stratified IFRs increased steeply with age, following an approximately log-linear relationship (**Figure 3**). Among the ten studies included, the oldest age group in Sweden had the highest IFR estimate whilst the lowest was in Geneva, Switzerland (**Supplementary Table 6**). Using these age-specific IFR estimates across studies, we calculated a pooled IFR estimate for five-year age bands that represented our best estimate of the true IFR when site-specific information was not available (**Table 2**). It is important to note that the uncertainty intervals around these estimates are predictive intervals rather than confidence intervals, meaning they show the plausible range of IFRs that can be expected in a new study population, rather than showing our degree of certainty in the average IFR over all studies. Finally, we standardized these age-specific IFR estimates across four age-demographics representative of median countries in the LIC, LMIC, UMIC, and HIC wealth brackets to demonstrate the wide range of the IFR depending on the age-structure in the population (**Table 2; Supplementary Materials: Pooled IFR Calculation**). Pooled log linear models fit with demographic weights by age groups resulted in similar age-specific pooled IFR estimates (not shown).

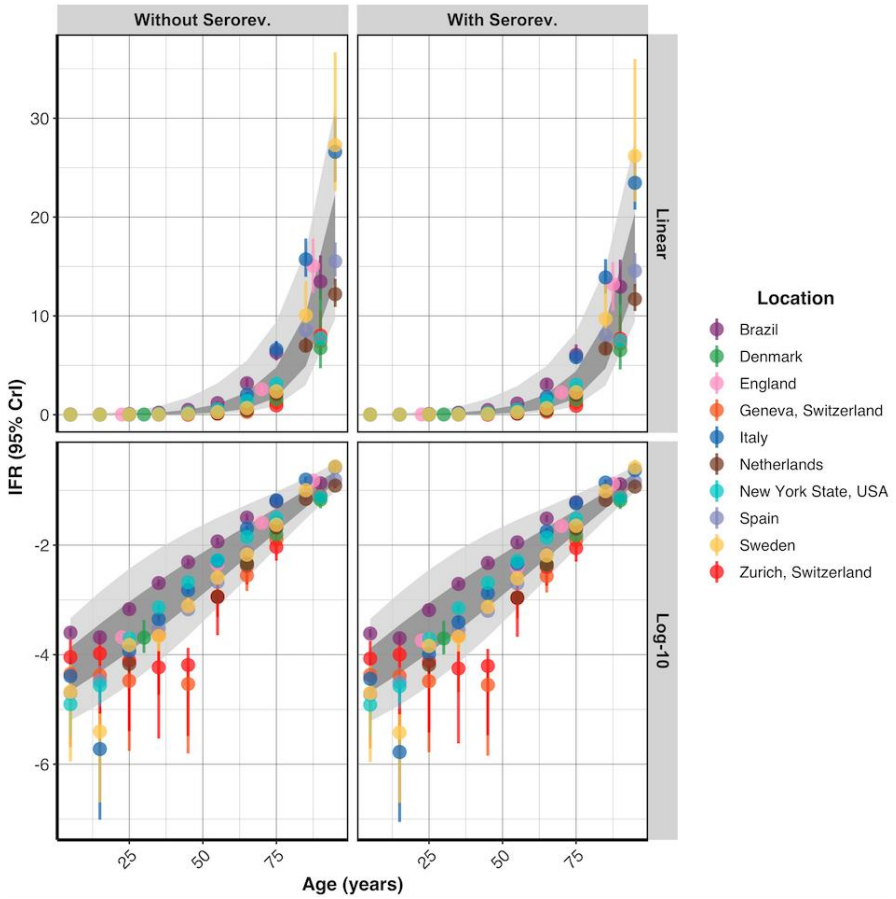

Figure 3 - Age-Stratified Infection Fatality Ratio Estimate: The age-specific modelled IFR (%) estimates with and without seroreversion plotted on a linear and log-10 scale (mean age within each age-group plotted). The 95% prediction intervals (light grey) and the 80% prediction intervals (dark grey) calculated from the age-specific pooled IFR estimates are shown for each model. The IFR appears to increase in a log-linear fashion with age. The model with the potential for seroreversion was considered as a sensitivity analysis.

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Table 2 - Pooled-Estimates of the Infection Fatality Ratio: IFR estimates were calculated by combining study- and age-specific IFR estimates in a log-linear model. The median predicted estimate and corresponding 95% prediction intervals (PIs) are shown above. Predictive intervals were used to express the plausible range of IFRs that can be expected in a new study population, rather than showing our degree of certainty of our estimates with confidence intervals. For the 90+ age-group, we assumed a maximum age of 100 years. The overall IFR estimates were standardized by the population structure in a representative low-income country (LIC), low-middle income country (LMIC), upper-middle income country (UMIC), and high-income country (HIC), assuming equal attack rates across age-groups.

Age-Band (years)	IFR (%) without Seroreversion (95% PI)	IFR (%) with Seroreversion (95% PI)
0-4	0.00 (0.00, 0.03)	0.00 (0.00, 0.03)
5-9	0.01 (0.00, 0.06)	0.01 (0.00, 0.06)
10-14	0.01 (0.00, 0.11)	0.01 (0.00, 0.10)
15-19	0.02 (0.00, 0.18)	0.02 (0.00, 0.17)
20-24	0.03 (0.00, 0.3)	0.02 (0.00, 0.28)
25-29	0.04 (0.00, 0.46)	0.04 (0.00, 0.44)
30-34	0.06 (0.01, 0.71)	0.06 (0.01, 0.67)
35-39	0.10 (0.01, 1.03)	0.09 (0.01, 0.98)
40-44	0.16 (0.02, 1.47)	0.15 (0.02, 1.37)
45-49	0.24 (0.03, 2.03)	0.23 (0.03, 1.88)
50-54	0.38 (0.05, 2.74)	0.36 (0.05, 2.52)
55-59	0.60 (0.10, 3.64)	0.57 (0.10, 3.32)
60-64	0.94 (0.18, 4.79)	0.89 (0.18, 4.34)
65-69	1.47 (0.35, 6.27)	1.39 (0.34, 5.64)
70-74	2.31 (0.65, 8.21)	2.17 (0.64, 7.35)
75-79	3.61 (1.21, 10.81)	3.39 (1.19, 9.65)
80-84	5.66 (2.23, 14.37)	5.3 (2.19, 12.81)
85-89	8.86 (4.06, 19.36)	8.28 (3.98, 17.25)
90+	17.37 (9.7, 31.12)	16.19 (9.44, 27.78)
Overall (LIC)	0.23 (0.14, 0.42)	0.22 (0.14, 0.39)
Overall (LMIC)	0.4 (0.26, 0.67)	0.37 (0.25, 0.61)
Overall (UMIC)	0.61 (0.40, 0.99)	0.57 (0.38, 0.92)
Overall (HIC)	1.15 (0.78, 1.79)	1.06 (0.73, 1.64)

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4. Discussion

Estimating the IFR of a novel infectious disease is inherently challenging due to the dynamic and imperfect nature of the available data. Here we have developed a statistical framework to account for key uncertainties in the data to provide robust estimates of the IFR of COVID-19. While our results highlight substantial variation in the overall estimated IFR between settings and surveys, we found a comparatively consistent pattern across ages, with age-stratified IFRs demonstrating an approximately log-linear relationship with increasing age. These results are consistent both with early reports [6–8] and more recent meta-analyses [4,12], although our pooled estimate of the IFR in high income countries is slightly higher.

Regions with higher attack rates within serosurveys -- hit hardest by the pandemic -- did not have substantially higher IFRs. For example, we found no evidence that the Lombardy province in Italy had a higher IFR than the rest of the country despite its much higher seroprevalence and likely healthcare saturation. Similarly, London and New York City did not have a higher IFR than other areas in the rest of England, and New York state, respectively.

Without representative serological data in care homes, we could not distinguish between a high attack rate or a high IFR in the care home population, but excluding care home deaths (when available) substantially reduced the IFR. Estimating the attack rate in care homes from serological data may be challenging, as older individuals may have compromised humoral immune responses, which suggests that seroprevalence might underestimate the attack rate [22]. Data based on COVID-19 case-reporting suggests that attack rates in care homes are higher than the general population [23]. In addition, given the variety of definitions of a care home and differences in geriatric clinical management across countries, estimates of COVID-19 deaths in the elderly may be underreported [9]. Further data and work is needed to properly characterize transmission and fatality dynamics within the vulnerable care home population, which has borne a huge burden of the COVID-19 pandemic and may explain much of the heterogeneity in overall population IFRs [4].

We found that a model-based approach was needed in order to account for biases in estimating the IFR even after adjusting for test sensitivity and specificity. For example, we found that the IFR was typically biased downwards for serosurveys conducted early in the epidemic, when infections are growing, whilst the IFR was typically biased upwards when serosurveys were conducted after the initial epidemic wave passed and seroreversion became more likely (*i.e.* decay in antibody titres leading initially seropositive individuals to become seronegative).

Identifying the true specificity of a seroassay in the general population is critical early in an outbreak when seroprevalence may consist of more false than true positives. Given that some regions will have few deaths and few infections, regional-disaggregated data offer insight into the real-world specificity of tests when used in large studies of the general population. For the studies that had region-disaggregated seroprevalence data, we found that our estimates of test specificity were sometimes lower than estimates derived from assay validation studies.

Serological test sensitivity may also be lower in the general population than in assay validation studies. Assays are often validated in hospitalised patients with more recent severe disease, whilst the majority of infections in the population are milder and may produce a lower [24] or sometimes no antibody response [25]. As a result, if the true sensitivity in the general population is lower than the reported

sensitivity -- possibly in part due to a cell-mediated immune response -- the IFR may be overestimated. However, serologic test sensitivity has been found to be relatively high in non-severe cases [21,26], and our seroreversion sensitivity analysis indicated that even a rapid rate of antibody waning had a limited effect on our IFR estimates. Furthermore the high seroprevalence of approximately 50-80% observed in some settings suggests that a large proportion of infected individuals mount an antibody response upon infection [27,28].

For a subset of studies, our estimates of age-specific and overall IFRs were uncertain due to studies reporting both a low seroprevalence and low specificity. This level of uncertainty is appropriate, as sensitivity and specificity can skew estimates of the cumulative infection incidence derived from seroprevalence surveys, particularly when infection is not widespread and positive results may be dominated by false-positives. For example, Denmark appears to have a lower IFR than other countries from crude estimates (0.33%) but was consistent with other countries after we re-estimated test specificity from regional data and incorporated uncertainty: 0.52% (0.37, 1.01).

Later in the epidemic, seroreversion may lead to an increasing loss of sensitivity to detect previously infected individuals using serological surveys [29,30]. Using published data on serial antibody titres from previously diagnosed non-hospitalised COVID-19 patients [21], we estimated that over four months, an average of 52.15% individuals would serorevert after seroconverting when tested with the Abbott assay. We used the Abbott assay for our sensitivity analysis to examine a maximum effect of seroreversion, as it was the assay with the fastest rate of decay in a recent comparison of serological tests [21]. In addition, our model assumes that everyone will eventually serorevert. Our assumptions represent a deliberately extreme view on antibody waning that leads to conservative IFR estimates in this sensitivity analysis (only the Italian study used the Abbott assay; seroreversion rates will differ by assay). When accounting for potential seroreversion, we found that IFR decreased most significantly in Italy with an approximately 12% relative reduction in the IFR: Italy experienced an early first wave of the epidemic and the serological survey was conducted some months after the first peak. However, among the other studies, the IFR was only marginally affected when considering seroreversion, indicating that not enough time had passed for a substantial proportion of infected people to serorevert. Although the time to seroconversion does not appear to be affected by disease severity [31], future and ongoing studies are needed to characterise the impact of seroreversion on the sensitivity of the numerous assays in widespread use and clarify the extent of the risk of reinfection with COVID-19 [32].

A major limitation of our study was rooted in the serological data available: 4/10 (Denmark; Netherlands; Sweden; Zurich, Switzerland) of the studies that we considered only had seroprevalence data from blood donors, which may not be representative of the general population. In addition, the seroprevalence study in New York State recruited participants at grocery stores, which may represent a biased study population (**Supplementary Table 1**). A recent study estimated a higher IFR in New York City based on case data and assuming the seroprevalence in shoppers was higher than the general population [33]. We used seroprevalences in contiguous age-groups to estimate seroprevalence in age-groups missing from studies, or assumed uniform seroprevalences across ages when no age stratification was provided. A second limitation was the use of reported deaths. Quantifying deaths from COVID-19 has been challenging for many countries, due to death counts being revised over time or countries differing in approaches to counting COVID-19 deaths. In some instances, particularly in LICs and LMICs, cases of death underreporting have been identified [34,35] whilst in other instances, large

increases in excess deaths have been noted [36–38]. Most countries included in our study reported deaths amongst test-positive cases only, but England also reported probable COVID-19 deaths [39]. In England, most probable deaths without laboratory confirmation occurred in care homes, so the difference between using probable and confirmed deaths is likely to be greater for IFR estimates including care home deaths. Separately, a recent analysis found a positive relationship between COVID-19 mortality rates and excess deaths mortality rates in high income countries, suggesting that missed COVID-19 deaths did not explain differences in the mortality rates between these countries [4]. In our modelled IFR estimates we did not explicitly account for death as a competing hazard with seroconversion, as the observed seroprevalence (*i.e.* model data input) is inherently calculated among surviving individuals. This might mean our estimates of the IFR in the oldest age groups are overestimates.

In summary, we estimate that the overall COVID-19 IFR ranges from 0.14 - 0.42% in low income countries to 0.78 - 1.79% in high income countries, with the differences in those ranges reflecting the older demography of high income settings. The IFR is also likely to vary depending on available healthcare and underlying health conditions. Our results suggest that the overall risk of death from COVID-19 doubles with approximately every eight years of age. Our estimates of the IFR of COVID-19 are consistent with early estimates and remain substantially higher than IFR estimates for seasonal influenza (<0.1% in the USA) [40]. To the best of our knowledge, this is the first study accounting for seroreversion as part of IFR estimation as well as simultaneously accounting for uncertainty in serological test characteristics and delays from infection to death and seroconversion. As the pandemic progresses, it will be important to continue to update these estimates to capture changes driven by improvements in care and potential genetic mutations in the virus.

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6. Data and code

The R-package, `COVIDCurve`, is publicly available on Github (mrc-ide/COVIDCurve). In addition, all the code needed to re-generate these analyses are publicly available on Github (mrc-ide/reestimate_covidIFR_analysis). Similarly, all of the data with the exception of raw data for the onset to seroreversion analysis is publicly available on Github (mrc-ide/reestimate_covidIFR_analysis). The onset to seroreversion data is available upon request (Sara Jenks).

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