

Serology-informed estimates of SARS-CoV-2 infection fatality risk in Geneva, Switzerland

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The infection fatality risk (IFR) is the average number of deaths per infection by a pathogen and is key to characterizing the severity of infection across the population and for specific demographic groups. To date, there are few empirical estimates of IFR published due to challenges in measuring infection rates.^{1,2} Outside of closed, closely surveilled populations where infection rates can be monitored through viral surveillance, we must rely on indirect measures of infection, like specific antibodies. Representative seroprevalence studies provide an important avenue for estimating the number of infections in a community, and when combined with death counts can lead to robust estimates of the IFR.

We estimated overall and age-specific IFR for the canton of Geneva, Switzerland using age-stratified daily case and death incidence reports combined with five weekly population-based seroprevalence estimates.³ From February 24th to June 2nd there were 5'039 confirmed cases and 286 reported deaths within Geneva (population of 506'765). We inferred age-stratified (5-9, 10-19, 20-49, 50-65 and 65+) IFRs by linking the observed number of deaths to the estimated number of infected individuals from each serosurvey. We account for the delays between infection and seroconversion as well as between infection and death.⁴ Inference is drawn in a Bayesian framework that incorporates uncertainty in seroprevalence estimates (supplement).

Of the 286 reported deaths caused by SARS-CoV-2, the youngest person to die was 31 years old. Infected individuals younger than 50 years experienced statistically similar IFRs (range 0.00032-0.0016%), which increases to 0.14% (95% CrI 0.096-0.19) for those 50-64 years old to 5.6% (95% CrI 4.3-7.4) for those 65 years and older (supplement). After accounting for demography and age-specific seroprevalence, we estimate a population-wide IFR of 0.64% (95% CrI 0.38-0.98).

Our results are subject to two notable limitations. Among the 65+ age group that died of COVID-19 within Geneva, 50% were reported among residents of assisted care facilities, where around 0.8% of the Geneva population resides. While the serosurvey protocol did not explicitly exclude these individuals, they are likely to have been under-represented. This would lead to an overestimation of the IFR in the 65+ age group if seroprevalence in this institutionalized population was higher than in the general population (supplement). Further, our IFR estimates are based on current evidence regarding post-infection antibody kinetics, which may differ between severe and mild infections. If mild infections have significantly lower and short-lived antibody responses, our estimates of IFR may be biased upwards.⁵

Estimates of IFR are key for understanding the true pandemic burden and for weighing different risk reduction strategies. The IFR is not solely determined by host and pathogen biology, but also by the capacity of health systems to treat severe cases. Despite having among the highest per capita incidence in Switzerland, Geneva's health system accommodated the influx of cases needing intensive care (peak of 80/110 ICU-beds including surge capacity) while maintaining care quality standards. As such, our IFR estimates can be seen as a best-case scenario with respect to health system capacity. Our results reveal that population-wide estimates of IFR mask great heterogeneity by age and point towards the importance of age-targeted interventions to reduce exposures among those at highest risk of death.

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Supplementary Material

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1 Deriving the infection fatality risk

We derive the infection fatality risk (IFR) from available epidemiological data. Let $D(t)$ be the observed cumulative number of deaths up to time t , $I(t)$ the cumulative number of infections, $C(t)$ that of reported cases and $I^{sero}(t)$ the number of seroconverted people in the population at time t . We note that $I^{sero}(t)$ is estimated from serosurvey data and incorporates uncertainty on test specificity and sensitivity as well [12]. We have that the cumulative number of deaths is:

$$D(t) = IFR \int_0^t I(t - \tau) f_D(\tau) d\tau,$$

where $f_D(t)$ is the probability density function (PDF) of the time from infection to death. Similarly we have:

$$I^{sero}(t) = \int_0^t I(t - \tau) f_{sero}(\tau) d\tau,$$

where $I^{sero}(t) = \theta_t \cdot P$ is the seroconverted population given by the seroprevalence at time t , θ_t , and the population P , and $f_{sero}(t)$ is the PDF of the time from infection to seroconversion. Taking the ratio between these two equations we have that:

$$IFR = \frac{D(t)}{I^{sero}(t)} \frac{\int_0^\infty I(t-\tau) f_{sero}(\tau) d\tau}{\int_0^\infty I(t-\tau) f_D(\tau) d\tau}. \quad (1)$$

$I(t)$ is unobservable, however we can reconstruct it using $C(t)$:

$$C(t) = \alpha \int_0^\infty I(t-\tau) f_C(\tau) d\tau,$$

where α is the probability of infection reporting (proportion of infections that lead to symptomatic and detected COVID-19 cases), and f_C is the PDF of time from infection to reporting, which accounts both for the incubation period and the delay between symptom onset to reporting. An estimate of $I(t)$ up to a constant of proportionality can be obtained by inverting the convolution:

$$\begin{aligned} \mathcal{F}\{C\} &= \mathcal{F}\{\alpha I\} \mathcal{F}\{f_I\} \\ \mathcal{F}\{\alpha I\} &= \mathcal{F}\{C\} / \mathcal{F}\{f_I\} \\ I &= \frac{1}{\alpha} \mathcal{F}^{-1} \{ \mathcal{F}\{C\} / \mathcal{F}\{f_I\} \} \\ I &= \frac{1}{\alpha} I^*, \end{aligned}$$

were \mathcal{F} and \mathcal{F}^{-1} are respectively the Fourier transform and its inverse. In the presence of noise the deconvolution can be numerically unstable due to noise amplification caused by large values of $1/\mathcal{F}\{f_I\}$ at high frequencies. We therefore regularize $\mathcal{F}\{f_I\}$ by applying a threshold under which the values are set to the threshold while preserving their phase, also called water level regularization [1, Chapter 8.3]. Here we use the threshold value of 0.05.

The infection fatality ratio can therefore be expressed as:

$$IFR = \frac{D(t)}{I^{sero}(t)} \frac{\int_0^\infty I^*(t-\tau) f_{sero}(\tau) d\tau}{\int_0^\infty I^*(t-\tau) f_D(\tau) d\tau}, \quad (2)$$

where α cancel out. In practice we do not have continuous values of epidemiological variables, but counts by discrete time periods. In this study data were available at a daily time step (Fig. 1). We therefore replace integrals in eq. 2 with sums over discrete time delays as:

$$IFR = \frac{D(i)}{I^{sero}(i)} \frac{\sum_{j=0}^T I^*(i-j) p_{sero}(j)}{\sum_{j=0}^T I^*(i-j) p_D(j)}, \quad (3)$$

where i is the day on which deaths and seroprevalence are measured, T is the total number of days since the start of the epidemic, and $p_{sero}(j)$ and $p_D(j)$ are respectively the probabilities of seroconversion and death during day j after infection computed using the distribution functions of seroconversion and death F_{sero} and F_D : $p_{sero}(j) = F_{sero}(j+1) - F_{sero}(j)$ and $p_D(j) = F_D(j+1) - F_D(j)$. The values of I^* are also computed using discrete time steps.

To infer the IFR we considered a binomial likelihood for the number of deaths $D(i)$ occurring among the fraction of the infected population at risk of dying on day i , $I^{sero}(i)\phi(i)$, where $\phi(i) = \frac{\sum_{j=0}^T I^*(i-j) p_D(j)}{\sum_{j=0}^T I^*(i-j) p_{sero}(j)}$ as:

$$\mathcal{L}(IFR|\theta_{1...T}) = \prod_{i=1}^T \binom{I^{sero}(i)\phi(i)}{D(i)} IFR^{D(i)} (1 - IFR)^{I^{sero}(i)\phi(i) - D(i)}, \quad (4)$$

were \mathcal{L} is the likelihood of IFR given the data and the seroprevalences at each sampling time i , $\theta_{1...T}$, recalling that $I^{sero}(t) = \theta_t \cdot P$ with P the population. To incorporate uncertainty in the seroprevalence estimates one can integrate over the seroprevalence posterior at time t , $f_t(\theta)$:

$$\mathcal{L}(IFR) = \prod_{t=1}^T \int \mathcal{L}(IFR|\theta_t) f_t(\theta) d\theta$$

We approximate the integral by Monte Carlo integration using M posterior draws θ_t^m from our seroprevalence analysis [12]:

$$\mathcal{L}(IFR) \approx \prod_{t=1}^T \frac{1}{M} \sum_{m=1}^J \mathcal{L}(IFR|\theta_t^m).$$

Finally, the log-likelihood, ll is:

$$ll \approx \sum_{t=1}^T -\log(M) + \log \left\{ \sum_{m=1}^J \mathcal{L}(IFR|\theta_t^m) \right\}.$$

2 Inference

2.1 Bayesian framework

We aim at inferring the IFR by age class. We use the age-classes in our previous analysis: 5-9, 10-19, 20-50, 50-65, and 65+. Inference is drawn using a Bayesian framework, where we assume that the IFR for age class a , IFR_a , has a Beta prior distribution with age-specific parameters α_a and β_a :

$$IFR_a \sim \text{Beta}(\alpha_a, \beta_a).$$

We reparametrize the prior following [6, Chapter 5]:

$$\begin{aligned} \gamma_a &= \frac{\alpha_a}{\alpha_a + \beta_a} \\ \lambda_a &= \alpha_a + \beta_a, \end{aligned}$$

with hyper-priors:

$$\begin{aligned} \gamma_a &\sim \text{Beta}(1, 6.5) \\ \lambda_a &\sim \text{Pareto}(0.1, 1.5). \end{aligned}$$

We use for the mean of the IFR prior, γ , a beta distribution which has a median of ≈ 0.1 to account for the fact that current estimates situate around 1%, with more vulnerable age classes around 10%.

Posterior draws were obtained using a Hamiltonian Monte Carlo sampler as implemented in the Stan programming language [3], through the package `rstan` [11] in R. Chain convergence was assessed using the Gelman-Rubin \hat{R} statistic [5]. The code used in the analysis is available at <https://github.com/HopkinsIDD/sarscov2-ifr-gva>.

2.2 Data

Epidemiological data for each age class was provided by the canton of Geneva's public health authority, the Direction Générale de la Santé (DGS) (Fig. 1). Population data [9], and the number of people living in assisted care centers [8] were obtained from the statistics office of the canton of Geneva. The parameter values for the delay distributions are given in Table 1.

2.3 Population-level post-stratification

The population-level IFR was estimated by post-stratification using the estimates by age class a , IFR_a :

$$IFR_{pop} = \frac{1}{I^{sero}} \sum_a I_a^{sero} \cdot IFR_a, \quad (5)$$

where I^{sero} is the estimated number of seropositives in the canton of Geneva on the last available serosurvey week (May 6th), and I_a^{sero} is the estimated number of seropositives in age class a from our previous analysis [12]. We note that this estimate accounts for differences in attack rates across age classes.

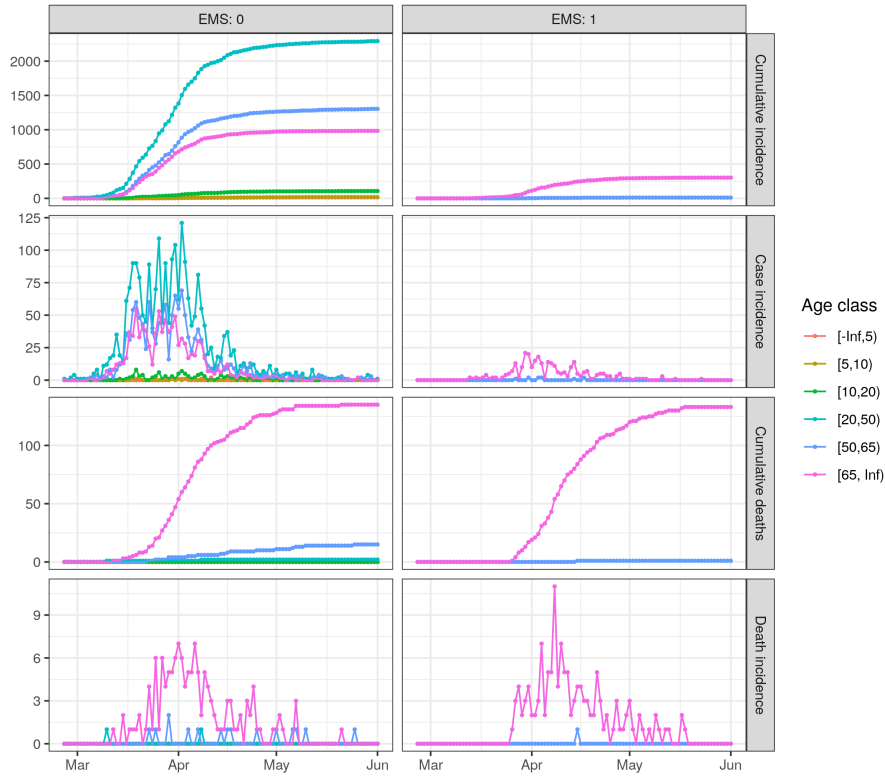


Figure 1: Age-stratified COVID-19 daily epidemiological data in the canton of Geneva, Switzerland in the general population (left column) and within assisted care facilities (EMS) (right column).

Table 1: Parametrization of delay distributions. The distribution of delays were parameterized using log-normal distributions either as reported in the cited references, or computed to match reported mean and standard deviation (denoted with †). Delay combinations (like infection to symptom onset and symptom onset to reporting), were computed by convolution (denoted by $*$). All distributions are shown in Fig. 2.

Distribution	Parameters		Description	Source
	$\log \mu$ (mean)	$\log \sigma$ (sd)		
f_{inc}	1.57 (5.94)	0.65 (4.31)	Incubation period	[2]
f_{report}	1.50 (5.60)	0.45 (4.20)	Symptom onset to reporting	[10] †
$f_{sympsero}$	2.34 (11.2)	0.38 (4.40)	Symptom onset to seroconversion	[12]
$f_{reportdeath}$	2.1 (11.9)	0.87 (12.7)	Reporting to death	DGS
f_C	$f_{inc} * f_{report}$		Infection to reporting	-
f_{sero}	$f_{inc} * f_{sympsero}$		Infection to seroconversion	-
f_D	$f_{inc} * f_{report} * f_{reportdeath}$		Infection to death	-

3 Results

Primary results. Results discussed in the main text are presented in Table 2, with IFR posterior draws given in Fig. 3.

Accounting for assisted care facilities/nursing homes. The true seroprevalence in assisted care facilities remains unknown. If we consider only deaths and infections that occurred in the general population older than 65, the age-specific IFR for this group decreases to 2.7% (95% CrI 1.6-4.6). Excluding this population (both infections and deaths) leads to an overall IFR estimate in Geneva of 0.32% (95% CrI 0.17-0.56), half of what we estimate in our primary analyses (Table 3).

Sensitivity analyses. We fit the model using a uniform instead of a Beta-distributed IFR prior and results were very similar, except for a wider 95% CrI for the 5-9 age class. Finally we fit the model using only to the last serosurvey week which yielded IFR posteriors had the same means but wider 95% CrIs.

Reported COVID-19 deaths and excess mortality Analysis of excess mortality trends have been suggested to provide a more accurate estimate of COVID-19 mortality due to confirmed death under-reporting [7]. The cantonal department of public health (DGS) reported the number of excess mortality during the weeks of the epidemic, estimating to 261 excess deaths during weeks 12-18 among the 65 and older age group, and no statistically significant excess mortality in the younger population [4]. In the same period there were 255 reported COVID-19 deaths in the 65+ age class. This suggests that COVID-19-related deaths were not significantly under-reported.

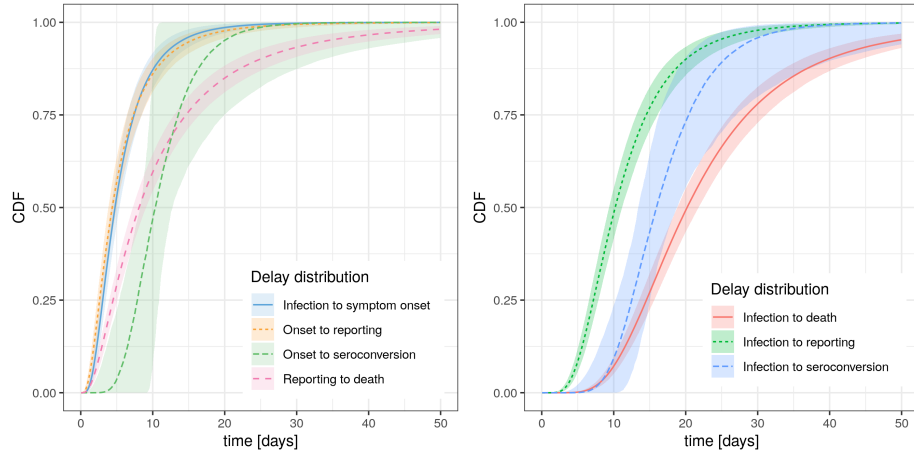


Figure 2: Cumulative probability distributions of delays to key events. *Left*: Delay distributions for which estimates were available from data. *Right*: Un-observable delays estimated using convolutions (Table 1). Distributions are shown in terms of the MLE parameter estimates (lines) and the 95% confidence intervals (shadings).

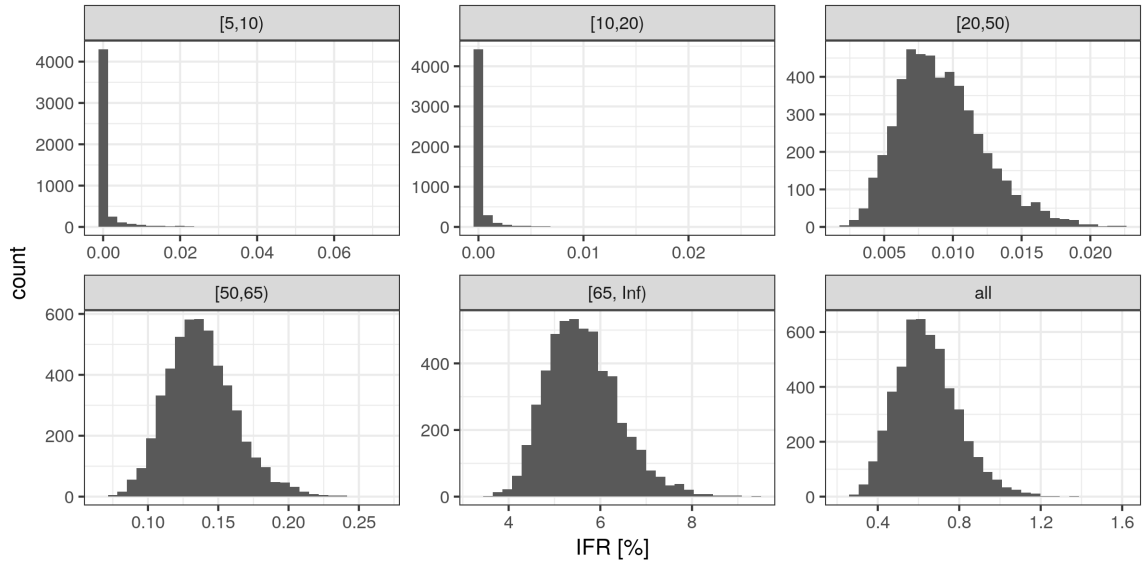


Figure 3: IFR posterior distributions by age class.

Table 2: Age-stratified estimates of the infection fatality risk (IFR) of SARS-Cov-2 in the canton of Geneva, Switzerland.

Age class	Population	Seroconverted population as of May 6th (95% CrI)	Deaths as of June 1st	IFR [%] (95% CrI)
5-9	26'466	1'200 (400-2'400)	0	0.0016 (0-0.019)
10-19	53'180	6'100 (3'900-8'800)	0	0.00032 (0-0.0033)
20-49	219'440	28'800 (21'400-37'300)	2	0.0092 (0.0042-0.016)
50-64	98'528	10'300 (7'200-13'900)	16	0.14 (0.096-0.19)
65+	83'574*	5'700 (3'200-8'800)	268	5.6 (4.3-7.4)
all	506'765	54'800 (41'300-70'700)	286	0.64 (0.38-0.98)

* of which $\sim 4'065$ (4.9%) live in assisted care facilities (EMS).

Table 3: Age-stratified estimates of the IFR without accounting for the deaths in assisted care facilities. Results for age classes younger than 65 are the same as in Table 2, and estimates for the 65+ age class and the overall population were recomputed by not considering the population living in assisted care facilities.

Age class	Population	Seroconverted population as of May 6th (95% CrI)	Deaths as of June 1st	IFR [%] (95% CrI)
65+	79'509	5'400 (3'000- 8'400)	135	2.7 (1.6-4.6)
all	502'700	54'800 (41'300-70'700)	152	0.32 (0.17-0.56)

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