Bayesian evidence synthesis on COVID-19 mortality risk in HCT volunteers

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Contents

1 Introduction

This short document is a technical appendix to the paper discussing COVID-19 risks in human challenge trial. Here, we show how a Bayesian model can synthesise information on many infection fatality rates (IFRs) into a single estimate. This estimate is specific to certain age groups and can be further adjusted by e.g. co-morbidity status. The analysis presented here is a form of Bayesian meta-analysis , in that our primary objective is to weigh sources of evidence in a way that captures both variability (here, heterogeneity in real IFRs across different settings) and uncertainty (here, the fact that we do not know the IFRs in each setting precisely).

The ultimate objective of this model is to characterise risk in a way that is useful for design of HCTs. Therefore, as a minimum, we want to incorporate variability across different populations into our prediction. Even better would be to understand how different factors can drive heterogeneity: *a priori* we hypothesise that the three main drivers of differences in IFRs are time-specific, population-specific and otherwise country-specific.[1]

To characterise differences in observed IFRs we first develop a Bayesian model and apply it to publicly available summary data on IFRs from multiple countries and contexts, with particular focus on the impact of age. This is covered by Section 2. We then use a simple model to hypothesise reduction in risk that may be achieved by screening individuals for comorbidities; this is Section 3. We summarise all results in Section 4.

[1]The role of time may be due to new treatments, improvements over time in our ability to treat Covid-19 or selection pressures which may lead to more benign versions of the virus. Country-specific or location-specific factors in IFR data may be driven by under-reporting, health care factors (including access to health care services) or underlying distributions of known risk factors. Additionally, some unknown risk factors (e.g. genetic) may also be operating, in which case controlling for age and co-morbidities will be not sufficient to account for cross-location differences.

2 Age-specific risk of COVID-19 mortality

2.1 Bayesian evidence synthesis model

What follows is an adaptation of typical methods of Bayesian evidence synthesis to analysis of IFRs. IFR is the ratio of deaths to infections in a given population. Early estimates of Covid-19 mortality risk, e.g. by Verity et al. (2020), placed it at over 0.6%; however, it was also evident from data that IFR could be orders of magnitude higher in particular high risk groups, especially in the elderly, than in the general population.[2]

By definition, our data on IFRs is a combination of data on deaths with data on infections. Typically, these are disjoint samples, in that numbers of infections are estimated (typically very imprecisely) on select subpopulation, while deaths are recorded in the general population (at a level of country, administrative region etc.). There are clear reasons to believe that IFRs will differ across studies (e.g. due to age, comorbidity status, time, genetic factors, quality of healthcare etc.). To address this, we will use a Bayesian hierarchical modelling framework to assume that the setting-specific estimates of IFR_k can differ from each other but are linked through some common parameters. (By k's we denote different populations; note that sometimes we may have multiple IFR's from different age groups in the same location.)

The most straight-forward and "canonical" way to implement such a Bayesian model is by modelling log odds of the event.[3] Deeks (2002) present a general treatment of such approach in medical statistics. Note, that for very rare events the odds of mortality are very similar to probability of mortality, but we model events on odds scale as a good "generic" approach to modelling binary data (in this case death following infections).[4]

Basic models for this type of analysis of binary data can be implemented using existing statistical analysis packages (see, for example, *metafor* package in R or *baggr* by Więcek and Meager (2020)), by treating IFR as a logit-normal parameter to meta-analyse. However, note that when no deaths are observed, analysis of IFR (equal to observed deaths divided by modelled infections) is problematic. Therefore we propose a "custom" model that built in Stan which treats deaths and *prevalences* (rather than the IFRs) as data.

Let d_k denote observed deaths for data point k and assume that logit of corresponding prevalence estimate is p_k is a parameter (typically obtained from a statistical modelling papers, government reports etc.). Total population in k-th setting is n_k. Total number of estimates is K. Then the model likelihood is as follows:

$$d_k \sim \text{Binomial}(n_k, p_k IFR_k) \tag{1}$$

$$\text{logit}(p_k) \sim \mathcal{N}(\mu_k^{(p)}, (\sigma_k^{(p)})^2) \tag{2}$$

where $\sigma_k^{(p)}$ and $\mu_k^{(p)}$ are parameters obtained from the literature (or converted from these parameters – see next section). The k data points collected can span many locations (studies); we denote them by loc_k and the total number of locations by K_{loc} (with $K_{loc} < K$).

In this model we can also account for various covariates impacting the IFRs (let's denote their total number by N_p), such as age groups (which we identify with median age of the population being studied, MedianAge_k). We code them in a design matrix X. To center our X at the value of interest in our model (risk in 20-30 year olds), we use a transformation `MedianAge/10 - 2.5` to construct our matrix X. We denote all of the covariates using a design matrix X and denote by N_p the number of columns in X. We assume the impact on IFR is on logit scale, same as in the "canonical" logistic models of binary data that we mentioned above:

[2] Various estimates published since suggested that the relationship of mortality risk to age is consistent across different countries.

[3] It is also possible to work with IFR_k parameters and treat them as derived from Beta distribution with some "hyperparameters" α and β of Beta distribution, as done by e.g. Carpenter (2016). That approach, however, does not offer an easy way of modelling impact of covariates (e.g. age and co-morbidities) on the rates.

[4] Another advantage of such a model is that it can use either individual-level or summary data and work with covariates (such as gender, age, time of the study, co-morbidities), captured as odds ratios or risk ratios. If only summary data are available, covariates can be defined as study level distributions (e.g. % male)

$$\text{logit}(IFR_k) = \theta_{\text{loc}_k} + X\beta, \tag{3}$$

$$\theta_j \sim \mathcal{N}(\tau, \sigma^2), \text{where } j = 1, \ldots, K_{loc}. \tag{4}$$

This means θ spans location-specific (random) effects on IFR while β is N_p dimensional vector of (fixed) covariate effects.

We implement our model in Stan and assume weakly informative priors on all parameters, with prior for τ centered at 1 death per 10,000 cases.

```
model {
  //Uncertain prevalence estimates (mu^p and sigma^p above):
  logit_prevalence ~ normal(mean_prevalence, sd_prevalence);
  //Likelihood of mortality (d_k = obs_deaths, p_k = prevalence):
  obs_deaths ~ binomial(population, prevalence .* ifr);
  //Hierarchical component of the model (location-specific theta):
  //logit_ifr = theta_k[loc] + to_vector(X*beta);
  theta_k ~ normal(tau, sigma);

  //Priors:
  tau   ~ normal(logit(.0001), 5);
  sigma ~ normal(0, 10);
  beta  ~ normal(0, 10);
}
```

2.2 Data

We used estimates originally collected by Levin, Cochran, and Walsh (2020) to construct the first version of analysis dataset, which we then supplemented with more values extracted from other studies. **Write-up of data collection here OR REFERENCE DATA COLLECTION ELSEWHERE.** The input data into our model consists of deaths (treated as known) and prevalences (treated as logit-distributed parameter with known mean and SD) in all reported age groups in all studies[5].

All of input data are given in Table 2. The analysis dataset contains 114 data points from 23 studies, each containing between 3 and 11 different age groups. We made only minimal modifications to source data, by 1) imputing the values in Italian study (**David to describe**?), 2) imputing population size in Maranhao (as ratio of the reported number of infections and the mean infection rate) which were not reported and 3) assuming that uncertainty in prevalence 0-29 age group in Iceland is same as in the 30-39 age group since data were missing.

As mentioned, our model treats number of Covid-attributable deaths as measured without error (due to lack of data) but accounts for uncertainty in infection rates, which are always model-based estimates extracted from various available data sources. In preparing data, we assumed that logits of prevalence estimates from available studies are normally distributed, which seems to reproduce majority of data very well, see Figure 5 in the Supplement. There are some discrepancies with studies that allowed for prevalence estimates to be 0, something that our logit model does not allow.

For each study we construct a median age scalar defined as **David to detail this: for now leaving blank as it might change with sensitivity analyses**.

Our approach of regressing on the median age and use of all available data (rather than the subset of data available in younger adults only) is necessitated by data limitations: out of 114 data points comprising age-specific estimates of prevalence (or IFR) and counts of deaths, 24 contain individuals aged 20-30 who are of primary interest to us. However, the populations are mixed with regards to age, with typical age groupings

[5]This basic approach exaggerates uncertainty, as we treat different 95% intervals reported in the study as uncorrelated.

such as 19-49, 20-49, 20-39, 0-49 used instead. In fact, we find only one estimate out of 24 that is entirely specific to the 20-29 age group (Brazilian state of Maranhao), while one more has median age falling between 20 and 30 but is not specific to that age group.

2.3 Results

There were no issues with convergence of the Bayesian model. We set number of iterations to 5,000 and used 4 chains, with `max_treedepth` option set to 15. There were no divergent transitions and effective sample size was greater than 3348 for all of 368 modeled parameters (this number includes fitted prevalences, IFRs, θ's and their transformations into/from logit scales). For the three main parameters in the model we obtained the following:

```
## Inference for Stan model: ifr_with0.
## 4 chains, each with iter=5000; warmup=2500; thin=1;
## post-warmup draws per chain=2500, total post-warmup draws=10000.
##
##          mean se_mean   sd  2.5%   25%   50%   75%   98% n_eff Rhat
## tau     -8.67       0 0.15 -8.97 -8.77 -8.66 -8.57 -8.36  9819    1
## sigma    0.67       0 0.12  0.48  0.59  0.66  0.74  0.96 10086    1
## beta[1]  1.07       0 0.01  1.05  1.07  1.07  1.08  1.09  4328    1
##
## Samples were drawn using NUTS(diag_e) at Sat Oct 31 14:54:41 2020.
## For each parameter, n_eff is a crude measure of effective sample size,
## and Rhat is the potential scale reduction factor on split chains (at
## convergence, Rhat=1).
```

The mean coefficient of beta 1.07 corresponds to 2.93-fold increase in mortality risk following an infection per each extra decade of age (95% uncertainty interval is 2.87-2.99).

From these parameters we can predict average risks for subjects of any given age x, by using the posterior distribution of $\tau + (10x + 2.5)\beta$ (where 2.5 and 10 refer to the transformation that we applied to `MedianAge` inputs).

2.4 Average infection fatality risk in young subjects

Since we centered our `MedianAge` at 25 years in constructing our matrix X, we can now obtain model-estimated risk for a typical HCT population (aged 20 to 30, with median 25) by ignoring the β coefficient and examining τ and σ only. We find that the average IFR for this group (equal to $\frac{\exp(\tau)}{\exp(1+\tau)}$) is 1.75×10^{-4} (with 95% interval from 1.27×10^{-4} to 2.33×10^{-4}). That means, on average, slightly under 2 deaths per 10,000 infections in the studied datasets.

2.4.1 Heterogeneity in IFRs

However, there is a considerable variability in IFRs across different locations/dataset that we should consider. To take into account parameter σ, we can generate draws from the $\mathcal{N}(\tau, \sigma^2)$ distribution, corresponding to a hypothetical IFR in a new source of data. 95% interval for such model runs from 4.46×10^{-5} to 7.03×10^{-4}. Since the model works a logistic scale, another way of interpreting the across-dataset variability is reporting the fold-impact of σ on the mean IFR; here, we obtain on average a 3.96-fold increase (decrease) in IFR per 2σ increase (decrease).

The lower end of the 95% interval, 4.46×10^{-5}, is not extreme given input data, where the "crude" mean IFR (based on mean prevalence only) is below 7 per 10,000 for all data except for South Florida, and as low as 0 for some countries that did not record deaths (Belgium, New Zealand, Korea, Iceland) in various age groups including 20-29 year olds or 1.4 per 10,000 in Utah, in the population aged 19-44. (Please refer to Table 2 for complete list of inputs.)

We can assess this heterogeneity by inspecting the distribution of random effects in the model transformed into IFRs, i.e. the inverse logit transformation θ parameters. The largest (posterior mean) IFR value of θ is 6.29×10^{-4} in Castiglione d'Adda. The smallest posterior mean for 20-29 year olds is 5.74×10^{-5} in Belgium.

2.4.2 Predictive checks for the model

We constructed posterior predictive distributions for number of deaths in each of the inputs by using the `generated quantities` functionality of Stan. Figure 1 compares the posterior means and 95% intervals with observed deaths. Out of 114 observations that were used to fit the model, 108 were within 95% intervals of the posterior predictive distributions. We observed the largest discrepancies occurred in Spanish data. Overall, we conclude that the simple binomial model we used here is flexible enough to capture both age-specific risk increases and heterogeneity in IFRs across settings/countries.

2.5 Sensitivity analyses

WW: I WILL WORK ON THIS IN NOV-DEC 2020. ALL 4 OF THESE ARE ESSENTIAL

- Exclusion of small studies and test & trace data
- Median age: exclusion of 80+ population (non-linear behaviour on logit IFR?)
  - Could also check exclusion of children and teenagers, due to imprecise prevalence numbers
- Median age: different method of age imputation
- Model with time

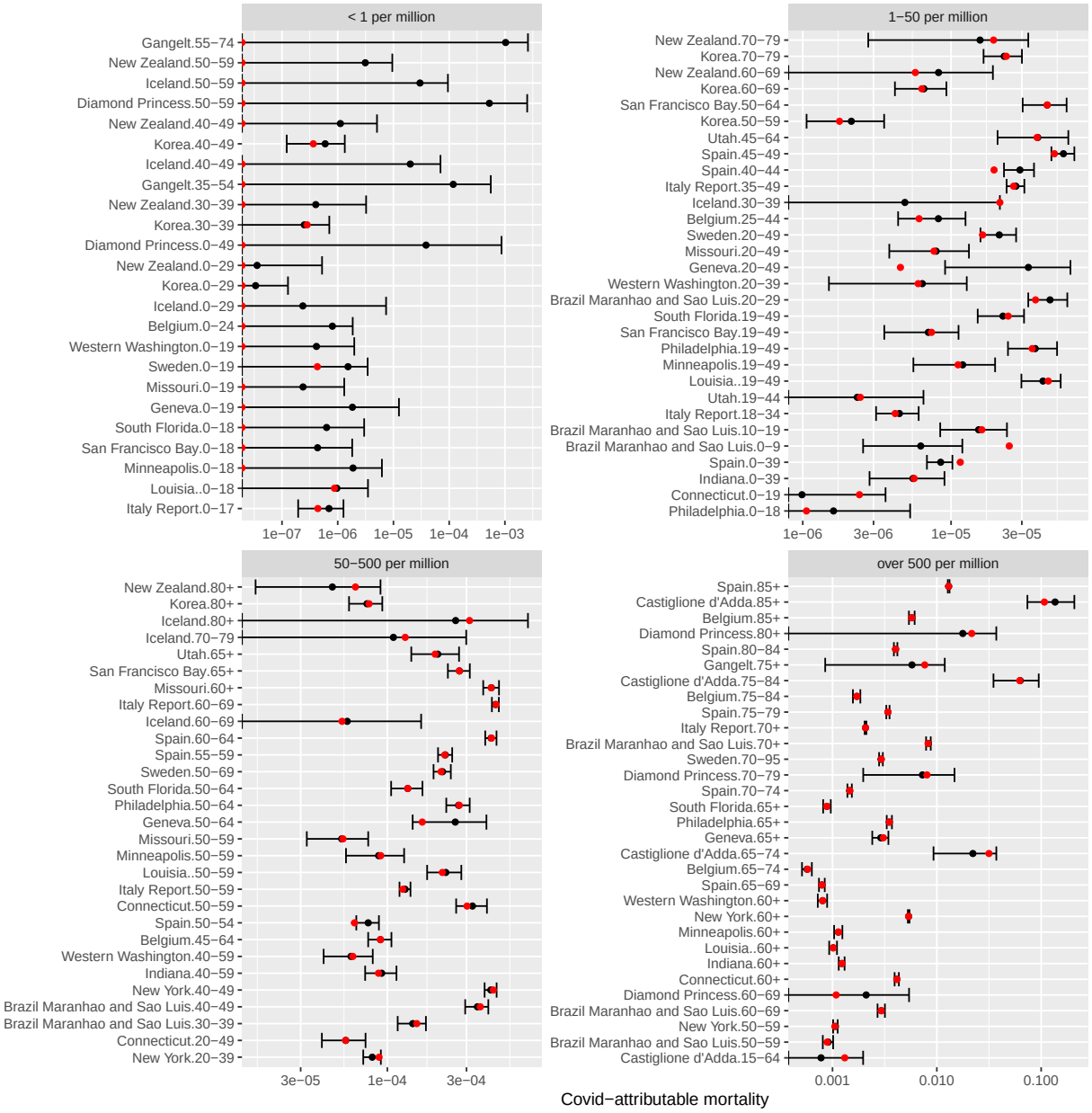

Figure 1: Comparison of model estimates (black) with observed mortality (red), compared on logarithmic scale. Bars are 95% posterior interval; point is the mean. For better clarity, we grouped the plot into four panels according to observed mortality. X axes on each panel differ. For many low-risk populations no deaths were reported: we indicate this by plotting a red point on the left-hand side of the panel plot.

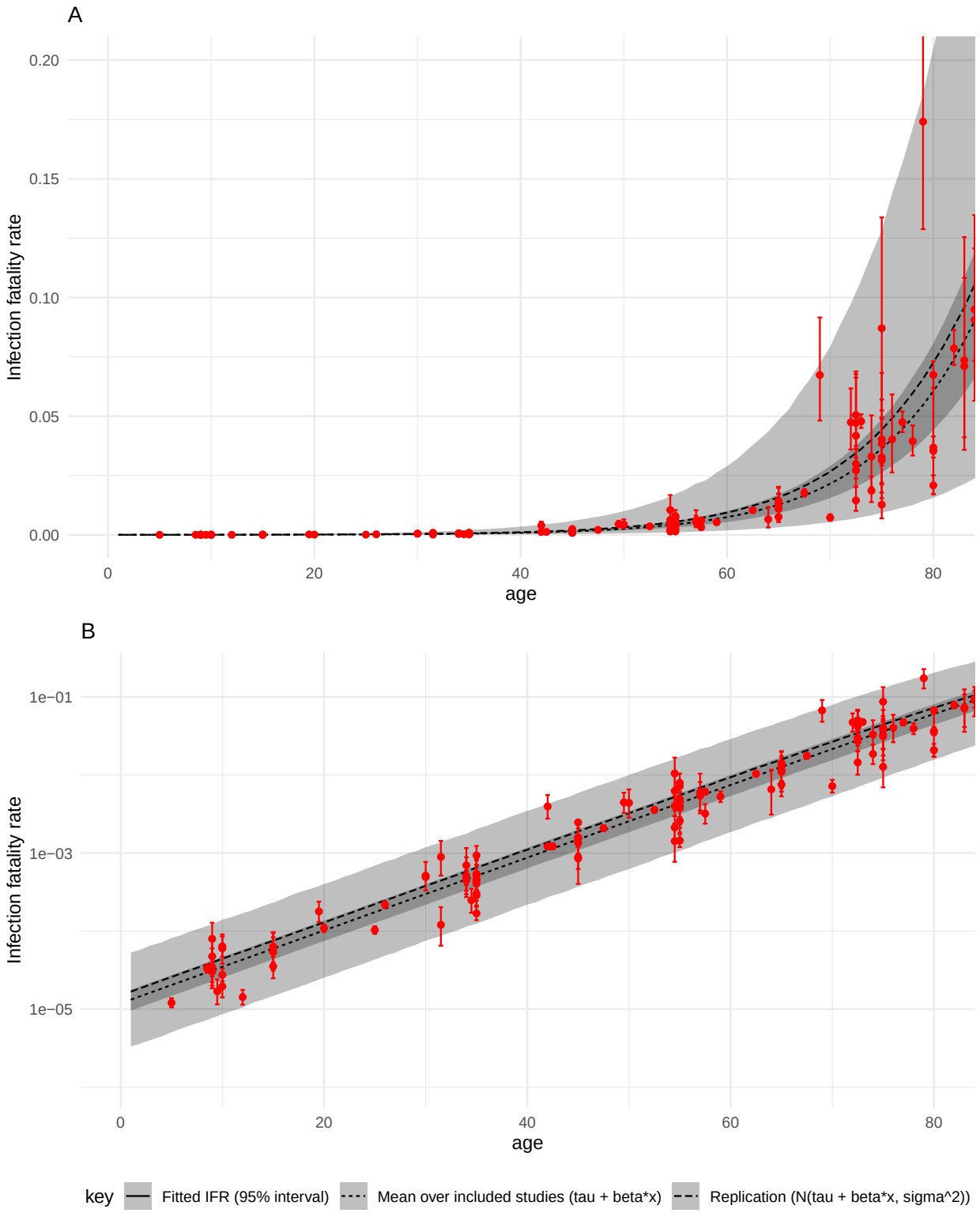

Figure 2: IFR as a function of age. Narrower ribbon corresponds to the 95% posterior interval of average across all included studies (tau parameter in the meta-analysis model), while the wider band takes into account heterogeneity (tau and sigma). Lines are means. Red points are model estimates of mean IFRs in partciular studies, with bars representing 95% posterior intervals. Panel A is untransformed data and panel B is same data on log 10 scale.

3 Risk reduction in healthy individuals

We now turn our attention to the question of how much a human challenge trial designer could reduce the mortality risk by using simple screening methods, as discussed in the main paper.

Data for this section has been provided by OpenSAFELY (https://opensafely.org/) and was used by Williamson et al. (2020) to characterise Covid-19 mortality risk factors for 10,926 Covid-19 deaths in England. We group the total of 21,444,863 individuals into high and low risk groups as follows: **Definition of co-morbiditiy goes here (David/team).** For brevity we define population without one of the pre-defined comorbidities as "healthy". In contrast to the cited publication, we include records of individuals under 18 in our assessment. Counts grouped by age are presented in Table 1. Complete data (broken down by gender) are in Table 3 at the end of the document.

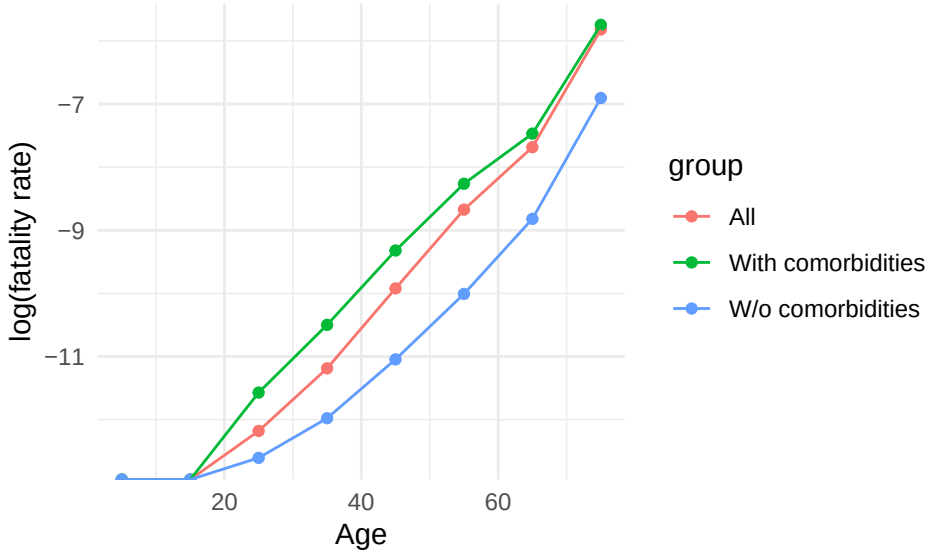

Figure 3: Fatality rates as a function of age in OpenSAFELY data.

As shown in Table 1, for the age group of 20-29 the crude risk ratio (of general population vs the healthy subset only) is 1.53, but, due to low number of events in both healthy and general population, with a very wide 95% interval from 0.6 to 5.65.[6] As data on relative risks in other age groups is clearly related to the relative risk in 20-29 age group, we use another meta-analysis model to improve our estimate. Additionally, relative risks are higher in women than in men – something that we can account for in our model too.

In our modelling we make a strong assumption that infection rates in population with comorbidities are the same as in the general population. In other words, we assume that denominator for IFR is same in both populations. We then specify a generic partial pooling model of fatality rates (FR, defined as number of deaths in the entire population, without regards to infection status) such that

$$\text{logit}(\text{FR}_k) \sim \mathcal{N}(\alpha_{\text{age}_k}\text{comorb}_k + \beta\text{male}_k + \gamma_{\text{age}_k}), \tag{5}$$

$$\alpha_i \sim \mathcal{N}(\mu, \sigma) \text{ for all } i, \tag{6}$$

where, for k-th observation, age_k is the age group, and comorb_k and male_k are indicator variables. This means that each age group is assigned different "baseline" fatality rates.

[6] We obtain the interval using a simulation approach. Using normal approximation of log(RR) statistic we obtain a narrower 0.57 to 4.1, perhaps due to poor quality of approximation for rare events.

Table 1: Data from the OpenSAFELY database grouped by age.

	Population		Fatalities		FR per 100k		
Age group	All	Healthy	All	Healthy	All	Healthy	RR
0 to 9	2,160,958	2,007,997	0	0	0.00	0.00	NaN
10 to 19	2,428,494	2,000,761	0	0	0.00	0.00	NaN
20 to 29	2,530,792	1,788,907	13	6	0.51	0.34	1.5
30 to 39	2,960,611	1,909,227	41	12	1.38	0.63	2.2
40 to 49	2,849,984	1,565,935	140	25	4.91	1.60	3.1
50 to 59	3,051,110	1,243,728	522	56	17.11	4.50	3.8
60 to 69	2,392,392	622,357	1,101	92	46.02	14.78	3.1
70 to Inf	3,070,522	317,238	9,109	318	296.66	100.24	3.0

Note that the assumption of FRs varying across age groups that we just mentioned differs from the model of age-specific IFRs in Section 2. This is because we hypothesised that infection rates (which are used as denominators in the IFR model of Section 2) will vary across age groups. This is borne out by Figure 3.

Summary of the main model parameters is as follows:

```
##            mean se_mean    sd   2.5%    25%   50%    75%    98% n_eff Rhat
## mu         1.43 0.00286 0.199   1.03   1.33   1.4   1.53   1.85  4866    1
## sigma      0.36 0.00543 0.230   0.12   0.22   0.3   0.44   0.95  1803    1
## alpha[3]   1.32 0.00411 0.323   0.62   1.14   1.3   1.52   1.93  6175    1
## beta       0.40 0.00019 0.019   0.36   0.39   0.4   0.42   0.44 10105    1
## gamma[3] -13.05 0.00372 0.338 -13.73 -13.27 -13.0 -12.81 -12.41  8238    1
```

We find that the mean risk ratio between population with comorbidities and healthy sub-population in 20-29 age group (exponent of α_3 above) is 3.93, with wide 95% uncertainty interval of 1.86 to 6.92.[7]

Next, using the posterior samples we calculate the event rate in total population (i.e. $\theta* = (\theta_1 n_1 + \theta_2 n_2)/(n_1 + n_2)$, where subscripts 1 and 2 are healthy and comorbid sub-populations) and then divide it by ratio in healthy population to obtain an estimate of risk reduction possible by selecting healthy volunteers only. The mean posterior value is 1.87, with 95% uncertainty interval from 1.26 to 2.75. Due to use of Bayesian hierarchical model over many age groups, the uncertainty interval is much narrower than on the risk reduction factor calculated on 20-29 age group only.

To validate the model, we conducted a simple posterior predictive check for numbers of deaths in different age groups and genders. The graphical check is presented in Figure 4. Overall we find that the simple model has no problem with reproducing observed data.

[7] Using simple models that assumed identical risk ratios in all age groups would lead to a mean RR of similar magnitude but a much less uncertain estimate, due to more rigid model assumptions; similarly, assuming some linear age structure on risks, such as in the main meta-analysis model above, would may lead to a different RR, but we do not think such an assumption is justified here. We do not include outputs of these models in this short write-up.

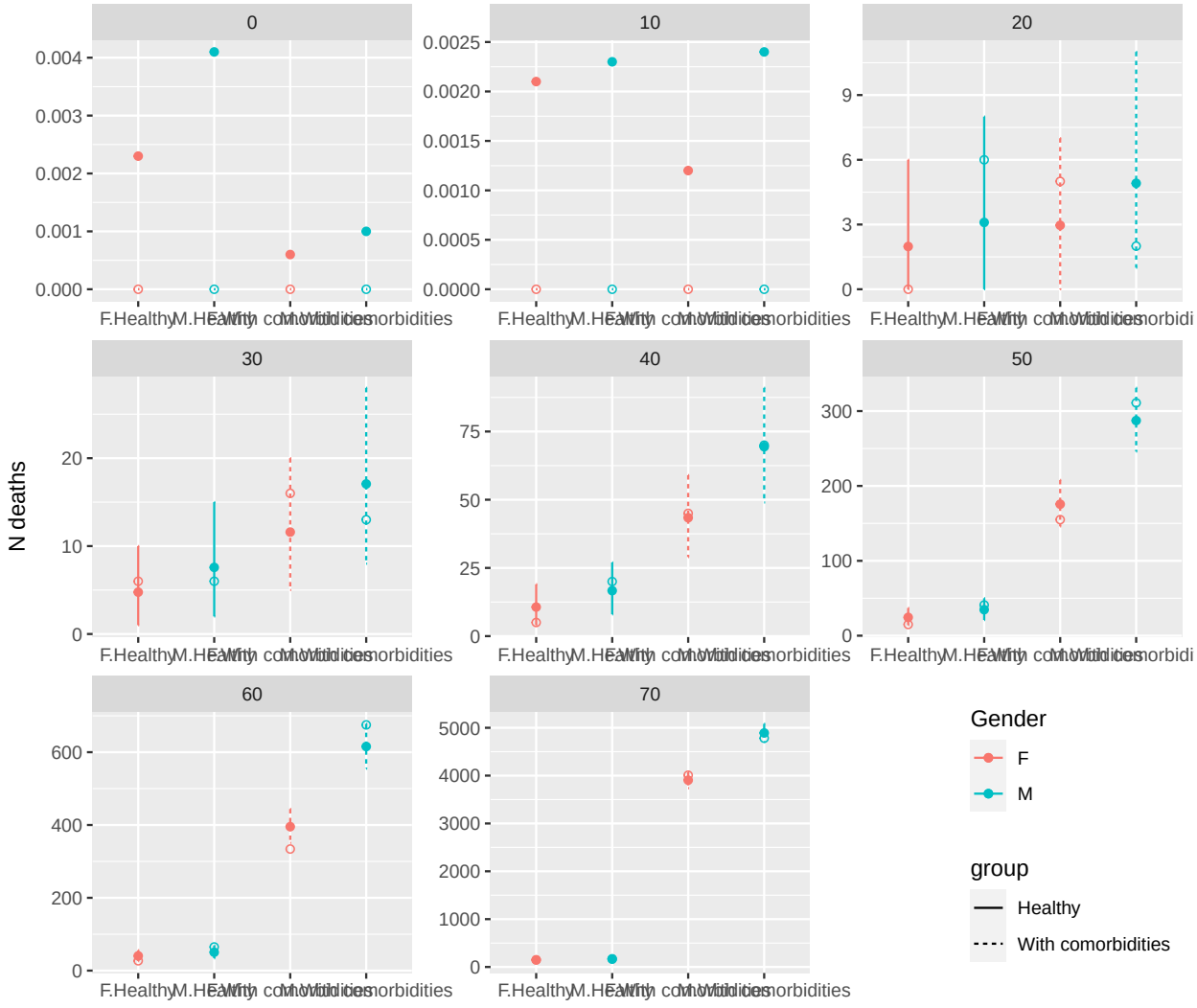

Figure 4: Comparison of posterior predictive numbers of deaths from the fitted Bayesian model (mean and 95% intervals) with data inputs (circles). For each age grouping we have 4 estimates: male/female and healthy (`No.Comorbidities` equal to 1) vs general population (0)

4 Conclusion and summary of results

In conclusion:

- We find that average IFR in 20-29 age group for the studies included in this analysis is 1.75×10^{-4} with 95% interval from 1.27×10^{-4} to 2.33×10^{-4}.
  - It is feasible that the mean IFR can be decreased as much as 3.96-fold (2σ impact on the IFR according to hyper-SD parameter in the meta-analysis model).
  - It is easy to argue that a HCT designer would be able to achieve IFR at least as low as within any of the large-scale studies included in our sample of populations. The smallest posterior mean for 20-29 year olds is 5.74×10^{-5}, fitted to data from Belgium.
- In healthy population (defined as lack of co-morbidities listed above), the average mortality risk is 1.87 times lower than in the general population, with 95% uncertainty interval from 1.26 to 2.75.
  - Our 1.87 estimate is a bit higher than the mean "crude" risk ratio of 1.53 because we use Bayesian hierarchical model.
- Combining the smallest posterior IFR for 20-29 year olds with our estimated fold-reduction due to excluding individuals with co-morbidities from the population would lead to a mean infection fatality risk of 3.21×10^{-5} with 95% Bayesian interval from 1.98×10^{-5} to 4.79×10^{-5}.

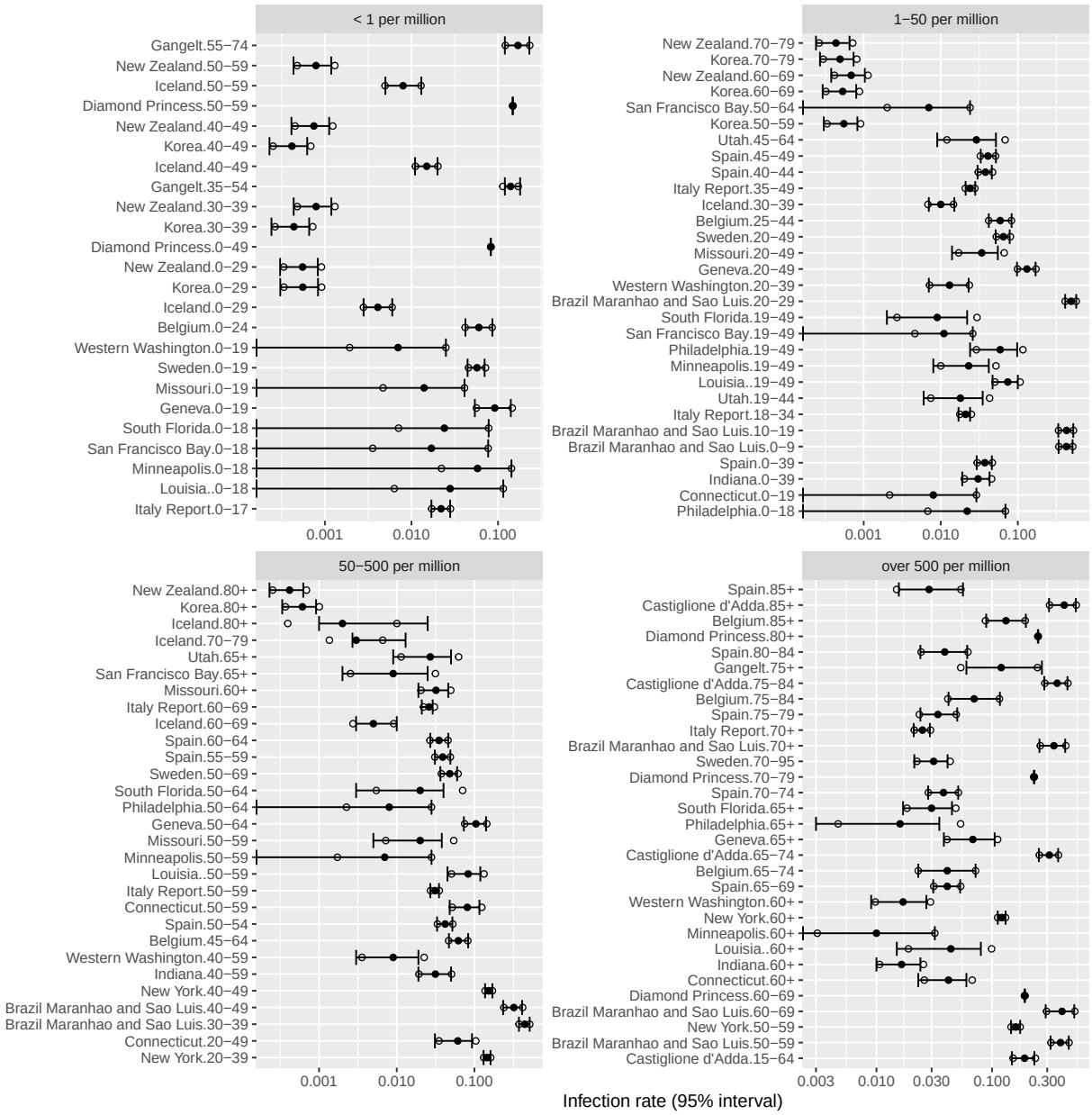

Figure 5: Comparison of model-estimated prevalences (95% CI's reported by modelling studies) collected by Levin, Cochran, and Walsh (2020) and our distributional assumptions: additional circles show 95% CIs recreated by assuming logit-normal distribution of prevalence. We group studies into 4 bands of mortality to mirror earlier figures. Please note that this approach produces discrepancies in a number of US estimates where the confidence intervals were skewed toward including 0. However, since we do not have access to source data, we decided to use the logit-normal assumption for all estimates. This assumption may have an effect of overestimating mortality risk in settings where prevalence was very low.

Table 2: Complete table of inputs used by the meta-analysis model and crude IFR's.

							Infection rate (%)			
Study location	Scale	Type	End date	Age	Deaths	N	Mean	2.5%	97.5%	IFR/100k
Brazil Maranhao and Sao Luis	Region	Seroprevalence	NA	0-9	29	1.2e+06	42.60	51.30	33.80	0.06
Italy Report	Country	Seroprevalence	2020-08-01	0-17	5	1.0e+07	2.20	2.80	1.70	0.02
Louisia.	USState	IFR	2020-05-06	0-18	1	1.1e+06	2.80	11.50	0.00	0.03
Minneapolis	USState	IFR	2020-06-04	0-18	0	9.7e+05	5.80	14.30	0.00	0.00
Philadelphia	USState	IFR	2020-05-17	0-18	1	9.4e+05	2.20	6.90	0.00	0.05
San Francisco Bay	USState	IFR	2020-05-25	0-18	0	1.6e+06	1.70	7.70	0.00	0.00
South Florida	USState	IFR	NA	0-18	0	1.3e+06	2.40	7.80	0.00	0.00
Missouri	USState	IFR	2020-05-23	0-19	0	1.5e+06	1.40	4.10	0.00	0.00
Connecticut	USState	IFR	2020-05-28	0-19	2	8.3e+05	0.80	2.90	0.00	0.30
Geneva	City	IFR	2020-06-01	0-19	0	8.0e+04	9.17	14.06	5.40	0.00
Sweden	Country	IFR	2020-06-18	0-19	1	2.3e+06	5.73	7.00	4.45	0.01
Western Washington	USState	IFR	NA	0-19	0	1.0e+06	0.70	2.50	0.00	0.00
Belgium	Country	IFR	2020-05-16	0-24	0	3.2e+06	6.00	8.60	4.20	0.00
Brazil Maranhao and Sao Luis	Region	Seroprevalence	NA	10-19	21	1.3e+06	43.00	52.40	33.50	0.04
Iceland	Country	IFR	2020-06-14	0-29	0	1.4e+05	0.41	0.60	0.28	0.00
Korea	Country	IFR	2020-07-11	0-29	0	1.6e+07	0.06	0.08	0.03	0.00
New Zealand	Country	IFR	2020-07-09	0-29	0	1.9e+06	0.06	0.08	0.03	0.00
Indiana	USState	IFR	NA	0-39	20	3.5e+06	3.05	4.30	1.90	0.18
Spain	Country	IFR	2020-07-15	0-39	225	1.9e+07	3.73	4.60	2.93	0.31
Brazil Maranhao and Sao Luis	Region	Seroprevalence	NA	20-29	47	1.3e+06	49.20	57.30	41.10	0.08
Italy Report	Country	Seroprevalence	2020-08-01	18-34	43	1.0e+07	2.10	2.40	1.70	0.20
New York	USState	IFR	2020-05-23	20-39	482	5.4e+06	14.60	16.10	13.10	0.61
Western Washington	USState	IFR	NA	20-39	8	1.3e+06	1.30	2.30	0.70	0.46
Philadelphia	USState	IFR	2020-05-17	19-49	51	1.4e+06	5.90	9.80	2.40	0.60
Utah	City	IFR	2020-06-19	19-44	3	1.2e+06	1.80	3.50	0.60	0.14
Louisia.	USState	IFR	2020-05-06	19-49	85	1.9e+06	7.40	10.00	4.70	0.61
Minneapolis	USState	IFR	2020-06-04	19-49	18	1.6e+06	2.30	4.20	0.80	0.48
San Francisco Bay	USState	IFR	2020-05-25	19-49	25	3.4e+06	1.10	2.60	0.00	0.67
South Florida	USState	IFR	NA	19-49	61	2.5e+06	0.90	2.20	0.20	2.70
Missouri	USState	IFR	2020-05-23	20-49	18	2.3e+06	3.40	5.50	1.40	0.23

Table 2: Complete table of inputs used by the meta-analysis model and crude IFR's. *(continued)*

Study location	Scale	Type	End date	Age	Deaths	N	Mean	2.5%	97.5%	IFR/100k
Belgium	Country	IFR	2020-05-16	25-44	18	3.0e+06	5.90	8.30	4.20	0.10
Brazil Maranhao and Sao Luis	Region	Seroprevalence	NA	30-39	163	1.1e+06	44.40	51.40	37.40	0.34
Connecticut	USState	IFR	2020-05-28	20-49	75	1.3e+06	6.10	9.30	3.10	0.92
Diamond Princess	Small	IFR	2020-04-01	0-49	0	1.2e+03	8.26	8.28	8.24	0.00
Geneva	City	IFR	2020-06-01	20-49	1	2.2e+05	13.12	17.00	9.75	0.03
Iceland	Country	IFR	2020-06-14	30-39	1	4.7e+04	1.00	1.50	0.70	2.13
Korea	Country	IFR	2020-07-11	30-39	2	7.1e+06	0.04	0.07	0.02	0.64
New Zealand	Country	IFR	2020-07-09	30-39	0	6.2e+05	0.08	0.12	0.04	0.00
Sweden	Country	IFR	2020-06-18	20-49	63	3.9e+06	6.50	7.84	5.16	0.25
Castiglione d'Adda	Small	IFR	NA	15-64	4	3.1e+03	19.10	23.24	14.86	6.86
Italy Report	Country	Seroprevalence	2020-08-01	35-49	334	1.3e+07	2.40	2.80	2.10	1.10
Spain	Country	IFR	2020-07-15	40-44	78	4.0e+06	3.80	4.60	3.00	0.51
Brazil Maranhao and Sao Luis	Region	Seroprevalence	NA	40-49	290	8.0e+05	32.20	41.00	23.40	1.13
Gangelt	Small	IFR	NA	35-54	0	3.6e+03	14.00	18.00	12.00	0.00
Iceland	Country	IFR	2020-06-14	40-49	0	4.3e+04	1.50	2.00	1.10	0.00
Korea	Country	IFR	2020-07-11	40-49	3	8.2e+06	0.04	0.06	0.02	0.88
New York	USState	IFR	2020-05-23	40-49	1026	2.4e+06	15.30	17.00	13.70	2.85
New Zealand	Country	IFR	2020-07-09	40-49	0	5.9e+05	0.07	0.11	0.04	0.00
Spain	Country	IFR	2020-07-15	45-49	196	3.9e+06	4.10	5.20	3.30	1.21
Indiana	USState	IFR	NA	40-59	148	1.7e+06	3.14	5.00	1.90	2.81
Western Washington	USState	IFR	NA	40-59	69	1.1e+06	0.90	1.90	0.30	6.88
Spain	Country	IFR	2020-07-15	50-54	230	3.6e+06	4.20	5.20	3.30	1.51
Louisia.	USState	IFR	2020-05-06	50-59	126	5.9e+05	8.30	11.90	4.50	2.59
Minneapolis	USState	IFR	2020-06-04	50-59	47	5.2e+05	0.70	2.80	0.00	13.03
Missouri	USState	IFR	2020-05-23	50-59	43	8.0e+05	2.00	3.80	0.50	2.70
Philadelphia	USState	IFR	2020-05-17	50-64	290	1.1e+06	0.80	2.80	0.00	33.95
Utah	City	IFR	2020-06-19	45-64	24	6.3e+05	2.90	5.20	0.90	1.31
Belgium	Country	IFR	2020-05-16	45-64	280	3.1e+06	6.20	8.30	4.70	1.47
Brazil Maranhao and Sao Luis	Region	Seroprevalence	NA	50-59	533	6.0e+05	39.10	46.10	32.10	2.27
Connecticut	USState	IFR	2020-05-28	50-59	157	5.2e+05	8.10	11.60	4.80	3.73
Diamond Princess	Small	IFR	2020-04-01	50-59	0	4.0e+02	14.82	14.90	14.70	0.00

Table 2: Complete table of inputs used by the meta-analysis model and crude IFR's. *(continued)*

Study location	Scale	Type	End date	Age	Deaths	N	Mean	2.5%	97.5%	IFR/100k
Iceland	Country	IFR	2020-06-14	50-59	0	4.2e+04	0.80	1.30	0.50	0.00
Italy Report	Country	Seroprevalence	2020-08-01	50-59	1196	9.6e+06	3.10	3.50	2.70	4.00
Korea	Country	IFR	2020-07-11	50-59	15	8.5e+06	0.06	0.08	0.03	3.20
New York	USState	IFR	2020-05-23	50-59	2764	2.6e+06	16.00	17.50	14.60	6.58
New Zealand	Country	IFR	2020-07-09	50-59	0	6.3e+05	0.08	0.12	0.04	0.00
San Francisco Bay	USState	IFR	2020-05-25	50-64	66	1.5e+06	0.70	2.40	0.00	6.37
South Florida	USState	IFR	NA	50-64	169	1.3e+06	2.00	4.00	0.30	6.64
Geneva	City	IFR	2020-06-01	50-64	16	9.9e+04	10.45	14.11	7.31	1.55
Spain	Country	IFR	2020-07-15	55-59	758	3.4e+06	3.90	4.90	3.10	5.69
Sweden	Country	IFR	2020-06-18	50-69	504	2.4e+06	4.81	5.98	3.64	4.38
Spain	Country	IFR	2020-07-15	60-64	1249	2.9e+06	3.50	4.60	2.70	12.14
Gangelt	Small	IFR	NA	55-74	0	3.1e+03	17.00	23.00	12.00	0.00
Brazil Maranhao and Sao Luis	Region	Seroprevalence	NA	60-69	1155	3.9e+05	40.30	51.40	29.10	7.28
Diamond Princess	Small	IFR	2020-04-01	60-69	1	9.2e+02	19.18	19.30	19.10	5.65
Iceland	Country	IFR	2020-06-14	60-69	2	3.8e+04	0.50	1.00	0.30	10.66
Italy Report	Country	Seroprevalence	2020-08-01	60-69	3274	7.2e+06	2.60	2.90	2.10	17.40
Korea	Country	IFR	2020-07-11	60-69	41	6.5e+06	0.05	0.08	0.03	11.91
New Zealand	Country	IFR	2020-07-09	60-69	3	5.2e+05	0.07	0.10	0.04	8.33
Spain	Country	IFR	2020-07-15	65-69	1905	2.4e+06	4.10	5.30	3.10	19.35
Castiglione d'Adda	Small	IFR	NA	65-74	17	5.4e+02	31.30	37.30	25.40	100.95
Belgium	Country	IFR	2020-05-16	65-74	663	1.1e+06	4.10	7.20	2.30	14.10
Connecticut	USState	IFR	2020-05-28	60+	3633	8.8e+05	4.20	6.00	2.30	98.77
Indiana	USState	IFR	NA	60+	1864	1.5e+06	1.65	2.40	1.00	74.71
Louisia.	USState	IFR	2020-05-06	60+	1053	1.0e+06	4.40	8.00	1.50	23.07
Minneapolis	USState	IFR	2020-06-04	60+	928	8.1e+05	1.00	3.20	0.00	114.11
Missouri	USState	IFR	2020-05-23	60+	620	1.5e+06	3.20	4.60	1.90	13.21
Spain	Country	IFR	2020-07-15	70-74	3230	2.2e+06	3.80	5.10	2.80	38.56
Western Washington	USState	IFR	NA	60+	700	8.7e+05	1.70	2.70	0.90	47.31
New York	USState	IFR	2020-05-23	60+	24376	4.5e+06	12.10	13.10	11.20	44.33
Geneva	City	IFR	2020-06-01	65+	257	8.4e+04	6.82	10.53	3.83	45.09
New Zealand	Country	IFR	2020-07-09	70-79	7	3.6e+05	0.04	0.07	0.02	44.30
Diamond Princess	Small	IFR	2020-04-01	70-79	8	1.0e+03	23.05	23.20	23.00	34.90

Table 2: Complete table of inputs used by the meta-analysis model and crude IFR's. *(continued)*

Study location	Scale	Type	End date	Age	Deaths	N	Mean	2.5%	97.5%	IFR/100k
Iceland	Country	IFR	2020-06-14	70-79	3	2.3e+04	0.30	1.30	0.27	42.71
Korea	Country	IFR	2020-07-11	70-79	84	3.6e+06	0.05	0.07	0.03	47.89
Philadelphia	USState	IFR	2020-05-17	65+	2374	6.8e+05	1.60	3.50	0.30	219.23
San Francisco Bay	USState	IFR	2020-05-25	65+	333	1.2e+06	0.90	2.50	0.20	30.20
Utah	City	IFR	2020-06-19	65+	71	3.7e+05	2.70	5.00	0.90	7.19
South Florida	USState	IFR	NA	65+	1060	1.2e+06	3.00	4.50	1.70	29.38
Spain	Country	IFR	2020-07-15	75-79	6175	1.8e+06	3.40	5.00	2.40	100.28
Sweden	Country	IFR	2020-06-18	70-95	4485	1.5e+06	3.12	4.12	2.13	94.03
Castiglione d'Adda	Small	IFR	NA	75-84	25	4.0e+02	36.60	44.90	28.30	170.34
Belgium	Country	IFR	2020-05-16	75-84	1182	6.9e+05	7.00	11.70	4.20	24.45
Brazil Maranhao and Sao Luis	Region	Seroprevalence	NA	70+	2788	3.4e+05	34.30	42.90	25.70	24.07
Gangelt	Small	IFR	NA	75+	9	1.2e+03	12.00	27.00	6.00	63.83
Italy Report	Country	Seroprevalence	2020-08-01	70+	21271	1.0e+07	2.50	2.90	2.10	83.00
Spain	Country	IFR	2020-07-15	80-84	5192	1.3e+06	3.90	6.10	2.40	103.33
Diamond Princess	Small	IFR	2020-04-01	80+	5	2.2e+02	25.00	25.10	24.90	86.42
Iceland	Country	IFR	2020-06-14	80+	4	1.3e+04	0.20	2.50	0.10	156.56
Korea	Country	IFR	2020-07-11	80+	144	1.9e+06	0.06	0.09	0.03	127.21
New Zealand	Country	IFR	2020-07-09	80+	12	1.9e+05	0.04	0.06	0.02	153.85
Spain	Country	IFR	2020-07-15	85+	21248	1.6e+06	2.85	5.60	1.56	455.37
Castiglione d'Adda	Small	IFR	NA	85+	16	1.5e+02	42.10	53.10	31.10	255.07
Belgium	Country	IFR	2020-05-16	85+	1878	3.3e+05	13.20	19.60	8.90	43.55

Table 3: Data from the OpenSAFELY database grouped by age and broken down by gender.

		Population		Fatalities		FR per 100k		
Age group	Gender	All	Healthy	All	Healthy	All	Healthy	RR
Female								
0 to 9	F	1,052,302	988,343	0	0	0.00	0.00	NaN
10 to 19	F	1,176,606	990,232	0	0	0.00	0.00	NaN
20 to 29	F	1,225,905	875,401	5	0	0.41	0.00	Inf
30 to 39	F	1,451,654	921,582	22	6	1.52	0.65	2.33
40 to 49	F	1,383,764	763,003	50	5	3.61	0.66	5.51
50 to 59	F	1,500,670	637,807	170	15	11.33	2.35	4.82
60 to 69	F	1,206,084	339,283	361	27	29.93	7.96	3.76
70 to Inf	F	1,679,738	182,735	4,156	147	247.42	80.44	3.08
Male								
0 to 9	M	1,108,656	1,019,654	0	0	0.00	0.00	NaN
10 to 19	M	1,251,888	1,010,529	0	0	0.00	0.00	NaN
20 to 29	M	1,304,887	913,506	8	6	0.61	0.66	0.93
30 to 39	M	1,508,957	987,645	19	6	1.26	0.61	2.07
40 to 49	M	1,466,220	802,932	90	20	6.14	2.49	2.46
50 to 59	M	1,550,440	605,921	352	41	22.70	6.77	3.36
60 to 69	M	1,186,308	283,074	740	65	62.38	22.96	2.72
70 to Inf	M	1,390,784	134,503	4,953	171	356.13	127.13	2.80

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