A systematic review and meta-analysis of published research data on COVID-19 infection-fatality rates

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Abstract

An important unknown during the COVID-19 pandemic has been the infection-fatality rate (IFR). This differs from the case-fatality rate (CFR) as an estimate of the number of deaths as a proportion of the total number of cases, including those who are mild and asymptomatic. While the CFR is extremely valuable for experts, IFR is increasingly being called for by policy-makers and the lay public as an estimate of the overall mortality from COVID-19.

Methods

Pubmed and Medrxiv were searched using a set of terms and Boolean operators on 25/04/2020. Articles were screened for inclusion by both authors. Meta-analysis was performed in Stata 15.1 using the metan command, based on IFR and confidence intervals extracted from each study. Google/Google Scholar was used to assess the grey literature relating to government reports.

Results

After exclusions, there were 13 estimates of IFR included in the final meta-analysis, from a wide range of countries, published between February and April 2020.

The meta-analysis demonstrated a point-estimate of IFR of 0.75% (0.49-1.01%) with significant heterogeneity ($p<0.001$).

Conclusion

Based on a systematic review and meta-analysis of published evidence on COVID-19 until the end of April, 2020, the IFR of the disease across populations is 0.75% (0.49-1.01%). However, due to very high heterogeneity in the meta-analysis, it is difficult to know if this represents the 'true' point estimate. It is likely that different places will experience different IFRs. More research looking at age-stratified IFR is urgently needed to inform policy-making on this front.

Introduction

2020 saw the emergence of a global pandemic, the disease COVID-19, caused by the SARS-CoV-2 virus, which began in China and has since spread across the world. One of the most common, but difficult questions to answer during the COVID-19 pandemic has been regarding the true infection-fatality rate (IFR) of the disease. While case-fatality rates (CFR) are eminently calculable from various published data sources (1), it is far more difficult to extrapolate to the proportion of all infected individuals who have died due to the infection because those who have very mild, atypical or asymptomatic disease are frequently left undetected and therefore omitted from fatality-rate calculations (2). Given the difficulty of obtaining accurate estimates, it is not unexpected that there are wide disparities in the published estimates of infection. This is an issue for several reasons, most importantly in that policy is dependent on modelling, and modelling is dependent on assumptions. If we do not have a robust estimate of IFR, it is challenging to make predictions about the true impact of COVID-19 in any given susceptible population, which may stymie policy development and may have serious consequences for decision-making into the future. While CFR is a more commonly-used statistic, and is very widely understood among experts, IFR provides important context for policy makers that is hard to convey, particularly given the wide variation in CFR estimates. While CFR is naturally a function of the denominator – i.e. how many people have been tested for the disease – policy-makers are often most interested in the total burden in the population rather than the biased estimates given from testing only the acutely unwell patients.

This is particularly important when considering the reopening of countries post 'lockdown'. Depending on the severity of the disease, it may be reasonable to reopen services such as schools, bars, and clubs, at different timings. Another salient point is the expected burden of disease in younger age groups – while there are likely long-term impacts other than death, it will be important for future planning to know how many people in various age groups are likely to die if the infection becomes widespread across societies. Age-stratified estimates are also important as it may give countries some way to predict the number of deaths expected given their demographic breakdown.

There are a number of methods for investigating the IFR in a population. One method used successfully for influenza has been retrospective modelling studies predicting the 'true' number of cases and deaths from influenza-like illness records and/or excess mortality estimates (3, 4). This is in part due to the general difficulty in attributing influenza cases to subsequent mortality, meaning that CFRs may both overestimate and equally underestimate the true number of deaths due to the disease in a population (5). The standard test for COVID-19 involves polymerase chain reaction testing (PCR) of nasopharyngeal swabs from patients suspected of having contracted the virus. This can produce some false negatives, with one study demonstrating almost a quarter of patients experiencing a positive result following up to two previous false negatives (6). PCR is also limited in that it cannot test for previous infection. Serology testing is more invasive, requiring a blood sample, however it can determine if there has been previous infection and can be performed rapidly at the point of care (PoC). Serology PoC testing cannot determine if a person is infectious, or if infection is recent and there is risk of misinterpretation of results (7).

Given the emergence of COVID-19 as a global pandemic, it is somewhat unlikely that these issues are directly mirrored for the newer disease, but there are likely similarities between the two. Some analysis in mainstream media publications and pre-prints has implied that there is a large burden of deaths that remains unattributed to COVID-19. Similarly, serological surveys have demonstrated that there is a large proportion of cases that have not been captured in the case numbers reported in the U.S., Europe, and potentially worldwide (8-10).

This paper presents a systematic effort to collate and aggregate these disparate estimates of IFR using an easily replicable method. While any meta-analysis is only as reliable as the quality of included studies, this will at least put a realistic estimate to the IFR given current published evidence.

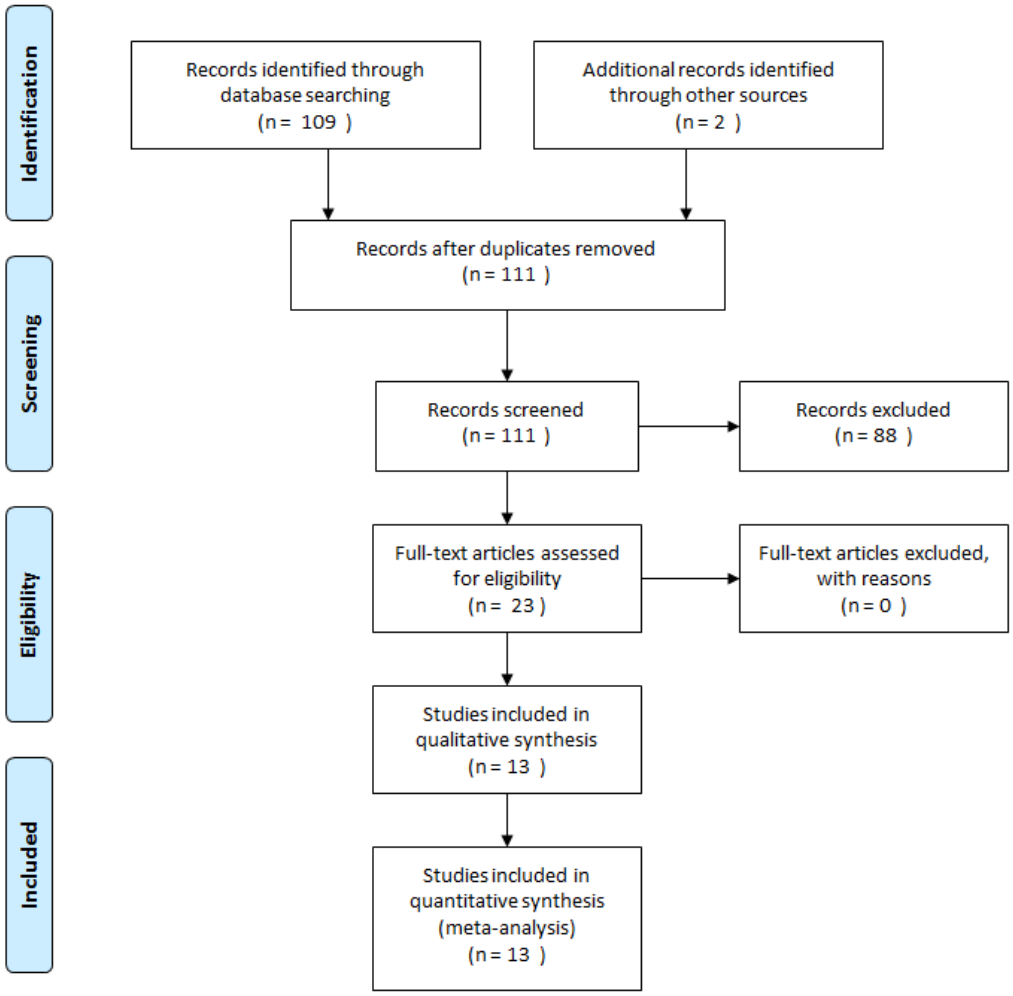
Methods

This study used a simple systematic review protocol. PubMed and Medrxiv were searched on the 25/04/2020 using the terms and Boolean operators: (infection fatality rate OR ifr) AND (COVID-19 OR SARS-CoV-2). While Medrxiv would usually be excluded from systematic review, given that the papers included are not peer-reviewed, during the pandemic it has been an important source of information and contains many of the most recent estimates for epidemiological information about COVID-19. Inclusion criteria for the studies were:

- Published in English
- Regarding COVID-19/SARS-CoV-2 (i.e. not SARS-CoV-1 extrapolations)
- Presented an estimated infection-fatality rate

Titles and abstracts were screened for eligibility and discarded if they did not meet the inclusion criteria. GMK then conducted a simple Google and Google scholar search using the same terms to assess the grey literature, in particular published estimates from government agencies that may not appear on formal academic databases. LM assessed the articles to ensure congruence. If these met the inclusion criteria, they were included in the systematic review and meta-analysis. Similarly, Twitter searches were performed to assess the evidence available on social media. Estimates for IFR and the confidence interval were extracted for each study.

All analysis and data transformation was performed in Stata 15.1. The meta-analysis was performed using the metan command for continuous estimates, with IFR and the lower/upper bounds of the confidence interval as the variables entered. This model used the DerSimonian and Laird random-effects method. The metan command in Stata automatically generates an I^2 statistic that was used to investigate heterogeneity. Histograms were visually inspected to ensure that there was no significant positive or negative skew to the results that would invalidate this methodology. For the studies where no confidence interval was provided, one was calculated.



A PRISMA flow diagram of the search methods

Sensitivity analyses were performed stratifying the results into the type of study – observational, modelling, or pre-print – by country, and by month of calculation. A further sensitivity analysis was conducted excluding outliers to examine the affect this had on the point estimate and range.

All code and data files are available (in .do and .csv format) upon request.

Results

Initial searches identified 109 studies in both databases. Searches on Google and social media revealed a further two estimates to include in the study. There were no duplicates specifically, however two pre-prints had been published and so appeared in slightly different forms in both databases. In this case, the published study was used rather than the pre-print. Results are collated in table 1.

After screening titles and abstracts, 88 studies were removed. 23 papers were assessed for eligibility for inclusion into the study, resulting in a final 13 to be included in the qualitative synthesis and meta-analysis.

Studies varied widely in design, with 4 entirely modelled estimates (11-14), 4 observational studies (8, 15-17), 4 pre-prints (2, 18-20), and one published estimate from a government report that has been widely reported and cited in a number of studies (21).

The main result from the random-effects meta-analysis is presented in Figure 1. Overall, the aggregated estimate across all 13 studies indicated an IFR of 0.75% (95% CI 0.49-1.01%), or 75 deaths per 10,000 infections. Heterogeneity was extremely high, with the overall I^2 exceeding 99% ($p<0.0001$).

Within distinct study types, there was a difference in the point-estimates for IFR. Published research had a much lower point-estimate (modelling: 0.45%, 0.22-0.69%, observational: 0.52%, 0.14-0.90%) than pre-prints (1.06%, 0.81-1.3%), although the lowest heterogeneity was seen in the pre-print research. The sensitivity analysis by month from Figure 3 showed a similar finding, with later estimates showing a higher figure (although not lower heterogeneity).

Analysing by country of origin did not appear to have a substantial effect on the findings, with both those studies from within and outside of China showing similar aggregate estimates in Figure 2. There was very significantly lower heterogeneity in studies published using Chinese data ($I^2 = 0\%$, $p>0.5$)

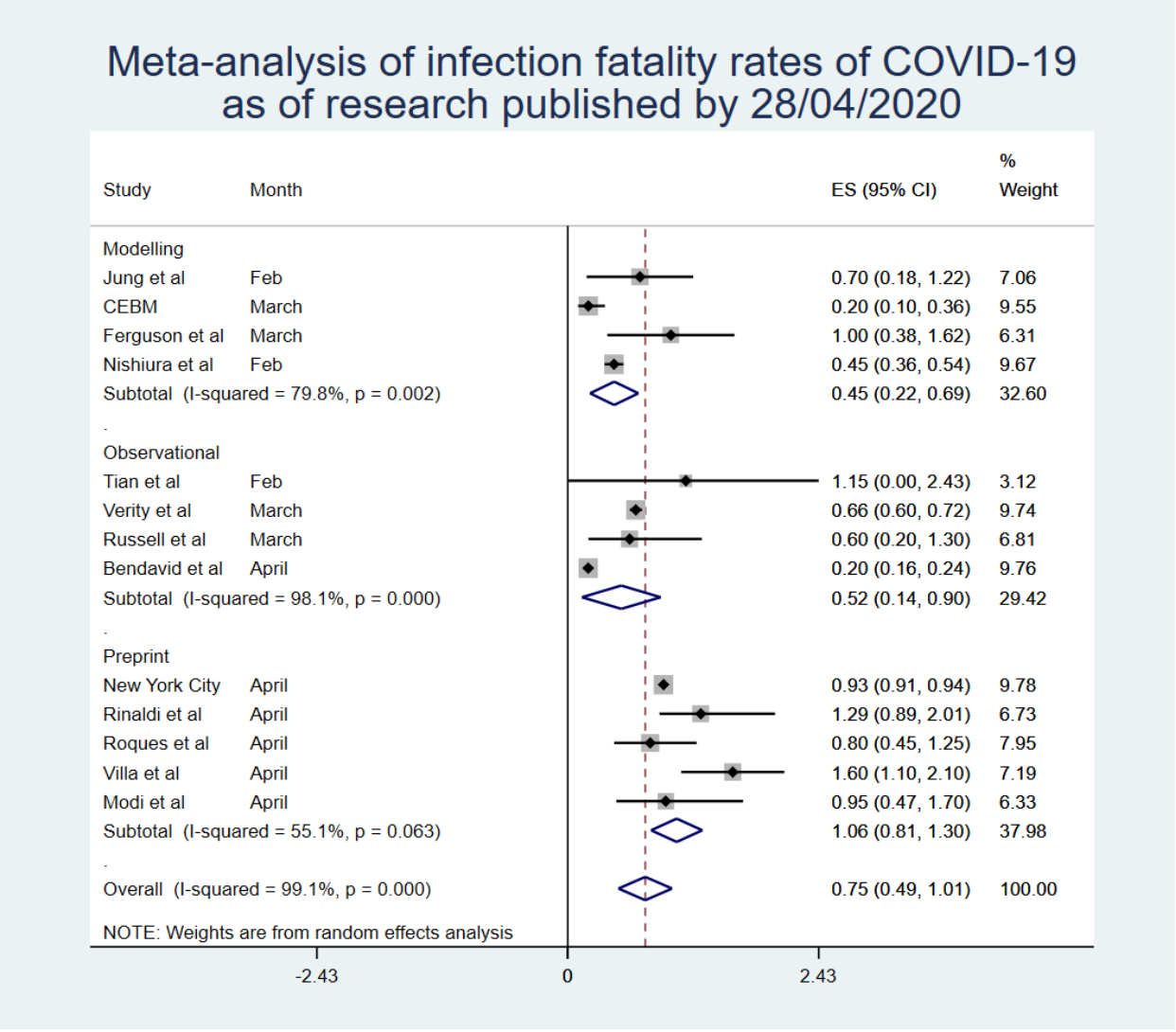


Figure 1

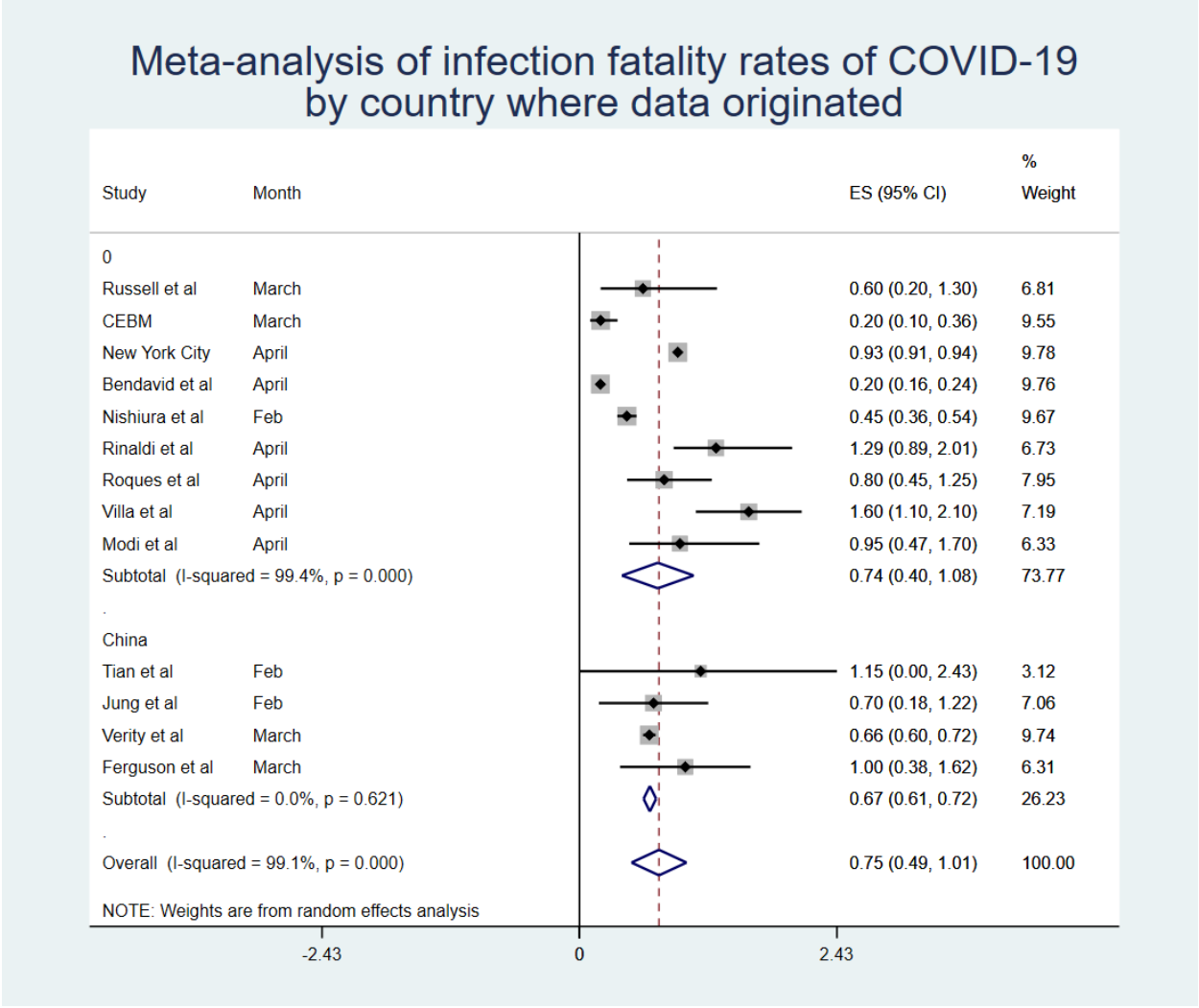


Figure 2

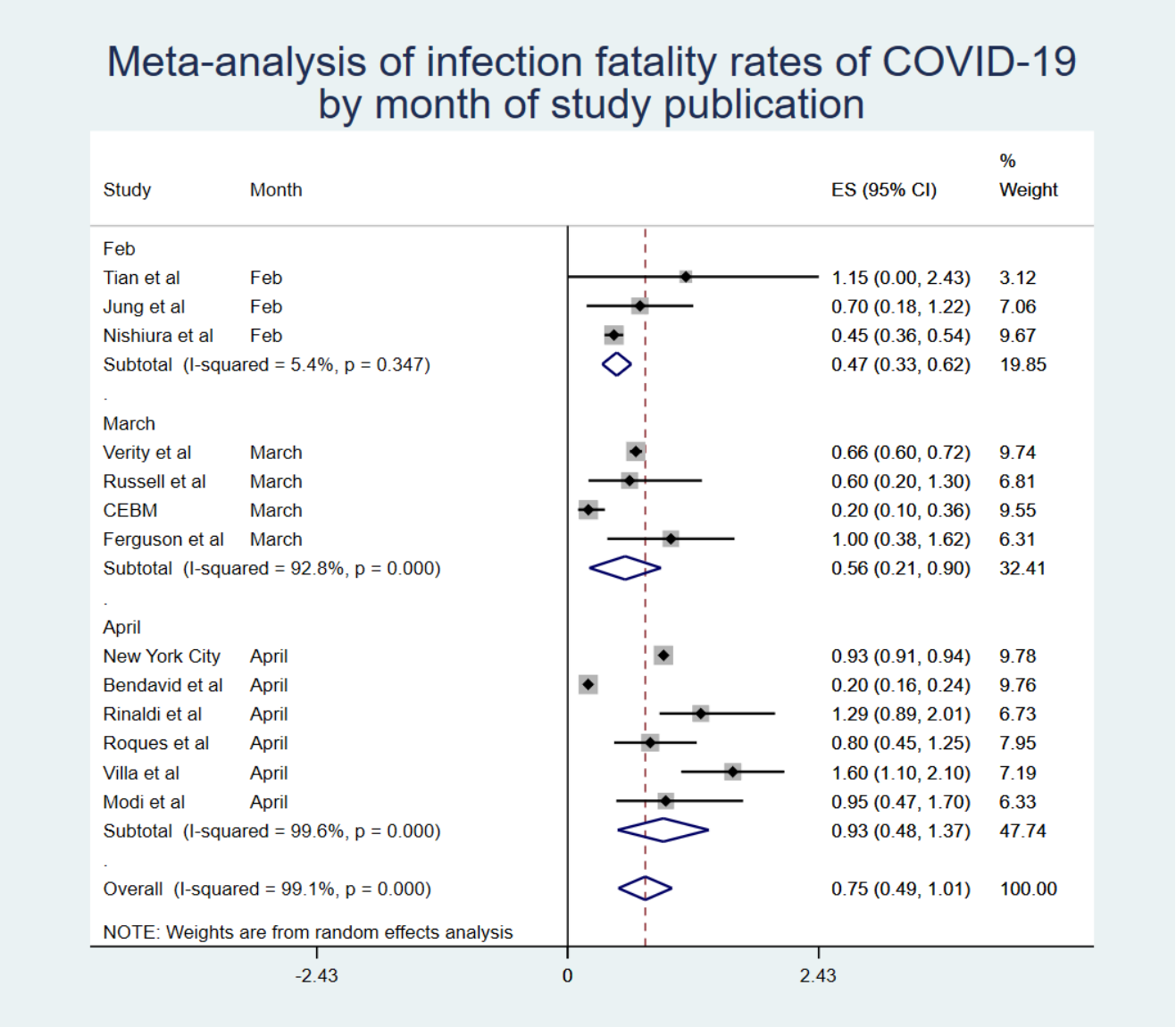


Figure 3

There were not sufficient data in the included research to perform a meta-analysis of IFR by age. However, qualitatively synthesizing the data that was presented indicates that the expected IFR below the age of 60 years is likely to be reduced by a large factor. This is supported by studies examining the CFR which were not included in the quantitative synthesis, that demonstrate a strong age-related gradient to the death rate from COVID-19.

Discussion

As pandemic COVID-19 progresses, it is useful to use the IFR when reporting figures, particularly as some countries begin to engage in enhanced screening and surveillance, and observe an increase in positive cases who are asymptomatic and/or mild enough that they have so far avoided testing (22). It has been acknowledged that there is asymptomatic carriage and that asymptomatic transmission may also be possible with COVID-19 (13, 23) and use of IFR would aid the capture of these individuals in mortality figures. IFR modelling, calculation and figures, however, are inconsistent.

The main finding of this research is that there is very high heterogeneity among estimates of IFR for COVID-19 and therefore it is difficult to draw a single conclusion regarding the number. Aggregating the results together provides a point-estimate of 0.75% (0.49-1.01%), but there remains considerable uncertainty about whether this is a reasonable figure or simply a best guess. It appears likely, however, that the true IFR from COVID-19 will lie somewhere between the lower bound and upper bounds of this estimate.

One reason for the very high heterogeneity is likely that different countries will experience different death rates due to the disease. It is very likely, given the evidence around age-related fatality, that a country with a significantly younger population would see fewer deaths on average than one with a far older population, given similar levels of healthcare provision between the two. For example, Israel, with a median age of 30 years, would expect a lower IFR than Italy, with a much higher median age (45.4 years). The sensitivity analysis by country hinted at this possibility – while there were too few studies from any one individual country to aggregate except for China, the studies only using Chinese data came to very similar conclusions.

Some included studies (2, 20) compared fatality during COVID-19 pandemic with previous years' average fatality, determining that mortality has been higher during pandemic and whilst correlation doesn't necessarily equate to causation, it is reasonable to link the events as causal given the high CFR observed across countries. It is highly likely from the data analysed that IFR increases with age-group, with those aged over 60 years old potentially experiencing the highest IFR, in one case close to 15% (20). Given the elderly are the most vulnerable in society to illness and likely to carry a higher disease burden owing to increased susceptibility and comorbidity (24, 25), the lower IFRs observed in the younger populations may skew the figure somewhat.

While not included in the quantitative synthesis, one paper did examine the extreme lower bound of IFR of COVID-19 in situations where the healthcare system has been overwhelmed. This is likely to be higher than the IFR in a less problematic situation but demonstrates that the absolute minimum in such a situation cannot be lower than 0.2%, and is likely much higher than this figure in most scenarios involving overburdened hospitals.

There are a number of limitations to this research. Importantly, the heterogeneity in the meta-analysis was very high. This may mean that the point-estimates are less reliable than would be expected. It is also notable that any meta-analysis is only as reliable as the data contained within – this research included a very broad range of studies that address slightly different questions with a very wide range of methodological rigor, and thus cannot represent certainty of any kind. While the studies were not formally graded, at least one (8) has already been critiqued for simple mathematical errors, and given that many were pre-prints it is hard to ascertain if they have provided accurate representations of the data.

This research has a range of very important implications. Some countries have announced the aim of pursuing herd immunity with regards to COVID-19 in the absence of a vaccination. The aggregated IFR would suggest that, at a minimum, you would expect 0.45-0.53% of a population to die before the herd immunity threshold of the disease (based on R0 of 2.5-3 (17)) was reached. As an example, in the United States this would imply more than 1 million deaths at the lower end of the scale.

This also has implications for future planning. Governments looking to exit lockdowns should be prepared to see a relatively high IFR within the population who are infected, if COVID-19 re-emerges. This should inform the decision to relax restrictions, given that the IFR for people infected with COVID-19 appears to be not insignificant even in places with very robust healthcare systems.

Conclusions

Based on a systematic review and meta-analysis of published evidence on COVID-19 until the end of April, 2020, the IFR of the disease across populations is 0.75% (0.49-1.01%). However, due to very high heterogeneity in the meta-analysis, it is difficult to know if this represents the 'true' point estimate. It is likely that, due to age and perhaps underlying comorbidities in the population, different places will experience different IFRs due to the disease. More research looking at age-stratified IFR is urgently needed to inform policy-making on this front.

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Table 1: number: Results of systematic review of published research data on COVID-19 infection-fatality rates

Study	Location	Study period	Method and sample size	Results
Basset *et al* 2020	New York (NYC) (USA), Madrid, Lombardy	Until 22nd April 2020 (commence date not provided)	Utilised R_0 of 2.4 to calculate a predicted infection rate of 81% (UK and USA).	Over the 3 regions, the IFR (using predicted total infection rate of 81%) was calculated at 0.17%, for each region specifically, using the same predicted

				infection rate: NYC 0.22%, Lombardy 0.15%, Madrid 0.14%.
Bendavid *et al* 2020	Santa-Clara Country	2 days	Serological testing of 3,300 local adults and children. Volunteer sampling. Bootstrap procedure used for weighted and unweighted prevalence estimates.	Crude prevalence rate 1.5% (95%CI 1.1-2.0%), unweighted population prevalence 1.2% (bootstrap 95%CI 0.7-1.8%), weighted population prevalence 2.8% (95%CI 1.3-4.7%). Number of infections estimated to be greater than number of recorded cases. IFR 0.17%.
CEBM 2020	Global	Updating as pandemic progresses	Utilises data available from official sources in countries listed.	Iceland infection rate 0.5-1%; IFR 0.05% UK IFR 0.9% (95%CI 0.4-1.4%) Diamond Princess Cruise ship IFR 1.2% (95%CI 0.38-2.7%) and CFR 2.3% (95%CI 0.75-5.3%) China CFR 1.1% (95%CI 0.3-2.4%) and IFR 0.5% (0.2-1.2%).
Ferguson *et al* 2020	USA/Great Britain (GB)	Not specified	Utilised data from China to produce age-stratified IFR. Assumptions of severity and critical care requirements based upon expert opinion.	Using R_0 of 2.4, estimated 81% of GB and USA populations will be infected over the course of the epidemic. IFR calculated to be

				in the range 0.25-1.0%.
Jung *et al* 2020	Cases exported from China and diagnosed outside China	16 days	A total of 51 cases diagnosed between 24/09/2020 and 09/02/2020. Data collected from government websites or media quoting government announcements.	Mean time from illness onset to death was 20.2 days. Estimated incidence in China on 24/01/2020 was 4718 (95%CI 3328-6278) and CFR 5.3% (95%CI 3.5-7.6%). IFR 0.5-0.8%.
Modi *et al* 2020	Italy (1688 towns)	Used data from 01/01/2015-28/03/2020	Utilised data from the Italian Institute of Statistics. Compared death rates during the COVID-19 pandemic to previous death rates by age and region.	Clear increase in deaths was noted for early 2020. IFR increases with age. Range 0.02% (40-49 years old) to 15.1% (>90 years old).
Nishiura *et al* 2020	Japanese "evacuees" returning to Japan from Wuhan	3 days	A total of 565 individuals screened for symptoms and tested for COVID-19 (PCR).	A total of 8 passengers tested PCR positive for COVID-19 (1.4%). Estimated ascertainment rate of 9.2%. Estimated IFR 0.3-0.6%.
Rinaldi *et al* 2020	Northern Italy (10 municipalities in Lombardy)	Utilised 5-year death data until April 2020	Collected data from the Italian Institute of Statistics. The total population of the included municipalities was 50563. Bayesian model used to estimate IFR.	Deaths between February and April 2020 were 5-fold the 2015-2019 average (341 versus 70). IFR 1.29% (95%CI 0.89-2.01), increasing to 4.25% for those >60 years old (95%CI 3.01-6.39%)

Roques *et al* 2020	France	54 days	Obtained data on positive cases and deaths from Johns Hopkins University Centre for Systems Science and Engineering and data on tests performed from Santé Publique France, deaths from nursing homes were added to the official count.	Calculated IFR 0.5% (95%CI 0.3-0.8), when nursing home residents were adjusted for estimated IFR 0.8% (95%CI 0.45-1.25). Estimated ratio between those actually infected and those observed was 8 (95%CI 5-12).
Russel *et al* 2020	Diamond Princess Cruise Ship	14-17 days	A total of 3711 passengers and staff were tested (PCR) whilst in quarantine. Utilised data from the World Health Organisation situational reports.	There were 619 confirmed cases (17%), 318 of whom were asymptomatic (51%). Corrected CFR was 2.6% (95%CI 0.89-6.7%). Corrected IFR was 1.3% (95%CI 0.38-3.6%). CFR increased with age (3.6% for those aged 60-69, 95%CI 3.2-4.0) and 14.8% for those >80 years, 95%CI 13.0-16.7).
Tian *et al* 2020	Beijing, China	21 days	262 cases retrospectively enrolled and characteristics compared between severe, mild and asymptomatic patients using Mann-Whitney U tests and Wilcoxon tests.	Five patients died and 46 were classified as severe. IFR in Beijing was lower than nationally; 0.9% versus 2.4% (p<0.001).
Verity *et al* 2020	Mainland China and 37	56 days	Age-stratified CFR estimates on 1334	Mean time from illness onset to

	countries outside of mainland China		cases outside mainland China. Used prevalence data from PCR-confirmed cases in international residents repatriated from China to determine IFR.	death 17.8 days (95%CI 16.9-19.2). CFR in China 1.38% (95%CI 1.23-1.53), increasing with age to 6.8% in those aged >65 years (95%CI 5.7-7.2%) and 13.4% in those aged >80 years (95%CI 11.2-15.9%). IFR 0.66% (95%CI 0.39-1.33%).
Villa *et al* 2020	Italy	32 days	Collected data from Italy's Civil Protection Agency from each of Italy's 20 regions.	Estimated an IFR of 1.1% (95%CI 0.2-2.1%) and a CFR of 12.7%.