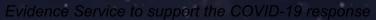
The Centre for Evidence-Based Medicine





Global Covid-19 Case Fatality Rates

March 17, 2020

Jason Oke, Carl Heneghan Updated data 7th Oct 2020

Lay Summary by Mandy Payne, Health Watch [https://www.healthwatch-uk.org/publications/covid-19/202-

covid-19-13.html]

This page is updated regularly as new information emerges. It sets out the current Case Fatality Rate (CFR) estimates, the country-specific issues affecting the CFR, and provides a current best estimate of the CFR, and more importantly, the Infection Fatality Rate (IFR).

The IFR estimates the fatality rate in all those with infection: the detected disease (cases) and those with an undetected disease (asymptomatic and not tested group).

Case Fatality Rates:

The total number of cases and the total number of deaths from COVID-19 outbreak data was drawn down (scraped) from https://www.worldometers.info/coronavirus/].

The proportion of deaths to the total numbers of cases was meta-analysed using the R function *metaprop*, using fixed-effect inverse-variance weighting. Estimates from the cruise ship 'Diamond Princess' as well as countries with **fewer than 1000 cases** are excluded from the analysis. (updated 9th April). We present country-level case fatality as a percentage along with 95% confidence intervals in a forest plot. Estimates of heterogeneity and a 95% prediction interval are presented, but a pooled overall estimate is suppressed due to heterogeneity. (<u>understanding data in meta-analysis</u>). [https://blogs.plos.org/absolutely-maybe/2017/07/03/5-tips-for-understanding-data-in-meta-analyses/]

*case fatality rate is the number of reported deaths per number of reported cases (Updated 26th May)

We previously reported estimates from meta-analyses using fixed-effect inverse-variance weighting. We still believe this to be the most appropriate for this context but have added an option to let users of this app explore how changing the method of weighting to Generalized linear mixed models (GLMMs [https://stats.idre.ucla.edu/other/mult-pkg/introduction-to-generalized-linear-mixed-models/]) impacts the prediction interval and estimated IFR.

Between countries, case Fatality rates vary significantly, and over time, which suggests considerable uncertainty over the exact case fatality rates.

- The number of cases detected by testing will vary considerably by country;
- <u>Selection bias [https://catalogofbias.org/biases/selection-bias/]</u> can mean those with severe disease are preferentially tested;
- There may be delays between symptoms onset and deaths which can lead to underestimation of the CFR;
- There may be factors that account for increased death rates such as coinfection, more inadequate healthcare, patient demographics (i.e., older patients might be more prevalent in countries such as Italy);
- There may be increased rates of smoking or comorbidities amongst the fatalities.
- Differences in how deaths are attributed to Coronavirus: dying with the disease (association) is not the same as dying from the disease (causation).

China:

In China, the CFR was <u>higher in the early stages of the outbreak</u> [https://www.worldometers.info/coronavirus/coronavirus-death-rate/#ref-12] (17% for cases from 1 to 10 January) and reduced to 0.7% for patients with symptom onset after 1 February.

Summary of a Report of 72 314 Cases From the Chinese Center for Disease Control and Prevention. [https://jamanetwork.com/journals/jama/fullarticle/2762130?guestAccessKey=bdcca6fa-a48c-4028-8406-7f3d04a3e932&utm_source=For_The_Media&utm_medium=referral&utm_campaign=ftm_links&utm_content=tfl&utm_term=022420 &mod=article_inline]. Reported in (China CDC weekly_[http://weekly.chinacdc.cn/en/article/id/e53946e2-c6c4-41e9-9a9b-fea8db1a8f51].). Update 21st March:

The epidemic curve of onset of symptoms peaked around January 23rd to 26th, then began to decline up to February 11th. Most cases were aged 30 to 79 years of age (87%), 1% aged \leq 9 years, 1% aged 10 to 19 years, and 3% 80 years or older.

The CFR was 2.3% (1023 deaths/44 672 confirmed cases). Reported CFRs by age were

Age (deaths/cases)	CFR (95% CI)
≤ 9 years (0/416)	0%
10 to 19 years (1/549)	0.18% (0.03 to 1.02%)
20 to 49 years (63/19790)	0.32% (0.25% to 0.41%)
50 to 59 years (130/10,008)	1.3% (1.1% to 1.5%)
60 to 69 years (309/8583)	3.6% (3.2% to 4.0%)
70 to 79 years (312/3918)	8.0% (7.2% to 8.9%)
≥80 years (208/1408)	14.8% (13.0% to 16.7%)

Patients with comorbid conditions had much higher CFR rates. Those with no comorbidites had a CFR of 0.9%. Critical cases had a CFR of 49%, no deaths occurred among those with mild or even severe symptoms.

- Critical cases: respiratory failure, septic shock, and/or multiple organ dysfunction/failure.
- Severe: dyspnea, respiratory rate ≥30/min, oxygen sats ≤93%, PaO₂/FiO₂ ratio
 <300, lung infiltrates >50% within 24–48 hrs

Limitation: some variables (i.e., comorbid condition and case severity) are not required fields in the Chinese CDC Infectious Disease Information System, some records have missing data.

Why is cardiovascular disease (CVD) so prevalent in those who died with COVID-19?

Most acute viral infections have three short-term effects on the CVD system: the inflammatory response can increase the risk of an acute coronary syndrome; depression of the myocardium can worsen heart failure, and inflammation can unmask heart arrhythmias. Seasonal influenza infections can increase CVD deaths significantly, and community-level rises in Influenza-like illness (ILI) lead to rises in CVD mortality:

Nature Medicine: Estimating the clinical severity of COVID-19

[https://www.nature.com/articles/s41591-020-0822-7] from the transmission dynamics in Wuhan, China~:

- Those with coronavirus symptoms in Wuhan, China, had a 1.4% (95% CI, 0.9% to 23.1%) chance of dying,
- 29th February, the crude CFR case risk, outside Hubei was 0.85%,
- Risk of symptomatic infection increased with age, maybe preferential ascertainment of older and more severe cases. *

*Because Wuhan prioritized the admission of more severe cases, the sCFR will be substantially lower than the HFR. *sCFR (s for symptomatic) defines a case as someone who is infected and shows certain symptoms; HFR (hospitalized) defines a case as someone who is infected and hospitalized.

Italy:

In Italy, there are several reasons why the CFR is higher. The age structure of the Italian population (2nd oldest in the world); highest rates of antibiotic resistance deaths in Europe (Italy tops the EU for antibiotic-resistance deaths, with nearly 1/3rd of the deaths [http://www.ansa.it/english/news/science_tecnology/2019/11/19/italy-top-in-eu-in-antibiotic-resistance_369e0123-0107-445e-8c17-f11932c9d27c.html] in the EU). Smoking also seems to be a factor associated with poor survival — in Italy, 24% smoke, 28% men. In the UK, for instance, 15% are current smokers.

Coronavirus: Is Covid-19 the cause of all the fatalities in Italy?

[https://www.stuff.co.nz/national/health/coronavirus/120443722/coronavirus-is-covid19-really-the-cause-of-all-the-fatalities-in-italy] Sarah Newy reports Italy's death rate might also be higher because of how fatalities are recorded. In Italy, all those who die in hospitals with Coronavirus are included in the death counts.

In this <u>article_[https://www.stuff.co.nz/national/health/coronavirus/120443722/coronavirus-is-covid19-really-the-cause-of-all-the-fatalities-in-italy]</u>, Professor Walter Ricciardi, Scientific Adviser to, Italy's Minister of Health, reports, "On re-evaluation by the National Institute of Health, only 12 per cent of death certificates have shown a direct causality from coronavirus, while 88% patients who have died have at least one pre-morbidity – many had two or three."

Recording the numbers of those who die **with** Coronavirus will inflate the CFR as opposed to those that died **from** Coronavirus, which will deflate the CFR.

Report from the Italian National Institute of Health: a

[https://www.epicentro.iss.it/coronavirus/bollettino/Report-COVID-2019 17 marzo-v2.pdf].nallysed 355 fatalities and found only three patients (0.8%) had no prior medical conditions. See Table 1 in the paper; (99% who died had one pre-existing health condition): 49% had three or more health conditions; 26% had two other 'pathologies', and 25% had one.

The most common problems in the 355 who died were: 76% high blood pressure; 36% diabetes, and 33% ischemic heart disease.

The average age of deceased and COVID-19 positive patients was 79.5 years (median 80.5, range 31-103). The median age of those that died was >15 years higher than patients who contracted the infection (median age: died 81 years – infected 63 years).

Case-fatality rate estimates by age and sex.

Data comes from cases diagnosed by regional reference laboratories (N = 73,780).

Source [https://www.epicentro.iss.it/coronavirus/bollettino/Bollettino-sorveglianza-integrata-COVID-19 26-marzo%202020.pdf]

Produced by the Istituto Superiore di Sanità (ISS) the data is collected through a dedicated web platform and includes all the cases of COVID-19 diagnosed by the regional reference laboratories. The data are updated daily by Region although some information may take a few days to come through.

Age effects by age band:*

*The Statistical model used is a grouped-binomial logistic regression with log-link function with main effects for age-band and sex (no two-way interaction terms). Deviance statistic is 30.9 on 6 degrees of freedom.)

	Females		Males	
Age band	CFR (%)	95% CI	CFR (%)	95% CI
30-39	0.26	0.16 to 0.42	0.43	0.27 to 0.69
40-49	0.55	0.43 to 0.70	0.91	0.72 to 1.16
50-59	1.23	1.08 to 1.40	2.05	1.81 to 2.33
60-69	4.02	3.71 to 4.34	6.67	6.22 to 7.15
70-79	11.86	11.26 to 12.50	19.71	18.98 to 20.47
80-89	17.94	17.11 to 18.80	29.81	28.78 to 30.87
>=90	19.41	18.05 to 20.88	32.26	30.01 to 34.68
Marginal estimates of the case-fatality rate by age.				

The risk ratios give the ratio of case-fatality rate in one age-band with the case-fatality rate in the reference age-band (here set to age 60-69).

Category	Risk ratio	95% CI
Age 30-39	0.06	0.038 to 0.10

Category	Risk ratio	95% CI	
Age 40-49	0.14	0.11 to 0.17	
Age 50-59	0.31	0.27 to 0.35	
Age 60-69 (Reference)	1.00	_	
Age 70-79	2.95	2.7 to 3.2	
Age 80-89	4.47	4.1 to 4.8	
Age 90+	4.83	4.4 to 5.3	
Female	1.00	_	
Male	1.66	1.58 to 1.74	
Rate ratio estimates (95% CI) for CFR under independence model			

For example, a ratio of 4.47 (aged 80 to 89) means that the case fatality rate is 4.47 times higher than those aged 60 to 69. For people aged 40 to 49 the case fatality rate is (1-0.14)*100 = 86% lower than in people aged 60-69. Similarly, the case-fatality rate for men was 66% higher than the case-fatality rate in women.

Health professionals only

Age band	Cases (n)	Deaths	CFR (%)
18-29	474	0	0.00
30-39	1068	0	0.00
40-49	1819	0	0.00
50-59	2193	5	0.23
60-70	780	6	0.77
Total	6334	11	0.17

Distribution of cases, deaths and case-fatality in health professionals - data is in the consolidation phase and does not include cases with unknown age

Iceland: (Update 28th March)

<u>Iceland has tested a higher proportion [https://nordiclifescience.org/covid-19-first-results-of-the-voluntary-</u> screening-on-iceland/] of people than any other country (9,768 individuals), equivalent to 26,762 per million inhabitants the highest in the world (as a comparison, South Korea has tested 6,343 individuals).

Screening suggests 0.5% are infected; the correct figure is likely higher due to asymptomatics and many not seeking testing: estimates suggest the real number infected is 1% [https://nordiclifescience.org/covid-19-first-results-of-the-voluntary-screening-on-iceland/].

Iceland, (1st May) reports ten deaths in 1798 patients, CFR. 0.56%. If we assumed 1% of the population (364,000) is infected, then the corresponding IFR would be 10/3640 = 0.3%. Iceland's test and quarantine measures may have shielded the elderly group, and deaths may still go up as they lag infection by about two weeks.

Iceland's higher rates of testing, the smaller population, and their ability to ascertain all those with Sars-CoV-2 means they can obtain. an accurate estimate of the CFR and the IFR during the pandemic (most countries will only be able to do this after the pandemic).

Current data from Iceland suggests their IFR is somewhere between 0.3% and 0.56%.

United Kingdom:

Impact assessment of non-pharmaceutical interventions (NPIs) to reduce COVID-19 mortality and healthcare demand [https://spiral.imperial.ac.uk:8443/handle/10044/1/77482]

Imperial College, London, modelled the impact of COVID-19, interventions to reduce the spread and case fatality.

Summary of their assumptions: <u>Impact assessment of non-pharmaceutical interventions</u> (NPIs) to reduce COVID-19 mortality and healthcare demand pdf. [https://www.cebm.net/wp-content/uploads/2020/03/Impact-assessment-of-non-pharmaceutical-interventions-NPIs-to-reduce-COVID-19-mortality-and-healthcare-demand-.pdf]

Infection Fatality Rate (IFR) estimates were based on <u>Verity et al.</u>

[https://www.medrxiv.org/content/10.1101/2020.03.09.20033357v1] and adjusted for a non-uniform attack rate to give an IFR of 0.9% (95% credible interval 0.4%-1.4%).

Published in MedRxiv [https://www.medrxiv.org/content/10.1101/2020.03.09.20033357v1] (preprint and not been peer-reviewed) [https://www.medrxiv.org/content/what-unrefereed-preprint]. Verity obtained agestratified CFR estimates from China and individual data on 1,334 cases identified outside of mainland China. Verity et al. [https://www.medrxiv.org/content/10.1101/2020.03.09.20033357v1] estimated an overall IFR for China of 0.66% (0.39%,1.33%) that increased with age.

Comparison with Swine Flu

The overall case fatality rate as of 16 July 2009

[https://www.reutosurveillance.org/content/10.2807/ese.14.33.19309-en] (10 weeks after the first international alert) with pandemic H1N1 influenza varied from 0.1% to 5.1% depending on the country. The WHO reported that swine flu ended up with a <u>fatality rate of 0.02%</u> [https://www.reuters.com/article/us-health-flu-who/world-must-prepare-for-inevitable-next-flu-pandemic-who-says-idUSKBN1QS1EP].

An analysis of the new pandemic influenza A/(H1N1)pdm09

[https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4910438/#R10].virus reported, a total of 18,631 deaths among the laboratory-confirmed cases, yielding a fatality rate of 2.9% (95% CI 0.0-6.7%), with an estimated fatality rate of 0.02% among all infected individuals.

Effect of concurrent infections

Highest peak rate ratios for admissions [https://academic.oup.com/jpubhealth/article/30/1/91/1577196] are in those years where the confirmed simultaneous circulation of Influenza LIke Illness (ILI) and acute bronchitis occur. Between 1990–91 to 2004–05 respiratory admissions of ≥65 years in England and Wales were analysed. The ILI peaked was highly variable: the earliest during mid-November (week 46, 1993–94) and the latest, late February/early March (week 7, 1997–98).

Diamond Princess Cruise Ship

On the *Diamond Princess*, initial estimates reported six deaths out of 705 who tested positive: CFR of 0.85%. All six deaths six occurred in patients > 70. No one under 70

Estimating the infection and case fatality ratio for COVID-19

[https://www.medrxiv.org/content/10.1101/2020.03.05.20031773v2] using age-adjusted data from the outbreak on the Diamond Princess cruise ship. Comparing deaths onboard with expected deaths based on naive CFR estimates using China data estimated a CFR 1.1% (95% CI: 0.3-2.4%); IFR 0.5% (95% CI: 0.2-1.2%).

Nature published an update on <u>what the cruise-ship outbreaks reveal about COVID-19</u>
[https://www.nature.com/articles/d41586-020-00885-w]

Japanese officials performed > 3,000 tests on the Diamond Princess. <u>Estimating the infection and CFR for COVID-19 [https://www.medrxiv.org/content/10.1101/2020.03.05.20031773v2] using age-adjusted data from the outbreak on the Diamond Princess cruise ship using the age structure of the onboard population and modelled that on naive CFR estimates using China data reported:</u>

- Onboard CFR as 2.3% (0.75%-5.3%),
- Onboard IFR as 1.2% (0.38-2.7%),
- Estimated China CFR as 1.1% (95% CI: 0.3-2.4%); and IFR as 0.5% (95% CI: 0.2-1.2%).

By the 14 April, 14 people had died who were passengers on the ship. The last of these, a Japanese male in his 70s dies nearly 3monhs after the ship outbreak.

By May 1st over 40 cruise ships

[https://en.wikipedia.org/wiki/2020 coronavirus pandemic on cruise ships#Summary of confirmed cases on board] have had confirmed positive cases of coronavirus.

Estimating COVID-19 Case Fatality Rates (CFR) Update 9th April:

As of the 30th April, the CFR prediction interval is 0.82-9.64% – the lowest end of the current prediction is 0.82% interval and in line with several other estimates.

Evaluating CFR during a pandemic is, however, a very hazardous exercise, and highend estimates should be treated with caution as the H1N1 pandemic highlights that original estimates were out by a factor greater than 10.

We now want to draw your attention to the flaws in CFR estimation due to the changing nature of the testing regimes.

Italy: A <u>change in strategy on Feb 25 [http://www.cidrap.umn.edu/news-perspective/2020/03/italian-doctors-note-high-covid-19-death-rate-urge-action].</u> Ilimited testing to patients who had severe signs and symptoms also resulted in a 19% positive rate (21,157 of 109,170 tested as of Mar 14) and an apparent increase in the death rate—from 3.1% on Feb 24 to 7.2% on Mar 17—patients with milder illness were no longer tested.

In the UK, only patients deemed ill enough to require at least one night in hospital met the criteria for a COVID-19 test. Modes. are also starting to accrue that suggest the number of people infected is much higher than [https://www.edgehealth.co.uk/post/covid23march2020] what testing alone identifies, and that the number infected is much higher in denser populations.

CFRs across countries are, therefore, highly variable, depending on who is tested for what reasons. There is no consistency. See CFR figures by countries over time:

- CFRS 0% to 4% by country 15/04/2020 [https://www.cebm.net/wp-content/uploads/2020/03/tsplotparta2020-04-15.pdf]
- CFRS more than 4% by country 15/04/2020 [https://www.cebm.net/wp-content/uploads/2020/03/tsplotpartb2020-04-15.pdf]

Estimating COVID-19 Infection Fatality Rates (IFR)

The current COVID outbreak seems to be following previous pandemics: initial CFRs start high and trend downwards. For example, In Wuhan, the CFR has gone down from 17% in the initial phase to near 1% in the late stage. It is increasingly clear that current testing strategies are not capturing everybody. In South Korea, considerable numbers who tested positive were also asymptomatics- likely driving the rapid worldwide spread. [https://www.wbay.com/content/news/Asymptomatic-people-may-be-driving-spread-of-coronavirus-568831221.html]

CFR rates are subject to selection bias as more severe cases are tested – generally those in the hospital settings or those with more severe symptoms. The number of currently infected asymptomatics is uncertain: estimates put it at least a half are asymptomatic; the proportion not coming forward for testing is also highly doubtful (i.e. you are symptomatic, but you do not present for testing). Therefore we can assume the IFR is significantly lower than the CFR.

Emerging evidence suggests many more people are infected. than tested. In Vo Italy [https://www.theguardian.com/commentisfree/2020/mar/20/eradicated-coronavirus-mass-testing-covid-19-italy-vo], at the time the first symptomatic case was diagnosed, about 3%, had already been infected — most were completely asymptomatic.

We could make a simple estimation of the IFR as <u>0.35%</u>, based on halving the lowest boundary of the CFR prediction interval in Europe. However, the considerable uncertainty over how many people have the disease, the proportion <u>asymptomatic</u> [https://www.cebm.net/covid-19/covid-19-what-proportion-are-asymptomatic/].(and the demographics of those affected) means this IFR is likely an overestimate.

In Swine flu, the IFR ended up as 0.02%, fivefold less than the lowest estimate during the outbreak (the lowest estimate was 0.1% in the 1st ten weeks of the outbreak). In Iceland, where the most testing per capita has occurred, the IFR lies somewhere between 0.03% and 0.28%.

Taking account of historical experience, trends in the data, increased number of infections in the population at largest, and potential impact of misclassification of deaths give a presumed estimate for the COVID-19 IFR somewhere between 0.1% and 0.35%.*

Data from COVID deaths in Gangelt, Germany, suggests an IFR of 0.37%. <u>A random sample of 1,000 residents of Gangelt [https://www1.wdr.de/nachrichten/rheinland/grosse-resonanz-auf-coronastudie-gangelt-100.html]</u> found that 14% were carrying antibodies (2% were detected cases), which led to the lowering of the IFR estimates

*Demographic changes in the population will vary the IFR significantly. If younger populations are infected more the IFR will be lower. Comorbidities will have a significant

impact to increase the IFR: the elderly and those with ≥ 3 comorbidities are at much higher risk.

A single estimate of IFR across all age groups is unhelpful particularly given the significant changes in risk of death with age. The IFR will also vary substantially based on country demographics such as age.

Modelling the data on the prevalence of comorbidities is also essential to understand the CFR and IFR by age (the prevalence of comorbidities is highly age-dependent and is higher in socially_deprived_[https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(12)60240-2/fulltext] populations). It is also not clear if the presence of other circulating influenza illnesses acts to increase the IFR (testing for co-pathogens is not occurring). And whether certain populations (e.g., those with heart conditions) and also in areas of high social deprivation put people at more risk of dying.

- In those without pre-existing health conditions, and over 70, the data suggests the IFR will likely not exceed 1%.
- Mortality in children seems to be near zero (unlike flu) which is also reassuring and will act to drive down the IFR significantly.

It is now essential to understand whether individuals are dying with or from the disease. Understanding this issue is critical. If, for instance, 80% of those over 80 die with the disease then the CFR would be near 3% in this age group as opposed to 15%. Cause of death information from death certificates is often inaccurate and incomplete

[https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4808686/], particularly for conditions such as pneumonia.

These factors would act to lower the IFR.

Antibody testing will provide an accurate understanding of how many people have been infected so far, and permit a more accurate estimate of the IFR.

We do not currently have a good understanding of <u>What proportion are asymptomatic?</u>

[https://www.cebm.net/covid-19/covid-19-what-proportion-are-asymptomatic/]

We are tracking excess mortality (<u>Assessment of Mortality in the Covid-19 outbreak to understand this phenomenon</u>) [https://www.cebm.net/covid-19/england-and-wales-mortality-during-the-covid-19-outbreak/] to determine how many excess deaths occur during the pandemic. Accurate data on deaths and cause of death (which is not forthcoming) is vital to determine the effect of the COVID pandemic.

*Estimating CFR and IFR in the early stage of outbreaks is subject to considerable uncertainties, the estimates are likely to change as more data emerges.

See Lancet report: [https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(20)30195-X/fulltext? fbclid=lwAR0z2mTiZ4D4itGAzVM9WhiNgSYuYIH48MDIYIWXqXqGLn1Xdblwcsk2wM4]. CFRs on mortality rate estimates can be misleading if the CFR is based on the number of deaths per number of confirmed cases at the same time.

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We welcome more critiques/questions on this article, and we are keeping the CFR under daily review.

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Estimating Case fatality rates in the early stage of outbreaks is subject to considerable uncertainties, the estimates are likely to change as more data emerges.

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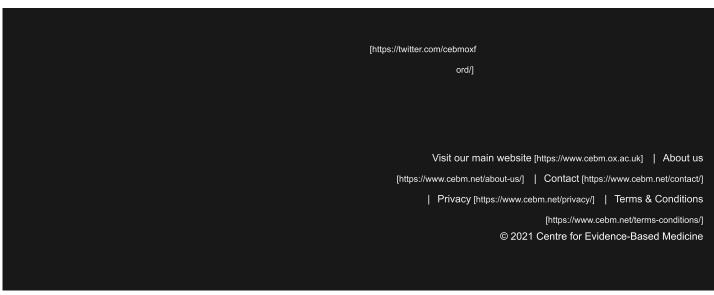


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