

## Coronavirus Pandemic

# As COVID-19 cases, deaths and fatality rates surge in Italy, underlying causes require investigation

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### Abstract

COVID-19 case fatalities surged during the month of March 2020 in Italy, reaching over 10,000 by 28 March 2020. This number exceeds the number of fatalities in China (3,301) recorded from January to March, even though the number of diagnosed cases was similar (85,000 Italy vs. 80,000 China). Case Fatality Rates (CFR) could be somewhat unreliable because the estimation of total case numbers is limited by several factors, including insufficient testing and limitations in test kits and materials, such as NP swabs and PPE for testers. Sero prevalence of SARS-CoV-2 antibodies may help in more accurate estimations of the total number of cases. Nevertheless, the disparity in the differences in the total number of fatalities between Italy and China suggests that investigation into several factors, such as demographics, sociological interactions, availability of medical equipment (ICU beds and PPE), variants in immune proteins (e.g., HLA, IFNs), past immunity to related CoVs, and mutations in SARS-CoV-2, could impact survival of severe COVID-19 illness survival and the number of case fatalities.

**Key words:** novel coronavirus; COVID-19; Italy; Case Fatality Rates, SARS-CoV-19; immunity.

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In five weeks, the number of COVID-19 deaths in Italy jumped from 21 to an astounding 3,200 by 20 March and increased to over 9,000 deaths by 28 March 2020 [1-3]. In absolute terms, this exceeds the January to March COVID-19 epidemic in China, where less than 3,301 COVID-19 deaths were reported [3]. In terms of case fatality rates (CFR), Italy now stands at a CFR of 10.6% and China has a CFR of 4% [4]. The extraordinary differential of absolute numbers of fatalities and the large differences in CFR has many seeking the underlying causes in the large differences between the two countries.

To put the situation into perspective and to accurately calculate the CFR, the total number of cases and infections has to be determined. At present, the number of laboratory-confirmed cases of COVID-19/SARS-CoV-2 in Italy stands at 92,472 and in China about the same number at 82,230 [3] (See Table 1). Are these accurate numbers for the total number of cases in each country? That question has been raised many times and the reality is that these numbers are likely

underestimates of the total number of cases. The cases now are defined as positive for viral infection using a test for SARS-CoV-2 viral nucleic acids, usually PCR based. China had at one point used a different method of case definition; however, cases are now defined as PCR positive. Are the number of cases accurate for Italy? First, the number of asymptomatic cases is unlikely to be tested if individuals were community infections. Second, during peak surge times for testing, it is unlikely people with mild cases of COVID-19 will seek testing or medical care. Third, even serious cases of COVID-19 disease may be unable to seek testing and receive medical attention. Fourth, there could be limiting factors in testing itself; for example, the test kits may be limited as was the case in the United States for much of the early stages of the epidemic in the USA, or material needed to do testing, such as nasopharyngeal swabs (NP swabs), may be in short supply, which is true in Italy, Spain, the USA, Canada, and probably more countries. Furthermore, PPE (especially N95 masks) are globally in short supply,

limiting the number of protected health-care workers who can take samples safely hence limiting the number of samples taken.

Other methods of estimating the total number of cases are needed. One very instrumental method is measuring sero prevalence of antibodies specific for SARS-CoV-19/COVID-19 in the general population. While these numbers will not cover fatalities, they will give good estimates of the number of people who have had the infection and recovered. This data will also be useful for vaccine design and implementation. To accomplish sero testing will require available reagents coming online and concerted efforts from governments and their general populations to obtain representative statistics of key groups. Several commercial kits are now available, so the data should begin coming in over the next few weeks to months.

Even though the total number of COVID-19 cases in Italy is subject to question, the total number of COVID-19 deaths is reliable [2,3] and large in comparison to the total number of deaths in China. Certainly, differences in demographics may play a role in case fatalities. Italy has one of the oldest populations in the world with a medium age of 45-6 [5], and given that the mean age of COVID-19 deaths is 81 [2], it is understandable that Italy would have higher numbers than China. Interestingly, Italy has an excellent health-care system based on world comparisons [6]; however, ICU beds were at 90% capacity before the COVID-19 surge in Northern Italy [7]. Sadly, the advancement in treatments in cardiovascular disease over the past 20 years may have resulted in a fertile population for SARS-CoV-2 infection and serious COVID-19 disease in Italy. Over 90% of the deaths in Italy had at least one underlying illness [2] and cardiovascular disease was found in greater than 70% of patients where data was available [3].

Of course, other factors may be important for the increased number of fatalities. A shortage in ICU beds and ventilators is easy to identify as contributing to

increased risk of death during epidemic surges and probably resulted in increased fatalities in Italy and Spain. For future reference, reassessment of hospital needs during epidemic/pandemic surges will need to be formulated. Some crucial numbers may be the number of ICU or hospital beds per high-risk populations and not necessarily ICU beds per capita (e.g., 100,000 people). In the case of Italy, the number of ICU beds for COVID-19 per age group may be more helpful in building models for pandemic preparedness.

The differences between Italy and China regarding host immune responses may also be dependent on past exposure to related coronaviruses viruses and establishing partial immunity to COVID-19/SARS-CoV-2. Once again, sero surveillance studies examining the prevalence of antibodies to related viruses may help in deciphering the importance of pre-existing immunity. Mutations in circulating strains of SARS-CoV-2 in Italy must be examined to ensure the Italian virus does not have increased virulence.

Lastly, population distribution of HLA types and other variations in immune proteins could possibly determine the tempo of host immune responses to SARS-CoV-2/COVID-19 and survival from infection. Research studies on a global scale will be necessary to answer many of these questions. For now, the absolute number of deaths due to COVID-19 is much higher and the apparent CFR is much higher in Italy than it is in China.

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**Table 1.** Case Fatality Rate comparison among most impacted countries.

Country	Total Cases	Deaths	CFR (%)
Italy	92,472	10,023	10.8
Spain	72,248	5,690	7.9
France	37,575	2,314	6.2
United Kingdom	17,089	1,019	6.0
China	82,230	3,301	4.0
USA*	123,828	2,231	1.8
Germany	52,547	389	0.7

Data from WHO.INT (March 29, 2020). \*USA data from <https://www.worldometers.info/coronavirus/country/us/> March 29, 2020.

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