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Excess Mortality from COVID-19: Lessons Learned from the Italian Experience

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Abstract

There is much discussion among clinicians, epidemiologists, and public health experts about why case fatality rate from COVID-19 in Italy (at 13.3% as of April 20, 2020, versus a global case fatality rate of 6.9%) is considerably higher than estimates from other countries (especially China, South Korea, and Germany). In this article, we propose several potential explanations for these differences. We suggest that Italy's overall and relative case fatality rate, as reported by public health authorities, is likely to be inflated by such factors as heterogeneous reporting of coronavirus-related fatalities across countries and the iceberg effect of under-testing, yielding a distorted view of the global severity of the COVID-19 pandemic. We also acknowledge that deaths from COVID-19 in Italy are still likely to be higher than in other equally affected nations due to its unique demographic and socio-economic profile. Lastly, we discuss the important role of the stress imparted by the epidemic on the Italian healthcare system, which weakened its capacity to adequately respond to the sudden influx of COVID-19 patients in the most affected areas of the country, especially in the Lombardy region.

Keywords: COVID-19; case fatality rate; Italy; testing; health care system; demographics; comorbidites; epidemiological trends

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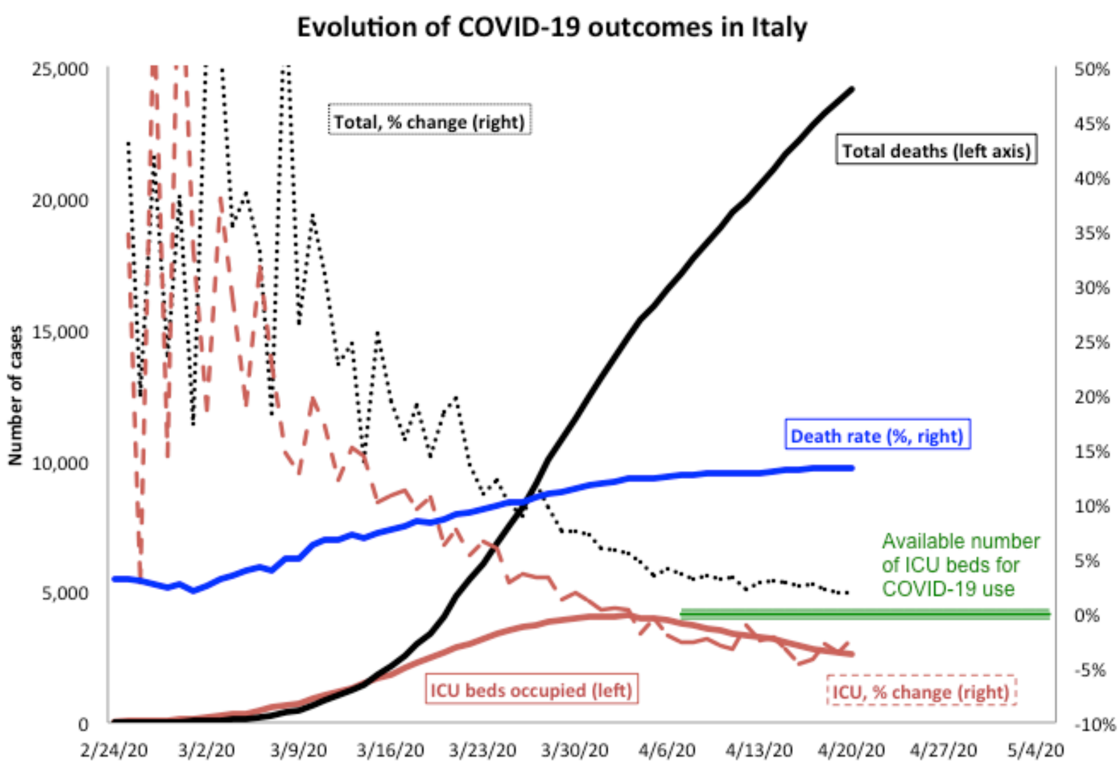
There is much discussion among clinicians, epidemiologists and public health experts about why case fatality rates from COVID-19 in Italy (at 13.3% as of April 20, 2020, blue solid line in Figure 1, versus a global case fatality rate of 6.9% [1]) are considerably larger than in other countries (especially China, South Korea, Germany, and Japan). In this article, we attempt to put forward several potential explanations underlying these differences in case fatality rates across countries, with special emphasis on the apparent excess fatalities from COVID-19 in Italy.

Figure 1. *COVID-19 case fatality rates in Italy*

Calculations by the authors from data available at [19] through April 20, 2020. Specifically, *total deaths* (black solid line, left axis, plotted versus date) is the cumulative total number of deaths Italy is attributing to COVID-19 in its daily DPC news release; *ICU beds occupied* (red solid line, left axis) is the cumulative total number of ICU units occupied by COVID-19 patients according to this report; the corresponding daily *% changes* are plotted (black dotted and red dashed lines, respectively) on the right axis; the *available number of ICU beds for COVID-19 use* (green shaded line, left axis) is estimated at 4,125, i.e., a 55% utilization of the total available supply of ICU beds in Italy prior to the pandemic (7,500, given an estimate of 12.5 ICU beds per 100,000 inhabitants [11], on the basis of a population of 60 million); lastly, the *death rate* (blue solid line, right axis) is the ratio of cumulative total deaths to cumulative total positive COVID-19 tests, also from Italy's DPC.



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1. Demographics

As widely reported, the novel Severe Acute Respiratory Syndrome CoronaVirus-2 (SARS-CoV-2) appears to be most harmful to male elderly [2] and Italy has one of the oldest populations globally, with a relatively large percentage of older adults (≥ 65 years of age), corresponding to nearly one fourth of the general population [3]. Thus, while in Italy the novel coronavirus spread quickly among its oldest, in other nations such as South Korea (a younger country to begin with) the coronavirus spread among the (younger female) members of a fringe religious group before reaching the general population.

In addition, Italy's elderly population is well-integrated within Italian society. For instance, Italian elderly usually live with their extended, multi-generation families, and actively participate in the life of their communities [4]. While socially beneficial, this integration may have facilitated the exposure of this vulnerable population subgroup to infection much more than in other high-income countries.

Lastly, many Italian elderly live in small towns, where access to testing and high-quality medical care may not have been immediate. Accordingly, data from the Italian Istituto Superiore di Sanità (ISS) clearly showed the skewed distribution of the demographic profile of COVID-deceased individuals in Italy, with median age of around 81 years [2].

2. Chronic comorbidities

The novel coronavirus appears to be especially harmful to people with pre-existing chronic conditions, which are highly prevalent in the general population and especially among the elderly [2]. For example, hypertension, type 2 diabetes, ischemic heart disease, atrial fibrillation, cancer, chronic kidney disease, stroke and COPD were among the most common comorbidities consistently associated with COVID-19 related Italian fatalities in the ISS reports [2] [5].

More specifically, in terms of background risk for respiratory disease [6] [7], Italy's elderly population appears to display these conditions at a much greater rate than Germany and at a greater rate than other European countries (see, e.g.,

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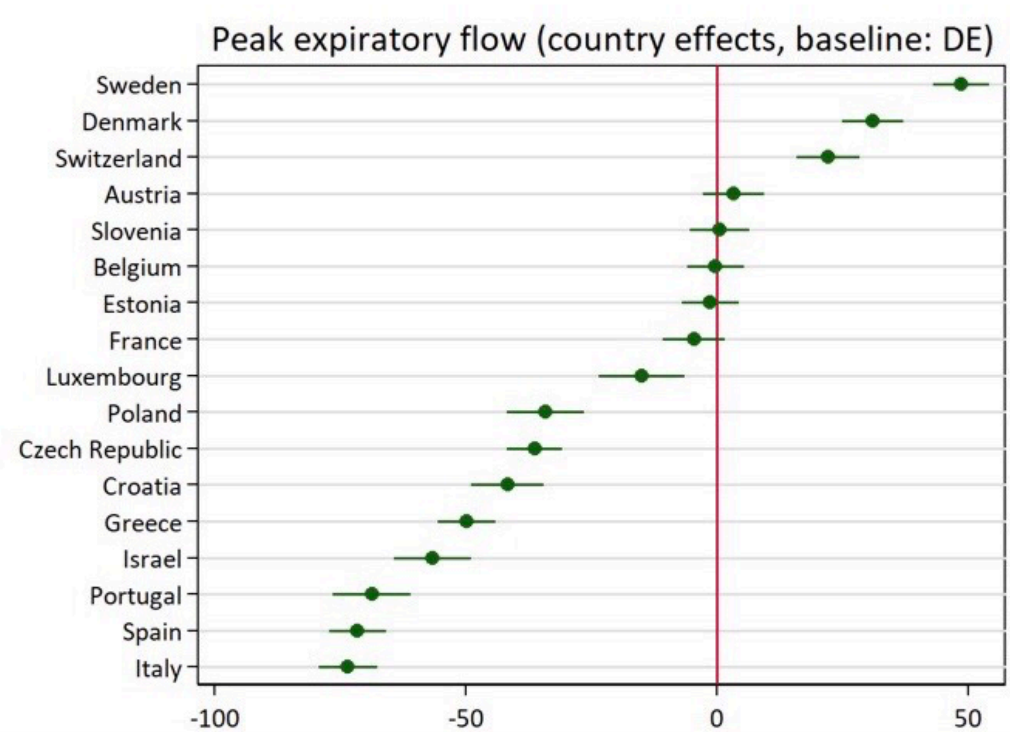
Figure 2; PEF = Peak Expiratory Flow [6]), perhaps because of smoking habits (including possibly a large prevalence of former smokers among male elderly) or high-degree of air pollution in Northern Italy. China (also a country with high prevalence of male smokers) has much higher rates of both, but its population is also much younger.

Figure 2. *Peak Expiratory Flow (PEF) relative to Germany*

Estimation based on a cross-country panel regression of PEF data (38,295 observations) in Wave 6 of the Survey on Health, Ageing and Retirement in Europe (SHARE) after controlling for age, self-reported health, gender, weight, and height [6].



3. Definition of COVID-related deaths

In absence of consistent international guidelines [8] [9], there may be considerable discrepancies among countries in distinguishing deaths from other causes while being infected with COVID. In particular, to our understanding, Italy is currently labeling a COVID-related death as any death where the patient had tested positive to the virus, independent of the primary underlying cause of morbidity. The cumulative total number of so-labeled deaths in Italy (black solid line in Figure 1) has reached 24,114 as of April 20, 2020 (D in the Appendix), although its growth has considerably slowed down in the last few weeks (black dotted line in Figure 1). Other countries may be using a much less expansive definition of COVID-death, e.g., as one that is induced directly by the virus (as in Germany), which might further explain some of the inconsistencies in case fatality rates observed worldwide.

Accordingly, many experts recommend caution when estimating case fatality rates as the ratio of total deaths to total infected individuals *during* an epidemic, since (as we discuss further next) at the time it is calculated there is likely a non-trivial portion of both patients and outcomes that are going underreported. For instance, Battegay et al. [10] go as far as to state that "*a precise estimate of the case fatality rate is therefore impossible at present*."

4. Effect of COVID-19 on the Italian National Health System

One of the most worrisome aspects of the novel coronavirus pandemic is the stress it has been imposing on the local provision of health care.

In particular, intensive care units (ICUs) of local and regional hospitals in Italy in general, and especially the Lombardy region, had to deal with thousands of patients with severe acute respiratory syndromes induced by COVID-19. This nearly exhausted the available provision not only of ICU beds (see red solid versus green shaded lines in Figure 1; despite being among the largest per capita in Europe, albeit well behind Germany [11]), but also of respirators and ventilators [12].

In addition, the epidemic progressed at a speed that made adding capacity challenging, at a time when the global supply chain is stretched and in some cases broken [13]. This suggests that some patients may not have received the best possible care, leading to worse health outcomes. These events are remarkable, since Lombardy is one of the wealthiest regions in Europe while the Italian Health System is widely considered among the best in the world in terms of access as well as for quantity and quality of care provided to patients [14]. The quality of health care is also one important reason for the high life expectancy of the Italian population, alongside lifestyle and diet, among other factors [15]. However, the longevity of the Italian population (alongside the lowest birth rate in the world [16]) has also generated a skewed demographic profile, made of a relatively large proportion of elderly and fragile individuals, which overlaps closely with the most vulnerable subgroups to COVID-19 [2].

It is equally important to emphasize that COVID-related case fatality rates *within* Italy display significant heterogeneity, e.g., are as high as 18.5% in Lombardy, also the most populous region of Italy, and as low as 4.3% in Umbria, among the least populated of Italian regions. This heterogeneity translates into a high cross-region dispersion of death rates of 3.4%, which amounts to 36% of those rates' equal-weighted cross-regional average (9.5%; authors' calculations based on data from [17] through April 20, 2020). Obviously, regional discrepancies in case fatality rates across Italy are also function of the different stages of the COVID-19 epidemic curve, with Lombardy and other Northern regions being at later stages of the outbreak as compared to the rest of the country.

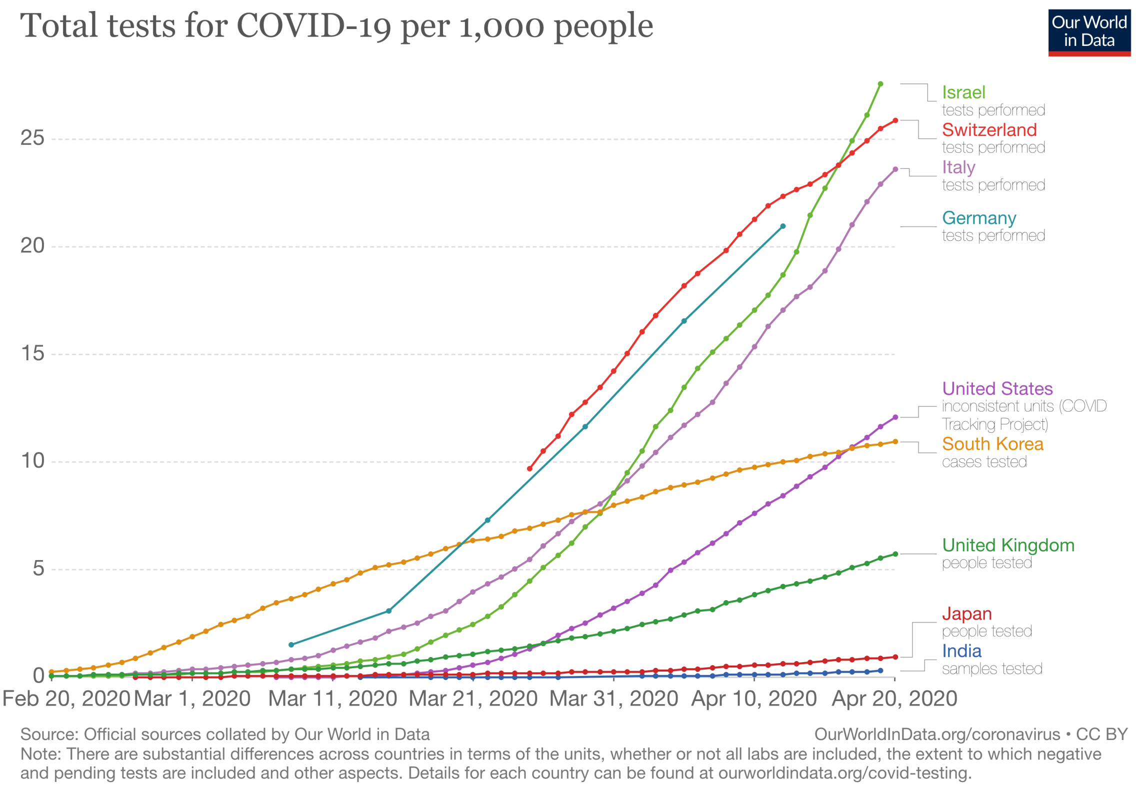
Nevertheless, and consistent with the above discussion, the regional case fatality rate is also highly positively correlated (up to 68%) with the regional-level number of hospitalized symptomatic and/or ICU-admitted COVID-19 patients, once again suggesting that case fatality rates spiked as hospitals' capacity (and presumably their ability to provide quality care) diminished with the progression of the epidemic.

Accordingly, numerous news reports have suggested that, in the early stages of the epidemic, a few small medical facilities, perhaps overwhelmed by the number of symptomatic hospitalized patients and the severity of their conditions, may have failed to follow safety procedures and so furthered the spread of the virus among other patients with serious illnesses as well as to visitors and medical personnel [18].

5. Extent of testing for COVID-19 and the tip of the iceberg

Italy and South Korea (along with Germany) are among the countries where the largest numbers of tests per thousand people for COVID-19 have been performed (see Figure 3).

Figure 3. *Number of COVID-19 tests per thousand people*
Data in linear scale as of April 20, 2020 for selected countries [31].



In particular, Italy has tested almost 950,000 people for COVID-19 as of April 20, 2020 [19]. Of course, running more tests implies in principle that a larger portion of the coronavirus iceberg (and its health outcomes) would be observed, including infected but asymptomatic individuals, relative to other countries where COVID-19 is stealthily spreading and killing. Accordingly, we would expect (and actually estimate) the cross-country correlation between total coronavirus tests per million population and the corresponding mortality rate to be nontrivially negative (-18%, with a *t*-statistics of -2.31; authors' calculations based on the closest available data to April 20, 2020 from 166 countries and territories affected by the coronavirus [1]). However, Italy has only been testing symptomatic people over the last several weeks, while it has been widely reported that South Korea (and more recently Germany) has been adopting extensive contact tracing by testing several asymptomatic people for each symptomatic one on the basis of their immediate proximity to him or her [20]. Nevertheless, the "South Korean testing approach", similar to that adopted by other Asian countries (e.g. Taiwan) has also raised concerns for the potential violation of privacy and human rights; hence, its applicability to Western countries is uncertain [21] [22] [23].

On the basis of these observations and the fact that roughly z = 1.9% of people tested in South Korea resulted in a coronavirus infection (authors' calculations based on [24]), we propose in the Appendix a simple model to estimate the Italian coronavirus under-testing and iceberg as of April 20, 2020 as a function of recent estimates of the asymptomatic proportion (y) of infected individuals [25] [26]. For example, according to our model on the basis of data from Japanese citizens evacuated from Wuhan, China [25], if Italy had followed the more proactive South Korean coronavirus testing approach it should have tested between as few as 10 and as many as 23 asymptomatic people for each symptomatic one it did test (i.e., a *test ratio* TR = 10.0 to 23.3 for y = 8.3% to 58.3%; see equation [A-4] in the Appendix). Such more widespread testing would have yielded between as few as 16,403 (i.e., Q^ in equation [A-2] for y = 8.3%) and as many as 253,372 (for y = 58.3%) additional coronavirus-positive (yet asymptomatic) individuals, i.e., a coronavirus iceberg between one-tenth to more than two times larger than its observed tip (i.e., an *iceberg ratio* IR between 1.1 and 2.4; see equation [A-5]). Qualitatively similar inference ensues from unreported analysis based on data from the unique circumstances of coronavirus cases on board the cruise ship "Diamond Princess" anchored in Yokohama, Japan [26].

In other words, our model indicates that there are likely many more COVID-19 infected people in Italy than it is reported by current testing, leading to an underestimation of the mortality denominator (i.e. total number of infected individuals, including asymptomatic cases and those with mild symptoms). Hence, this would translate in a non-trivial over-reporting of the current COVID-19 case fatality rate in Italy, as compared to countries (like South Korea) adopting proactive and extensive contact tracing. For instance, our model implies that under the assumption of a proportion of asymptomatic individuals among those infected y = 33.3% [25], there would be more than 270,000 individuals positive to the virus in Italy at the present (Q^ + P = 271,706 in equation [A-5], instead of the reported P = 181,228) out of more than 14 million tested (N^ = 14,300,324; see equation [A-1]), and an *estimated case fatality rate* of slightly less than 9% (ECFR = 8.9%; see equation [A-6]), i.e., about one-third lower than the current one and more in line with global numbers. Others have suggested even higher degrees of underestimation of the prevalence of COVID-19 in the population [27], which would further decrease the overall case fatality rate in Italy and other countries with comparable testing protocols.

6. Socioeconomic Order

The impact of socio-economic heterogeneity in affecting case fatality rates of an epidemic cannot be underestimated.

Italy is a Western democracy where restrictions to daily liberties are difficult to enforce in a draconian fashion. The entire country has been in lockdown since March 9, paralyzing the economy. The diffusion of the Internet and related technologies is low among the elderly, the most at-risk category [28].

Relative to Italy, China has managed to effectively seclude a city (Wuhan) and the surrounding Hubei province that is as large in population size as Italy, while keeping the rest of the country functioning economically and supporting that effort. South Korea's population is highly tech-literate and tech tools have helped the local authorities track the infected and limit the spread of the virus to at-risk categories, such as the elderly and/or people with pre-existing conditions.

Obviously, the long-term economic sustainability of extreme public health measures, as national lockdowns in Italy and other western countries, is a major concern, and may further exacerbate socioeconomic inequalities with additional negative impact on the wellbeing of the most vulnerable population subgroups.

7. Lessons learned from the Italian experience

We conclude that Italy's overall case fatality rate, as reported by public health authorities, is likely to be inflated for possibly several different factors including the iceberg effect of under-testing, yielding a distortedly inflated view of the global severity of the COVID-19 pandemic, although we acknowledge that deaths in Italy are still likely going to be higher than in other equally affected countries due to its unique demographic and socio-economic profile. In addition, we cannot ignore the stress on the health care system imposed by COVID-19 sudden pandemic in the most affected areas of the country, in terms of death toll.

Therefore, we caution from ignoring the lessons that the Italian circumstances may offer, especially for similarly affected Western countries. The COVID-19 pandemic has exposed several intrinsic structural limitations of the national public health care systems across Western countries, especially a lack of coordinated and timely response mechanisms for enabling rapid actions for the health crisis, like those deployed in several Asian countries. There is a need to expand public and private investments in infectious disease control and surveillance, as well as in epidemic preparedness.

Adequate community response, which is critical for epidemic containment, has been lacking in Italy, with dramatic consequences on local hospitals, many of which have eventually been overwhelmed in the most affected areas. We also need to rebalance the epidemiology and public health training, mostly centered on chronic non-communicable diseases, to enhance capacity in infectious disease epidemiology and control. We should strive to capitalize on new data analytics and technology tools to facilitate proactive case identification, like in some Asian countries (e.g., South Korea and Taiwan, among others [23] [29]).

Communication with the public is crucial to offset misinformation and fake news, which can be extremely detrimental in managing a health crisis of this nature. International partnerships and rapid sharing of data among national authorities and within the scientific community (e.g., unlike the delays that plagued communications from China at the first onset of the coronavirus epidemic [30]) are also crucial, and should be further encouraged and enhanced in the future.

In a context of limited evidence and significant uncertainty, Italy is running a massive public health intervention that is unique in the history of Western democracies. We all have to hope that it succeeds.

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Appendix

We propose a simple model to infer the iceberg of COVID-19 cases in Italy and ensuing mortality rate from observed testing and outcome data stemming from the more widespread coronavirus testing approach followed in South Korea.

Using data as of April 20, 2020, we begin by defining:

N ≡ actual number of people tested for coronavirus in Italy = 943,151

P ≡ actual number of coronavirus-positive individuals among those tested in Italy = 181,228

D ≡ actual number of coronavirus deaths in Italy = 24,114

x ≡ fraction of asymptomatic individuals tested in South Korea

y ≡ fraction of asymptomatic individuals among those yielding a positive test

z ≡ fraction of all (symptomatic and asymptomatic) individuals tested in South Korea who yielded a positive test = 1.9%

N^ ≡ estimated total number of all (symptomatic and asymptomatic) individuals that Italy would have tested if it had followed the South Korean testing approach.

Next we assume that, as discussed in Section 5, Italy has only been testing symptomatic individuals, i.e., that the number P of coronavirus-positives in Italy reported above is made exclusively of symptomatic individuals. We also assume that if Italy had followed the South Korean testing approach, it would have tested the same fraction x of asymptomatic individuals and experienced the same fraction z of positive tests among all (symptomatic and asymptomatic) individuals as those recorded in South Korea. It then straightforwardly ensues from the above definitions that:

$$\hat{N} \equiv x \cdot \hat{N} + (1 - x) \cdot \hat{N} = x \cdot \hat{N} + N = N / (1 - x) \qquad \text{[A-1]}$$

The above assumptions and definitions also imply that the fraction z of all (symptomatic and asymptomatic) individuals who should have been tested in Italy according to the South Korean testing approach can now be explicitly expressed as:

$$z \equiv [z*y*N\hat{} + z*(1 - y)*N\hat{}] / (N\hat{}) = (Q\hat{} + P) / (N\hat{}) \qquad [A-2]$$

where, to simplify notation, we further define Q^ ≡ z*y*N^ as the number of asymptomatic positives that Italy would have identified if it had followed the South Korean testing approach.

We can then use equation [A-1] to express x as a function of a given y:

$$x = 1 - [z*N*(1 - y) / P] \qquad [A-3]$$

Lastly, equations [A-1] to [A-3] straightforwardly allow us to express N^ = P / [z*(1 – y)], Q^ = P*y / (1 – y), and Q^ + P = P / (1 – y), such that we compute the *test ratio* TR of asymptomatic people tested versus symptomatic ones:

$$TR \equiv (N\hat{} - N) / N = \{P / [z*(1 - y)*N]\} - 1 \qquad [A-4]$$

as a function of y for a given z, as well as derive the *iceberg ratio* IR of estimated total positives over symptomatic positives and the resulting *estimated case fatality rate* ECFR:

$$IR \equiv (Q\hat{} + P) / P = \{[y*P / (1 - y)] + P\} / P = 1 / (1 - y) \qquad [A-5]$$

$$ECFR \equiv D / (Q\hat{} + P) = D*(1 - y) / P \qquad [A-6]$$

as a function of y alone.