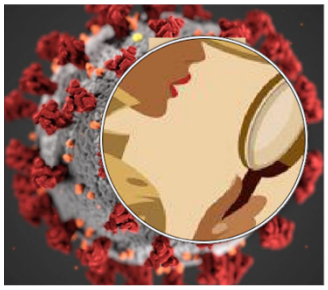
THE EPIDEMIOLOGY ADVENTURE: BEING A DISEASE DETECTIVE
9.04.2020



Episode 4: How virulent is the virus? Looking at mortality as a measure of disease severity

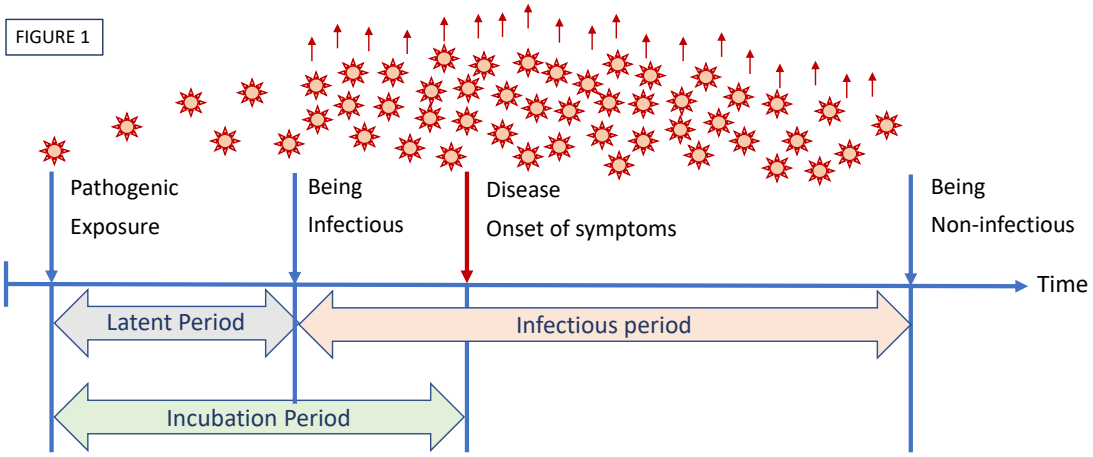
There is actually an open debate about how the to accurately measure severity of the disease. Assessing the severity of COVID-19 is very important in order to determine the most appropriate mitigation strategies and moreover allow to plan for healthcare needs as the epidemic develops. However, as you will see, it is a big challenge to accurately gather and assess the rapidly changing data in the middle of such a "pandemic storm".

How to measure virulence: understanding basic measures

There are different concepts, facts & figures to show the severity of disease:

- **Incubation and Infectious period**: [FIGURE 1]. Incubation period, defined as time from infection to onset of symptoms, is estimated on average between 5-6 days. Noteworthy is that the infectious period starts before the onset of symptoms.
- **Progression of the disease**: The median time from onset of symptoms to clinical recovery for mild cases is ±2 weeks and for severe or critical cases 3-6 weeks.[1]
- **Hospitalization & intensive care**: From the infected population (cases), ±15% are severe requiring hospitalization and oxygen, of which ±5% need intensive care requiring ventilation, while 80% of the infections are mild or asymptomatic [FIGURE 3]. Median time from illness onset to hospital admission was 4 days among cases, and 6 days for those reported as deceased. [2]
- **Time to death**: among patients who have died, the mean duration from onset of symptoms to death ranges between 14 to 18 days[3] and is shorter for people older than >70 years.

FIGURE 1



- ***Incubation period:*** *on average 5-6 days [2,14] (Lauer et al., 2020; Lai et al., 2020; WHO)*
- ***Viral shedding (contagiousness)****: Scientists reported the median duration of viral shedding was 20 days in survivors, but the virus was detectable until death in non-survivors. The longest duration in survivors was 37 days (Zhou et al., 2020)*

How to measure virulence: the speed of the (cycle of) transmission

- **The serial interval** is the period between the onset of symptoms between a primary and a secondary infected case [FIGURE 2]. For COVID-19 the median serial interval is 4 days, and a short serial interval indicates a rapid cycle of transmission. When the serial interval is shorter than the incubation period, pre-symptomatic transmission is likely to be more frequent than symptomatic transmission[4]. For, the serial time for SARS was estimated to be

1 WHO China joint mission report 20 February 2020

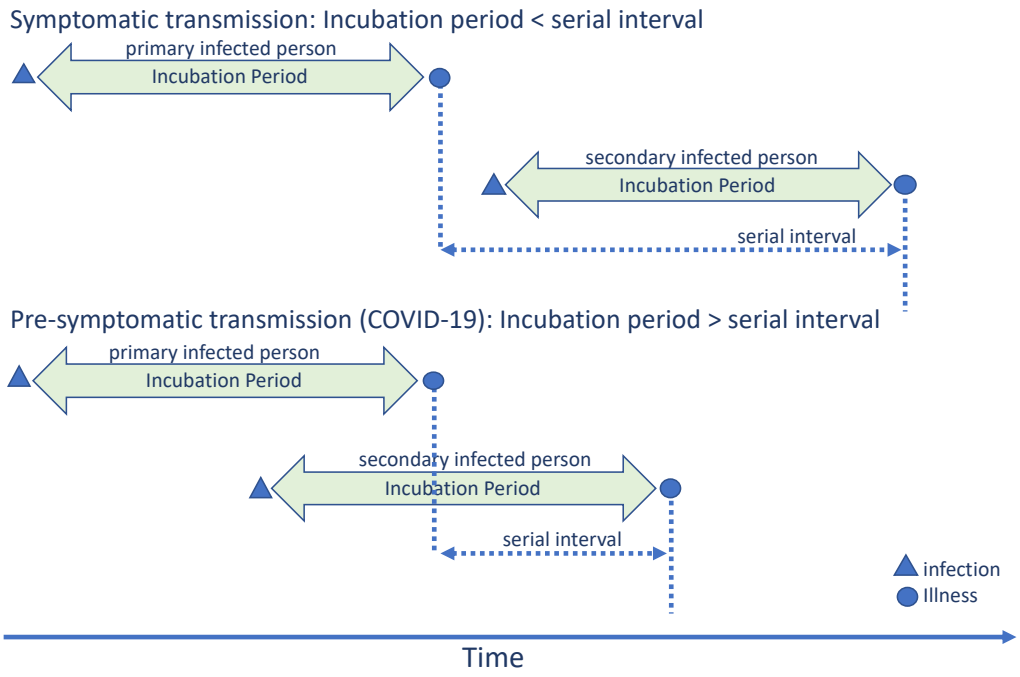
2 WHO ; OFSP ; Grasseli et al., 2020; Remuzzi et al., 2020 ; Linton et al., 2020

3 [95%CI, 16.9-19.2] ; Verity et al., 2020 ; Lai et al., 2020 ; Zhou et al., 2020

4 Nishiura et al, 2020

around 8 days with similar incubation period[5]. FIGURE 2 illustrates how for shorter serial intervals, second infected cases will more quickly become ill. Furthermore, for COVID-19, as the infection can be transmitted before the onset of symptoms, many people (~80%) may not be aware they are infected and that they are infecting other people.

FIGURE 2: Relationshiop between the serial time interval and incubation period



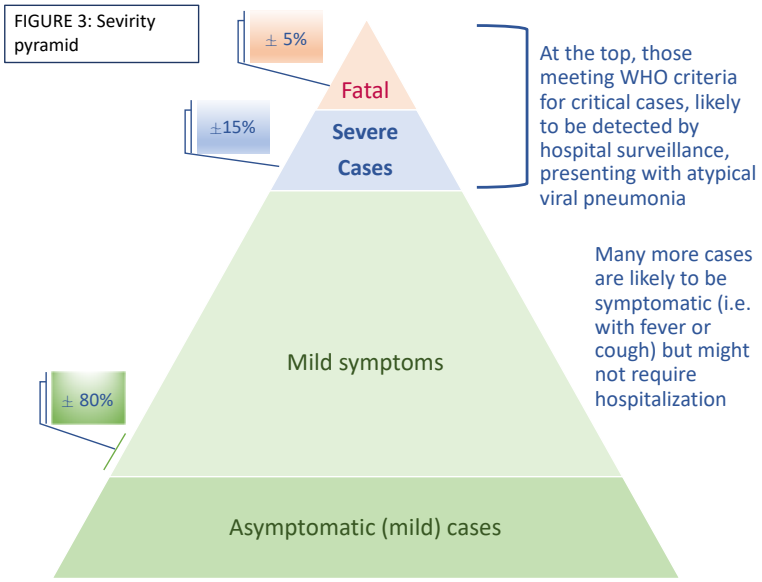
How to measure virulence by using case fatality ratios (CFR)

For fatal diseases death is a criterion of severity, and epidemiologists use two common measures: case-fatality ratio (CRF) and mortality rates. CFR is the proportion (%) of infected persons (identified cases) who die of the disease while the mortality rate a is the number of deaths per year or any other time period in a given population (rate per year). We must make sure we compare apples with apples and look how the data is collected. In practice, most of the data comes from regional or national statistics and there are many challenges to reporting accurate data:

- We are in the middle of a pandemic storm and there are potentially many sources of error that can lead to over- or under-reporting. However, these data can still be very useful to identify and compare trends and distributions of outcomes. **CFR is easily subject to miscalculation as it is a number that evolves**. At start of a **newly emerging epidemic**, diagnostic capacity is still low, and the initial data is obtained from hospitals and thus likely to represent patients with more severe illness, those that came to the hospital with atypical pneumonia or acute respiratory distress. Hence when we calculate a CFR at the start of an epidemic, **CFR will be higher**: Imagine 10 died from 500 reported cases, i.e. 2%; but imagine now that we managed to identify 500 more cases with mild symptoms, i.e. 10 died from 1000 reported cases, i.e. 1%. You realize this becomes a challenge. Therefore, authorities do try to report realistic estimates, but it is important to be aware that these can vary. We previously saw it is estimated that 80% of infected COVID-19 persons will only show mild or no symptoms. So, the overall reported CFR might be a ratio representing the death among the more severe infected persons (the top of the iceberg) and if measured on a population level the figure will be lower [FIGURE 2].[6]

5 Lipsitch et al., 2003 ; Li et al., 2020 ;Vink et al., 2014

6 Also, death numbers lag new cases by approximately 14-18 days (patients that die today were new cases ±14 days ago). While unadjusted this may potentially lead to an under-estimation of the CFR (as the pandemic continue to unfold, there will be more cases now compared to are more than 14 days ago), most scientific research will adjust for this in their statistical analysis.



Source: Verity et al., 2020; WHO; RIVM; Zhou et al., 2020

- Therefore, current CFR figures probably may not be representative yet of the "full" disease spectrum of COVID-19, and they will differ between countries (depending on testing and identifying cases). They will also **change over time.** Eventually even the most up-to-date case fatality ratio is expected to **decrease** as diagnosis of infected people are improving/increasing. Nevertheless, CFR figures are useful as a **common measure particularly for the short-term severity** of an acute disease and allows for an assessment of the effectiveness of an intervention.

TABLE 1 provides a general overview of CFR estimates from different scientific publications and how and what they were measuring. Our overall results range between 2% and 3.8%, with the median at 2.5%, and most authors indicate these figures will change over time, probably downwards, as the epidemic advances and more cases are identified.

TABLE 1: Overview scientific published evidence

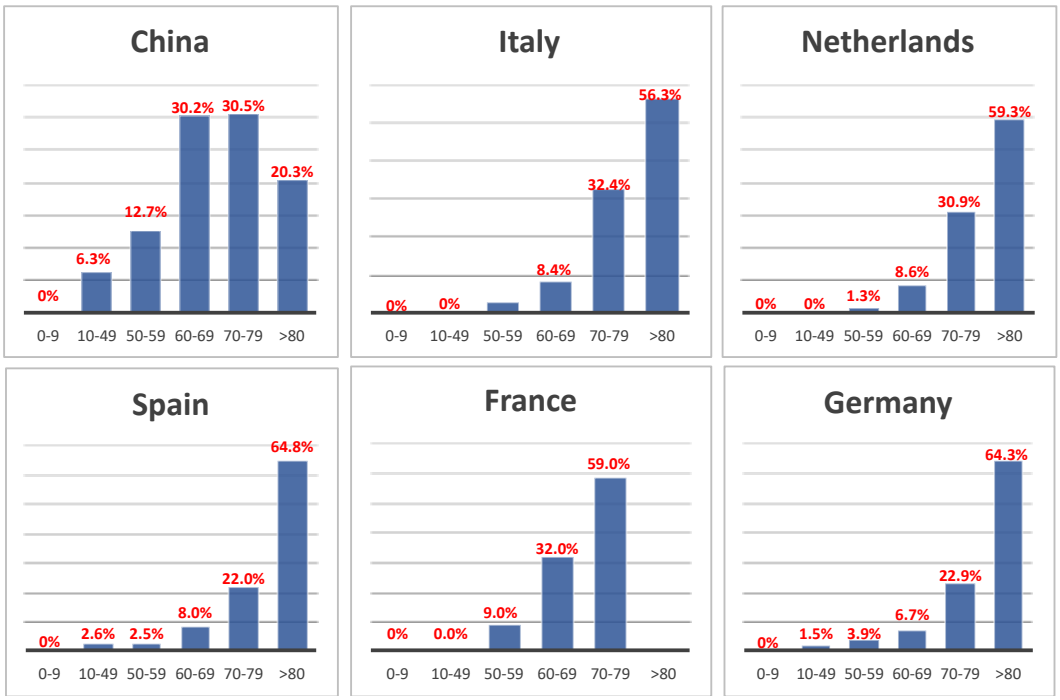
Author/report	Findings	Comments
Baud et al., 2020	Among Chinese patients, mortality rate of 3.6%	These rate is based on number deaths/confirmed cases which is not representative of actual death rate as full denominator remains unknown
Lai et al., 2020	Taiwan Center disease control reported CFR 2.5% and for mainland China 2.5%	
Lipsitch et al., 2020	Estimated CFR among medically attended patients is approximately 2%	The true ratio may not be known for some time as simple counts can be misleading if only severe patients are tested or problem of bottlenecks in laboratory testing
Surveillances V., 2020 (Article in Chinese, Feng et al)	For China overall CFR of 2.3%. The >80 age group had the highest CFR at 14.8%	
Verity et al, 2020	Within China CFR 3.7%; after adjusting for demography, severity and under-ascertainment CFR 1.4%	With substantial higher ratios for older age groups
WHO China joint mission report 20 Feb '20	CFR 3.8% but varies by location and stage of outbreak: 5.8% Wuhan vs 0.7% other areas in China; Early stage 17.3%, reduced over time to 0.7%	The joint mission acknowledges the known challenges and biases of reporting crude CFR early in an epidemic
WHO, Situation report-30/3/20	Within China: CFR 2.3%	CFR does not include the number of mild infections

Source: Google scholar

- CFR data broken down by **age-distribution** for China and European countries are shown in TABLE 3 and illustrated by the FIGURES. We observe that fatality cases in Europe impact the elderly far more severely. It can be seen that from age 50 years onwards the risks of dying are significantly higher. Furthermore, around 80% of deaths are above >70 years old.

TABLE 3: Death distribution per age group

Age, years	China (11/2/'20)	Italy (11/3/'20)	Netherlands (29/3/'20)	Spain (27/3/'20)	France (23/3/'20)	Germany (30/3/'20)
0-9	0%	0%	0%	0%	0%	0%
10-49	6.3%	0%	0%	2.6%	0.0%	1.5%
50-59	12.7%	2.8%	1.3%	2.5%	9.0%	3.9%
60-69	30.2%	8.4%	8.6%	8.0%	32.0%	6.7%
70-79	30.5%	32.4%	30.9%	22.0%	59.0%	22.9%
>80	20.3%	56.3%	59.3%	64.8%		64.3%
Sources:	*Surveillance et al., 2020*	*Remuzzi et al, 2020*	*RIVM (Gvt Neth.)*	*ISC (Gvt Spain)*	*Santé Publique France*	*Koch Institute*



One of the reasons why China death-age distribution is different compared to Europe is the age-structure of the population. We can observe a more pronounced "aging-population" in Europe compared to China [TABLE 2].

TABLE: demographics, Age structure

Age, years	China		Italy	Netherlands	Spain	France	Germany
0-14	17.2%	>	13.6%	16.3%	15.3%	18%	13%
15-24	12.3%	>	9.6%	12.0%	9.7%	11.8%	10.0%
25-54	47.8%	>	41.8%	39.2%	44.5%	37.5%	39.9%
55-64	11.4%	<	13.3%	13.4%	12.4%	12.4%	15.0%
65 and over	11.3%	<	21.7%	19.1%	18.2%	19.8%	22.4%

Source: https://www.indexmundi.com/germany/population_distribution.html

- A second consideration is the presence of **co-morbidities**. Co-morbidities increase with age. The main co-morbidities present in COVID-19 fatalities are hypertension (30%), diabetes (19%), followed by coronary heart disease and chronic respiratory diseases, with a high prevalence of overweight and obesity. Overall, it can be observed that patients with co-morbidities have between 1.3x and 2.0x higher risk of dying [TABLE 3]. Hence, both the age structure and the health status of the population play an important role.

TABLE 4: Country mortality with co-morbidities & RR

Country	Co-Morbidities		Relative Risk
	Yes	No	Yes/No
China	67%	33%	2.0
France	57%	43%	1.3
Italy	66%	34%	1.9
Netherlands	58%	42%	1.4
Spain	57%	43%	1.3

Sources: France National stats, Italy Remuzzi et al., 2020; Netherlands National stats, Spain National stats, China Zhou et al. 2020

How to measure virulence: looking at infected cases and clinical severity

Although the elderly, those older than 70 represent the majority of the deaths, it is also important to look at the which age range is affected the most among cases: the range of 50-60 years [TABLE 5]. In China, the median age of the infected was 59 years, in Switzerland 53 years and in Germany 49 years with most cases between 15 and 59 years old[7]. More than half of the hospital cases are in the group of 49 years and above. In France for example we could observe 50% of cases in intensive care are below age 64 and in Spain 33% in intensive care are below age 60. Hence the challenge for public health is not just about isolating the elderly. This is important when planning for health-care needs but also considering economic impacts as a much larger and younger age-group, part of the workforce, is also impacted by the severity of the disease.[8]

TABLE 5: age-distribution for CASES

Age, years	Netherlands	Spain	Germany	Switzerland
0-14	1%	1%	3%	3%
15-59	42%	50%	71%	62%
60- +80	57%	48%	20%	35%

Source: National statistics (RIVM, Sp Gvt, RKI, OFSP)

How COVID-19 virulence compares with SARS 2003

The SARS outbreak has also originated from animals sold in a live animal market in China. SARS resulted in more than 8'000 cases and 800 deaths in 8 months, while COVID-19 reached 82'000 cases and 2'800 deaths after just 2 months. **(1)** The infectious period is different. Peak viral shedding in SARS was seen after patients were already quite ill with respiratory symptoms and these patients could be easily identified and isolated. No transmission occurred from patients with mild symptoms. For COVID-19 there is evidence of pre-symptomatic transmission during the early phase of illness. Mild **cases** are more common (80%) and these patients **spread the disease silently** as they are not identified and not isolated**. (2)** Different speed of transmission. The mean incubation period is similar, but the serial interval is ±4 days for COVID-19 versus ±8 days for SARS. For COVID-19 it is shorter than the 6-days incubation period, increasing the cycle of transmission. **(3)** The current CFR for COVID-19 is estimated around 2%-3.8%, increasing with age but still far lower than SARS [10%][9]. Yet this is not very reassuring, because a **highly transmissible disease** will result in many more cases, and ultimately more deaths, even with a low CFR.

Discussion

There are different ways to measure the severity of the disease, each with advantages and limitations. Mortality figures differ because there is no common nor final denominator. CFR increases substantially with age and co-morbidities. The severity of illness and distribution of cases should also carefully be considered, as the mean age is in the range of 50-60 years, with many requiring hospitalization and intensive care.

Furthermore, CFR is also likely to be strongly influenced by the **availability of healthcare facilities**. It is also worth investigating the potentially substantial under-ascertainment of cases in younger age groups in cities where healthcare systems have been quickly overwhelmed. Also, when hospitals are overwhelmed and cannot accept new patients anymore, severe cases may not be properly isolated and could continue transmission of infection in communities.

More measurements have to be considered to quantify the severity of the disease, especially those related to mild and asymptomatic cases. **Serological testing** in this group will be crucial to understand the importance of this group in **driving population transmission**.

Please excuse any oversights I may be blind to
and feel free to contact me and let me know of any "errors and omissions" in this article[10].

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7 The fact that Germany is actively testing, may explain that more younger cases are identified.

8 Data are from French Natl Statistics 31 March 2020 & Spanish Natl Statistics as of 6 April 2020; Verity et al., 2020

9 Wider-Smith et al., 2020

10 List of sources and references available