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COVID-19: Past, present and future

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The world is emerging from coronavirus disease 2019 (COVID-19), but only slowly and with many relapses. What can be concluded at this time is that past efforts to contain this new infection were far from perfect and that emerging viruses remain a present threat with the future being conditional on what is done now. Wearing facemask, keeping distance and large-scale lockdowns are difficult to enforce, and cannot be as effective as immunological protection. It is thus clear that only sustained vaccination programmes with full coverage can successfully prevent proliferation of the virus.

Although COVID-19, caused by the severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2), has caused years of worldwide suffering and death, the devastation does not measure up to that of the Spanish flu - the H1N1 influenza pandemic of 1918-1920 (Berche, 2022). These two infections are decidedly different with respect to age: the Spanish flu resulted in high mortality in young age groups but not in the elderly, while COVID-19 has had the opposite outcome. Surviving the former could be a manifestation of remaining immunity after a previous such infection in those old enough to have been infected before, while the impact of the latter seems to be due to frailty of old age combined with absence of any immunological memory of coronaviruses. The high susceptibility to SARS-CoV-2 is somewhat surprising, as we live in an environment with various coronaviruses that frequently cause common colds and other upper respiratory infections, especially in young children and the elderly (Geller *et al*., 2012). Is SARS-CoV-2 a very different coronavirus or is short-term immunity to blame for the inability to mount even partial cross-reactive immunity? The apparent absence of herd immunity and widespread infections despite repeated vaccine doses and/or previous infections support the latter premise.

Because severe symptoms and death counteract the spread of any virus, mutant variants causing only gentle disease win out, as illustrated by the reappearance of a modified H1N1 virus (recently together with the H3N2 variety) in the form of seasonal influenza epidemics of low significance (Brüssow, 2022). The mild symptoms and the much better survival rates of those infected by the current SARS-CoV-2 Omicron variants can be interpreted as a sign that this virus is set on a similar course. Auspiciously, in one of the first experimental investigations of the pathology of the disease in an animal model Armando *et al*. (2022) confirmed that the Omicron variants generally cause a clinical picture more like influenza and other less serious upper respiratory tract infections. Still, a definite move along this route cannot be counted on as waves of more deadly forms can arise after long intermissions.

The various waves of infection we have witnessed can have many causes: new virus variants; poor vaccination status; general fatigue of rules and regulations; and spread of infection by people unaware that they are infected. Importantly, even if COVID-19 did first seem similar to ordinary influenza, it turned out to be a systemic infection and thus capable of infecting any organ in the body, a particular legacy of the ominous Delta variant. Caution is therefore *de rigueur* and what can be learnt from COVID-19 might well be of vital importance when the next pandemic strikes. Judging from the unusual emergence, within less than 20 years, of three deadly coronaviruses, *i.e*. the severe acute respiratory syndrome (SARS), the Middle East respiratory syndrome (MERS) and now COVID-19, this might not be far off. Indeed, the risk of viruses crossing the animal/human divide is enhanced by increased human intrusions into the world's last surviving wild-animal habitats leading to close contact with potential animal carriers (Wells and Flynn, 2022). Shifting disease distributions are also promoted by the ongoing climate change.

Diagnosis and risk analysis

Each diagnosis is individual, but the accumulation of results covering specific areas or time periods produces measures that can pinpoint hotspots, indicate directions of disease spread and document how many people are infected at any given time. In the early stages of the COVID-19 pandemic neither direct testing nor serology were applied at a large scale resulting in unreliable information. In addition, following the arrival of effective vaccines at the end of 2020, indirect testing was no longer useful.

Interestingly, wastewater testing enables the monitoring of whole urban agglomerations, something of value for risk review. Since the SARS-CoV-2 virus replicates in the digestive system and is stable and detectable in sewage despite the dilution effect, increased implementation of this approach is highly useful (Mallapaty, 2020; Michael-Kordatou *et al*., 2020). In addition, sewage surveillance is not only a major epidemiological step forward but also an approach that can shed light on the spread of new variants through genetic sequencing.

Although not a diagnostic in the strict sense, risk assessment is still an important adjunct to efforts encumbering the spread of infectious diseases, *e.g*., by assisting the separation of high-risk regions from safer ones. Michal *et al*. (2022) reduced a perceived assessment bias by combining four different metrics into one and concluding that knowledge about what makes this metric increase or decrease helps evaluating the importance of observed infection trends.

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Fatality rates

The number of deaths due to a disease is expressed by the case fatality rate (CFR) and the infection fatality rate (IFR). The former is related to the number of clinically defined cases, while the latter is based on passive diagnosis as well as surveys and therefore inevitably also includes infected people without symptoms. These two measures, particularly the CFR, remain the most reliable indicators of the impact of COVID-19. Based on the cumulative, global number of deaths due to COVID-19 (currently 6.5 million) and that of reported cases (610 million) (https://www.worldometers.info/coronavirus), the CFR stands close to 1%. Although still a comparatively high number, the beginning of the pandemic was more worrying with this measure rapidly passing 7% in July 2020 before dropping below 3% a few months later (Bergquist *et al.*, 2020), followed by further levelling off when vaccines were launched towards the end of 2020 (Figure 1). This graph is increasingly influenced by the current stepped-up testing, where the timeline represents an ongoing move from CFR towards IFR; *i.e.* fatality rates progressively diluted by people diagnosed through positive tests rather than symptoms. For example, the comparatively high number of tests carried out in Denmark (Table 1) may explain the unusually high number of cases per million inhabitants reported there, something that would not be expected to differ greatly from those of the other Nordic countries.

The IFR tells us that COVID-19 infections must be more common than the case counts say. That this was the case already during the early stage of the pandemic is shown in a study involving 15 countries, where the real infection numbers were on average 6.2 times higher than the official records, even reaching 17.5 times in one area (Phipps *et al.*, 2020). Thus, the 1% CFR figure discussed above could be 10 times too high resulting in a global fatality rate of only 0.1%, which is supported by today's more contagious and less pathological Omicron variants. This may be good news but mortality at this level is still much higher than that caused by other common infections, *e.g.*, influenza that normally does not exceed 0.01%, as reported by Wong *et al.* (2013) based on a systematic review of 50 published papers dealing with the H1N1pdm09 influenza pandemic of 2009-2010.

Considering the fact that all deaths due to COVID-19 cannot be clinically verified, reports concerning its impact now also use excess mortality (EM), a metric produced by comparing the total number of

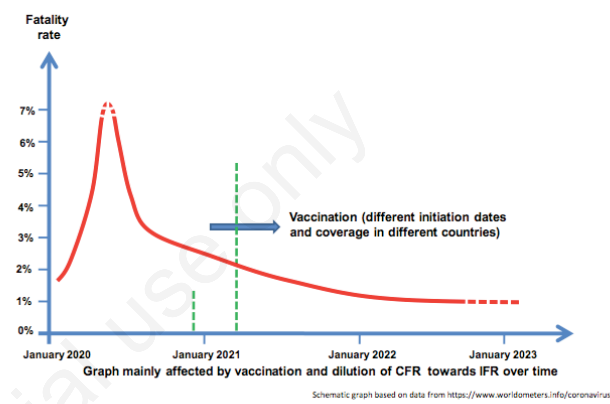

Figure 1. Seriousness of COVID-19 over time.

Table 1. Impact of COVID-19 in the Nordic countries.

Country	Cases per million (no.)*	CFR per million (no.)*	Excess mortality (%)**	Tests per million (no.)*
Denmark	527,971	1170	10-15	21,950,562
Finland	222,883	962	0-5	2,030,472
Norway	264,642	706	10-15	1,996,426
Sweden	249,396	1905	0-5	1,837,146

CFR, case fatality rate; *https://www.worldometers.info/coronavirus/; **https://ec.europa.eu/eurostat/statistics-explained/index.php?title=File:Map01_Excess_Mortality_2022_Jun.png.

Table 2. Impact of COVID-19 in key countries in the Americas and Europe.

Country	Cases per million (no.)*	CFR per million (no.)*	Excess mortality (%)	Tests per million (no.)*
Austria	530,784	2117	10-15[a]	2,966,664
Brazil	158,515	2337	22[b]	295,553
France	522,120	2337	0-5[a]	4,139,864
Germany	375,411	1731	10-15[a]	1,450,269
Italy	357,012	2890	0[a]	3,983,785
Poland	162,894	3096	0-5[a]	976,684
Spain	284,364	2392	>15[a]	10,066,355
Switzerland	454,409	1607	10-15[a]	2,502,858
UK	341,205	2711	11[c]	7,612,391
USA	285,406	3198	15[d]	3,289,896
Average	330,939	2215	-	-

CFR, case fatality rate; *https://www.worldometers.info/coronavirus/; [a]https://ec.europa.eu/eurostat/statistics-explained/index.php?title=File:Map01_Excess_Mortality_2022_Jun.png; [b]https://www.vitalstrategies.org/resources/excess-mortality-in-brazil-a-detailed-description-of-trends-in-mortality-during-the-COVID-19-pandemic/; [c]calculated for England + Wales for the period March 2020 to December 2021 based on data available at https://www.gov.uk/government/statistics/excess-deaths-in-england-and-wales-march-2020-to-december-2021 and https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/bulletins/deathsregistrationsummarytables/2021; [d]https://www.cdc.gov/nchs/nvss/vsrr/COVID19/excess_deaths.htm deaths during an epidemic to the average rate during the immediately preceding 2-4 years. However, when comparing one area (or country) with another, the result can be affected by various factors, such as ethnicity, demography and applied measures to stop COVID-19 spread; age groups can also be of different size and/or be affected by specific diseases at different times. The Nordic group of countries have similar cultural characteristics, but only Finland shows a low CFR per million inhabitants with a corresponding low EM (Table 1). Sweden's relatively high CFR coupled with a low EM and Denmark's and Norway's reversed data in this respect (Table 1) could possibly be expected if a high proportion of those deceased in Sweden, in contrast to the other two countries, belonged to an age group with a short life expectancy. Interpretation of provided estimates is thus difficult and exploration of the causes to the differences noted is needed, a request strengthened by similar discrepancies when data from a larger number of countries are consulted (Table 2).

According to the World Health Organization (WHO), the global EM was close to 15 million between 1 January 2020 and 31 December 2021 (WHO, 2022). However, the global, cumulative CFR reported as directly attributable to COVID-19 by the end of August 2022 amounts to only 6.5 million (https://www.worldometers.info/coronavirus). Naturally, EM data covering all countries on the planet cannot be equally reliable, and the same goes for the number of deaths reported. Furthermore, death rates have more causes than COVID-19 and gaps in underlying datasets and non-aligned factors in the preceding years, such as climate change, immigration dynamics, *etc*., also affect outcomes.

Long-term consequences

We are still in the learning phase of COVID-19 with various new trends coming to light. Long COVID, a post-acute, multidimensional clinical state lasting weeks or months (Brightling and Evans, 2022) came to the forefront last year. An early systematic review reported a 73% median of patients with symptom(s) ≥2 months after diagnosis or ≥1 month after perceived recovery (Nasserie *et al*., 2021), while a recent comment in *Nature* (https://www.nature.com/articles/d41586-022-01702-2) refers to a range of 5-50%. Furthermore, Douaud *et al*. (2022) reported on magnetic resonance imaging (MRI) of the brain of 401 patients testing positive for COVID-19. These patients had all undergone a previous MRI (with no connection to SARS-CoV-2 infection) and when they were scanned again at an average of 141 days after the diagnosis, a large number of them had widespread degeneration of the grey matter including the olfactory cortex. The possibility of viral spread through the olfactory pathways is of particular interest as anosmia has been a common complaint of those infected. Whether these effects will persist or subside over time remains to be followed-up.

As outlined in the preceding paragraphs, we are not only in the dark about the cumulative number of infections since the start of the pandemic, but also with respect to the pathological processes caused by COVID-19 and their length. Even patients with a longer disease perspective may not seek medical advice if symptoms are mild, which complicates the situation; if they could all be accounted for, the Long COVID prevalence rate would most probably be at the higher end of the range mentioned above.

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