Covid-19

End of the beginning?

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Introduction

The limited case cluster of atypical pneumonia detected in central China in December 2019, now known as Coronavirus Disease 2019 (Covid-19), converted into a million confirmed cases worldwide in only 10 weeks. Declared a pandemic by the World Health Organization (WHO) on 11 March 2020 (WHO, 2020) and passing the 3 million mark on 27 April, the world is under formidable strain with respect to public health, economy and personal life. Time and again we are alerted about unforeseen, new effects of this disease, which brings to mind the terms "known unknowns" and "unknown unknowns" used by former U.S. Secretary of Defense Donald Rumsfield when referring to the lack of evidence of weapons of mass destruction in Iraq ahead of the second Gulf war, a fitting vocabulary as we again are faced with mass destruction, though this time of a different kind.

Critical questions

Rumsfield's statement conceptualizes the distinction between the questions we are aware of and those not even considered. Most of them are fortuitously known unknowns, e.g., what is the origin of this virus? How much longer will this pandemic go on? why do men develop serious symptoms more often than women? Are childhood infections with other coronaviruses preventing infections in young people? Can non-infected people be sheltered by those who have recovered (herd immunity)? And perhaps the most important one, can lives be saved without killing the economy? There are also many unknown unknowns, such as the recent understanding that the lungs are not the only target organ (El Boussadani et al., 2020; Magro et al., 2020; Matías-Guiu et al., 2020; Yao et al., 2020). This raises the question of whether Covid-19 is a systemic disease, something supported by reports of cardiac involvement, embolism and hypotension, which has changed about 5% of all cases into life-threatening emergencies (Wadman et al., 2020). Indeed, the

virus acts very differently from influenza and can even lead to stroke in young patients (Oxley et al., 2020). On the other hand, a large proportion of patients show only mild symptoms. While the pathological reactions could be explained by a high viral load, such as that sustained by some doctors and nurses, that might release what has been called a 'cytokine storm' in spite of (or perhaps rather because of) a strong immunity, a minor viral challenge could allow sufficient time for the immune system to mask the infection because of the longer incubation time of Covid-19 compared to influenza and the common childhood infections. This supposition could also explain the dual wave pathology expressed by clinicians with regard to patients who are initially hospitalized with modest symptoms, then improve only to experience widespread pathology later on. Overall, these observations and conjectures illustrate that we remain in the dark regarding how Covid-19 operates.

At what stage of the pandemic are we?

The totality of active and recovered cases as shown in Figure 1 indicates that the increase of active cases is starting to slow down, while the number of people who have recovered is rising faster than before. Although this mainly applies to hospitalized and tested patients, it suggests that the red curve will eventually go down and in doing so predominantly move individuals into the blue curve. Thus, there will be a meeting point of the two curves, but when this will occur is too early to say. Even if we accept the view of the Centre for Evidence-Based Medicine (CEBM) at the University of Oxford, UK (CEBM, 2020) that a large proportion of infections are silent, a rough estimate indicates that less than 30 million people have so far been infected - a sobering thought against the background that the Spanish flu reached 55% of the world's population, (Taubenberger & Morens, 2019).

As reported by China's National Health Commission, the country reached a peak of Covid-19 cases on 12 February 2020 followed by elimination of local dissemination by 19 March. South Korea was not far behind with no new domestic cases reported since 29 February. Indeed, all Southeast Asian countries as well as Japan, New Zealand and Australia have reported only modest numbers of confirmed cases and comparatively few deaths, something seen also in South Africa where the low median age (27 years) has been used as an explanation. In Europe, the situation is quite different with high death counts and continued new Covid-19 infections in nearly all countries. The low number of deaths in Germany is, however, surprising as this country has one of the highest median ages in the world (47 years). Overall, however, even the European countries have reached the beginning of a plateau with respect to new cases (https://www.worldometers.info/ coronavirus/) and many are planning to begin opening up after the lockdown that clearly flattened (and prolonged) the curve relieving pressure on hospitals and intensive care.

Why is there such a difference with respect to Covid-19

between Europe and the U.S. on the one hand, and the Far East on the other - is it just a question of management? Since a large number of pandemics originated in Asia, innate immunity against coronaviruses might be more common there than in the rest of the world. Are we witnessing a replay of the the last 500 years of the seafaring explorers who brought smallpox to the Americas (Henderson *et al.,* 1999) and took syphilis back to Europe (Harper *et al.,* 2008)? Antibody studies will contribute to elucidating this conjecture.

The lack of clear metrics makes it difficult to estimate the true fatality risk of Covid-19. The daily published figures refer to the Case Fatality Rate (CFR), which is based on confirmed cases in hospitals and mainly does not include people cared for in their own homes or in care homes. Antibody tests will eventually enlarge the base by adding those with silent infections, thereby moving closer to what is called the Infection Fatality Rate (IFR), a measure that is, by definition, lower than the CFR. Interestingly, the latter seems to very recently have reached a plateau (perhaps even a peak) at 7%, which not only signals a break in the deadly attacks of the disease but also establishes a ceiling for the risk. The IFR will probably turn out to be not much higher than that for common influenza even considering the 5% with extraordinary symptoms and the fatalities in the old-age group. However, the high mortality in people with chronic medical problems and the elderly, the latter possi-
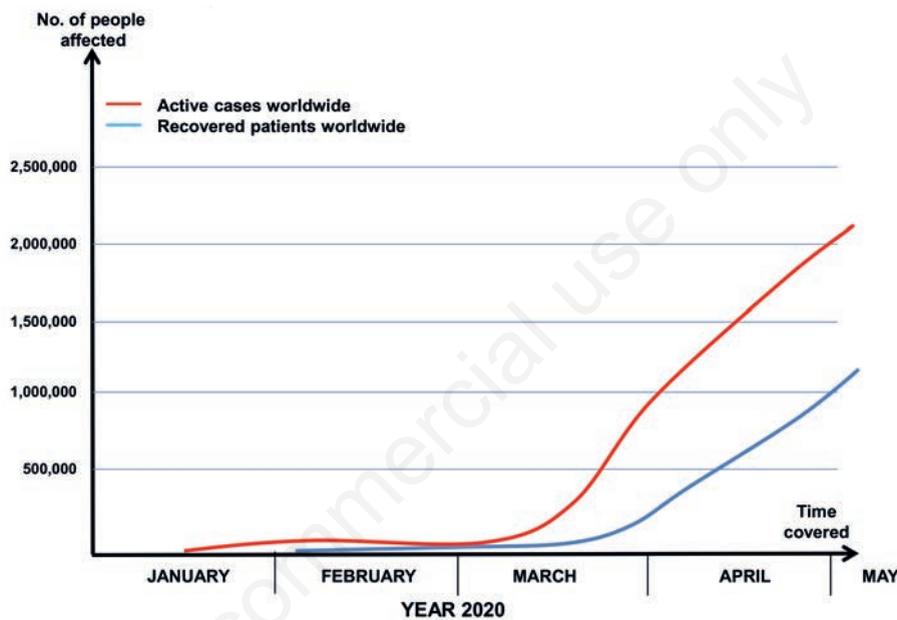

Figure 1. When will these curves cross?

Table 1. A 100+ years of viral threats by influenza and coronaviruses.

Time and name of infection wave	Viral species (subtype)	Reproductive ratio (R_0)	World population (billion)	People infected (million)	Number of deaths (million)	Case fatality rate (%)	Reference	Impact[a]
1889-1990 Russian flu[b]	Influenza A (H3N8/H2N2)	2.1	1.5	300-900	1	0.1-0.3	Valleron *et al.*, 2010	5
1918-1920 Spanish flu[b]	Influenza A (H1N1)	1.8	1.8	500-1,000	50-100	2-3	Taubenberger & Morens, 2006, 2019	9
1957-1958 Asian flu[b]	Influenza A (H2N2)	1.7	2.9	500	1-4	<0.2	Hilleman, 2002	4
1968-1969 Hong Kong[b]	Influenza A (H3N2)	1.8	3.5	500	1-4	<0.2	Hilleman, 2002	4
2002-2004 SARS[c]	SARS-CoV	2.8	6.4	$8,098 \times 10^{-6}$	774×10^{-6}	9.6	CDC, 2005	1
2009-2010 Swine flu[b]	Influenza A (H1N1/09)	1.5	6.9	100-200	$18,500 \times 10^{-6}$ $284,500 \times 10^{-6}$	0.03	WHO, 2011; Dawood *et al.*, 2012	2
2012-cont. MERS[c,d]	MERS-CoV	<1	7.8	$2,519 \times 10^{-6}$	866×10^{-6}	34.4	WHO, 2020a	1
2020-2021? Covid-19[b]	SARS-CoV-2	2.6[e]	7.8	3.6[f]	0.2[f]	7.0[f]	Worldometer[g]	10?

[a]on a scale of 0-10; [b]Pandemic; [c]Epidemic; [d]Still ongoing epidemic but with few new cases; [e]https://www.cebm.net/covid-19/when-will-it-be-over-an-introduction-to-viral-reproduction-numbers-r0-and-re/; [f]as of 6 May 2020; [g]https://www.worldometers.info/coronavirus/.

bly due to immunosenescence as suggested by Lambert *et al.* in influenza (2012), makes one wonder if it will ever be possible to extract confounding factors and produce an unequivocal fatality rate for the general public.

Previous pandemics

Historically, viruses have emerged time and again only to disappear when immunity developed in the affected population. Indeed, epidemics, let alone pandemics, may not have been a problem until humans first gathered in cities about 5000 years ago as viruses require continuous access to immunologically naive people. If so, a brief video of the growth of habitation from 3,700 B.C. until modern days (http://metrocosm.com/history-of-cities/) not only shows the origin of cities, but also visualizes the growing prospects for viral outbreaks. The reflection that humankind has grown by 410% over the last 100 years (https://ourworldindata.org/world-population-growth) is disturbing as this has also increased human encroachment into habitats previously belonging to other species. This has brought humans in closer contact with wildlife potentially harbouring new and unknown viruses, increasing the risk of animal virus's jumping species boundaries to infect humans This fact alone, ensures that Covid-19 is likely to be followed by future zoonotic events and other pandemics in the not too distant future.

The major pandemics of the last century all emerged, in one way or another, from animal viruses that have adapted to humans. However, as seen in Table 1, mortality rates have held well below 1% lately (WHO, 2011) with, counterintuitively, the Swine flu turning out to have had an unusually low case fatality rate (CFR) even though it infected more people than any previously known pandemic in spite of a comparatively low reproductive ratio (R_0=1.7). How does Covid-19 fit into this list?

In contrast to the Spanish and Asian flu pandemics that mainly hit those below 30 years of age with older people probably protected by remaining immunity from infections in their youth, older people suffer the greatest risk this time around. For Covid-19, the high R_0 (2.6) stands out as does the CFR, which has led to a political response affecting mobility tough enough to slow down the general economy so strongly that the overall impact of this pandemic is overtaking that of the Spanish flu.

Case tracing

One of the papers on Covid-19 published in this issue of *Geospatial Health* regards the large population exchange between Wuhan - the epicentre of this disease, the Yangtze River Delta area and Zhejiang Province concluding that identification of the spatiotemporal trends of this kind should be the first step when developing effective policies to manage epidemics (Ye and Hu, 2020). This exchange can be followed in detail by electronic surveillance as discussed in the preceding editorial. A way to do so with minimal managerial effort and time loss would be to analyze geolocated Twitter traffic as suggested by Bisanzio *et al.* (2020). These authors show that data generated by social media can be used to predict the spatiotemporal spread of infectious diseases based on a study cohort of Twitter users. They studied human mobility patterns with reference to Covid-19, paying special attention to air-

ports with scheduled flights from Wuhan using a validated Infectious Disease Vulnerability Index (IDVI) to identify the capacity to prepare for and respond to infectious disease threats in countries receiving travellers from this city.

Digital solutions for case tracing are now being developed and tested in many countries, where citizens are engaged to assist the health authorities' epidemiological surveillance of the spread of Covid-19 infection in their country. The applications speed up contact with people exposed and can help support decisions concerning a safe and data-based, gradual opening of society. Examples include the development of national smartphone app-based approaches to trace the virus, such as the 'C-19 Covid Symptom Tracker' (https://covid.joinzoe.com/) in use in UK since March 2020, the 'Covidmeter' (https://www.mobihealthnews.com/news/europe/danish-government-launches-covidmeter-tracking-service-lockdown-restrictions-are-lifted) in Denmark, 'smittestopp' (https://helsenorge.no/coronavirus/smittestopp) in Norway and 'Covidsafe' in Australia (https://www.health.gov.au/resources/apps-and-tools/covidsafe-app) in April. These apps let citizens voluntarily self-report symptoms and other health-related data. A similar system will soon be available in Italy under the name 'Immuni', while Germany has chosen to support an approach available from Google and Apple based on a decentralized software architecture with the data stored in the users' own phones.

The question of immunity

An early, significant step forward was the sequencing and sharing of the SARS-CoV-2 genome in a sample from a Chinese patient on 5 January 2020 (Zhang and Holmes, 2020). The virus causing Covid-19 turned out to be a single, positive-stranded RNA with close to 30,000 nucleotides, which was later confirmed by sequenced samples from other countries. This early success helped develop the first diagnostic assays and has been crucial for the ongoing vaccine development. Interestingly, specific IgG and IgM antibodies were followed in a limited number of Covid-19 patients and revealed seroconversion after 11 and 14 days, respectively, with IgG reaching its highest concentration four weeks after the onset of symptoms (Oxley *et al.*, 2020). Detection of specific antibodies against SARS-CoV-2 indicates previous infection by this virus, but to be epidemiologically useful testing must be based on sufficiently large samples. This approach is now coming to the fore after delays due to problems with assay production and distribution. The very first test results of s indicate that the virus had come the U.S. prior to the previously notified first cases in Washington State as positive results were recovered from two persons in Santa Clara, California who died in early and mid-February 2020 (https://www.nytimes.com/2020/04/22/us/coronavirus-first-united-states-death.html). It is also plausible that the virus has been circulating in China long before the first reported case, a 55-year-old individual from Hubei Province in China diagnosed in mid-November 2019 (Ma, 2020).

The importance of immunity might soon be recognized in the U.S. as some States have begun opening up, prematurely according to the experts, while others remain in lockdown. Extended antibody detection in randomly selected samples of people in New York and Stockholm has already been carried out. According to News-casts (https://www.nytimes.com/2020/04/23/nyregion/coronavirus-antibodies-test-ny.html) 20% positivity, presumably corresponding to a similar level of immunity, has been found. This is

promising though too low to be useful as herd immunity (at least >60% needed). Future testing will hopefully show higher levels, which is important as the SARS-CoV-2 virus will never disappear completely and may return at any time depending on the general status of immunity, the longevity of which will remain unknown for a long time.

That transmission of the disease seems to have stopped in China as well as in some other countries in the region, and the fact that the lockdown in Wuhan was lifted without undue results is good news. The slower climb of mortality in Europe together with indications that the rate of new cases generally does not increase further is supporting evidence, but only large-scale testing for specific antibodies can provide a clear answer regarding the role of immunity. Individual quarantine should not be lifted before research has conclusively shown that the presence of specific antibodies corresponds to immunity. So far, the strongest confirmation of the development of immunity comes from a preprint of a paper based on experiments with a few Rhesus macaque monkeys (Bao *et al.*, 2020) and the news release of successful, extended testing of a prototype vaccine in the same species of animal at the Jenner Institute at Oxford University, UK (http://www.cubasi.cu/en/news/covid-19-oxford-university-vaccine-proves-effective-monkeys).

Vaccine(s) or drug(s)

There are basically two ways of stopping an infectious disease, be it a due to a virus, a bacterium or a parasite. An effective drug provides immediate relief, while a vaccine can prevent reinfection in the long term.

With respect to drug development, nucleotide inhibitors have been shown to be active against RNA viruses (Elfiky, 2020). Incidentally, hydroxychloroquine is one of these but its usefulness has not been borne out and the U.S. Food and Drug Administration (FDA) cautions against its use with Covid-19 outside hospital settings due to the risk of heart rhythm problems. There are several other compounds that also interfere with viral reproduction by binding to the viral RNA-dependent RNA polymerase (the enzyme that catalyzes RNA replication). One of them, Remdesivir™, is currently in Phase 3 clinical studies (testing large numbers of people in the field) to evaluate the safety and efficacy in adults diagnosed with Covid-19. Initial results are said to be positive, but have yet to be published.

Regarding vaccines, there are now more than 100 candidates (Thanh *et al.*, 2020), but only a few have reached an advanced stage and only three are in clinical trials for safety (Phase I). However, even if efficacy can be demonstrated, scaled-up production will become a bottleneck given the high number of doses needed to keep the world safe. Therefore, even if it is plausible that an efficacious prototype vaccine could be ready before the end of this year, experience based on distribution of other vaccines indicates that a tentative date for commercial release of large numbers of doses would still be another year away, with the possibility of vaccination perhaps becoming available earlier for risk groups. Nevertheless, access to the virus genome has reduced the laboratory work from decades to months and further savings will be achieved as many of the steps normally required before a vaccine is released for public use will probably be cut short once safety has been shown. Vaccine evaluation can therefore be expected to move almost directly from Phase I to Phase IV (continued studies after the commercial release of a product).

The main editorial for this May issue of *Geospatial Health* was published the last day of April 2020, unusually early affected by the advent of Covid-19. It is now followed by this addendum, again unprecedented and due to the speed of new developments and publications related to this new disease.

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