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The evolving epidemiology of SARS-CoV-2

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ABSTRACT

Pandemics usually start with a bang following the emergence of a new pathogen that is both sufficiently infectious and virulent to pose a substantial threat and warrant an emergency response. The very fact that a pandemic involves a new or substantially changed infectious agent means the initial response is hampered by limited epidemiological data and a large amount of uncertainty. It was in this context that COVID-19 infections spiralled in many countries in early 2020, overwhelming health systems and driving excess mortality. Without reliable data it was initially unclear who was most at risk of, and from, infection, or of transmitting the virus to others. Over the course of the pandemic global research efforts have gradually pieced together the complex epidemiology of SARS-CoV-2 infections and longer-term sequelae, but there is still much work to be done. The situation also continues to evolve as the virus mutates, public health responses change, effective treatments become available, and population level immunity is acquired and matures. Although the onset of a pandemic is usually explosive and undisputed, the end is rarely as dramatic or as certain. Tracking the changing epidemiology of SARS-CoV-2 in the transition from pandemic to endemic is essential and remains a significant task.

Keywords: COVID-19, disease control, epidemiology, infectious disease, pandemic preparedness, public health, SARS-CoV-2.

Introduction

The epidemiological definition of 'pandemic' is actually quite general: 'an epidemic occurring over a very wide area, crossing international boundaries and usually affecting a large number of people' (p. 209).[1] However, the defining characteristic of a pandemic that prompts a coordinated global emergency response is the combined threat of rapid transmission, simultaneous outbreaks in multiple countries, and severe illness and high fatality rates.[2] This is most likely to occur with the emergence of a new pathogen, or where there has been a substantial change in a pathogen that renders existing population immunity ineffective. Pandemics end when the disease is brought under control – either eradicated, which is rarely possible, or it becomes endemic as the pathogen and humans co-adapt.

The SARS-CoV-2 virus, and the COVID-19 disease it causes, was first reported in early 2020, though it likely was causing diseases some months earlier,[3] and marked the beginning of the first truly global pandemic of the 21st century.[2] Although we had previously had to contend with SARS and MERS which were caused by related coronaviruses,[4] this new coronavirus presented key epidemiological differences that would affect transmission dynamics and our ability to control and contain the morbidity and mortality that would follow.

The main routes of transmission of the coronaviruses causing COVID-19, SARS and MERS appeared similar in the very early stages of the pandemic (aerosol transmission detection increased with later SARS-CoV-2 variants), but SARS and MERS had higher case fatality rates (~10 and 35%, respectively) compared with COVID-19 (averaging 2.5% in the pre-vaccine phase[5]). Global case fatalities estimates ranged from 1.7 to 39.0% in February–March 2020, falling below 0.3% by August 2022, a relative risk reduction of 96.8% over 2.5 years (95% confidence interval 95.6–97.6[6]).

However, it was the efficiency of transmission of SARS-CoV-2 and the resultant high infection rates globally that led to an estimated seven million deaths attributed to COVID-19 at the time of writing (reported at https://www.worldometers.info/coronavirus/, accessed 15 January 2024) compared with the substantialy lower total global reports for deaths from MERS (806 deaths) and SARS (774 deaths).[5] Fundamental differences in the epidemiology among these coronaviruses (length of incubation period, viral load and when it peaks, infectious period commencing before symptoms, variability in infection and severe disease susceptibility, case fatality rates and so on) had to be understood to assess the potential need for, and likely effectiveness of, public health interventions. SARS-CoV-2 also stands out from SARS and MERS as it has not only spread to all countries but has also persisted within most populations for 4 years or more. Over this time, key aspects of the epidemiology have changed with the succession of variants and subvariants and the development of population immunity.

The inevitable path to endemicity

SARS-CoV-2 is not amenable to eradication globally, or elimination at a local level, as we do not have a sterilising vaccination, natural immunity following infection wanes, and transmission can occur before or in the absence of symptoms limiting the effectiveness of public health measures.[7] Furthermore, there are multiple animal reservoirs that can seed reintroductions into the human population and accelerate the evolution of new subvariants in the cross-species spillover process.[8] Endemicity is the only other option, and is defined as 'the constant occurence of a disease, disorder, or noxious infectious agent in a geographic area or population group; it may also refer to the chronic high prevalence of a disease in such area or group' (p. 92).[1]

One of the ongoing misunderstandings is what endemicity means in practical terms. When a disease is classified as 'endemic', it does not imply that it not a significant or ongoing public health threat, nor does it preclude waves where infection rates spike or localised outbreaks occur. Rather, it signals that we have shifted from the emergency phase of the disease response, usually focussed on dampening community transmission to protect lives and prevent health system overload while vaccines and treatments are developed and distributed, to managing the disease in a sustainable way given the likelihood of persistence.[9] From late 2021, countries that had previously tightly managed international boarders to limit transmission began to open, including Australia. By early 2023, it was widely acknowledged that the world was transitioning to an endemic phase, with the World Health Organization (WHO) declaring the emergency phase over in May of that year.[10]

From dominant variant of concern to omicron subvariant soup

As SARS-CoV-2 established itself globally during the COVID-19 pandemic, we saw a succession of waves driven by the emergence of new variants with different combinations of mutations that, at various times, rendered the virus more or less virulent, more transmissible (generating higher viral load, binding affinity, upper respiratory infection sites) or instilled immune escape advantages (for example, changes to the spike protein increasing immune escape ability).[11] Most original COVID-19 waves were dominated by a single new variant, but by late 2021 when Omicron emerged, we saw a new pandemic phase with this single Variant of Concern dominating across waves, and multiple Omicron subvariants emerging, co-existing and persisting in communities.

The rate of transition from one SARS-CoV-2 variant to the next has been shown to be associated with vaccination rates, number of co-circulating variants, and convalescent immunity.[12] A mix of subvariants circulating concomitantly also creates a more complex epidemiological picture, further compounded by variable levels of immunity, vaccination- and infection-derived, within and across populations, and variable susceptibility to severe disease depending on age, comorbidity and immunity.[12]

Heterogeneity in infection and disease risk within populations and over the course of the pandemic challenges risk quantification and communication as the risk itself becomes more individualised and population averages less informative. The estimation of risk is further complicated when rapid transmission of a pathogen through the population, or rapid vaccine and treatment rollouts, makes it difficult to capture important comparative data from individuals before they are exposed. This is particularly important for comparison studies of acute and long-term disease risk in pandemics where the disease profile is variable in both severity and the symptoms that present, and the symptoms overlap those of pre-existing conditions.

Even in epidemiologically stable contexts, risk can be very challenging to communicate during a public health emergency and there can be significant consequences for public adherence to public health measures if risks are communicated poorly. Risk is more than the epidemiological likelihood of an infection occurring or the calculation of the effectiveness of an intervention containing transmission, it is a construct that draws together notions of hazard and outrage, and it is therefore essential that risk communication is inclusive and engages with the population where these views are formed and acted upon.[13]

The end of population-wide transmission control measures

In 2020, the ancestral variants required stringent public health measures, including international border closure, lockdowns and behavioural and mobility restrictions, to successfully limit community transmission to the levels required for disease control in an immunologically naïve population.[14] With increasing transmissibility and immune escape properties of subsequent variants, and shorter incubation periods, these same control measures have become less effective, particularly with the emergence of the highly transmissible Omicron variant and successive subvariants.[15]

Adherence to population level public health orders also cannot be assumed to be an endless commodity to call upon, especially among those who have been informed they are less at risk of severe illness or have experienced mild illness previously.[16] Non-pharmaceutical interventions also carry risk of other negative effects on health, healthcare access, population health and health inequalities,[17] and so the public health policy risk calculus supporting interventions shifts as the risks associated with infection reduce with increasing population immunity, and treatment options expand and improve.

The range of symptoms that can present in a COVID-19 infection, together with variability in severity and time to onset of symptom, make it hard to know exactly where the virus is circulating in the community. This is further exacerbated when infections remain symptom-free throughout. All have become more common with the emergence of Omicron, and in highly immune populations,[18] making the identification and management of infections, and of people in their infectious period, more challenging. A study of 210 people who tested positive on serology indicating a recent SARS-CoV-2 infection during the Omicron era reported that the majority (56%) were unaware that they had been infected,[19] compared with 44% in a large US population-based sample from early 2022,[20] and an estimated 35% of cases early in the pandemic.[21] More recently, data from late 2022 to January 2023 were combined from three prospective US cohort studies with 2959 participants with active testing not subject to biases associated with symptom presence or severity. Of the 426 infections discovered, 56.8% were asymptomatic, and symptomatic infections were mainly reported among those either not vaccinated, or who had only received the original monovalent vaccine.[22]

Recent research[23] has also shown that viral load rises later, on average, during Omicron infections compared with earlier in the pandemic where the highest viral load in throat swabs was reported at the time of symptom onset, and the inferred infectiousness peaked on or before symptom onset.[24] The viral load in Omicron infections was found to most commonly peak on the third or fourth day after symptoms developed.[23] This might seem epidemiologically beneficial if cases are less likely to be at their most infectious before symptoms emerge and can manage their risk of exposing others to the virus. However, it also means that Rapid Antigen Tests (RAT) are now more likely to generate false negative results even a few days into the symptomatic period.[23]

Earlier in the pandemic, a single negative RAT taken soon after symptoms developed had a meaningful negative predictive value, but with later viral load peaks and reduced RAT sensitivity until a few days into the symptomatic period, a negative result may lead people with COVID-19 to wrongly conclude that their symptoms must be due to another cause. What disease control benefits there may be in cases having more time to register that they have an infection before they reach peak infectiousness is lost if symptoms are so mild or vague that they are missed or not recognised as COVID-19. Asymptomatic infection, mild signs and symptoms or symptoms not readily recognisable as COVID-19 are all likely to result in more cases failing to recognise and manage their infection. This will only be further exacerbated if there is a higher risk of false negatives on RATs taken, even after symptoms appear. Individuals at high risk of severe disease, and their close contacts, now need to increasingly rely on repeat RAT testing to manage exposure risk.

Conclusion

The WHO announcement on 5 May 2023 declaring that COVID-19 was no longer an international public health emergency[10] officially signalled the SARS-CoV-2 transition from pandemic to endemic. Endemic diseases that pose a significant health burden, such as COVID-19, remain a public health priority and require ongoing surveillance and application of analytical methods to address the ever-increasing complexity of the epidemiology that occurs in the transition. Surveillance and analysis are vital in tracking local and global changes in epidemiology, and providing reliable estimates of risk to inform public health responses and support effective public health messaging to keep populations informed and actively engaged in health protection.

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Assoc. Prof. Hassan Vally is an epidemiologist with considerable experience in both academia and in government. He has expertise in the analysis and interpretation of health data, and in the understanding and critiquing of evidence in the health domain. He has background in a number of disciplines in addition to epidemiology, including molecular biology, virology and immunology. Dr Vally is an expert in risk and risk communication and has been involved in consulting for both the State and Federal Governments as well as the World Health Organization. In recent years, Dr Vally has been heavily involved in science communication and has been actively involved in media engagement.