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Are we coming out of the COVID-19 Pandemic?

A widespread outbreak spreading pervasively across the world is the hallmark of a pandemic. With good medical support, the case-fatality of SARS-CoV-2 has not been particularly high, in comparison with other high consequence emerging pathogens, such as Ebola and MERS.[1] However, its efficient transmission in modern human populations have proved devastating in almost all countries alike before the availability of vaccines.[2] All pandemics eventually end. However, when and how the Covid-19 pandemic will end is ultimately decided by nature rather than human proclamations.

When an emerging zoonotic virus jumps into a new host, it is expected to undergo a period of rapid adaptation under the selection pressure of the new environment. With progressive adaptation to the human host, the fitness cost of further mutations should increase and the chance of a new variant outcompeting the prevailing one(s) decreases. Since the fast-spreading Omicron variant emerged in November 2021, despite its descendant sublineages now accounting for 99.9% of uploaded genomes[3], no new variant of concern has been designated by the World Health Organization in last the 11 months. Instead, the Omicron sublineage viruses show convergent evolution, involving multiple overlapping mutation combinations that favour their persistence, despite substantial population immunity from past infection or immunization.[4]

Population immunity builds up either through natural virus circulation or vaccination. However, unlike smallpox, infections by many respiratory viruses do not confer long-lasting immunity and SARS-CoV-2 is no exception.[5] The short latent period before an acquired re-infection is able to retransmit probably does not allow sufficient time for recall of memory cells after neutralizing antibody and cellular immunity drops three to six months after the previous infection.[6] Despite the waning of immunity, there appears to be some residual immune protection even in the presence of immune-escape variants.[7] After a massive outbreak caused by Omicron BA.2.2 in Hong Kong in early 2022, reinfection stayed at less than 2% of all infections during the BA.5 wave in August and September (Figure).[8] Similarly, out of around 20 million accumulated cases in England less than 1.3 million (6.5%) were due to reinfection.[9]

Immune escape Omicron sublineages, like BA.2.75.2, BF.7 and BQ.1.1, have led to raised concerns as to whether another pandemic wave is coming in the winter. Although rebounds in the number of daily cases were reported in United Kingdom, Germany and Singapore[10], they cannot be fully attributed to the emergence of these new variants. Partial waning of herd immunity around 3 months after the last wave could partly contribute as witnessed by the rebound of Omicron BA.2.2 in June after its March peak in Hong Kong (Figure). Other contributory factors may include increased population mixing after schools reopen and relaxation of masking requirement indoor. Whatever the cause, there is perhaps no need for panic at the moment. Assuming the basic reproductive number, R0, of these omicron lineages is around 9.5[11] with a serial interval of 3.5 days[12], unless the number of infections double faster than weekly after full relaxation of control measures, the effective reproductive number, R, is less than 1.42 or 15% of the R0. This suggests that the herd immunity is still protecting more than 85% of the population.

The COVID-19 pandemic is likely evolving into an endemic stage after nearly three years of intensive circulation in the human population.[2] The public and political desire everywhere to return to living "normally" with the virus is high, and pandemic restrictions in most countries have been relaxed. However, declaring the pandemic over does not mean the threat disappears. Regions with high levels of circulating infection could still experience considerable disruption and ill-health. Even in areas where levels of infection are low, the situation could change rapidly as SARS-COV-2 has demonstrated its ability to spread very fast under the right conditions.

COVID-19 continues to disproportionately affect vulnerable groups such as the elderly, those with pre-existing medical conditions, immunosuppression, as well as disadvantaged socioeconomic groups such as ethnic minorities and the poor. Whilst existing vaccines and antivirals can help to reduce disease severity diseases and death, but they are far from perfect or universally accessible. In Hong Kong, the case-fatality ratio for COVID-19 remains well over 1% among those aged 80 or above despite 3 doses of vaccines[13]. Various forms of long COVID are still affecting tens of million persons many months after their infection.[14]

The transition of the COVID-19 pandemic into an endemic is also asynchronous, depending on the extent of natural virus circulation that helps to build up a major part of herd immunity in different parts of the world. As existing vaccines cannot effectively control transmission of the immune escape variants, all previously zero-COVID areas faced a massive outbreak when the containment measures failed. Containment cannot last forever, both because of increased transmissibility of the virus and deepening population fatigue or economic pressure. Updated vaccines to reduce transmission and high vaccine coverage of the old or chronically ill are therefore needed to avoid an explosive outbreak and safeguard the health care system before the last remaining zero-COVID areas reopen.

Major antigenic shift could still occur at an unpredictable time, with the potential of triggering yet another major global pandemic wave. A clearer seasonal pattern may also emerge, for a variety of reasons such as longer viability of SARS-CoV-2 under low temperature or more favorable patterns of human mixing in winter or waning of population immunity. Minor antigenic drift and diversification of the viral genome are also likely to continue, just as in the case of seasonal influenza. The threat, whilst muted by vaccinations, therefore remains.

Consequently, it is high time for countries to address the serious global inequity and lack of prosocial cooperation that have hindered effective global responses so far.[2] The development of updated vaccines well-matched to the circulating strains is likely to help to protect against both infection and severe disease.[15] But, this is not enough - a global mechanism to allow the rapid distribution of updated COVID-19 vaccines against evolving virus is also critical. This includes boosting vaccination coverage in low-income countries where vaccination rates have remained low. We are not safe until all are safe.

Key points: ,

1. After nearly three years of intensive circulation, SARS-CoV-2 is showing signs of adaptation to the new human host and no new variant of concern has been

designated by the World Health Organization since the Omicron variant emerged 11 months ago.
2. Herd community is also building up with natural virus circulation and vaccination asynchronously in different parts of the world.
3. While the Covid-19 pandemic is likely evolving into an endemic stage, there are continuing threats related to the waning of immunity and emergence of immune escape variants.
4. We need to address the serious global inequity and lack of prosocial cooperation that have hindered effective global responses so far: we are not safe until all are safe.

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Reference

1. COVID-19 Forecasting Team. Variation in the COVID-19 infection-fatality ratio by age, time, and geography during the pre-vaccine era: a systematic analysis. Lancet. 2022;399:1469-1488.
2. Sachs JD, Karim SSA, Aknin L, Allen J, Brosbøl K, Colombo F, et al. The Lancet Commission on lessons for the future from the COVID-19 pandemic. Lancet. 2022:S0140-6736(22)01585-9.
3. World Health Organization. Weekly epidemiological update on COVID-19 - 5 October 2022, https://www.who.int/publications/m/item/weekly-epidemiological-update-on-COVID-19---5-october-2022, last accessed 6 October 2022.
4. Upadhyay V, Patrick C, Lucas A, Mallela KM. Convergent Evolution of Multiple Mutations Improves the Viral Fitness of SARS-CoV-2 Variants by Balancing Positive and Negative Selection. Biochemistry. 2022;61:963-980.
5. Hansen CH, Michlmayr D, Gubbels SM, Mølbak K, Ethelberg S. Assessment of protection against reinfection with SARS-CoV-2 among 4 million PCR-tested

individuals in Denmark in 2020: a population-level observational study. Lancet. 2021;397:1204-1212.
6. Dan JM, Mateus J, Kato Y, Hastie KM, Yu ED, Faliti CE, et al. Immunological memory to SARS-CoV-2 assessed for up to 8 months after infection. Science. 2021;371: eabf4063.
7. Altarawneh HN, Chemaitelly H, Ayoub HH, Hasan MR, Coyle P, Yassine HM et al. Protective Effect of Previous SARS-CoV-2 Infection against Omicron BA.4 and BA.5 Subvariants. N Engl J Med. 2022 Oct 5. doi: 10.1056/NEJMc2209306. Epub ahead of print. PMID: 36198139.
8. https://www.scmp.com/news/hong-kong/health-environment/article/3192179/when-COVID-19-bites-twice-hong-kong-reinfections, last accessed 10 October 2022
9. https://coronavirus.data.gov.uk/details/cases?areaType=nation&areaName=England, last accessed 10 October 2022
10. WHO COVID-19 Dashboard, https://COVID19.who.int/table, last accessed 10 October 2022
11. Liu Y, Rocklöv J. The effective reproductive number of the Omicron variant of SARS-CoV-2 is several times relative to Delta. J Travel Med. 2022;29: taac037.
12. Backer JA, Eggink D, Andeweg SP, Veldhuijzen IK, van Maarseveen N, Vermaas K, et al. Shorter serial intervals in SARS-CoV-2 cases with Omicron BA.1 variant compared with Delta variant, the Netherlands, 13 to 26 December 2021. Euro Surveill. 2022;27:2200042.
13. Centre for Health Protection of the Department of Health of Hong Kong SAR, China. Provisional Data Analysis on COVID-19 Reported Death Cases, https://www.COVIDvaccine.gov.hk/pdf/death_analysis.pdf, last accessed on 10 October, 2022
14. Sørensen AIV, Spiliopoulos L, Bager P, Nielsen NM, Hansen JV, Koch A, et al. A nationwide questionnaire study of post-acute symptoms and health problems after SARS-CoV-2 infection in Denmark. Nat Commun. 2022;13:4213.
15. Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurtman A, Lockhart S, et al. Safety and efficacy of the BNT162b2 mRNA COVID-19 vaccine. N Engl J Med. 2020;383:2603-2615.

Figure: Epidemic curve of cases tested positive for SARS-CoV-2 virus in Hong Kong from 31 December 2021 to 1 October 2022