The transition of COVID-19 from a pandemic to an endemic disease

James Ayukekbong, BMLS, MSc, PhD, CIC
Editor-in-Chief, *Canadian Journal of Infection Control*

The emergence of Coronavirus Disease 2019 (COVID-19), caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), has led to an unprecedented global health crisis [1]. Within a few months, the disease that started in a small locality of China in December 2019, had spread to numerous countries around the world, and on March 11, 2020, the World Health Organization (WHO) classified the disease as a public health emergency of international concern [1]. As of March 2023, the COVID-19 pandemic was associated with more than 6.8 million deaths out of more than 681 million confirmed cases worldwide [2]. This number of confirmed cases is likely to be an underestimate because of the proportion of asymptomatic infected persons who may not have sought laboratory testing. Further, the global burden of the disease has been difficult to establish due to differences in surveillance, testing strategies, reporting methods, and other health-seeking behaviours which vary from country to country [3]. Overall, the pandemic has led to a major global health crisis causing significant disruption in social and economic activities.

By late 2020, there was a big change in the trajectory of the pandemic with the emergence of variants of interest (VOIs) and variants of concern (VOCs), which posed an increased risk to global public health [4], starting with the Alpha (B.1.1.7), Beta (B.1.351), Gamma (P1), Delta (B.1.617.2), and then Omicron (B.1.1.529), which was first identified in November 2021 [5, 6]. The transmission of Omicron VOCs led to significant intra-VOC evolution resulting in descendant lineages with different genetic constellations of mutations. Over the last year, there has been significant changes within the Omicron lineage, resulting in sub-lineages such as BA.1, BA.2, BA.3, BA.4, BA.5, BA.2.12.1, BA.4/5, BF.7, BA.4.6, BA.2.75.2, BQ.1, BQ.1.1, XBB.1, XBB.1.5 [5]. The XBB.1.5 sub-variant, otherwise referred to as the "Kraken", is thought to be the most transmissible sub-variant that has yet been detected [5]. Overall, the Omicron lineage carries an unusually high number of mutations on the spike protein – the main antigenic target of antibodies generated by either infection or vaccine – compared to the Delta variant [7, 8]. These mutations lead to increased transmission efficiency and escape from neutralizing antibodies [7-9]. A study from South Africa, however, found that the risk of severe disease by Omicron infection was lower than that of the Delta [10]. In yet another in vitro study, authors found that the Omicron variant had a low replication efficiency in tissue culture cell lines compared to the Delta, and suggested that this decreased replication capacity could explain its reduced disease severity [11]. Despite the high number of mutations, there is no impact on the capability of most molecular tests to detect Omicron variants as the majority of mutations occur in the spike protein (S-gene), but most PCR assays target both the nucleocapsid (N-gene) and S-gene. Where one genetic target has reduced sensitivity due to a mutation, the tests are still able to detect the virus on the other gene target [5, 12].

Although the virus has evolved significantly over the years, the key clinical features of the disease have not changed [13]. The symptoms of the disease, caused by recent variants, are still consistent with symptoms of early variants. These symptoms include fever, cough, general weakness/fatigue, headache, myalgia, sore throat, coryza, dyspnea, anorexia, and sometimes nausea and diarrhea [13]. Besides changes in virus property, which may account for the lower disease severity and mortality of the Omicron variants, the role of immunity from past infection or vaccination cannot be ignored.

In recognition of the relatively lower disease burden, WHO Director General, Tedros Adhanom Ghebreyesus stated that "there is no doubt that we're in a far better situation now" than a year ago – when the highly transmissible Omicron variant was at its peak. "We remain hopeful that in the coming year, the world will transition to a new phase in which we reduce hospitalizations and deaths to the lowest possible level," he added [14]. This announcement came after the WHO advisory panel suggested that the pandemic may be nearing an "inflection point" where higher levels of immunity can lower virus-related deaths. Notwithstanding, he concluded that COVID-19 still remains a global health emergency of international concern. This is, however, obvious as, unlike other epidemic or pandemic coronaviruses such as SARS and MERS, the transmission was successfully interrupted in many areas around the world [15], but the transmission of SARS-CoV-2 is still ongoing even after three years with new variants emerging.

https://doi.org/10.36584/cjic.2023.001.01.16.18

In this editorial, I discuss the anticipated shift in response strategies of COVID-19 with focus on surveillance, diagnostic strategies, booster vaccines and therapeutics as the disease eventually transitions from a pandemic to an endemic disease.

First, as the perception of COVID-19 changes from a pandemic to an endemic disease, the following must be put in place to manage the disease effectively during this phase:

1) **Surveillance and testing:** For the past three years, SARS-CoV-2 dominated the respiratory viral ecology space causing a disproportionately high number of outbreaks and infections. During the peak period of the COVID-19 pandemic, the circulation of other respiratory viruses was more or less suppressed. SARS-CoV-2 may continue to mutate and evolve, but not all mutations will lead to stable new forms of the virus with an evolutionary advantage. Alpha, Delta, and Omicron gained this evolutionary advantage and caused significant waves. The Beta and Gamma variants, on the other hand, also affected the trajectory, but to a lesser extent, and their evolutionary advantage was not sufficient to maintain global dominance. Omicron, to date, is the most infectious SARS-CoV-2 virus as a result of its mutation efficiency [5, 9]. More mutations may confer future variants the ability to evade immunity and become even more infectious, thereby maintaining dominance. As SARS-CoV-2 becomes sustained in the population, there is need for ongoing surveillance of acute respiratory infections especially in vulnerable settings. It must be recognized that with the transition of the disease from a pandemic to an endemic disease, other respiratory viruses are gradually reclaiming their position within the niche and also causing the characteristic acute respiratory infections [16]. With this in mind and coupled with the fact that symptoms of COVID-19 mimics that of other respiratory viruses, multiplex viral diagnostic panels must be expanded to include SARS-CoV-2 along with other respiratory viruses such as Influenza, Parainfluenza, Respiratory Syncytial virus (RSV), seasonal Coronavirus, Rhinovirus, Human metapneumovirus, Enterovirus, and Adenovirus. The surveillance and tracking of new variants must continue.
2) **Vaccination:** Vaccines will continue to be the best means of preventing adverse outcomes from SARS-CoV-2 infection. Essentially, the current COVID-19 vaccines mainly target the spike protein, but it must be recognized that with an increasing number of mutations, including deletions and insertions in the spike protein, this may dramatically enhance the variant's ability to evade current vaccines. Therefore, future vaccine formulations must recognize the ongoing mutations in the spike protein. Additionally, any formulation that includes a cocktail with both the annual flu vaccine and COVID-19 booster may improve uptake as public interest in the frequent COVID-19 boosters is likely to decline over time [17]. Without continued immunization, population immunity (natural and vaccine-induced immunity) will lessen over time. Although the full extent of waning immunity against Omicron is unknown, evidence indicates that those who have received the booster benefit from protection against severe disease [12]. Finally, as efforts to stop the spread of COVID-19 continues, two critical questions remain about the duration of protection and how often will boosters be required?
3) **Treatment:** This key intervention will continue to be required to reduce the mortality and morbidity of the disease. When initiated early, treatments can either support immune response against the virus or directly neutralize the virus. Treatment also can help address excessive immune responses and hyper-coagulability [12]. Nirmatrelvir/ritonavir (Paxlovid™) has been shown to significantly reduce hospitalization or death especially among unvaccinated high-risk adults when treatment was initiated within three days of symptom onset [18]. Paxlovid and other COVID-19 therapeutics are now widely available for use. Increasing the availability and timely utilization of effective therapeutics is an important step in the transition toward managing endemic COVID-19.

Together, COVID-19 will only become a truly endemic disease when it exists at a predictable level that is not influenced by public health interventions. When this occurs, public health mandates must be recalibrated as a means to balance public health directives and the social and psychological wellbeing of the population. For example, in healthcare settings isolation measures should be restricted only to those who are positive or symptomatic. Testing should be reserve for those who are symptomatic or high-risk contacts as part of an outbreak response. Masking in the public must be voluntary and only required for those who are symptomatic or test positive. Finally, endemic COVID-19 does not mean that the disease poses no risk, it simply means co-existence. Therefore, current infection prevention and control measures in vulnerable settings must be sustained post-pandemic.

ACKNOWLEDGEMENT

Sincere thanks to Dr. Devon Metcalf, Associate Editor of the *Canadian Journal of Infection Control*, for her review and useful suggestions.

REFERENCES

1. Cucinotta, D., Vanelli, M. (2020). WHO declares COVID-19 a pandemic. *Acta Biomedica,* 91:157-60. https:\\doi.org/10.23750/abm.v91i1.9397.
2. Worldometer: COVID Live – Coronavirus Statistics. (2022). Retrieved March 1, 2023, from https://www.worldometers.info/coronavirus.
3. Alrasheedi, A. (2022). The spread of COVID-19 in Africa and its comparison with the global spread: an examination after thirty-three months. *Azerbaijan Medical Journal*, 62,3917-27.

4. Aleem, A., Akbar Samad, A.B., Slenker, A.K. (2022). Emerging Variants of SARS-CoV-2 And Novel Therapeutics Against Coronavirus (COVID-19). In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing. PMID: 34033342.
5. National collaborating centre for infectious diseases. Updates on COVID-19 Variants of Concern (VOC). Retrieved February 20, 2023, from https://nccid.ca/covid-19-variants.
6. World Health Organization. Tracking SARS-CoV-2 variants. Retrieved on February 20, 2023, from https://www.who.int/activities/tracking-SARS-CoV-2-variants.
7. Chakraborty, C., Bhattacharya, M., Sharma, A.R., Mallik, B. (2022). Omicron (B.1.1.529) – A new heavily mutated variant: Mapped location and probable properties of its mutations with an emphasis on S-glycoprotein. *International Journal of Biological Macromolecule,* 219,980-997. https://doi.org/ 10.1016/j.ijbiomac.2022.07.254.
8. Harvey, W.T., Carabelli, A.M., B. Jackson, B., Gupta, R.K., Thomson, E.C., Harrison, E.M., Ludden, C., Reeve, R., Rambaut, et al. (2021). SARS-CoV-2 variants, spike mutations and immune escape. *Nature Reviews Microbiology,* 19,409-424. https://doi.org/10.1038/s41579-021-00573-0.
9. Jung, C., Kmiec, D., Koepke, L., Zech, F., Jacob, T., Sparrer, K.M.J, Kirchhoff, F. (2022). Omicron: What Makes the Latest SARS-CoV-2 Variant of Concern So Concerning? *Journal of Virology,* 96(6):e0207721. https://doi.org/10.1128/jvi.02077-21.
10. Jassat, W., Abdool Karim, S.S., Mudara, C., Welch R., Ozougwu, L., Groome, M.J., Govender, N., Gottberg, A., Wolter, N., Wolmarans, M., Rousseau, P., Blumberg, L., Cohen C. (2022). Clinical severity of COVID-19 in patients admitted to hospital during the omicron wave in South Africa: a retrospective observational study. *Lancet Global Health*, 10 (7): e961–69. https://doi.org/10.1016/S2214-109X(22)00114-0.
11. Zhao, H., Lu, L., Peng, Z., Chen, L.L., Meng, X., Zhang, C., Ip, J.D., Chan, W.M., Chu, A.W., Chan, K.H., Jin, D.Y., Chen, H., Yuen, K.Y., To, K.K. (2022). SARS-CoV-2 Omicron variant shows less efficient replication and fusion activity when compared with Delta variant in TMPRSS2-expressed cells. *Emerging Microbes and Infections,* 11(1),277-283. https://doi.org/10.1080/22221751.2021.2023329.
12. Grant, J.M., Chan, J., Lother, S.A., Barrett, L., Bonnar, P.E., Findlater, A.R., Kassim, S.S., Lam, J.C., Vinh, D.C. (2022). AMMI Canada Practice Point: Treatments for adults with COVID-19 in 2021-2022. *Journal of the Association of Medical Microbiology and Infectious Disease Canada,* 27,7(3):163-169. https://doi.org/10.3138/jammi-2022-08-08.
13. World Health Organization. (2022). COVID-19: Case Definitions. Retrieved March 1, 2023, from https://apps.who.int/iris/bitstream/handle/10665/360579/WHO-2019-nCoV-Surveillance-Case-Definition-2022.1-eng.pdf.
14. CBC News. WHO says coronavirus remains a global health emergency. Retrieved on February 20, 2023 from https://www.cbc.ca/news/health/who-coronavirus-update-emergency-1.6730397.
15. Ayukekbong, J., Ntemgwa, M., Ayukekbong, S., Ashu, E., Agbor, T. (2020). COVID-19 compared to other epidemic coronaviruses and the Flu. *World Journal of Clinical Infectious Disease,* 10:1-18.https://doi.org/10.5495/wjcid.v10.i1.1.
16. University of Bristol. (2022). Increase in non-COVID-19 respiratory infections predicted this winter. *ScienceDaily*. Retrieved on February 20, 2023 from www.sciencedaily.com/releases/2022/08/220809101800.htm.
17. MacDonald, N.E. (2015). SAGE Working Group on Vaccine Hesitancy. Vaccine hesitancy: Definition, scope and determinants. *Vaccine*, 33(34):4161-4. https://doi.org/10.1016/j.vaccine.2015.04.036.
18. Najjar-Debbiny, R., Gronich, N., Weber, G., Khoury, J., Amar, M., Stein, N., Goldstein, L.H., Saliba, W. (2023). Effectiveness of Paxlovid in Reducing Severe Coronavirus Disease 2019 and Mortality in High-Risk Patients. *Clinical Infectious Disease,* 76(3):e342-e349. https://doi.org/10.1093/cid/ciac443.