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# Considerations for Population Immunity and Endemicity

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## Key Points

- Reaching a critical population immunity threshold to eliminate ongoing SARS-CoV-2 transmission is not likely achievable, due to a variety of factors including waning immunity and the emergence of new variants that escape immunity from prior infection and vaccination.
- As such, population immunity should be thought of as being a continuum (i.e. decreasing rates of infection and/or severe disease with increasing immunity within the population).
- There is currently a lack of a definitive correlate of protection for SARS-CoV-2 (immunological marker associated with protection from an infectious agent following previous infection or vaccination), which limits the ability to determine the extent of population immunity.
- Vaccinations will likely continue to play an ongoing role in sustaining a level of immunity in the population required to maintain endemic equilibrium and minimize the negative consequences of SARS-CoV-2 infection.

## Background

Population immunity refers to a proportion of the population that is immune to infection (either through vaccination or prior infection), with higher levels leaving fewer people susceptible to being infected and transmitting to others.[1-3] Current evidence indicates that while eradication or elimination of SARS-CoV-2 does not appear feasible, the level of immunity in the population will play a crucial role in disease control and the transition to an endemic state in which SARS-CoV-2 will be consistently present in a population in a "maintenance" phase, but still experience waves due to seasonality or new variants.[4,5]

In this context, population immunity should be considered as something that is "continuous" and dynamic (i.e. level of immunity in the population is proportional to decreases in incidence of infection and may vary across regions or sub-populations) as opposed to dichotomous (i.e. whether or not it can be achieved). Public Health Ontario's (PHO) Evidence Brief on "What does it mean for COVID-19 to be 'endemic' and when will we get there?" provides an overview of the literature on this topic.[5] This document describes considerations for population immunity including disease severity and duration of immunity as it relates to COVID-19 becoming endemic and the challenges of determining population immunity due to lack of a definitive correlate of protection (CoP) for COVID-19 at this time.

# Methods

This document summarizes relevant literature that was previously included as part of PHO's Evidence Brief on Endemicity and a recent systematic review of the literature on SARS-CoV-2 correlates of protection (CoP).[5,6] PHO Library Services conducted updated searches of the literature in Ovid MEDLINE, Embase, Scopus, Global Health and preprints for both of these topics on January 25, 2022. The Public Health Agency of Canada Omicron Monitoring Report was also reviewed for vaccine effectiveness literature.[7]

# Critical Vaccine Threshold and Waning of Immunity

The population immunity or 'herd immunity' threshold is achieved when there is sufficient immunity in the population (whether through vaccination or prior infection) such that each person who acquires the infection transmits it to less than one person on average.[8] The critical vaccine threshold required to achieve population immunity incorporates a measure for vaccine effectiveness (VE) and surpassing this threshold theoretically results in a decline in the incidence of infection (see Appendix for calculations and assumptions).[9] The population immunity threshold for COVID-19 includes the proportion of the population that requires vaccination in order to achieve this threshold. Estimating this threshold is imprecise given the dynamic nature of virus transmission, uncertainty of level of immunity due to infection, changes in implementation and adherence to public health measures, uncertainties in vaccine effectiveness (including against transmission), waning of immunity and emergence of new variants of concern (VOC) with increased transmission, severity and immune escape . Additionally, because currently available vaccines do not result in sterilizing immunity (i.e. where an individual's immune system is able to prevent a virus from replicating), SARS-CoV-2 will continue to circulate in the population, particularly in individuals that are unvaccinated, medically vulnerable or immunocompromised, thereby providing the virus potential to evolve and/or evade immune responses.[10]

For these reasons, meeting the threshold needed to eliminate ongoing transmission of SARS-CoV-2 infection will not be achievable. Instead, SARS-CoV-2 will become endemic meaning that while overall rates may become stable, the incidence may not necessarily be low and there will be peaks of infection due to seasonality, new variants and/or the unclear effects of waning of immunity and long-term durability of protection with resulting disease not necessarily being mild.[11] Population immunity estimates will vary based on the above assumptions and also depending on the variant. For example, assuming a VE of 87% against Delta and a reproduction number (R0) of 6.3, the critical vaccination threshold was estimated at 96.7% of the total population, which is practically impossible to achieve especially as not all age groups are currently eligible for vaccination (e.g. less than 5 years old).[12] A Spanish study estimating population immunity for Delta using R0 of 4.02–8.96 found that this would result in a population immunity threshold of 90% but that since vaccines do not completely prevent the transmission of the virus, even with 90% vaccine coverage, the population immunity threshold would unlikely be reached.[13] Another study using a model incorporating waning of immunity, a similar R0 of 6 for Delta and VE of 80%, and assuming 83% population immunity (64% from vaccination and 19% from infection) concluded that elimination of COVID-19 would be highly unlikely.[14] An American study estimating population immunity to SARS-CoV-2 over 2020-21 found that while 86% of the population has a history of infection or vaccination, when accounting for waning of immunity, the effective protection rate against infection for with prevalent strains as of October 31 2021 was 50% and 77% against severe disease.[15]

In light of these considerations, a review of the evidence for vaccination strategies to increase population immunity emphasized that vaccination targets should be set to levels to reduce disease burden to a level that is manageable for a country's healthcare system with minimum public health measures in place. In order to protect vulnerable populations at risk of severe outcomes, targets should be higher for these groups over and above that for the general population.[16]

These observations are particularly relevant in the context of the Omicron variant which has higher transmissibility (i.e. a higher reproductive number) than Delta, potentially due to a combination of factors including immune escape, inherent transmissibility, and other differential characteristics such as shortened serial interval (time from symptom onset in the index case to symptom onset in a secondary case).[17,18] VE against symptomatic disease after time has elapsed from an mRNA primary series appears to be very low for Omicron and modest following a booster,19-22 VE against hospitalization is 52-78% after 2 doses of mRNA vaccine increasing to about 90% after 3 doses which further supports setting vaccination targets aimed at reducing hospitalizations to avoid overwhelming healthcare capacity.[20,22-24]

Vaccinations will continue to play an ongoing role in sustaining a level of immunity in the population required to maintain endemic equilibrium which is reached when R0 is less than or equal to one. This is due to the possibility of COVID-19 re-infection with different variants, that mild or asymptomatic infection may result in more rapid waning of immunity than symptomatic or severe disease and evidence showing that vaccination is safer than infection.[5,25,26] However, since waning of vaccine-derived immunity and correlates of protection are not well understood and it is unknown what level of protection current vaccines may provide against new VOCs, there is uncertainty around optimal booster schedules including which populations will require boosters, whether the aim is to prevent infection, hospitalization or other outcomes and the potential for updated vaccines targeted at VOCs.[5]

# Correlates of Protection

A correlate of protection (CoP) is an immunological marker associated with protection from an infectious agent following previous infection or vaccination.[27] Being able to identify a SARS-CoV-2 CoP would enable a better understanding of the extent of immunity at an individual and population level, which could be used to help inform vaccine schedules, public policy and adaptations to policy in response to new VOC in order to maintain an endemic state. There are different immune markers that can be CoPs; however, because cellular immunity is difficult to measure in clinical laboratories, antibody CoPs are the most common and easily measured.

A recent systematic review of the literature found that while an antibody CoP for SARS-CoV-2 may exist, there is currently no defined single correlate or protective threshold value. Without a defined CoP, serology tests which detect antibodies against SARS-CoV-2 in an individual can only be used to evaluate prior exposure to SARS-CoV-2 or COVID-19 vaccine and should be interpreted with caution with respect to immunity.[6]

However, the review indicated that if an antibody CoP exists and could be identified, it would likely have the following characteristics:[6]

- Is relative, where higher levels of antibody are correlated with higher levels of protection, rather than absolute, where protection is achieved above a defined threshold;
- Is specific to an outcome such as infection, symptomatic infection, or severe disease;
- Is specific to a SARS-CoV-2 lineage; for example, while there is currently a lack of data regarding an Omicron-specific CoP, studies suggest that a relatively higher concentration of antibody may be required to protect against Omicron compared to other variants.

Without a definitive CoP, it is difficult to measure the level of population immunity and therefore challenging to determine when the level of population immunity falls below the critical threshold where boosters or additional interventions may be required.

# Population Immunity and Endemicity

In addition to the considerations described in the above sections, the literature also underscores several other factors related to population immunity which favour the high likelihood of SARS-CoV-2 becoming endemic as opposed to being eliminated.[5] These factors include:

- Low and variable global vaccine coverage; currently, 39.4% of the world's population has not been vaccinated against SARS-CoV-2 and only 9.7% of people in low-income countries have received at least one dose,[28]
- Virus evolution leading to SARS-CoV-2 variants with increased immune escape potential,
- Availability of variant-based vaccines which may provide better VE against Omicron and other new variants in the future.[29,30]

# Summary and Implications

- Reaching a critical population immunity threshold against SARS-CoV-2 infection will not be achievable given factors such as the uncertainty about the level of immunity due to infection, lack of non-sterilizing immunity resulting from currently available vaccines, waning of immunity, and the emergence of new variants of concern (VOC) as well as the unknown role of animal reservoirs and/or human-to-animal transmission. In the context of SARS-CoV-2 becoming endemic, the notion of population immunity should be thought of as being "continuous" (i.e. level of immunity in the population required to achieve a desired outcome, such as acceptable level of infection or severe disease) and something that can be localized and vary by region.
- Several studies have emphasized the importance of maintaining a sufficient level of immunity in the population in order to facilitate a lower risk transition to endemicity where waves of infection would have progressively smaller peaks and runaway outbreaks could be avoided once public health measures are minimized. High levels of population immunity will also be crucial in maintaining endemic equilibrium in the future.[5,14,16]

- More research is required in order to establish a SARS-CoV-2 CoP. Serosurveys, which measure antibody levels against SARS-CoV-2 in the population, can be used to understand what proportion of the population have been exposed to COVID-19 or have been vaccinated, but have limited utility in assessing population immunity. Additionally, historical serosurveys based on previous waves of infection may not be useful in informing population level protection against new VOCs which have the ability to evade immune response.

- While there is uncertainty around optimal booster schedule and the availability of variant-specific vaccines in the future, vaccinations will likely continue to play an ongoing role in sustaining a level of immunity in the population required to maintain endemic equilibrium and minimize the negative consequences of SARS-CoV-2 infection. Vaccination targets should be aimed at reducing the burden of severe disease (e.g. requiring hospitalization) and minimizing transmission to vulnerable groups to avoid overwhelming healthcare capacity in the context of minimum public health measures. Higher target vaccination coverage may be required in certain populations.

# Appendix

**Calculation of Herd Immunity Threshold[9]**

Herd immunity (HI):

$$HI = (1 - \frac{1}{R_0})$$

The threshold for vaccination ($V_c$) required to achieve herd immunity is as follows and incorporates a measure for vaccine effectiveness:[5]

$$V_c = (1 - \frac{1}{R_0}) / E$$

Vc = critical vaccination level, which refers to the proportion of the population that must be vaccinated to achieve the threshold of herd immunity.

R0 = basic reproduction number, which refers to the number of transmissions or secondary cases generated by a typical infectious person when the rest of the population is susceptible. R can change over time (Rt) as a result of immunity due to infection in the population and implemented public health control measures.

E = vaccine effectiveness against transmission.

The formula for herd immunity threshold is built on the following assumptions:[8,9,31,32]

- Infection is transmitted from person-to-person with no animal reservoirs.
- There is homogeneity in transmission and susceptibility to infection across the population.
    - Herd immunity is impacted by distribution of immunity in the population. If groups at high risk of transmitting an infection attain a high level of immunity through vaccination, herd immunity may still be achieved despite a lower level of vaccine coverage for groups that do not engage in high-risk behaviours. However, this may result in clusters of unvaccinated persons who remain at risk of outbreaks.
- Vaccination prevents transmission in addition to protecting from infection.
    - Herd immunity will depend on the nature of the immunity induced by the vaccine, including the extent to which vaccination prevents transmission and the duration of such protection.
- Vaccination protects everyone to the same extent.
- Vaccination is administered uniformly throughout the population.
- Vaccination will be effective against variants that arise from mutations over time.
- Members of a population interact randomly.
- The reproduction rate of the infection remains stable.
- The herd immunity threshold is agnostic to source of immunity, whether it be from infection or immunization.

# References


1. Vaccine Knowledge Project. Herd immunity (herd protection) [Internet]. Oxford: Oxford Vaccine Group; 2019 [modified 2019 Aug 29; cited 2021 Jan 15]. Available from: https://vk.ovg.ox.ac.uk/vk/herd-immunity

2. World Health Organization. Coronavirus disease (COVID-19): herd immunity, lockdowns and COVID-19 [Internet]. Geneva: World Health Organization; 2020 [cited 2021 Jan 15]. Available from: https://www.who.int/news-room/q-a-detail/herd-immunity-lockdowns-and-covid-19

3. Government of Canada. Vaccines for children: deciding to vaccinate [Internet]. Ottawa, ON: Government of Canada; 2020 [modified 2021 Jan 13; cited 2021 Jan 15]. Available from: https://www.canada.ca/en/public-health/services/vaccination-children.html#vaccineeffectiveness

4. Telenti A, Arvin A, Corey L, Corti D, Diamond MS, García-Sastre A, et al. After the pandemic: perspectives on the future trajectory of COVID-19. Nature. 2021;596(7873):495-504. Available from: https://doi.org/10.1038/s41586-021-03792-w

5. Ontario Agency for Health Protection and Promotion (Public Health Ontario). What does it mean for COVID-19 to be 'endemic' and when will we get there? [Internet]. Toronto, ON: Queen's Printer for Ontario; 2021 [cited 2022 Feb 9]. Available from: https://www.publichealthontario.ca/-/media/documents/ncov/phm/2021/12/covid-19-what-does-endemic-mean.pdf?sc_lang=en

6. Perry J, Osman S, Wright J, Richard-Greenblatt M, Buchan SA, Sadarangani M, et al. Does a humoral correlate of protection exist for SARS-CoV-2? A systematic review. medRxiv 22269667 [Preprint]. 2022 Jan 23 [cited 2022 Feb 9]. Available from: https://doi.org/10.1101/2022.01.21.22269667

7. Government of Canada. Omicron monitoring report: report 5 – January 11 2022. Ottawa, ON: Government of Canada; 2022.

8. Omer SB, Yildirim I, Forman HP. Herd immunity and implications for SARS-CoV-2 control. JAMA. 2020;324(20):2095-6. Available from: https://doi.org/10.1001/jama.2020.20892

9. Fine P, Eames K, Heymann DL. "Herd immunity": a rough guide. Clin Infect Dis. 2011;52(7):911-6. Available from: https://doi.org/10.1093/cid/cir007

10. Chen J, Wang R, Wei G-W. Review of the mechanisms of SARS-CoV-2 evolution and transmission. ArXiv 08148 [Preprint]. 2021 Sep 15 [cited 2022 Feb 9]. Available from: https://arxiv.org/abs/2109.08148

11. Katzourakis A. COVID-19: endemic doesn't mean harmless. Nature. 2022;601(7894):485. Available from: https://www.nature.com/articles/d41586-022-00155-x

12. Ontario Agency for Health Protection and Promotion (Public Health Ontario). PHMT updates on Delta and Lambda [Webinar]. Toronto, ON: Queen's Printer for Ontario; 2021 [presented 2021 Jul 12; cited 2022 Feb 9].

13. García-García D, Morales E, Fonfría ES, Vigo I, Bordehore C. Caveats on COVID-19 herd immunity threshold: the Spain case. Sci Rep. 2022;12(1):598. Available from: https://doi.org/10.1038/s41598-021-04440-z

14. Dagpunar J, Wu C. A prototype vaccination model for endemic Covid-19 under waning immunity and imperfect vaccine take-up. medRxiv 21266002 [Preprint]. 2021 Nov 11 [cited 2022 Feb 9]. Available from: https://doi.org/10.1101/2021.11.06.21266002

15. Klaassen F, Chitwood MH, Cohen T, Pitzer VE, Russi M, Swartwood NA, et al. Population immunity to SARS-CoV-2 in US states and counties due to infection and vaccination, January 2020-November 2021. medRxiv [Preprint]. 2021 Dec 24 [cited 2022 Feb 9]. Available from: https://doi.org/10.1101/2021.12.23.21268272

16. Wei WE, Tan WK, Cook AR, Hsu LY, Teo YY, Lee VJM. Living with COVID-19: the road ahead. Ann Acad Med Singapore. 2021;50(8):619-28. Available from: https://dx.doi.org/10.47102/annals-acadmedsg.2021244

17. COVID is here to stay: countries must decide how to adapt. Nature. 2022;601(7892):165. Available from: https://www.nature.com/articles/d41586-022-00057-y

18. Ontario Agency for Health Protection and Promotion (Public Health Ontario). COVID-19 Omicron (B.1.1.529) variant of concern and communicability…what we know so far [Internet]. Toronto, ON: Queen's Printer for Ontario; 2022 [cited 2022 Feb 9]. Available from: https://www.publichealthontario.ca/-/media/documents/ncov/covid-wwksf/2022/01/wwksf-omicron-communicability.pdf?sc_lang=en

19. Tseng HF, Ackerson BK, Luo Y, Sy LS, Talarico CA, Tian Y, et al. Effectiveness of mRNA-1273 against SARS-CoV-2 omicron and delta variants. medRxiv 22268919 [Preprint]. 2022 Jan 21 [cited 2022 Feb 9]. Available from: https://doi.org/10.1101/2022.01.07.22268919

20. Buchan SA, Chung H, Brown KA, Austin PC, Fell DB, Gubbay JB, et al. Effectiveness of COVID-19 vaccines against Omicron or Delta symptomatic infection and severe outcomes. medRxiv 21268565 [Preprint]. 2022 Jan 28 [cited 2022 Feb 9]. Available from: https://doi.org/10.1101/2021.12.30.21268565

21. Willett BJ, Grove J, MacLean OA, Wilkie C, Logan N, Lorenzo GD, et al. The hyper-transmissible SARS-CoV-2 Omicron variant exhibits significant antigenic change, vaccine escape and a switch in cell entry mechanism. medRxiv 21268111 [Preprint]. 2022 Jan 26 [cited 2022 Feb 9]. Available from: https://doi.org/10.1101/2022.01.03.21268111

22. UK Health Security Agency. COVID-19 vaccine surveillance report week 4 [Internet]. London: UK Health Security Agency; 2022 [cited 2022 Feb 9]. Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1050721/Vaccine-surveillance-report-week-4.pdf

23. Thompson MG, Natarajan K, Irving SA, Rowley EA, Griggs EP, Gaglani M, et al. Effectiveness of a third dose of mRNA vaccines against COVID-19–associated emergency department and urgent care encounters and hospitalizations among adults during periods of Delta and Omicron variant predominance — VISION Network, 10 States, August 2021–January 2022. MMWR Morb Mortal Wkly Rep. 2022;71(4):139-45. Available from: http://dx.doi.org/10.15585/mmwr.mm7104e3

24. Tartof SY, Slezak JM, Puzniak L, Hong V, Xie F, Ackerson BK, et al. BNT162b2 (Pfizer–Biontech) mRNA COVID-19 vaccine against Omicron-related hospital and emergency department admission in a large US health system: a test-negative design. SSRN 4011905 [Preprint]. 2022 Jan 18 [cited 2022 Feb 9]. Available from: http://dx.doi.org/10.2139/ssrn.4011905

25. Veldhoen M, Simas JP. Endemic SARS-CoV-2 will maintain post-pandemic immunity. Nature Rev Immunol. 2021;21(3):131-2. Available from: https://dx.doi.org/10.1038/s41577-020-00493-9

26. Gargouri S, Souissi A, Abid N, Chtourou A, Feki-Berrajah L, Karray R, et al. Evidence of SARS-CoV-2 symptomatic reinfection in four health care professionals from the same hospital despite the presence of antibodies. Int J Infect Dis. 2022 Jan 10 [Epub ahead of print]. Available from: https://doi.org/10.1016/j.ijid.2022.01.006

27. Plotkin SA. Correlates of protection induced by vaccination. Clin Vacc Immunol. 2010;17(7):1055-65. Available from: https://doi.org/10.1128/CVI.00131-10

28. Ritchie H ME, Rodés-Guirao L, Appel C, Giattino C, Ortiz-Ospina E, Hasell J, et al. Coronavirus pandemic (COVID-19) [Internet]. London: Global Change Data Lab; 2020 [cited 2022 Feb 9]. Available from: https://ourworldindata.org/coronavirus

29. Pfizer Inc. Pfizer and BioNTech initiate study to evaluate Omicron-based COVID-19 vaccine in adults 18 to 55 years of age [Internet]. New York: Pfizer Inc.; 2022 [cited 2022 Feb 9]. Available from: https://www.pfizer.com/news/press-release/press-release-detail/pfizer-and-biontech-initiate-study-evaluate-omicron-based

30. ModernaTX Inc. A study to evaluate the immunogenicity and safety of mRNA-1273.211 vaccine for COVID-19 variants [Internet]. Bethesda, MD: US National Library of Medicine; 2021 [cited 2022 Feb 9]. Available from: https://clinicaltrials.gov/ct2/show/NCT04927065?term=NCT04927065&rank=1

31. Gomes MGM, Aguas R, King JG, Langwig KE, Souto-Maior C, Carneiro J, et al. Individual variation in susceptibility or exposure to SARS-CoV-2 lowers the herd immunity threshold. medRxiv 20081893 [Preprint]. 2021 Aug 1 [cited 2022 Feb 9]. Available from: https://doi.org/10.1101/2020.04.27.20081893

32. Vignesh R, Shankar EM, Velu V, Thyagarajan SP. Is herd immunity against SARS-CoV-2 a silver lining? Front Immunol. 2020;11:586781. Available from: https://doi.org/10.3389/fimmu.2020.586781

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