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COVID-19 Vaccines and a Pathway out of the Pandemic

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The development of COVID-19 vaccines occurred at lightning speed during the first year of the pandemic. Stringent public health and social measures had been used intermittently in most parts of the world in the first year of the pandemic, and vaccines represented a light at the end of the tunnel. That is because vaccines could be used to complement public health and social measures and reduce the impact of COVID-19 infections, with an expectation that they could eventually allow governments to relax all community-wide measures. However, expectations of vaccine performance had to be adjusted as the pandemic progressed and new SARS-CoV-2 variants emerged, while delays in the global sharing of vaccines led to discussions over equity. In the third year of the pandemic, it became clearer that repeated administration of COVID-19 vaccines will be key to protecting people, particularly older and more vulnerable individuals, as the disease continued to circulate globally into the summer of 2022.

A Brief History of Vaccines

Viruses such as SARS-CoV-2 require human or animal cells to reproduce and spread. When a person is infected with the SARS-CoV-2 virus, cells in their respiratory tract are invaded by the virus and used as virus-making factories to produce large numbers of copies of the virus. Those virus copies can then be emitted back out of the respiratory tract through breathing, talking, coughing, sneezing, vaping etc. and pass to another person. In this way, the virus propagates through a community.

Humans are born with an immune system that can fight off mild infections but can sometimes struggle to deal with more serious infections. Once the immune system notices that an infection is occurring, for example because cells are not performing their usual functions, an immune response is mounted with the aim of eliminating the virus from the body and repairing any damage that has occurred. A long-established observation in infectious diseases is that recovery from an infection can provide long-lasting immunity against re-infection. This long-lasting protection is due to the 'adaptive' component of our immune systems, including antibody-producing 'B cells' and killer 'T cells' that can hunt down and eliminate viruses and virus-infected cells. During infection, these cells learn to recognise the infecting pathogen and commit that recognition to a type of memory. One of the most important responses to a viral infection is the production by B cells of antibodies to that virus in case it is encountered again. Antibodies are small proteins that attach to the receptors on a virus surface and prevent the virus from being able to infect cells, as well as marking the virus as an intruder for other parts of the immune system to react to.

While immunity to common pathogens is clearly advantageous, acquiring that immunity through infection can be dangerous. Smallpox—caused by the virus *variola major*—killed 30 per cent of the people it infected, a remarkably high fatality rate. In China, an approach called variolation was used for many centuries to reduce the public health impact of smallpox. The dried scabs from smallpox survivors were collected and ground into a powder, which was then insufflated, i.e., blown up the nose. Another variolation approach spread from Turkey into Western Europe in the seventeenth and eighteenth centuries, which involved making superficial scratches or cuts in the skin and then exposing these either to scabs or contaminated clothes from an infected individual. The infections that resulted from variolation tended to be milder, although not without risk.

In the late eighteenth century Edward Jenner and other scientists noted the observation that milkmaids who contracted cowpox—an animal infection that was much milder in humans than smallpox—seemed to be immune to smallpox. Edward Jenner then demonstrated that deliberate infection with cowpox provided immunity to smallpox, and was safer than variolation. Since the pathogen causing cowpox was called *variolae vaccinae* (*vacca* is Latin for cow), Jenner named his procedure 'vaccination'. Interestingly, opposition to Jenner's vaccine grew into a huge anti-vaccination movement in the nineteenth century.[1] Ultimately, however, the mass global use of cowpox infection in the skin as a smallpox vaccine ultimately led to the eradication of smallpox by 1980.

While inoculation of one virus to provide immunity to another, more serious infection was the first approach to vaccination, it is not the most common. More than 20 vaccines are used worldwide to prevent human diseases caused by viruses, and most of these are made from either inactive viruses or non-infectious components of viruses.[2] Infection with attenuated (weakened) viruses has also been used as an approach to vaccination, most notably for polio. In more recent years, a new approach has been developed that involves genetically modifying one virus (including removal of disease-causing genes) and inserting part of the genetic code of a second virus. The first virus

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[1] Jess McHugh, 'The World's First Anti-Vaccination Movement Spread Fears of Half-Cow Babies', *Washington Post*, 14 November 2021, https://www.washingtonpost.com/history/2021/11/14/smallpox-anti-vaccine-england-jenner.

[2] Brian Greenwood, David Salisbury, and Adrian V. S. Hill, 'Vaccines and Global Health', *Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences* 366, no. 1579 (2011): 2733–2742, https://doi.org/10.1098/rstb.2011.0076.

is then used as a vector to carry the genetic material of the target virus and train our immune system to respond to future exposures to viruses with the same components. Because the vector virus is designed to be able to infect cells, it can also stimulate a robust cellular response in addition to the production of antibodies.

Rapid Development of COVID Vaccines

From the early days of the COVID-19 pandemic, it was clear that infections were so severe that unmitigated epidemics would lead to considerable loss of life. The three major toolboxes for mitigating viral epidemics and pandemics include (1) public health and social measures, (2) antiviral drugs and associated therapeutics for the treatment of infections, and (3) biological vaccines and prophylactics to prevent infections. Given that antivirals and vaccines were not initially available, most governments around the world could only rely on public health and social measures to suppress transmission in the early months of the pandemic.

The vaccine development cycle typically takes many years because of the sequence of steps required. The pre-clinical development of a candidate vaccine involves identifying a formulation of virus or virus components that could stimulate a protective immune response, as well as other necessary ingredients such as stabilisers and preservatives. Some vaccines also include chemicals known as adjuvants that can help to stimulate a stronger immune response to the vaccine. The clinical development process typically includes a series of trials in humans, starting with small trials to measure the immune response and common side effects, followed by larger trials to determine the effectiveness of the vaccine in preventing the disease of interest.

For COVID-19 vaccines, this cycle was compressed into less than a year, by speeding up the pre-clinical process and by moving through clinical trials at a record pace. Vaccine developers moved faster than usual, often running multiple trials in parallel, and setting up the next round of clinical trials while waiting for the previous round to finish in the expectation (or hope) that those results would be positive. Regulators such as the United States Food and Drug Administration provided rapid evaluation and emergency approvals. Vaccine manufacturing was also scaled up, often before the availability of clinical trial results and regulatory approval, taking the risk that the vaccine might not ultimately be approved. The rapid development of vaccines and scaling up of manufacturing capacity were generally supported by public funds. For example, the vaccines developed by Moderna and Johnson & Johnson were aided by American government funding under Operation Warp Speed.[3] The development of the

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[3] Lancet Commission on COVID-19 Vaccines and Therapeutics Task Force Members, 'Operation Warp Speed: Implications for Global Vaccine Security', *Lancet Global Health* 9, no. 7 (2021): E1017–E1021, https://doi.org/10.1016/S2214-109X(21)00140-6.

Oxford University/AstraZeneca vaccine was largely supported by funds from the UK government.[4]

Around 30 COVID-19 vaccines are being used around the world, from four major technology classes (Table 4.1). The mRNA vaccines developed by BioNTech/Pfizer/Fosun Pharma and Moderna could be considered the newest technology, since mRNA vaccines have never previously been used in mass vaccination campaigns, although mRNA vaccines for several other diseases have been tested in clinical trials.[5] This novel technology works by encoding the recipe for viral components, in this case, the spike protein of SARS-CoV-2, in mRNA form and using cellular machinery to adapt the recipe and produce spike proteins. In simple terms, injection with an mRNA vaccine allows our own cells to be used as factories for SARS-CoV-2 spike proteins, and our immune system can then mount an immune response to those spike proteins that will provide protection against future exposures. While live vaccines also use our own cells as factories to produce more viruses that our immune system can respond to, there is always a risk that a live virus vaccine might transmit infection between individuals, as has happened with the live oral poliovirus vaccine for example. Viral subunit vaccines such as the one produced by Novavax include individual viral spike proteins rather than complete viruses, and therefore do not infect cells but stimulate an immune response to those viral components.

The vaccines against COVID-19 provide two layers of defence in general. The first layer is protection against infection, mostly mediated by antibodies. The second layer is protection against severe disease, even if infection occurs. An infection in a vaccinated individual is sometimes called a 'breakthrough' infection, and breakthrough infections can tend to be milder in severity than infections in unvaccinated individuals because of this second layer of defence, mediated by T cells and other components of the immune system. Whereas SARS-CoV-2 variants have been able to escape the first layer of defence by evading antibodies against the original strain of the virus, the second layer of defence against severe disease has generally remained robust and provided sustained protection against severe COVID-19 in breakthrough infections.

There is a clear difference in the approaches taken in China, relying mostly on inactivated vaccines, compared to the approach in Europe and North America of using newer technologies to manufacture vaccines with higher efficacy against mild infection. All vaccine technologies were able to provide a high level of protection against severe COVID-19.

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4. Samuel Cross, Yeanuk Rho, Henna Reddy, Toby Pepperell, Florence Rodgers, Rhiannon Osborne, et al., 'Who Funded the Research behind the Oxford–AstraZeneca COVID-19 Vaccine?', *BMJ Global Health* (2021) 6: e007321, https://doi.org/10.1136/bmjgh-2021-007321.
5. Norbert Pardi, Michael J. Hogan, Frederick W. Porter, and Drew Weissman, 'mRNA Vaccines—A New Era in Vaccinology', *Nature Reviews Drug Discovery* 17 (2018): 261–279, https://doi.org/10.1038/nrd.2017.243.

Table 4.1: Overview of COVID-19 vaccine technologies

	mRNA	**Viral Sub-unit**	**Viral Vector**	**Inactivated Virus**
Example vaccines by manufacturer	BioNTech (Pfizer), Moderna	Novavax	AstraZeneca, Johnson & Johnson, CanSino	Sinovac, Sinopharm, Covaxin
Doses required to be 'fully vaccinated'[a]	Two	Two	Two	Two (<60y) or Three (≥60y)
Advantages	Very strong immune response	Very strong immune response	Broader and more durable immune response (in theory)	More traditional manufacturing approach
Disadvantages	Complex to develop and manufacture, stronger side-effects	Complex to develop and manufacture	Complex to develop and manufacture	Weak and short-lived immune response
Initial efficacy estimates against symptomatic COVID-19 with ancestral strain in large clinical trials	90%–95%	96%	76%	51%–78%
Initial efficacy estimates against severe COVID-19 with ancestral strain in large clinical trials	>99%	>99%	>99%	>99%

a. The definition of 'fully vaccinated' varies in different locations, here we refer to the World Health Organization recommendations for primary vaccination series.

Global Vaccination Uptake and Impact

As of August 2022, more than 12 billion doses of COVID-19 vaccines have been administered worldwide, and more than 68 per cent of the world's population has received at least one vaccine dose. In many higher-income countries, more than 70 per cent of the population have received at least two doses of vaccine, with many locations achieving high coverage with booster doses.

Israel was one of the first countries to achieve high vaccination coverage, and in February 2021 reached two-dose coverage of 84 per cent among persons ≥70 years of age. Substantial reductions in severe disease particularly in older adults were clear evidence of the impact of the vaccination programme.[6] As vaccination coverage continued to increase in Israel, by the end of March, levels of infection had dropped to a point where public health and social measures could be relaxed.[7]

However, a gradual loss of vaccine performance had become apparent by mid-2021, attributable to two specific phenomena. The first phenomenon was waning in immunity after vaccination, recognised for many vaccines, but not initially for COVID-19 vaccines because the focus of the earliest trials was short-term protection within a few months of receipt of initial vaccine doses. The second phenomenon was the emergence of SARS-CoV-2 variants. The first of these was the Alpha variant, first identified in the United Kingdom, and included a number of mutations on the spike protein that allowed the virus to infect individuals who already had antibodies against the original virus either through vaccination or infection, because of a mismatch between the antibodies against the original virus and against the mutated Alpha variant. A number of other variants were detected, each of which had the capacity to evade antibodies from prior infections or vaccinations, the most recent variant being Omicron.

Notwithstanding waning immunity and the emergence of variants, vaccines have saved many lives already, and will save many more in the coming years. One study estimated that almost half a million lives have been saved in the first 11 months of the vaccination programme in the European Union.[8] Another study conducted over a similar period estimated that vaccines have prevented more than 1 million deaths in the United States.[9]

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[6] Ehud Rinott, Ilan Youngster, and Yair E. Lewis, 'Reduction in COVID-19 Patients Requiring Mechanical Ventilation Following Implementation of a National COVID-19 Vaccination Program—Israel, December 2020–February 2021', *Morbidity and Mortality Weekly Report* 70, no. 9 (2021): 326–328, https://doi.org/10.15585/mmwr.mm7009e3.

[7] Stuart Winer, 'With Most Israelis Now Fully Vaccinated, Virus Spread Continues Sharp Drop-Off', *Times of Israel*, 25 March 2021, https://www.timesofisrael.com/with-most-israelis-now-fully-vaccinated-virus-spread-continues-sharp-drop-off.

[8] Margaux M. I. Meslé, Jeremy Brown, Piers Mook, José Hagan, Roberta Pastore, Nick Bundle, et al., 'Estimated Number of Deaths Directly Averted in People 60 Years and Older as a Result of COVID-19 Vaccination in the WHO European Region, December 2020 to November 2021', *Eurosurveillance* 26, no. 47 (2021): pii=2101021, https://doi.org/10.2807/1560-7917.ES.2021.26.47.2101021.

[9] Eric C. Schneider, Arnav Shah, Partha Sah, Seyed M. Moghadas, Thomas Vilches, and Alison Galvani, 'The U.S. COVID-19 Vaccination Program at One Year: How Many Deaths and Hospitalizations Were Averted?', Commonwealth Fund, 14 December 2021, https://doi.org/10.26099/3542-5n54.

However, vaccines have not been equally available everywhere in the world. The World Health Organization established the 'COVAX' programme to provide vaccines worldwide with costs varying by income status (see Chapter 2). The concept of this programme was to encourage higher and lower-income locations to purchase vaccines through the programme, as well as to receive donations, using the large programmatic budget as leverage to negotiate for discounts on vaccine purchases that could then be passed to the lower-income locations. Vaccines purchased through COVAX would then be distributed fairly to all participating countries. By mid-April 2022, the COVAX programme had shipped 1.4 billion vaccine doses to 145 countries, somewhat short of the initial aim of 2 billion doses by the end of 2021 but still a fantastic achievement.

While initial vaccine programmes aimed to provide adults (and, more recently, children) with two vaccine doses, the loss of immunity to infection with virus variants has led to third dose 'booster' programmes in many locations, and even more recently to fourth-dose campaigns. There is clear evidence that these additional doses provide improved protection against infection and severe disease. Where discussion remains is the optimal interval between booster doses, whether it be as short as 3 months, as long as 12 months, or perhaps somewhere in between.

Individual Immunity, Population Immunity, and Herd Immunity

As noted above, COVID-19 vaccines provide two layers of defence—against infection, and against the development of severe disease if we still get infected. For the ancestral strains of the virus, the mRNA vaccines were extremely effective in preventing even mild infections. If infection can be prevented, then there is of course no chance of severe disease occurring. With the emergence of virus variants, however, vaccine effectiveness against infection has declined, and the second layer of defence has come to the fore. In a recent study of Omicron BA.2 cases in Hong Kong, my colleagues and I estimated that two doses of the mRNA vaccine produced by BioNTech/Pfizer/Fosun Pharma provided adults 20–59 years of age with around 31 per cent protection against mild infection, but 95 per cent protection against severe disease. In comparison, two doses of the inactivated vaccine produced by Sinovac provided adults 20–59 years of age with around 18 per cent protection against mild infection, but 92 per cent protection against severe disease.[10] While it is not yet fully understood which exact immune mechanisms contribute to the different layers of protection, a common view is that antibodies play a major role in protection against infection, while cellular immunity has a greater role in protection from severe disease in breakthrough infections.

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[10] Martina E. McMenamin, Joshua Nealon, Yun Lin, Jessica Y. Wong, Justin K. Cheung, Eric H. Y. Lau, et al., 'Vaccine Effectiveness of One, Two, and Three Doses of BNT162b2 and CoronaVac against COVID-19 in Hong Kong: A Population-Based Observational Study', *Lancet Infectious Diseases* 22, no. 10 (2022):1435–1443, https://doi.org/10.1016/s1473-3099(22)00345-0.

Immunity can also be acquired through infection, of course, and there are ongoing scientific debates about which source of immunity might be stronger or more durable, depending as well on the sequence of vaccination first or infection first, and the types of vaccines. Where there is no debate is that vaccination is a safer process than natural infection, not only because of the risk of severe disease in natural infections but also because of the possibility of exacerbation of an underlying medical condition and the possibility of developing long-term symptoms after recovery ('long COVID').

The broad concept of 'population immunity' refers to the degree of immunity in the population as a whole, perhaps against infections, or perhaps measured against severe disease. For example, a population in which the vaccine coverage is very high is likely to have a high level of population immunity against severe disease, in the sense that rates of severe disease in any epidemic would be substantially reduced by the high vaccine coverage. Because the risk of severe disease is much higher in older adults than in younger individuals, it is possible that population immunity against severe disease could still be considered high in a population that has a high vaccine coverage in older adults but a low vaccine coverage in other groups. Immunity from natural infections should also be considered in an assessment of population immunity.

A more specific concept is 'herd immunity'. This is a technical term in the study of infectious diseases, referring to a level of population immunity against infection that is high enough to prevent an epidemic from occurring. An example of herd immunity for COVID-19 is when Israel achieved a high enough vaccine coverage—above 60 per cent, with a highly effective vaccine (the mRNA vaccine produced by BioNTech/Pfizer/Fosun Pharma)—that COVID-19 transmission ceased in the community in early 2021. Given that a small fraction of the population had likely been infected and had natural immunity, the herd immunity threshold was likely surpassed when somewhere between 60 per cent and 70 per cent of the population had immunity against infection.

For the newer variants of COVID-19, such as the Omicron variant, vaccines do not provide a high level of protection against infection, and herd immunity cannot be achieved by vaccination alone. Infections however do provide strong specific immunity—there are very few known cases of re-infection with the same strain of the virus—and many locations have now reached herd immunity against Omicron BA.1 and BA.2 following epidemics of these viruses in their communities. In fact, there are only two reasons why daily COVID-19 case numbers decline over a period of time. One reason is because of the implementation of public health and social measures, as happened around the world in 2020 bringing community epidemics under control. The other reason is that the herd immunity threshold has been surpassed (at around the time an epidemic curve peaks), and the virus essentially runs out of people to infect. It is important to recognise that not everyone would be infected in such a scenario, the cumulative proportion of the population infected in an epidemic would exceed the herd immunity threshold but would fall short of 100 per cent (see Chapter 5). In Hong Kong's large community epidemic of Omicron BA.2 in February, March and April 2022 my colleagues and I estimate that around two-thirds of the population was infected, while a further fraction of perhaps 15 per cent of the population already had immunity against infection provided by vaccination, with three doses of an mRNA vaccine providing a moderate level of protection against infection that was higher than the protection provided by two doses of that vaccine or two or three doses of an inactivated vaccine.

Looking into the future, it is unlikely that vaccines will be able to provide strong immunity against infection unless somehow the strains included in vaccines can keep up with viral evolution. New vaccine technologies might be able to provide stronger protection, but there is not likely to be any short-term change in the technologies used for COVID-19 vaccines. Infections do provide long-lasting immunity against re-infection with the same strain, and the large community epidemics of Omicron subvariants that have been occurring in early 2022 will ultimately confer herd immunity against those specific subvariants. However, that herd immunity against one subvariant would likely not translate to herd immunity against another, and that was why in April 2022, the world saw an increasing spread of the latest Omicron subvariants, such as BA.4 and BA.5.

As time goes on, population immunity against severe disease will tend to rise to higher and higher levels because of the infections that occur in community epidemics, aided by booster vaccines, particularly in high-risk groups. This means that COVID-19 will likely pose less of a threat to public health as time goes on. In Hong Kong's population of 7.4 million, seasonal epidemics of influenza cause between 500 and 1,000 deaths annually, far fewer than the 9,000 deaths and counting caused by Omicron in 2022. But in future years, the annual death toll of COVID-19 might reduce to a level more comparable to influenza.

Vaccine Recommendations and Mandates

When COVID-19 vaccines were first introduced, priority was generally given to individuals at the highest risk of severe disease, i.e., older adults and those with underlying medical conditions, as well as those at potentially higher risk of infection or with an important role in society such as healthcare workers and other key workers. Vaccines were subsequently made available to other age groups, and many countries now offer COVID-19 vaccines to children. While some aspects of vaccine recommendations can vary from one country to another, it is clear that COVID-19 vaccines have provided benefits to all age groups that have received them, and that re-vaccination from time to time will be recommended in the years to come.

Where controversy has arisen is in the use of coercive policies to increase vaccination uptake beyond what can be achieved voluntarily, with the recognition that higher vaccine uptake will reduce the health impact of COVID-19 epidemic waves in a community. For example, Israel introduced a 'green pass' that restricted the movements of unvaccinated individuals (noting that recovery from a documented infection was permitted as an alternative to vaccination).[11] In January 2022, Austria introduced a law requiring all adults to receive COVID-19 vaccination, but withdrew it in March.[12] As of April 2022, a number of countries only permit residents or visitors to arrive in the country if they are vaccinated. Vaccine mandates, or the implementation of vaccine passes or passports, have a number of ethical considerations.[13]

According to the World Health Organization, mandating vaccination or any other medical procedure requires strong justification such as an emergency situation. That is because vaccination is a medical procedure and requires an 'informed consent' process beforehand. Three key components of the informed consent process include (1) the consenting person is of sound mind; (2) the consenting person understands the risks and benefits of the procedure; and (3) the consenting person does so voluntarily. These principles are modified when applied to children or those unable to consent themselves for some reason. A well-informed person is fully entitled to refuse a medical procedure, even if it unequivocally offers more benefits than risks.

COVID-19 has been a clear public health emergency since the World Health Organization first declared the Public Health Emergency of International Concern on 30 January 2020 (see Chapter 2). Stringent public health and social measures were implemented around the world in the first year of the pandemic. Restriction of individual freedoms with a range of public health measures was justified based on the societal risk, and particularly the risk of substantial harm to the community if healthcare systems became overwhelmed with COVID-19 cases. Once vaccines became available, they presented an opportunity to protect individuals and healthcare systems even after the relaxation of those public health measures. That is because the immunity provided by COVID-19 vaccines, as well as any immunity in the population following previous infections, could substantially reduce the risk of severe COVID-19.

Given compelling evidence of the effectiveness of vaccines, most developed countries have been able to achieve high vaccination coverage in the segments of their population at the highest risk of severe COVID-19, namely the elderly and those with underlying medical conditions. In many cases, high coverage was achieved without a mandate. In circumstances where vaccine coverage had not reached high levels in high-risk subpopulations, a mandate could have been justified to protect the community as a whole, despite overriding individual freedoms. Differences in the social contract, discussed elsewhere in this book, would also play into the rationale for mandates in different locations. However, moving into 2022 there seems to be little justification for continuing vaccine mandates, vaccine passes or vaccine passports. Any need for them had passed.

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[11] Shelly Kamin-Friedman and Maya Peled Raz, 'Lessons from Israel's COVID-19 Green Pass Program', *Israel Journal of Health Policy Research* 10, no. 61 (2021), https://doi.org/10.1186/s13584-021-00496-4.

[12] Geir Moulson, 'Austria Suspends Vaccine Mandate before Enforcement Starts', *AP News*, 9 March 2022, https://apnews.com/article/covid-health-europe-austria-e0ebc5d6fa43913c8361f718a3688fb3.

[13] Mark A. Hall and David M. Studdert, '"Vaccine Passport" Certification—Policy and Ethical Considerations', *New England Journal of Medicine* 385 (2021): e32, https://doi.org/10.1056/NEJMp2104289.

Vaccines in the Era of COVID-19 'Epidemicity'

It is now clear that SARS-CoV-2 will not disappear but will continue to cause infections around the world in the coming years. Successive emergence of variants, most recently the Omicron variant, will likely continue as the virus evolves to escape population immunity. SARS-CoV-2 infections will occur in periodic epidemics, perhaps more likely in the winter months in temperate locations, and so the term 'endemic' may not be the right term as it means the virus would remain in a community year-round. It is possible that some parts of the world will see temporary disappearances of the virus, with travellers then introducing the latest strains that will go on to cause local epidemics. In that sense, 'epidemicity' might perhaps be a better word.

An interesting debate has revolved around the severity of infections, with Omicron often perceived as 'milder' than previous strains of SARS-CoV-2. However, this is not actually the case. In Hong Kong, unvaccinated adults infected with Omicron had roughly the same risk of severe disease or death as they did in early waves with the original strain of SARS-CoV-2.[14] In adults with pre-existing immunity, either from a prior infection or from vaccination, Omicron is a milder infection. As levels of immunity reach higher and higher levels, SARS-CoV-2 will appear to become a milder and milder infection whether or not there is any change in its intrinsic severity.

Given that most individuals around the world now have some degree of immunity from infections, vaccinations, or a combination of both, SARS-CoV-2 will pose less of a threat to public health and the integrity of healthcare systems than it did in the first two years of the pandemic. However, the danger has not completely passed. New variants will emerge and cause large numbers of infections. Even when most infections are mild, the small fraction of more severe cases can still be a large absolute number and pose challenges for weak healthcare systems as influenza does in some years. A priority now is to ensure that vaccination coverage remains high in vulnerable individuals, particularly older adults and those with underlying medical conditions.

Nevertheless, one major country, China, chose to maintain its control measures for COVID-19 into April 2022, despite achieving high vaccination coverage. In China, the 'Dynamic Zero COVID' approach has successfully minimised the number of infections, severe COVID-19 cases, and deaths during the first two years of the pandemic. There are two major components of this approach. The first is to keep infections out of the local community as much as possible, achieved through strict on-arrival quarantines not only for arrivals from outside China but also in some cases for inter-provincial travellers. The second is to identify any outbreaks as quickly as possible and respond as quickly as possible with very stringent measures to control the outbreak while it is still at a very early stage. At the time of writing in June 2022, a large outbreak in Shanghai had just been controlled although not eliminated through a prolonged lockdown of

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[14] Yonatan Mefsin, Dongxuan Chen, Helen S. Bond, Yun Lin, Justin K. Cheung, Jessica Y. Wong, et al., 'Epidemiology of Infections with SARS-CoV-2 Omicron BA.2 Variant, Hong Kong, January–March 2022', *Emerging Infectious Diseases* 28, no. 9 (2022): 1856–1858, https://doi.org/10.3201/eid2809.220613.

more than two months combined with frequent testing of the entire population. This has been extremely costly and disruptive to China's largest and wealthiest city. If outbreaks continue to occur in Chinese cities, it is unlikely that the local elimination policy can be sustained without enormous social and economic impact.

One of the reasons sometimes used to explain China's persistence with Dynamic Zero COVID is the relatively lower vaccine coverage in the elderly compared to other age groups. A number of factors have led to the relatively lower vaccination uptake in the elderly to date, perhaps one being the overall elimination strategy that minimises the risk of infection and therefore minimises the risk of severe COVID-19 even in unvaccinated individuals. Vaccines provide a pathway out of the pandemic, but high vaccine coverage in the elderly will be essential if China is to minimise the health impact of a transition away from its Dynamic Zero COVID strategy.[15]

Now that fourth doses are being administered in some locations, it would be a good time to review the optimal timing of vaccine doses. Administering vaccines 3–4 times per year is unlikely to be sustainable, but perhaps twice-annual vaccination for the highest risk could be weighed against annual vaccination, with advantages and disadvantages of both. Among the advantages of twice-annual vaccination would be the regular top-up in immunity, but its disadvantages would be the additional costs and perhaps only incremental benefits, especially if SARS-CoV-2 tends towards winter epidemics. Similar discussions have occurred for influenza vaccination. One final issue is whether there is any immunologic disadvantage of frequent vaccination, which remains a controversial topic for influenza vaccination.[16]

In conclusion, the rapid development of SARS-CoV-2 vaccines has already likely saved millions of lives worldwide and allowed safe relaxation of public health and social measures with minimal morbidity and mortality, particularly in parts of the world that were able to keep COVID-19 at bay for the first two years of the pandemic.

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15. Jun Cai, Xiaowei Deng, Juan Yang, Kaiyuan Sun, Hengcong Liu, Zhiyuan Chen, et al., 'Modeling Transmission of SARS-CoV-2 Omicron in China', *Nature Medicine* 28, no. 7 (2022): 1468–1475, https://doi.org/10.1038/s41591-022-01855-7.
16. Mark G. Thompson and Benjamin J. Cowling, 'How Repeated Influenza Vaccination Effects Might Apply to COVID-19 Vaccines', *Lancet Respiratory Medicine* 10, no. 7 (2022): 636–638, https://doi.org/10.1016/S2213-2600(22)00162-X.