Research Article

The Changing Trajectory of Covid-19 and How Immunity is Evolving with It

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The dynamic of the virus-host interaction is subject to constant evolution which makes it difficult to predict when the SARS-CoV-2 pandemic will become endemic. Vaccines in conjunction with efforts around masking and social distancing have reduced SARS-CoV-2 infection rates, however, there are still significant challenges to contend with before the pandemic shifts to endemic, such as the coronavirus acquiring mutations that allow the virus to dodge the immunity acquired by hosts. The continued emergence of variants and sub-variants poses a significant hurdle to reaching endemicity. This underscores the importance of continued public health measures to control SARS-CoV-2 transmission and the need to develop better second-generation vaccines and effective treatments that would tackle current and future variants. We hypothesize that the hosts' immunity to the virus is also evolving, which is likely to abet the process of reaching endemicity.

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Article Highlights

- This paper addresses the much-debated question of if and when the current Covid-19 pandemic will shift to endemic.
- The buildup of the hosts' immunity from natural infections and/or vaccination has led to milder infections, which could facilitate a transition to endemicity.
- Selective pressure acting on SARS-CoV-2 tends to select traits that favor the virus' survival, such as the ability to evade the hosts' immunity, which could increase the timeline to reach an endemic state.

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- The more widespread the transmission is, the more chance that this RNA virus will mutate; therefore, continued public health measures to control the transmission of the virus to reduce the chance of a more dangerous variant emerging and the development of better second-generation vaccines to tackle the currently circulating variants are of paramount importance.

Introduction

As the fourth year of the pandemic approaches, SARS-CoV-2 infections continue to spread, though the levels are variable and erratic in different parts of the world. More and more individuals are developing milder symptoms following infection with the virus, which has reduced the rates of hospitalization and fatalities [1]. The USA and most European countries did not see a surge this winter as was initially predicted. This has raised hopes that the Covid virus can soon become endemic. This paper discusses how the host's immunity is evolving and how this may facilitate a stable co-existence with the Covid virus.

The dynamic of the virus-host interaction is subject to constant evolution. Since SARS-CoV-2 is an RNA virus, the virus will mutate, and the emergence of new variants will occur as we have already seen over the last three years [2][3]. Suppose the virus morphs into a variant or subvariant that is more contagious and can evade the host's immunity; in that case, the rate of transmission can increase, which may lead to higher hospitalization and death rates. It must be emphasized that the more widespread the transmission is, the more likely this RNA virus will mutate. Of note, RNA viruses are characterized by their high mutation rate [4], which increases the risk that a new variant may emerge. While media coverage of Covid-19 has dwindled, the infection continues to significantly impact human health in parts of the world. For example, since the start of the pandemic in India, there have been 44,691,956 confirmed cases of Covid-19 with 530,789 deaths [5]. Moreover, this disease continues to do marked damage to at risk populations, such as those with weakened immunity or comorbidities [6], which means that the fight is still far from over.

Having considered the important advances in our knowledge regarding viral mutation and the host's immune response to emerging variants, this paper addresses whether SARS-CoV-2 could be here to stay, despite the presumed evolution of a stronger immune response in hosts over time. In this paper, we discuss different components of immunity impacting the Covid-19 virus including innate

immunity, T and B-cell mediated immunity, cross reactive immunity, the role of the host's genetics, and then hypothesize that the hosts' immunity to the virus is evolving, which is likely to support the process of reaching endemicity.

The Emergence of SARS-CoV-2 Variants

The continuous evolution of SARS-CoV-2 has resulted in the emergence of numerous subvariants that often exhibit growth advantages over previous variants. Since the emergence of Omicron in December 2021, several sub-lineages (BA.1, BA.2, BA.4, BA.5, and BA.2.12.1) have evolved, some of which demonstrate the ability to evade immunity from vaccination or previous infections. BA.4 and BA.5 exhibit the qualities of immune evasion; studies indicate that the variants can elude some of the antibodies produced after coronavirus vaccinations and infections, including infections caused by some earlier versions of Omicron (Figure 1A). The BA.5 sub-lineage can evade antibodies from both vaccination and prior infection [7]. This would explain the rapid spread of these variants despite widespread pre-existing immunity to the virus. In September 2022, scientists identified subvariant XBB, which is believed to be a recombinant of Omicron subvariants BA.2.10.1 and BA.2.75 [8].

Figure 1A: The Changing Landscape of the Covid-19 Pandemic

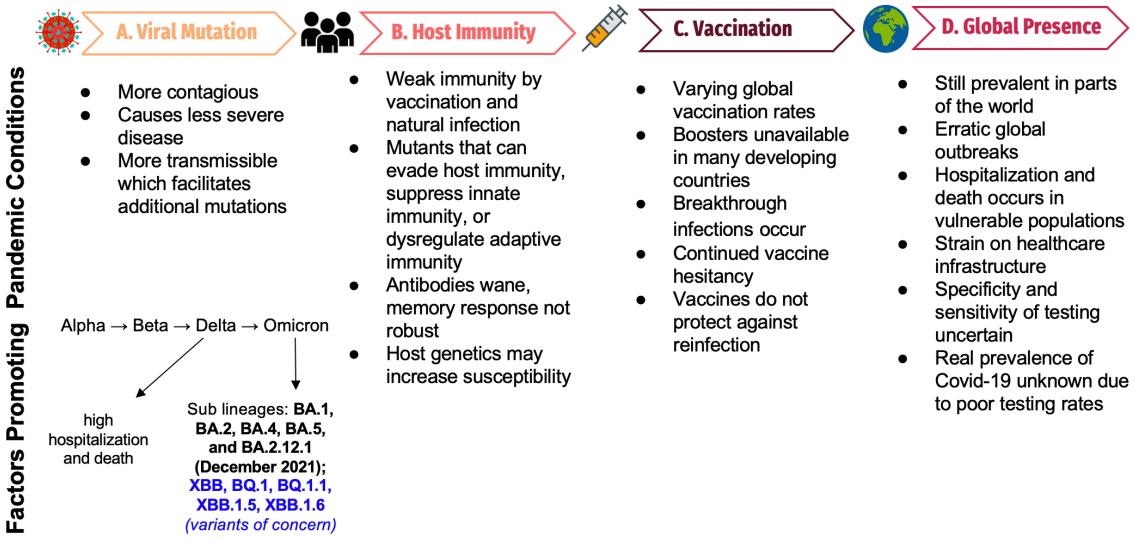

Figure 1A. The Changing Landscape of the Covid-19 Pandemic. This figure demonstrates the factors that will propagate a pandemic situation: Panel A lists viral mutations and characteristics that will promote a pandemic and demonstrates the characteristics of recent variants; Panel B demonstrates factors affecting host immunity and variations in susceptibility that would propagate the current pandemic; Panel C illustrates factors related to vaccination that would facilitate a continued pandemic state. Panel D demonstrates factors contributing to a pattern of continued, erratic global outbreaks attributed to a pandemic.

A new group of Omicron sub lineages (BQ.1, BQ.1.1, and XBB) is gaining ground across the USA and other countries. The BQ.1.1 variant, which has three spike mutations (N460K, K444T, and R346T), make BQ.1.1 more contagious than its closely related variants. Both of the BQ.1 and BQ.1.1 sub lineages are descended from BA.5, which has been dominant for months, while XBB comes from two different BA.2 lineages recombined into one [8]. The BQ.1 and XBB sub lineages are distinct enough from each other that they could end up co-circulating; if this turns out to be the case, infection outcomes should be monitored closely.

The newly emerged BQ.1.1 appears to have an advantage due to three major mutations on its spike protein that makes this variant more contagious than its predecessors. The researchers found that BQ.1.1 is able to evade antibodies from past BA.5 infections, which suggests it may also be able to dodge protection from vaccines [9]. The study also found that some monoclonal antibody drugs are less effective against BQ.1.1, compared to earlier strains of the virus. This is particularly concerning

since antibody therapies have proved popular and effective against other variants and subvariants of SARS-CoV-2. Public health officials fear that the ability for substantial neutralization escape can render antibody treatments like Evusheld, a Covid-19 treatment for severely immunocompromised individuals, and other monoclonal antibody treatments to be largely ineffective against these new variants. Of note, there is a long-standing controversy between the efficacy of therapeutic monoclonal antibodies and polyclonal preparations from convalescent plasma [10][11]. Data demonstrating a link between BQ.1 and increased disease severity is lacking; however, one pre-print study suggests that BQ.1 has shown substantial immune evasion potential compared to prior variants [12].

A recent preprint study demonstrates that this increased transmissibility could be attributed to a mutation on the spike protein that enhances the virus' ability to stick to the human ACE2 receptor [13]. Although there has been a rapid rise in XBB.1.5, the data does not suggest that this variant is more virulent than its cousins. Interestingly, the impacts of these sub variants may vary from place to place. For example, BA.2.75 caused a major spike in illness in India, while barely registering in other countries [14]. It is not clearly understood how the host's immune system adapts to the mixture of subvariants cocirculating at the same time in the hosts and how these processes are impacted by the varying types and rates of vaccination by country.

In March of 2023, a new variant known as XBB.1.6 (also known as Arcturus) was classified by the WHO as a variant under monitoring [15] and is causing increasing case counts in India, where it is the dominant subvariant. This variant has been identified in at least 31 countries, including the United States. It is very similar to its predecessor XBB.1.5 but has one additional mutation in the spike protein. The variant XBB.1.16 has a higher transmissibility rate than previous strains but doesn't appear to be more dangerous, however, symptoms of conjunctivitis in young patients have been reported in association with this newest variant. Currently, the dominant variant in the USA is XBB.1.5, with 53.8% of cases, followed by XBB.1.6, with 15.1% of cases, and XBB.1.9.1 with 11.8% of cases [16].

It seems that Covid-19 has become a more manageable disease as immunity from vaccination and prior infection, in conjunction with the fact that we haven't had a significantly new variant since late 2021 or early 2022, has led to the development of milder infections. Still, we cannot say how long the Omicron phase of SARS-CoV-2 evolution will persist. However, if a subvariant continues to spread and replicate, evolutionary pressure will ultimately cause the lineage to change further. The chance for the emergence of a new dominant variant, which causes more severe disease or has immune escape is still there, so continued monitoring is of paramount importance. On the other hand, if global immunity to

the subvariant builds, the emergence of a new lineage could take longer than a few months, as seems to be the case currently. Recent reports from the CDC show fewer than 500 deaths per week compared to more than 4,,000 deaths per day from Covid-19 in 2021 [16]. This may allow us to effectively adopt an annual/seasonal covid vaccination schedule, as is the case with the flu shot.

How Host Immunity is Evolving with SARS-COV-2

As we enter the fourth year of the Covid-19 pandemic, the immunity landscape is as complicated as ever due to the variability in infection rates, exposure to different viral variants, and disparate vaccination rates. The general trend seems to be that infections are getting milder as immune systems adapt to protect against serious disease [17]. However, many immunocompromised individuals are still developing severe symptoms that require hospitalization [18]. Moreover, the currently available vaccines do not protect against reinfection, and the immunity induced by vaccinations or natural infection tends to fade within eight months [19]. While the current vaccines may be sufficient to provide individual protection against severe disease, they have little effect on protection against infection and reduction in transmission, and therefore do not adequately generate community immunity [20] (Figure 1A). Without a reduction in transmission, the risk for a more contagious subvariant to emerge remains; the more the virus spreads and replicates, the more chances for a mutation to occur. The goal of reaching "herd immunity," remains elusive as the virus develops immune evasive characteristics and adapts to undermine the vaccines' protection [21][22]. SARS-Cov-2 immune evasion strategies include mutating key protein structures that are recognized by the body's immune system or, camouflaging its viral mRNA to mimic the host's mRNA to avoid immune detection. A recent study has shown that the SARS-Cov-2 RNA's genome contains a code for a viral five prime (5') cap which facilitates immune evasion [23].

Not only has SARS-CoV-2 acquired mutations to evade the hosts' immunity, but also those that inhibit the innate immune response [24]. Innate immunity is the first to respond to intruding pathogens and may exert a strong selection pressure on the Covid-19 virus, which could explain the rapid spread of the two most recent and dominant variants. One of the ways innate immunity protects the host against infection is to recruit antiviral proteins to combat invading viruses; studies have shown that SARS-CoV-2 can dampen the activation of these critical antiviral proteins [24]. This allows

SARS-CoV-2 to evade the body's initial lines of defense and could explain the virus' ability to infect vaccinated or previously infected people.

Several studies have shown that neutralizing antibodies can wane over time, however, the long-lasting B and T memory cells can persist in recovered individuals [25][26]. The initial spike in IgA antibodies drops significantly and the levels of IgG antibodies remain elevated for at least 3 months [27]. In a recent study, IgG antibodies against spike proteins were found to be stably produced for over 6+ months post-infection. SARS-CoV-2 CD4+ T cells and CD8+ T cells showed a half-life of 3-5 months in primary response [27][28]. However, in the secondary response, T-cell responses can persist in the blood long after antibody responses wane [29]. One study demonstrated that T-cell responses were detected up to 15 months after initial Covid-19 infection with 86% sensitivity [30][31]. Most antibody tests only look for one part of the virus (e.g., spike protein) [30]. T cells together can recognize many parts of the virus. The memory T cell response has better breadth and magnitude [32] (Figure 1B).

Figure 1B: The Journey of Covid-19, from Pandemic to Endemic:

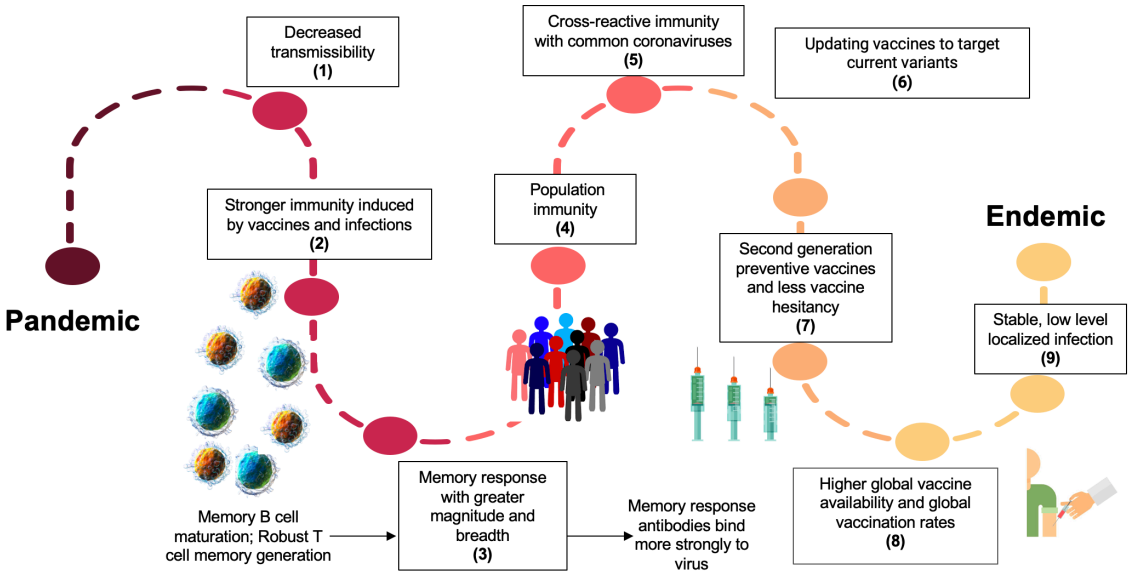

Figure 1B. The Journey of Covid-19, from Pandemic to Endemic: This figure demonstrates the factors that will eventually shift the current pandemic to an endemic situation: (1) decreased transmissibility of circulating virus, (2) increased immunity induced by vaccines and infections, (3) induction of a stronger memory immune response by stimulating memory B cell maturation and robust memory T cell generation, (4) more people in the community acquiring an immune response, (5) stronger cross-reactive immunity stimulated by the common coronavirus, (6) updating vaccines targeting the currently circulating virus, (7) the development of better second-generation vaccines preventing infection and wide vaccine acceptance, (8) increased global vaccine availability leading to local control and to impeding the spread of SARS-CoV-2 virus, (9) shifting to low stable localized infections facilitating the transition to endemicity.

A recent study compared the antibody mediated response between patients who had severe or mild disease and found that patients with severe disease demonstrated a more robust humoral immune response due to increased levels of B cell receptor activation and clonal expansion [33]. Interestingly, another study using inhibition assay found contrasting results which indicated that convalescent Covid-19 patients did not always generate spike specific and receptor binding domain (RBD) specific antibodies that inhibit RBD binding to ACE2 [34]. Clearly, SARS-CoV-2 infections can generate varying levels of antibody response [34]; however, it is not robust enough to induce protection against reinfection which has implications on studies seeking to measure vaccine-induced immune memory.

Kream and co-workers proposed that convalescent memory T cell immunity in individuals with mild or asymptomatic SARS-CoV-2 infection may result from an evolutionarily adapted immune response to coronavirus and the 'common cold' [35]. Furthermore, there is increasing evidence of the existence of SARS-CoV-2-reactive T memory cells in unexposed healthy individuals originating from previous immune responses to endemic coronaviruses that cause the 'common cold' in humans [36]. The patterns of SARS-CoV-2-specific $CD4^+$ and $CD8^+$ T cells responsive to HLA class I and class II epitopes found in multiple species of viral proteins were observed in a significant number of unexposed healthy donors [36][37]. These findings suggest a more extensive and persistent expression of SARS- CoV-2-reactive T memory cells in unexposed healthy individuals than previously believed, which could be attributed to multiple cross-reactive viral protein targets following previous exposure to circulating human endemic 'common cold' coronaviruses [37][38] (Figure 1B).

Assessment of global virus-specific T cell responses could be challenging. Compared to humoral immunity, the investigation of cellular responses against peptides presented through multiple HLA alleles in human populations is more complex [39]. However, some important progress has recently been made. A recent study has shown that spike mutations can lead to loss of T cell recognition within epitopes restricted by common HLA alleles [40]. This is potentially important, given that population immunity may not yet be sufficient to drive strong T cell selection [41]. The large number of mutations in the Omicron variant within the spike is likely to inactivate the presentation or recognition of some epitopes. At the current time, potential mechanisms by which viral proteins or RNA may act to directly suppress antigen presentation are unclear, although ORF8 was shown to downregulate the expression of HLA class I proteins [42]. Of note, ORF8 is a rapidly evolving accessory protein of SARS-CoV-2 that has been proposed to interfere with immune responses to the virus [43].

Interestingly, recent data showed the presence of non-spike cross-reactive memory T cells protecting SARS-CoV-2-naïve contacts from infection [44]; these findings suggest that vaccine manufacturers should include non-spike antigens that can target spike-antibody immune escaping variants when designing better second-generation vaccines (Figure 1B). In fact, recent scientific endeavors have been focused on the development of vaccines that could stimulate long lasting T cell responses and researchers have started comparing the T-cell responses between the currently available vaccines. It has been reported that the mRNA vaccines from Pfizer and Moderna (as well as two other vaccines that work by different mechanisms) produced relatively consistent levels of a key T cell in the six months

after vaccination [45]. Over the same period, antibodies generated by the Pfizer and Moderna shots faded. Researchers at the University of Tübingen in Germany have a trial going to investigate the safety of a vaccine made of SARS-CoV-2 proteins that are known to stimulate T-cell immunity [46]. A similar study at the Massachusetts Institute of Technology demonstrated that their mRNA vaccine, which targets highly conserved parts of the coronavirus, generates a robust T cell response that confers protection against morbidity and mortality in mice [47].

Host Genetics and Susceptibility to SARS-CoV-2

It has recently been shown that people with allergic conditions such as hay fever, rhinitis, and atopic eczema, may have a lower risk of Covid-19 infection, especially if they also have asthma [48]. This may be related to the decreased expression of *ACE2*, the gene encoding the SARS-CoV-2 receptor, which has been reported in people with asthma [48]. SARS-CoV-2, and human coronavirus NL63 (HCoV-NL63), utilize the human protein ACE2 as a cellular receptor to gain entry into human cells [49][50]. Genetic ACE2 variants are likely to correlate with the increase or decrease in their affinity. However, it is unknown whether these natural ACE2 variants decrease or increase their affinity for coronavirus spike protein and affect the susceptibility of individuals to infection. Several variations have been observed in the ACE2 gene, some of which have been significantly associated with arterial hypertension, diabetes mellitus, and coronary artery disease [51]. A recent study that assessed the impact of ACE2 single nucleotide polymorphisms (SNPs) on interactions with coronavirus S proteins and SARS-CoV-2 entry *in vitro* and *in vivo* has identified an SNP that potentially protects individuals against SARS-CoV-2 infection [52]. ACE2 polymorphism may alter human susceptibility to SARS-CoV-2 infection and contribute to ethnic and geographical differences in SARS-CoV-2 spread. Intact viruses can target their receptors on multiple cell types through conformational matching; this is followed by viral replication by an evolutionary modification of the ACE2 receptor required for the virus binding and host cell entry [53]. The ability to successfully escape immunity while maintaining its ability to bind to ACE2 may have potentially contributed to the rapid global spread of omicron subvariant BA.5 [54].

Although both genetic and environmental factors are certainly expected to impact the susceptibility of individuals, the HLA alleles can affect both the susceptibility and the severity of SARS-CoV-2 infection. The crucial role played by HLA molecules in the immune response, especially through

pathogen-derived peptide presentation, and the huge molecular variability of HLA alleles in the human populations could be responsible for the varying rates of infection in different patients following Covid-19 infection [55].

A recent genome wide association study reported genetic risk factors, such as six genes in a region of chromosome three, are associated with Covid-19 severity [56]. Another study found that patients with severe Covid-19 disease had genetic mutations that resulted in a deficient type 1 interferon (IFN) response or autoimmune antibodies affecting type I IFN [57]. In fact, recent studies highlighted that many of the genes associated with severe disease were associated with inflammation or immunoregulatory pathways [58], particularly those associated with the IFN signaling pathway [59]. These studies support the idea that human genetic variation can impact the susceptibility and pathogenicity of the Covid-19 virus in different geographic territories and ethnicities. Of note, most genome wide association studies conducted early on were skewed due to small sample sizes and the selection of severely ill patients. Clearly, further studies are required to better identify the genetic factors that influence Covid-19 disease pathology to define biomarkers for at-risk individuals and inform potential therapeutic targets.

Vaccines and the Role of Boosters

In most infectious diseases, with a few exceptions, the human immune system needs repeated exposure to natural infections to develop immunity, even in the case where the infectious agent does not mutate significantly. One known exception is cutaneous Leishmaniasis in which one primary natural infection may lead to life-long immunity [60]. Many individuals in Africa can develop a degree of natural immunity against malarial parasites after repeated exposure [61]. Immunity without repeated exposure wanes and exposure with smaller doses reduces the risk of overburdening the immune system.

Currently, scientists are debating how frequently bivalent vaccines need to be used across the population. A new study from Yale University and the University of North Carolina at Charlotte suggests healthy people should get annual Covid-19 boosters to prevent widespread outbreaks [62]. On the other hand, a recent paper in the New England Journal of Medicine challenges the use of mRNA boosters in healthy individuals who often develop mild infections. The author opined that protecting against Covid infection with the current mRNA technology is unrealistic, especially as new

coronavirus strains emerge every few months [63]. Of note, the bivalent booster was hurriedly introduced with limited data from pre-clinical animal studies. Furthermore, relatively few people in the U.S. have had updated boosters. As of February 6, 2023 only around 15% of people over age 5 had gotten them, according to the CDC [64].

Recently, there has also been an increased interest in the development of intranasal (IN) vaccinations for Covid-19. Recent studies have demonstrated that intramuscular vaccines are not effective at hampering viral replication and shedding in the upper respiratory tract, so while symptoms are milder, the virus can still be transmitted [65]. The appeal for IN vaccinations lies in the fact that they have shown promise to induce sterilizing immunity against mucosal pathogens [66], which could prevent virus infection, replication, shedding, and disease development, while also limiting viral transmission.

Vaccines-induced immune responses naturally wane over time. This in conjunction with the immune evasiveness of newly emerged variants, might explain why those particular subvariants were able to spread quickly regardless of vaccination status or prior infection [67]. These findings have lent urgency to policymakers to develop Omicron subvariant-targeted boosters (Figure 1A). In 2022, the CDC recommended using bivalent mRNA vaccines as boosters for human beings [68]. This vaccine targets both the original strain of SARS-CoV-2 and Omicron subvariants BA.4 and BA.5. The effect of this booster vaccine has been tested in mice and was found to generate a significant immune response against the new Omicron subvariant. Newly released data from Pfizer and BioNTech's ongoing clinical trial indicate that the booster stimulated an immune response against omicron's BA.4 and BA.5 subvariants; participants demonstrated elevated antibody levels against BA.4 and BA.5 just seven days after injection [69]. Although this booster is a bivalent vaccine made from the BA.4 and BA.5 omicron subvariants, it is expected to provide broad protection against newer variants as well. It is not yet clear if this new booster will stimulate protection against reinfection for a longer period, however, the most important point here is how well the vaccines can prevent severe disease with the currently circulating BQ.1 and XBB variants. The most recent (May 2023) recommendation from the WHO suggests that vaccine makers should drop ancestral strains and switch to a monovalent vaccine that only targets XBB variants [70].

Another recent study suggests that instituting yearly, population-wide booster vaccinations updated to predominant variants is beneficial, however, the study only focused on people with healthy immune

systems [62]. The authors of this study acknowledged that immunocompromised populations may require more frequent immune boosting and are conducting additional studies to evaluate the optimal vaccine interval for people with weakened immunity. It is not clear when individuals with weakened immune systems should be given the bivalent booster and how prolonged and robust the antibody response is generated. Many immunocompromised individuals have a lower number of B-cells [71], which play an essential role in antibody and cytokine production to protect against infection. Further studies are needed regarding the dose, frequency, and type of vaccine (e.g., mRNA, protein-based, or inactivated virus) in individuals with different demographics and health conditions.

Furthermore, there is a note of caution about the frequent use of booster shots with short gaps in between, which may overburden the immune system and lead to immune exhaustion, as has been observed in the case of HIV infections [72]. Of note, a recent study demonstrated that T-cell responses to various vaccines remain stable without showing any signs of T cell levels declining over time, and most notably, that boosters do not significantly affect the T cell responses [73]. If this is the case, then Covid-19 immunity could be maintained with only occasional boosting based on T cell levels. However, quantitatively measuring T cells is more difficult than antibody detection; There is a need to improve this technology and relate T cell monitoring to the development of future vaccines, boosters, and effective immunization schedules.

A recently published systematic review concluded that individuals who were vaccinated and infected (hybrid immunity) had the highest magnitude and durability of protection, and as a result, might be able to extend the period before booster vaccinations are needed [74]. Assessing the magnitude and durability of existing protection has become a challenge because of the varying rates and timings of past infections and vaccinations, availability of multiple types of vaccinations and varied dosing schedules, and variants of concern that can escape pre-existing immunity. These variables make it difficult to establish a standardized booster schedule as we have seen with other vaccinations.

While guidance for boosting remains unclear, the CDC has reported that Covid-19 is now one of the three leading causes of death among persons aged 65 and older [75], however, only 40% of that group has received updated booster shots [64]. Public health officials attribute the low uptake in boosters to the lower hospitalization and death rates as reported on social media. Yet another reason for the low booster rate could be a lack of trust in the shots, which has posed a significant obstacle since the introduction of these novel vaccines [2]. Stronger public health messaging by physicians, officials, and

advocates that pointedly address the various factors contributing to vaccine hesitancy would be beneficial (Figure 1A).

The efficacy of a vaccine booster to contain SARS-CoV-2 will depend upon whether the virus mutates again and whether antibodies generated against earlier strains will still be effective. Vaccines that induce antibodies against current and future SARS-CoV-2 variants in conjunction with therapeutics, including monoclonal antibodies and antiviral drugs, will be critical in the fight against Covid-19. Another challenge is that updating vaccines requires clinical testing; however, finding adults who have not been infected or vaccinated remains a challenge for conducting valid tests.

Experts do not expect the recent vaccination of children ages 6 months to 5 years old to alter the trajectory of the pandemic due to sustained vaccine hesitancy in parents; seven out of ten parents in the USA remain hesitant about vaccinating their children mainly due to the lack of transparency in the trial process and dosing determination [76][77]. Furthermore, many children may not be eligible for updated boosters as many of them have not yet received a primary dose of vaccine. Of note, vaccines developed for adults typically require in-depth research to calculate adequate dosages and investigate the short-term and long-term side effects before they are approved for use in children. Transparency and adequate messaging by physicians and public health workers targeted at parents might be helpful in the application of mass-scale vaccination, particularly with vaccines developed using new technologies (Figure 1A).

SARS-CoV-2 may eventually spread like endemic coronaviruses, where exposure to young children under the age of 5 can help bolster the immune system to prevent serious disease. Reinfection throughout adulthood is common for many viruses that were initially encountered in childhood. In the context of SARS-CoV-2 variants, this has raised hopes that repeated exposure throughout a person's lifetime can strengthen immune responses to new variants and accelerate the drifting of the virus toward lower virulency.

The Prospect of Covid-19 Shifting to Endemic

The transition from pandemic to endemic could take time and depends on how long humans retain immunity to the Covid-19 virus and how quickly the virus evolves (Figure 1B). Generation of robust host immunity to recent variants may accelerate the transition to endemic, which could lead to the SARS-CoV-2 virus becoming like other commonly circulating coronaviruses. However, we neither

know yet what degree of immunity is enough to contain Covid-19 nor to reduce transmission rates (Figure 1B).

We may continue to see disparate outcomes in severe disease and deaths between vaccinated and unvaccinated people for some period in different parts of the world. Development of "herd immunity" in enough people in a population who become immune to the virus could be helpful in the transition to endemicity. However, achieving herd immunity to the Covid-19 virus seems to be elusive because of the variable global vaccination rate and the ever-changing nature of SARS-CoV-2 in terms of infectivity [78][79].

As long as viral transmission remains widespread, the virus will continue to mutate, and more variants and subvariants will emerge (Figure 1B). Natural selection will favor mutations that give the virus the greatest survival advantage, so the selection of mutations that promote the evasion of the host's immunity is not surprising [80] and could delay the transition to an endemic state. Additionally, some of the new variants could be so different that the immunity induced by the currently available vaccines will fail to recognize them, and the virus will continue to replicate and transmit effectively in vaccinated and/or nonvaccinated individuals. The development of better second-generation vaccines capable of stimulating a robust immune response involving a full arsenal of both cellular and humoral immunity, which could be more effective in containing existing and future SARS-COV-2 variants, is critical. Many scientists have underlined the importance of developing universal covid vaccines [81]. An effective universal vaccine could be one that activates all the components of the immune system to work together to induce a high level of long-term immunity against SARS-CoV2.

The average case is getting much milder over time, however, endemic doesn't mean harmless. Tuberculosis and HIV, which are two well-known endemic diseases, cause millions of deaths each year around the world. Another endemic disease, influenza is an issue that public health workers must contend with seasonally. In most viruses, the use of treatments and vaccines causes them to evolve ways of escaping these protective measures so they can continue to spread [80][82]. It is not yet known what selective pressures exist for viruses to acquire the genetic material which facilitates the quick emergence of new variants. One theory is that while these viruses can hide from the immune system, they will survive longer to replicate, and may pick up new genetic material in replication. The selective pressures on the genome of a pandemic virus are likely to be variable in different parts of the world.

Conclusions

The transition for the Covid-19 virus to become endemic is still not certain at this stage, and it is hard to predict the timeline. However, if we can increase the number of people vaccinated with better second-generation vaccines, which match the currently circulating virus, and simultaneously reduce the transmission rates, we are likely to be able to start living more normal lives, perhaps in the coming months of this year. In the meantime, efforts should continue to develop more effective vaccines that reduce the reinfection level and treatments that can cure infected individuals, particularly for vulnerable populations. There are signs of optimism, and we speculate that SARS-CoV-2 will soon follow in a similar evolutionary trajectory to the four endemic coronaviruses that cause the "common cold". Eradication will be a different campaign, which requires the development of more effective vaccines that can protect against reinfection at a local and global level.

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