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Review Article

A Perspective on the Transition from the COVID-19 Pandemic to Endemicity

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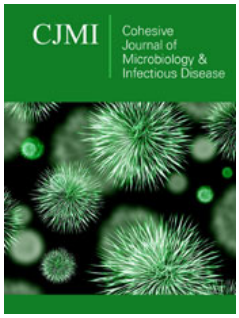

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Abstract

Since the current COVID-19 pandemic started in early 2020, despite strategic public health measures and the subsequent global development of COVID-19 vaccines, it can still be difficult to predict whether the current pandemic will turn into an endemic event. Variation in the pandemic measures could result in emergence of new SARS-CoV-2 variants, which may follow distinct evolutionary pathway compared to previous variants. Achieving herd-immunity threshold against SARS-CoV-2 infections can be difficult due to factors like vaccine hesitancy, vaccine inequity, etc. The current COVID-19 vaccines are primarily effective in preventing the disease symptoms in patients, and prevent hospitalizations and deaths, but strong evidence in favor of their ability to prevent new infections is weak, till date. Therefore, it is crucial to continuously develop efficient antiviral medications that can be taken at home. This will reduce the need for hospitalization and ICU admissions, which will relieve pressure on many countries' underdeveloped healthcare systems. Additionally, robust high-throughput genome surveillance in real-time will help to precisely profile SARS-CoV-2 variants in circulation. Urgent need also exists for a reliable and one-size-fits-all serological tests that will help in retrospective contact tracing, investigation of asymptomatic infections, and presence of humoral protective immunity in the population, along with SARS-CoV-2-specific T cell profiling in COVID-19 patients. The potential immunological parameters specific to COVID-19 disease pathology must be assessed in high-powered population surveillance studies to better manage the disease. Also, communication of comprehensive pandemic surveillance data must be communicated in simple languages to the public.

A Wide Range of Factors Determine the Stability and Safety of an Endemic State

Despite strategic public health measures, such as the global development of COVID-19 vaccines, since the start of the pandemic in late 2019, it is still possible that the current pandemic will not turn into a true global endemic event in the near future. Therefore, COVID-19's negative impacts will be felt by everyone in the world, at least throughout the transition from pandemic to endemic. The near-zero-COVID-19 goal must be achieved, and immediate action must be taken to define the necessities and develop practical approaches.

By definition, endemic disease means that a sizable portion of the population develops immune protection, either through vaccination or accidental natural infection, such that there will be less community transmission, along with much lower disease severity and mortality rate, even as the virus persists. This is in contrast to pandemic disease, which results in exponential increase in the number of cases encompassing a larger area due to widespread speedy transmission of the infectious disease [1,2]. The length of time it takes to reach an endemic condition thus depends on a number of factors, including the effectiveness and duration of immune protection in individuals, the effectiveness of vaccines, patterns of human contact, adherence to non-pharmaceutical public health measures, the rate of virus transmissibility, and the frequency of emergence of new variants [3-5]. Nevertheless, an endemic disease may potentially be dangerous. For example, malaria killed more than 600,000 people in 20205, tuberculosis resulted 1.5 million deaths in the same year, worldwide6, and endemic infection during measles outbreak in the U.S. in 2019 killed many people [6,7].

Thus, the progression from pandemic to endemic is therefore a crucial learning process, to better understand the efficacy of disease-specific interventional measures, such as range of

genomic surveillance [8] in the population, along with performance analyses, e.g., critical assessment of retrospective and prospective population surveillance data based on seroprevalence [9] findings and antiviral T cells profiling [10] together with hospitalization rates, Case Fatality Rates (CFR) and other metrics. Furthermore, results from clinical trials on emerging interventions, the temporal epidemiological landscape of infection spread, antibody neutralization data on new SARS-CoV-2 variants emerging from laboratories, periodic, predictive statistical modeling data [11] on disease propensity in the population, as well as an accurate evaluation of public health initiatives, are crucial for a better understanding of the pandemic to endemic trajectory. Additionally, information from previous infectious disease outbreaks can be used to predict how a particular virus, such as SARS-CoV-2, will evolve in the future, and whether COVID-19 will eventually develop into a well-known seasonal illness like influenza [12].

Another important factor in bringing a pandemic situation to an endemic level, is the development of efficient anti-viral medications [13,14] both prophylactic and therapeutic, that can be taken at home. This will reduce hospitalization rates and ICU admission rates, reducing the burden on underdeveloped healthcare infrastructure, especially in poor countries, and limiting the spread of the disease in places like African nations, where vaccination coverage is low primarily due to vaccine inequity [15,16].

Key Considerations for Bringing a Pandemic to an Endemic State

Furthermore, based on the past history of global pandemic events, it is difficult to predict whether SARS-CoV-2 will evolve over time to become less virulent and transmissible, causing endemic to occur. Evidence for any specific virus to become more benign over the years [17] following the course of evolution, is rare. In the best-case scenario, if an endemic condition arises sooner rather than later, its stability over an extended period of time needs to be ensured by careful evaluation of the holistic developments linked to the pandemic trajectory [18], to protect the society over an extended period of time. As a result, identifying and reaching agreement among public health experts on the acceptable disease burden to be considered as an endemic state [19], tracking of emerging SARS-CoV-2 variants by periodic genomic surveillance, limiting morbidity and deaths through home-based diagnostics [20], antiviral drug therapy, and holistic care for patients with "long COVID" [21-23], are the main considerations for managing an endemic COVID-19 state. Additionally, it is critical to use data from previous infectious disease epidemics [24] to build efficient interventional strategies for emerging pathogens like SARS-CoV-2.

More importantly, in contrast to other deadly coronaviruses like Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) and Middle East Respiratory Syndrome Coronavirus (MERS-CoV) [25], SARS-CoV-2 is not only more virulent, but also results in asymptomatic transmission of virus to other people in a higher frequency. It's probable that SARS-CoV-2's zoonotic origin [26] has led to substantial selection pressure for its adaption in the human host through greater transmissibility and immune evasion. For example, the D614G substitution [27] in SARS-CoV-2 and mutations in SARS-CoV-2 variants like B.1.1.7 (Alpha) and B.1.617.2 (Delta) have led to enhanced transmission in humans, as opposed to H1N1 influenza virus, which finally became seasonal, most likely because of reduced selection pressure emanating from the host. The unexpectedly low prevalence of influenza, the common human respiratory virus since the start of the ongoing COVID-19 pandemic [28], could be attributed to many of the preventive measures taken to slow the transmission of SARS-CoV-2. Finally, it is possible that SARS-CoV-2 and H1N1 influenza virus co-infect the host cells, resulting in the evolution of a new SARS-CoV-2 variant with less virulence and transmissibility [29,30].

This variant is likely to result from homologous and/or heterologous recombination, in which a donor sequence (in this case, influenza virus) is introduced into the genome of another virus such as SARS-CoV-2, which additionally offers evolutionary advantage for the long-term survival of the less lethal recombinant virus variant in the human host, out competing other lethal versions of SARS-CoV-2, resulting in the occurrence of a stable endemic situation [31-35]. Also, due to the complicated evolutionary behaviors of all viruses, it is often difficult to predict whether SARS-CoV-2 would finally be a seasonal winter virus during its trajectory from pandemic to endemic. Nevertheless, it is likely that immune memory from prior SARS-CoV-2 infections, leading to its adaptive immunological tweaking against a new variant, might conceivably push a pandemic event towards an endemic state [36,37]. Having said that, due to coronaviruses' high rate of viral RNA recombination, it is difficult to rule out the possibility of future recombination events between SARS-CoV-2 and other human coronaviruses, that can evade pre-existing immunity in the individuals, destabilizing the endemic state of the disease. Furthermore, people with compromised immune systems and/or immunosuppressed persons are unable to fully recover from SARS-CoV-2 infection, making them possible hidden reservoirs for the virus, which can then further evolve and spread through human-to-human contact [38,39]. Also, vaccination against COVID-19 may not be optimal in immunocompromised people [40]. Additional stochastic events may occur in a small percentage of immunosuppressed or vaccine-resistant people, which could lead to the emergence of future variants from infections [41,42].

Previous research on the emergence of viral mutants during pandemics seems to point to structural and functional plasticity in certain viral component regions, which has minor effects on the virus's overall structure and function and allows a specific viral variant to maintain its life cycle [43,44] and achieve evolutionary adaptation in the human host. For example, in the case of SARS-CoV-2, our current comprehension of the evolution of its variations is largely dependent on the mutational changes in the virus' spike protein. The selection pressure within the host [45-48] that particularly targets the virus' spike protein, has led to a lack of knowledge about the impact of mutations outside of this region. It's possible that any adjustments to the selection pressure

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brought on by increased population immunity that a particular variant experiences en route to an endemic state could lead to the emergence of newer mutants from viral components other than the SARS-CoV-2 spike protein, which would broaden the virus's fitness landscape [49,50].

It may therefore be premature to predict a potential synergy dialogue between the SARS-CoV-2 and the host [51] that might establish a stable equilibrium, causing stable endemicity and reducing uncertainties about the long-term course of the ongoing pandemic given the complex history of the ongoing pandemic [52], with its twists and turns. Additionally, variations in pandemic measures, particularly in troubled regions of the world, could have a direct impact on the appearance of new variants, which are likely to follow an altogether different evolutionary trajectory from earlier SARS-CoV-2 variants [53]. This is further compounded by the fact that intermediate host adaptation of SARS-CoV-2, such as in animals from humans, could generate new variants in the intermediate animal host, re-infecting individuals with more virulence and transmissibility, following human-animal-human infection pathway [54,55] further underscoring the importance of one health approach in bringing a pandemic state to stable endemicity.

The recent observations from the real world COVID-19 vaccine efficacy data, suggest achieving herd immunity against COVID-19 could be challenging [56-58]. Evidence for effective protection from SARS-CoV-2 infections in vaccinated individuals is mostly lacking [59-63]. Therefore, it appears that vaccines primarily work to stop disease symptoms in COVID-19 victims and to stop hospitalizations, but there is currently little convincing evidence supporting their potential to stop new infections or re-infections. In the middle of the lengthy pandemic, a straightforward estimate implies that the combined efficacy of vaccines in preventing B.1.351 spread in the U.S. may be only 50 percent [64]. Also, it is not clear, to what extent previous infections from one SARS-CoV-2 variant protect people from re-infection with new variants [65-67].

Key Approaches and Challenges in Bringing a Pandemic to an Endemic State

Importantly, in depth analysis of immunity type [68,69] (0-1) in vaccinated individuals like susceptibility to infection (IES), reduction of infectiousness (IEI), and pathological manifestations (IEP) needs to be carefully evaluated, to understand the pandemic-to-endemic trajectory-where '0' corresponds to complete reduction in susceptibility of infection/infectiousness/pathology, and '1' corresponds to complete sterilizing immunity/non-infectiousness/asymptomatic state. For example, measles, which likely provides lifetime sterilizing immunity in the vaccinated individuals (IES= 1), is entirely different in its trajectory compared to SARS-CoV-2, where immunity against it wanes over time with progressive changes in IES, IEI, and IEP. In spite of extensive vaccination in the population, SARS-CoV-2's R0 is primarily dependent on the dynamics of immune behavior in individuals. A slower waning of immunity will lead to faster endemic state with lower R0, resulting in much lower prevalence of infections. Thus, it is critical to continuously monitor the effective R0 in the population throughout the five stages [70] of a pandemic: (1) Pandemic, (2) Deceleration, (3) Control (Endemic), (4) Elimination and (5) Eradication.

In addition, there are numerous 'suspected' COVID-19 cases with similar Computed Tomography (CT) lung images and clinical symptoms that are reported to be missed by real-time RT-PCR detection. This raises technical challenges associated with the precise detection of SARS-CoV-2 that can be difficult to overcome [71-74]. As a result, a negative result does not rule out SARS-CoV-2 infection and should not be the only factor considered when making patient management decisions. Additionally, the gold standard of antibody testing for SARS-CoV-2 immunity in individuals, is not without flaws [75,76]. A recent data among 1497 fully vaccinated health care workers in Israel revealed that in 39 workers, who became infected after receiving their second dose of the BNT162b2 (Pfizer-BioNTech) vaccine, had lower levels of neutralizing antibodies as compared to their uninfected colleagues [77,78]. Although, antibody levels were associated with some degree of protection, the researchers were unable to specifically determine a threshold. None of the cases were severe, but antibodies were not totally protective against the virus.

Thus, individuals can have neutralizing antibodies, but can still get infected, underscoring the importance of determining the antibody threshold that protects vaccinated individuals from further infections [79,80]. Additionally, none of the authorized seroprevalence tests has the ability to distinguish between neutralizing and non-neutralizing anti-SARS-CoV-2 antibodies [81,82]. There is an urgent need for a dependable, universal serological test that will aid in the search for the natural reservoir and intermediate host(s) of SARS-CoV-2 as well as in the retrospective contact tracing, investigation of asymptomatic infections, case fatality rate, and presence of humoral protective immunity in both recovered COVID-19 patients and vaccinated individuals [83,84]. The convalescent plasma obtained from COVID-19 patients is used in several types of SARS-CoV-2 neutralization studies carried out in lab settings.

However, there doesn't seem to be agreement on a particular neutralization test type as of yet among: (1) life virus neutralization by plaque reduction assay [85], (2) a lentiviral vector based pseudo type neutralization assay [86], and (3) a competition ELISA-based Surrogate Virus Neutralization Assay (sVNT) [87,88] that closely mimics the SARS-CoV-2 neutralization pattern in individuals. In addition, viral neutralization assays must be performed in a Biosafety Level 3 (BSL3) facility, except for the pseudo type neutralization assay, which needs a Biosafety Level 2 (BSL2) facility. Another advantage of sVNT, is its ability to detect SARS-CoV-2 antibodies, in a species-independent manner. Since serological assays are superior to molecular detection because virus-specific antibodies remain in the body for a longer period of time than SARS-CoV-2 RNA, which has a relatively shorter shelf life, the sVNT assay will be perfectly suited for "COVID-19 hunting" in suspected intermediate host (s),

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such as in animals [89]. However, a general limitation of these assays is that they are only able to detect neutralizing antibodies, which only function by blocking the interaction between the RBD (Receptor Binding Domain) and ACE2 (Angiotensin-Converting Enzyme 2). Although the majority of SARS-CoV-2 neutralizing antibodies found in patients fit this description, some antibodies have been reported to use alternative pathways. Therefore, to screen plasma donation recipients for passive immunization, more sophisticated viral neutralization assays are required, which require additional technological advances [90].

Virus-specific humoral and cellular immunity act synergistically to protect individuals from viral infection [91,92]. Although, rapid induction and intensity of humoral responses are associated with increased disease severity, early Induction of Interferon (IFN)-γ-secreting SARS-CoV-2-specific T cells, is found in patients with mild COVID-19 disease [93,94], which might help COVID-19 patients in accelerating viral clearance. These results offer compelling evidence for the prognostic utility of early functional SARS-CoV-2-specific T cells, which has significant implications for immune surveillance [95]. A sufficient number of functional antiviral T cells (CD4+ and CD8+) can protect against developing severe COVID-19 disease due to breakthrough infection by quickly and effectively eradicating SARS-CoV-2 in the early stages of infection, even though humoral immunity from a prior infection or vaccination gradually declines over time. Interestingly, regulatory FoxP3 (Forkhead Box Protein 3) positive T cells (Tregs); a subset of CD4+ T cells, involved in preventing exaggerated immune responses, were found in severe COVID-19 patients, exhibiting cytokine storm including both Th1 and Th2 cytokines [96,97]. Thus, assessment of numbers and function of Tregs in COVID-19 patients, can shed light on SARS-CoV-2-mediated immune dysregulation, and prognosis of the disease in individuals. Additionally, it can offer critical insights into how to recognize patients at various disease stages or with various immune response traits and synchronize them with particular treatment approaches.

This means that a precision medicine approach based on 'immune health' profiling by examining SARS-CoV-2-specific T cells could be used to better tailor immunostimulatory treatment modalities. However, the lack of phenotypic characterization of the SARS-CoV-2 T-cell response is a significant issue that is frequently reported [98]. The most popular ex vivo ELISpot assay [99], which is used to characterize the SARS-CoV-2 T-cell response in convalescent subjects, is only able to detect the presence of SARS-CoV-2-reactive T cells in the majority of convalescent COVID-19 patients and is unable to resolve T cell phenotypes. Also, the pre-depletion assays using anti-CD4 and anti-CD8 coated antibody beads for FACS [100] (Fluorescence-Activated Single Cell Sorting) analysis, have low resolution. That said, despite the lack of SARS-CoV-2 neutralizing Abs in some COVID-19 patients, the presence of detectable SARS-CoV-2 specific T cell response suggests the significance of SARS-CoV-2-specific T cell profile in COVID-19 patients, which will further improve our current understanding of precisely defining an endemic condition.

Conclusions and Future Directions

Taken together, R0 is a reliable readout in tracking the pandemic-to-endemic trajectory in a population. In particular, efforts should be made to identify COVID-19-infected people who are likely to contribute more to the spread of infections and trigger an unexpected spike in R0 in a shorter period of time, such as super-spreaders, long-haul drivers, immunocompromised people, and people who are not responsive to SARS-CoV-2 vaccinations. Furthermore, large-scale population surveillance studies using sophisticated laboratory assays are required to confirm the causal relationships between key immunological parameters and disease prevalence, severity, and clinical characteristics to increase the effectiveness of the disease's intervention through personalized treatments. Additionally, this will help in the accurate assessment of the population's vaccination status. Moreover, a more precise definition of what herd immunity in a population needs to be looked at. Because the threshold for herd immunity is pathogen-specific, it would take agreement to declare a population herd immune in the event of a COVID-19 pandemic. It also seems difficult to fully achieve herd-immunity threshold against SARS-CoV-2 infections due to problems including vaccine hesitancy, vaccine inequity, the unexpected emergence of new SARS-CoV-2 variants, and the delayed introduction of immunizations for children. Thus, non-pharmaceutical interventions should continue to play a major role in keeping COVID-19 cases to a lower level.

Even if herd immunity cannot be achieved, the global campaign to immunize a substantial section of the population, which has led to a decrease in the number of COVID-19 hospitalizations and fatalities, is essential in driving the pandemic towards endemicity. There are several ways immunity might defend against an infection when it becomes endemic without eradicating the virus from the population, such as through Lowering Infection Susceptibility (IES) or Lowering Pathogenesis (IEP). Understanding the underlying mechanisms by which these various aspects of protection deteriorate over time, and how they are strengthened by natural infection and vaccination, will be especially important in the case of viruses, such as SARS-CoV-2, against which infection does not seem to produce life-long immunity. For instance, it would be intriguing to figure out the important epigenetic changes governing the immune genes that provide long-lasting protection from reinfection with SARS-CoV-2. Also, cellular mechanisms, such as the role of cellular senescence and the body's stem cell health, which can induce immuno genesis on demand with improved functions, to be better able to cope with the accidental infection with SARS-COv-2 during the state of endemicity, would also provide additional insight into the underlying mechanisms of vaccine-induced long-term immunity in a population. However, it is possible that in a complex multifactorial and multigenic disease like COVID-19, a number of genetic, epigenetic, and sociodemographic factors are modulating the susceptibility to reinfection as the disease transitions from a pandemic to an endemic state [101]. This would complicate the current state of understanding of long-term immunity in the susceptible population and call for systems thinking to maintain stable endemicity.

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Furthermore, in comparison to using only test-based confirmed infections to assess the pandemic trajectory, a prediction-based model that incorporates effective R0 along with other critical metrics will provide a more accurate real-world country-specific infection prevalence and mortality rate with a higher level of confidence in accurately defining the state of endemicity [102]. Moreover, to speed the transition from a pandemic event to a stable endemic state, periodic high-powered genomic surveillance employing a one health approach is required. Last but not least, clear and comprehensive language must be used to communicate surveillance data to the public effectively. It might be useful to create rating systems, where multiple parameters and co-variants are combined into a single rating (low, moderate, high, very high, extreme, that is communicated to the public and directly ties to public health policies to facilitate the establishment of more stringent control on the pandemic-to-endemic trajectory.

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