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REVIEW ARTICLE

COVID-19 Vaccination, Herd Immunity and The Transition Toward Normalcy: Challenges with The Upcoming Sports Events

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ABSTRACT

Background. The coronavirus disease 2019 (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has created an unprecedented and daunting challenge for humanity to survive. This has also affected the sporting events across the globe as the majority of the tournaments have been cancelled or postponed as a result. For life to return to pre-pandemic normalcy, an effective and safe vaccination program needs to be implemented, be readily accessible, widely available, and affordable at the same time. **Objectives.** In this review, we analyze various challenges which demonstrate that COVID-19 is far from over.**Methods.** A systematic literature search was conducted on PubMed, ScienceDirect, Medline, google scholar and Scopus from the commencement of the COVID-19 pandemic to 22 June 2021. The current report is a summary of data regarding challenges faced by the COVID-19 vaccination campaign and the challenges for a transition toward normalcy especially for big sports events. **Results.** The current COVID-19 pandemic has likely resulted in sporting events and tournaments being canceled, postponed, or held without or with restricted spectators around the world. A combination of measures including prompt vaccination with the beneficial impact of the vaccines in reducing the severity of disease, advances in treatment, expanded use of diagnostics and better implementation of public-health policies are a necessity. Following this implementation, a transition toward normality could be expected when the mortality rate of COVID-19 simulates the average influenza statistics, with public-health measures continuing to play an important role worldwide. **Conclusion.** The authors believe that COVID-19 will be endemic in the human population, similar to seasonal influenza, and that COVID-19 vaccines will be included as an add-on to seasonal influenza vaccinations, being administered every winter for at least the next few decades. With adequate vaccination, the sporting world will be able to withstand the challenges and resume global events, returning to pre-Covid levels of normalcy.

KEYWORDS: ***Pandemic, SARS-COV-2, Mutation, Olympic games, FIFA World cup.***

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INTRODUCTION

During the last twenty years, there were three main pathogenic zoonotic disease epidemics caused by beta coronaviruses (1, 2). Severe acute respiratory syndrome coronavirus (SARS-CoV) first emerged in 2002, infecting around 8,000 people with a mortality rate of nearly 10 percent. Middle East respiratory syndrome coronavirus (MERS-CoV) emerged in 2012 with about 2,300 people being infected and much higher mortality of nearly 35 percent (3). The third coronavirus in this group, now termed SARS-CoV-2, causing the severe respiratory disease coronavirus disease 2019 (COVID-19) was first reported in December 2019, in Wuhan, China. This ongoing global pandemic has affected over 180 million people around the world and caused over 3.8 million deaths to date (4).

The appearance of the COVID-19 outbreak at the start of 2020, has led researchers around the globe to innovate different methods, to both gain more understanding of this novel virus as well as to understand the containment of its spread (5, 6, 7, 8).

With the emergence of the pandemic, people were hopeful that herd immunity, as well as warmer weather in different parts of the world, would contribute greatly to overcome the disease (9). However, COVID-19 has been an exceptional challenge to different sectors of the healthcare system, more so to the public health departments and World Health Organization (WHO). Quite a few measures such as the compulsory use of masks in public, social distancing, mass testing, and contact tracing in addition to lock-down of states and countries for various lengths of time have been implemented and proven partially successful in curbing the spread of the virus so far (10, 11, 12). However, despite these efforts globally, COVID-19 continues to spread like wildfire across the globe with the first wave being followed by a second, and in some countries, even a third wave making it evident that these measures alone may not draw a curtain on this pandemic yet.

This pandemic has been having a lasting effect on every aspect of people's lives, such as education, business, and economy, social life, politics, and entertainment (7, 8, 13). The common goal of humanity is to curb the spread of this dreaded pandemic and restore normalcy. Furthermore, newer medications have been tried to help fight and cure COVID-19 infected patients and should help reduce the number of deaths and other adverse complications related to COVID.

The world scientists including public health physicians and epidemiologists have geared up their efforts to predict the future of the pandemic and restrain this outbreak by using different algorithms and epidemiological formulas. We know from the natural history of previous pandemics that it may either gradually disappear over decades after successful treatment or vaccination, as has happened in the past. Most nations' existing COVID-19 mitigation strategies appear insufficient to curtail the disease outbreak; however, the implementation of multiple new, safe, and effective COVID-19 vaccines has triggered hope for a resolution to this crisis. Vaccination is widely acknowledged to be one of the most effective methods of preventing and controlling infectious diseases. Researchers were successful in developing the fastest vaccines in medical history to alleviate the burden of this pandemic and save human lives.

People who have been fully vaccinated with an mRNA vaccine (Pfizer-BioNTech and Moderna) are less prone to developing an asymptomatic infection or spread COVID-19 to others, according to a growing body of evidence (14). Furthermore, these vaccines have been shown to reduce hospitalizations, severe outcomes, and related mortality (14). Whilst there is no doubt that vaccines will play a vital role in this fight against the pandemic, it certainly presents an enormous challenge in terms of the numbers being available in a timeframe to vaccinate over 7 billion people, globally and thus reaching a herd immunity.

As with any other infection, herd immunity can be achieved in two ways: A large percentage of the population is either infected or receives a protective vaccine. According to what we know so far about coronavirus, if we were to return to a pre-pandemic lifestyle, we would need at least 70% of the population to be immune to keep the rate of infection low ("achieve herd immunity") without imposing restrictions on activities (15). However, this level is determined by a variety of factors, including the virus's infectiousness (viral

variants that are more infectious can evolve) and how people interact with one another.

The proportion of people who must be vaccinated to achieve herd immunity varies depending on the disease. Herd immunity against measles, for example, necessitates the vaccination of approximately 95% of the population. The remaining 5% will be protected because measles will not spread among those who have been vaccinated. For polio, the threshold is around 80% (16). The proportion of the population that must be vaccinated against COVID-19 before herd immunity can be induced is unknown. This is an important area of study that will most likely differ depending on the community, the vaccine, the populations are given priority for vaccination, as well as other factors (16).

Ending the pandemic will mainly rely on reaching herd immunity works by achieving a population-level threshold immunity capable of theoretically cutting the transmission chain of a given infectious disease, whether obtained through natural infection or vaccination (16). This does not necessarily imply that a given individual is fully protected at all times or in all situations. It is the level of immunity that, when reached, can protect the majority, if not all, of a population in a given geographical area for a set period of time. The latter, on the other hand, would undeniably be dependent on the duration of individual-level natural or vaccine-induced immunity (17).

By the end of June 2021, 21.5% of the world population has received at least one dose of a COVID-19 vaccine. However, only 0.8% of people in low-income countries have received at least one dose (18). Based, on the current situation, we cannot be certain when this pandemic will end and how many more people will lose their lives.

Here, in this review, we discuss the numerous challenges which could potentially limit the possibility of eradication of COVID-19.

FAST-TRACKED VACCINES RELEASED IN RECORD TIME

The world has cheered announcements over the past few weeks by the well-renowned pharmaceutical companies - Pfizer, BioNTech, Moderna, and Astra Zeneca as their COVID-19 vaccine candidates having shown efficacy rates of up to 95% that were higher than many anticipated (19, 20). Pfizer-BioNTech and Moderna vaccines are mRNA vaccines coding for the COVID-19 spike protein whereas the AstraZeneca vaccine is an adenovirus vector-based vaccine that works by carrying spike protein genetic sequence into cells and inducing immunity. They constitute two doses to be administered 21 and 28 days apart respectively for Pfizer and Moderna for sustaining immunity in the host (19, 20).

Pfizer/BioNTech vaccine was judged safe for use in UK and USA after Emergency Use Authorization (EUA) by the authorities concerned, from the second week of December 2020, whilst the other successful vaccine candidates are lined up for the EUA soon (21). Higher efficacy provides greater benefit to any vaccinated individual and may help encourage uptake amongst a large segment of the population, thus improving herd immunity which is very much the need of the hour for us to overcome this pandemic. There are some other vaccines in stage-3 trials from which data and outcomes are expected in the coming weeks (21).

However, even though the safety records of the vaccines appear promising so far with no serious side effects reported, caution is warranted as the coming weeks will provide a fuller picture as the sample size grows. We remain uncertain about the durability of protection the vaccines offer. The vaccine trials are still underway in children under twelve years old (22), so are currently unlicensed for use in this age group. For us to successfully eradicate COVID-19, vaccination programs need to be solid and well supported. It has to be noted also that all the vaccine has been approved for only emergency use. However, none of them has been fully approved or licensed by the U.S. Food and Drug Administration (FDA).

LOGISTICS OF VACCINE ADMINISTRATION AND STORAGE

The two first available vaccines have to be administered in two doses, twenty-eight days apart, which needs robust follow-up systems to achieve adequate protection (19, 20). The storage of vaccines has been discussed in depth recently due to the logistical challenges involved. Moderna's vaccine is stable at refrigerated temperatures (2-8 degrees Celsius) for 30 days and six months at –20 degrees Celsius whereas Pfizer's vaccine can be stored in conventional freezers for up to five days or in its custom shipping coolers for up to 15 days with appropriate handling but any longer duration needs freezing at –70 degrees Celsius, necessitating specialized equipment (19, 20).

These drawbacks, together with other challenges generate a risk of delay and test the health systems' capabilities, especially in the developing world.

VACCINATION CAMPAIGN STATUS

By the end of June'21, 21.5% of the world population has received at least one dose of a COVID-19 vaccine. 2.6 billion doses have been administered globally, and 36.1 million are now administered each day (18). However, only 0.8% of people in low-income countries have received at least one dose (Figure 1; Figure 2).

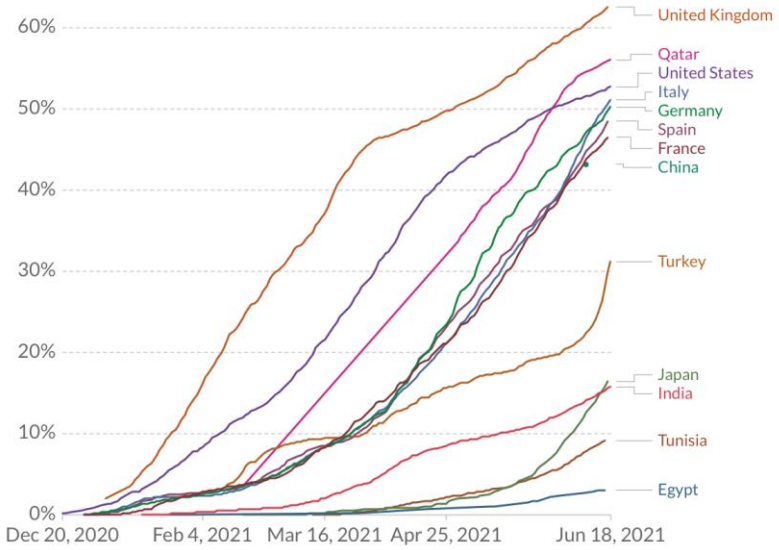

Figure 1. Share of people who received at least one dose of COVID-19 Vaccine (Official data collected by Word in data) (**18**)

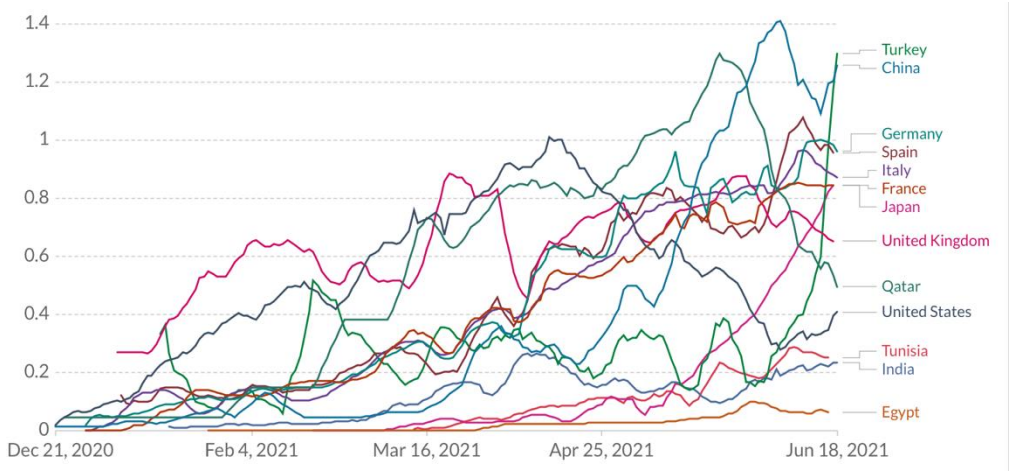

Figure 2. Daily COVID-19 vaccine doses administrated per 100 people (Official data collected by Word in data) (**18**)

VACCINE NOT LICENSED FOR USE IN CHILDREN

Globally, mass vaccination campaigns against novel coronavirus infection were primarily targeted at adults. However, by the 10th of May 2021, the FDA (Food and Drug Administration) has expanded the authorization of Pfizer-BioNTech vaccines to include adolescents aged 12 to 15 years old (22). It still unclear, when we will have the license for younger children which constitutes a very big proportion of the world population. This certainly pushes the increase in the percentage of the population needed to be immunized to achieve herd immunity from the initial figure of 45-65 percent (all ages) to 60-85 percent (adult only). This presents a huge epidemiological challenge, as children are shown to be asymptomatic carriers and perhaps more

contagious than adults, with a higher viral load, making them vectors of transmission (14).

POTENTIALLY SHORTER DURATION OF IMMUNITY

In the first few months of the pandemic, there was uncertainty regarding the duration of post-infection immunity, as it affects the percentage of the population needing to be vaccinated for herd immunity to be achieved. Ongoing population-level studies are researching the durability of immunity achieved, as rare cases of re-infection have been documented and published in the literature (23, 24). Studies in the United Kingdom (24, 25) have reported a 26 percent fall in antibody prevalence for three months. The association between declining antibodies and the risk of re-infection is yet to be determined. Emerging evidence reveals that the immune system may be able to accumulate a response using exclusive B-cell and T-cell immune pathways to lengthen the post-infection immunity to longer than six months, even with decreasing levels of COVID-19 antibodies (26).

ADVANCED THERAPEUTICS IN PROGRESS

Beyond vaccines, research and progress are being made in therapeutic intervention for COVID-19. Mentioning a couple of them, Eli Lilly's antibody Bamlanivimab was granted EUA by the US Food and Drug Administration on 9th November 2020, and Regeneron for its antibody cocktail REGN-COV2 for EUA was approved on 22nd November 2020. Emerging data on these antibodies suggest that they can reduce the need for hospitalization of high-risk patients and also have potential use in post-exposure prophylaxis for COVD-19 (27). While they are not recommended for use in hospitalized patients, these antibodies add to the growing armamentarium of treatments and protocols for COVID-19, where every incremental advance could help to reduce mortality. Collectively, these treatments and progress in clinical practice have lowered mortality for those hospitalized by over 18 percent.

MUTATION OF COVID-19

According to Dawood et al. (28), a new mutation in COVID-19 specifically in glycoproteins is expected, so health systems and governments should have a comprehensive preparation for this possibility.

Coronaviruses have genetic proof-reading mechanisms (29, 30) and COVID-19 sequence diversity is very low (31). Still, natural selection can act upon rare but favorable mutations. By analogy, antigenic drift results in a gradual build-up of mutations by the influenza virus during flu season, and the complex interplay between immunological resistance mutations and the fitness landscape enables antibody resistance to develop across populations (32), driving the need to develop new influenza vaccines every few seasons. Longer flu seasons have increased opportunities for selection pressure (33). Although COVID-19 shows evidence of some seasonal waning (34), the persistence of the pandemic may enable the accumulation of immunologically relevant mutations in the population even as vaccines are developed. Antigenic drift is seen among the common cold coronaviruses OC43 (35, 36) and 229E (37) and in SARS-CoV-1 (38, 39). Notably, a single SARS-CoV-1 amino acid change, Spike D480A/G in the receptor-binding domain (RBD), arose in infected humans and civets, becoming the dominant variant among 2003/2004 viruses. D480A/G escapes neutralizing antibody 80R and immune pressure from 80R *in vitro* could recapitulate the emergence of the D480 mutation (40). Although there is no evidence yet of antigenic drift for COVID-19, with the extended human-to-human transmission, COVID-19 could also acquire mutations with fitness advantages and immunological resistance. Attending to this risk now by identifying evolutionary transitions that may be relevant to the fitness or antigenic profile of the virus is important to ensure the effectiveness of the vaccines and immunotherapeutic interventions as they advance to the clinic. More recently, at the beginning of the third week of December 2020, a new variant of COVID-19 has been identified in the United Kingdom, which has exponential rises in coronavirus infections across London, Kent, parts of Essex, and Hertfordshire (41). There is evidence that this may be associated with the faster spread of the virus in the southeast of England, which is concerning, and further details are awaited as the authors write this article. Indeed, up to date, there are thousands of different Covid variants floating around the world. Viruses mutate all the time, and the majority of the changes are insignificant. Some of them even harm the virus. Others, on the other hand, can make the disease more infectious or dangerous - and these mutations tend to predominate. Those

with the most potentially concerning changes are referred to as "variants of concern" and are closely monitored by health officials (42). They include:

- The India or Delta variant (B.1.617.2), of which over 12,000 cases have been reported in the UK.
- The UK, Kent, or Alpha variant (also known as B.1.1.7) is common in Britain (over 200,000 cases have been identified), has spread to more than 50 countries, and appears to be mutating again.
- At least 20 other countries, including the United Kingdom, have identified South Africa or Beta variant (B.1.351).
- The Brazil or Gamma variant (P.1) has spread to over ten other countries, including the United Kingdom.

However, it is also still not known if the vaccines being rolled out, offer protection against the new strain of COVID-19 identified, which is very perturbing. Depending on how variants continue to develop, these could potentially be used to offer a booster vaccine to older or clinically vulnerable people later in the year.

CHALLENGES OF INFECTIOUS DISEASES!

Historically, pandemics have proven challenging to completely eradicate, whether it be bacterial, viral, or parasitic with these disease pathogens affecting people over the previous centuries, still existing.

The plague caused by the bacterium Yersinia Pestis has been one of the deadliest infectious diseases in human history (43). There have been countless local outbreaks and at least three documented plague pandemics over the last 5,000 years, resulting in millions of deaths worldwide, with the most devastating of them all being the "Back Death" of the mid-14th century. Politically, the gradual deterioration of the Mamluk Sultanate and its defeat by the Ottoman Empire was mainly attributed to the dramatic decrease in the population numbers, due to the plague pandemic.

Malaria is transmitted via a parasite (mosquito) and is almost as old as humanity, but still exerts a heavy disease burden in the world today with about 228 million cases and over 405,000 deaths worldwide in 2018 (44). Despite global programs to eradicate malaria since 1955, the disease remains endemic in many tropical countries, especially south of the equator.

Other diseases such as tuberculosis, measles, and leprosy have been with us for several centuries with eradication not imminent despite sustained efforts by the WHO (45).

Epidemiologically and historically, the only disease eradicated through mass vaccination was Smallpox (46). A campaign was successfully led by the WHO in the 1960/1970s. By 1980, smallpox was announced to be the first only human disease to be successfully eradicated. However, success stories like smallpox are unique and few and far between (32).

As the overall epidemiological picture becomes evident, it reveals that the global burden of disease and annual mortality caused by infectious diseases (most of which occur in the developing world) is nearly one-third of all deaths worldwide.

The authors think that COVID-19 will remain a threat in the form of an endemic infection with seasonal spikes like influenza, peaking in seasons and different parts of the world at different times, even with effective vaccination in place.

CHALLENGES WITH THE UPCOMING SPORTING EVENTS

Despite increasingly stringent protocols, COVID-19 outbreaks have resulted in multiple cancellations in the sporting world, such as the World Men's Handball Championship in January'21, the Australian Open in February'21, and the Indian Premier League (IPL) Cricket tournament being suspended midway in May'21 (47).

Tokyo Olympics games 2020. The Tokyo Olympics was postponed from 2020 and is planned to be held during July'21, when approximately 11,000 athletes and 4000 athletic-support staff from over 200 countries are planned to gather. Olympic athletes are encouraged (but not required) to be vaccinated against COVID-19 and will be undergoing testing at specified intervals after arriving in Japan, as per the International Olympic Committee (IOC) Tokyo 2020, which is intended to protect both participants and the population from COVID-19 infection (47). Pfizer and BioNTech have offered to donate vaccines to all Olympic athletes, but this remains a challenge as vaccine availability is lacking in over a hundred countries. Furthermore, some athletes may refuse vaccination due to concerns about the side effects of vaccination on their performance or other personal concerns. Athletes may become infected during the Olympics and pose a risk to others in their bubble, risking the stake of the tournament, as has

happened during the IPL tournament. Also, Paralympic athletes may be at a higher risk of serious health consequences from COVID-19, if infected.

FIFA World Cup 2022. The FIFA World Cup 2022 will be hosted in Qatar in December'22. This tournament is likely to a huge challenge for Qatar to host, as 1.5 million fans are expected to travel to Qatar during this time (48). Thus, a rigorous infection control protocol is needed to be implemented to curb the rate of COVID-19 transmission during this time.

The implementation of multiple public health interventions and policies specified to big sports events are required to prevent the spread of the virus during big competitions such as the upcoming Olympic Games and the upcoming FIFA world cup. Qatar has succeeded in December'20 to host a big sports event with 20,000 spectators under strongly controlled preventative measures (48). However, hosting a tournament with around 1.5 million visitors in a country with a population of 2.8 million habitants will need stronger preventive measures to protects players, spectators as well as for habitants. In this way, McLarnon et al. (49) proposed the creation of a new COVID-19 passport for professional athletes. This passport will contain information about the athletes' previous exposure to the virus, testing, results, and vaccination. McLarnon et al. (49) suggest a COVID-19 passport that could protect the athlete, their team, and contacts wherever they travel. It could also be held personally by the athletes, serving as a source of concise information to allow athletes to travel and manage any COVID-19 outbreaks in the run-up to and during the Summer Olympics 2021. This passport could also apply to spectators and will certainly help to track and mitigate the spread of the virus.

CONCLUSION

To control the risk of COVID-19, continual monitoring, annual vaccination campaigns, and treatment of isolated cases must be a priority. These measures will be part of standard infectious disease management, rather than the drastic social-distancing rules imposed globally. The challenges we overcome in the short term may enable us to optimistically hope for an end to the pandemic in 2022!

APPLICABLE REMARKS

- To significantly reduce deaths from COVID-19, a combination of measures including prompt vaccination (especially for the at-risk population) with the beneficial impact of the vaccines in reducing the severity of disease, advances in treatment, expanded use of diagnostics, and better implementation of public-health policies are a necessity.
- Following this implementation, a transition toward normality could be expected when the mortality rate of COVID-19 simulates the average influenza statistics, with public-health measures continuing to play an important role worldwide. There has to be a realistic view concerning the duration of immunity and long-term vaccine safety (given the limited data available so far). Herd immunity might take longer than expected to establish.
- The authors feel that COVID-19 will be endemic in the human population like seasonal influenza and COVID-19 vaccines would be incorporated in seasonal influenza vaccinations as an add-on, being administered every winter for the next few decades at least! With adequate vaccination implemented, the sporting world can withstand the challenges and hope to restart the global events getting back to normalcy as pre-COVID times.

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