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SARS-CoV-2: Unique Challenges of the Virus and Vaccines

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ABSTRACT

In November 2019, the highly infectious coronavirus SARS-CoV-2 emerged in Wuhan, China, and has since spread to almost all countries worldwide. Since its emergence, the COVID-19 infection has led to significant public health, economic and social problems. The current pandemic has inspired researchers to make every effort to design and develop an effective COVID-19 vaccine to provide sufficient protection against the virus and control the infection. In December 2020, the Pfizer vaccine was the first COVID-19 vaccine given Emergency Use Authorization (EUA), and the second FDA so-approved vaccine was the Moderna mRNA-1273 vaccine, which was introduced a week later. Both Pfizer and Moderna vaccines are mRNA-based vaccines, and are estimated to have an efficacy rate of more than 94%. The aim of this article is to provide a review of the attempts made to develop safe SARS-CoV-2 vaccines, highlighting potential challenges and concerns, such as disease enhancement, virus mutations, and public acceptance of the vaccine.

KEYWORDS

COVID-19; SARS-CoV-2; vaccine

Introduction

The management of highly contagious and potentially fatal infectious diseases has changed medicine's history over the centuries, and the COVID-19 pandemic will not be an exception. COVID-19 is the third significant coronavirus infection in the human population to occur in the twenty-first century, followed by severe acute respiratory syndrome (SARS) in 2002–2003 and MERS (Middle East respiratory syndrome) in 2012, both of which have not completely ended. In order to address these infections and in anticipation of the current pandemic, during the previous decade, the scientific community and vaccine industry have done their best to develop treatments and prevention for such viruses.

Coronaviruses are members of the Coronaviridae family that are uniformly positive-stranded RNA viruses with an external envelope. SARS-CoV-2, the causative virus of COVID-19, is capable of human-to-human transmission, which caused a pandemic by early 2020 as declared by the World Health Organization (WHO). SARS-CoV-2 is transmitted via respiratory aerosols and droplets from infected cases to oral, conjunctival, and respiratory mucosal cells. The entry into the host cell occurs via the interaction of angiotensin-converting enzyme 2 (ACE2) receptors with the cleavage of Spike (S) protein in the perfusion state by TMPRSS-2/furin proteases (Brian

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and Baric 2005). Following SARS-CoV-2 entry into the cell, downregulation of ACE-2 occurs, which results in the overproduction of angiotensin II, increases lung permeability and lung injury (Imai et al. 2005). A marked increase in proinflammatory cytokines follows with progression to adult respiratory distress syndrome (ARDS) and "cytokine storm" in some critically ill patients. Induction of a regulated host immune response against pathogens in general, and SARS-CoV-2 in particular, is essential to controlling and eliminating infection by employing adaptive and innate immune responses. Table 1 outlines the immune response of the human body to SARS COV-2 (Huang et al. 2020; Li et al. 2020; Liu et al. 2020; Qin et al. 2020; Tan et al. 2021; Wen et al. 2020). Efforts to decrease this virus's distribution have been challenging because of gaps in information regarding disease pathogenesis, host immune responses, and therapeutic interventions. Some knowledge deficits surrounding the host immune response are being closed through next-generation sequencing of former SARS-CoV strains (Huang et al. 2020).

As with many infections, there exist two potential approaches to build widespread immunity against SARS-COV-2. These include an effective vaccine or, alternatively, natural "immunization" of the global population or "herd immunity" to SARS-CoV-2. The second approach is practically impossible because of mortality rates and complications and thus is not recommended (Randolph and Barreiro 2020). Vaccination of the worldwide population is the most viable approach. There are many unanswered questions about optimal vaccine development and efficacy that are being addressed by the scientific community. Key issues include different mechanisms of host immune responses involved in the neutralization of the virus and/or the eradication of infected cells, and the effect of demographic characteristics, including gender, age, and comorbidities. Vaccines seem to be less effective at producing immunity than natural pathogens, but an effective vaccine is the safest approach to achieve widespread immunity. Therefore, if a COVID-19 vaccine shows 50–70% efficacy, as is the case for those receiving EUA, it will be a great success. This intervention could be mixed with other preventive and therapeutic interventions to reach an ideal success. As of December 11, 2020, researchers were evaluating 57 SARS-CoV-2 vaccines in human clinical trials, 15 of which entered the final phase of the study (2020).

Table 1. Immune response to the novel coronaviruses SARS COV-2.

Immune Response	Mechanism of Action	Reference
Innate immune response	• Decrease in Monocytes, Eosinophils, and Basophils • Decrease of absolute number of NK cells	(Qin et al. 2020)
Adaptive immune response	• Low percentage and count in T CD3+, CD4+, and CD8+ • Increase of Naïve T cells • Decrease of memory T cells • Decrease of Naïve B cells • Increase of plasma cells in peripheral blood • Positive virus-specific IgG and IgM	(Li et al. 2020) (Liu et al. 2020) (Qin et al. 2020) (Tan et al. 2021) (Wen et al. 2020)
Inflammatory cytokine reaction	• High plasma concentration of IL-1β, IL-1ra, IL-7, IL-8, IL-9, IL-10, basic FGF, G-CSF, GM-CSF, IFN-γ, IP-10, MCP-1, MIP-1α, MIP-1β, PDGF, TNFα, and VEGF • Higher plasma concentration of IL-2, IL-7, IL-10, G-CSF, IP-10, MCP-1, MIP-1α, and TNFα in ICU patients	(Huang 2020)

Abbreviation: SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; IL-1β, interleukin 1β; IL-1ra, Interleukin 1 receptor antagonist; IL-2, interleukin 2; IL-7, interleukin 7; IL-8, interleukin 8; IL-9, interleukin 9; IL-10, interleukin 10; IL-17, interleukin 17; basic FGF, Basic fibroblast growth factor; G-CSF, granulocyte-colony stimulating factor; GM-CSF, granulocyte macrophage-colony stimulating factor; IFN-γ, Interferon gamma; IP-10, IFN-γ-induced protein 10; MCP-1, monocyte chemoattractant protein 1; TNFα, Tumor necrosis factor α; MIP-1α, Macrophage Inflammatory Protein 1α; MIP-1β, Macrophage Inflammatory Protein 1β; PDGF, Platelet-derived growth factor; VEGF, Vascular endothelial growth factor

In this review, we attempt to clarify the unique concerns and problems associated with SARS-CoV-2 and the rapid and urgent developments of associated vaccines.

COVID-19 vaccine concerns

Vaccine hesitancy and acceptance

Segments of the population are hesitant to be given one of the new SARS-CoV-2 vaccines. While some individuals believe the anti-vaccination rhetoric that is propagated on social media, other individuals have concerns raised about these vaccines that also need to be considered. The rapidity with which vaccines are obtained with EUA in the United States has led some members of the public to express concerns about the true safety of these vaccines, even though the efficacy, at least in the short term, seems clear. As of February 2021, Van Tassel et al. described potential injuries that may be caused by many of the vaccine candidates against SARS-CoV-2 (Van Tassel et al. 2021). Moreover, there is concern that the political impetus to speed up vaccine development and acceptance processes could lead to the introduction of an unsafe vaccine for general use. Such a situation may lead to public refusal to accept potential vaccines in the future. Therefore, it is necessary to establish trust and efficient communication, and maintain public faith in the healthcare system, including accountability and regular reporting of reliable vaccine-related data (Jiang 2020).

There is also considerable fear that, as the vaccine is released for general use internationally, unexplained side effects could occur in the broader population that have not historically been identified in smaller study populations, even though 30,000–50,000 people have been included in those trials. In addition, given that a wide range of ages (>65 years and <16 years, depending on the study) and people with chronic conditions were not included in the population in the clinical trials, there is a risk that unanticipated side effects may be identified in those populations even though the vaccine is ready for use in the general adult population. The public can be reassured as post-marketing monitoring requirements guarantee that vaccines, as with all new medications and treatments, are monitored for certain side effects in the population (Sharma et al. 2020).

A recently performed study showed that the acceptance of the COVID-19 vaccine was affected by the effectiveness of the vaccine (Lazarus et al. 2021). Therefore, if a COVID-19 vaccine's efficacy was low, policymakers/governments should have introduced some strategies to persuade their vaccination population. Moreover, since acceptance was correlated with the potential risk of COVID-19, it was also essential to improve the perceived risk in communities (Harapan et al. 2020). Besides, every effort to find an effective vaccine with phase 3 trial pharmaco-vigilance infrastructure, such as surveillance for asymptomatic infection among vaccinated and unvaccinated persons, is required (Bar-Zeev and Moss 2020).

Vaccine design concerns

Preexisting immunity to adenoviruses is also a concern, notably in vaccine candidates using human adenoviruses, as this could produce a reduced immune response to the vaccine (Zhu et al. 2020). Adenovirus vectors may not be as effective, especially upon repeated dosing, compared with other vaccine approaches. When adenovirus platforms are used in vaccine design, anti-vector immune responses occur, with the potential for antibodies to be produced against the adenovirus vector, decreasing vaccine efficacy.

Another important design challenge is vaccine-induced "disease enhancement." Vaccine developers are working to understand the syndrome of "disease enhancement," which was reported in the past decades for a few viral vaccines. In those cases, immunized individuals suffered increased severity or death when they later encountered the virus. This issue was observed with certain SARS-CoV-1 vaccine candidates. This phenomenon was first identified in the 1960s when young children got an inactivated RSV (respiratory syncytial virus) vaccine. A few months after vaccination, when the vaccinated children became infected with natural RSV, the vaccine did not stop the infection, and 80% of the infected children needed hospitalization, and two died (Kim et al. 1969). Scientists also discovered that the vaccine-induced similar disease enhancement in animals with an immunopathological response generated by T helper cell type 2 (Th2) and antibodies with low neutralizing function (Connors et al. 1994; Delgado et al. 2009). Since then, animal models have been depended on to evaluate the safety of newly developed RSV vaccines. Animal models have allowed scientists to simulate human conditions to decrease the adverse effects of vaccines (Van Riel and De Wit 2020). Since pathology associated with enhanced RSV vaccine disease has been seen in animal models with certain SARS-CoV-1 vaccine candidates, there was also a fear that the related syndrome could be followed by vaccination in SARS-CoV-2-immunized individuals. In the case of COVID-19 due to SARS-CoV-2, it is not evident if any type of immune enhancement could have a role to play with vaccines under development. Experts have recommended that the evidence of some disease enhancement with any candidate vaccine after viral infection in animal models should not necessarily represent a no-go signal for progressing into early trials in the clinical development of a COVID-19 vaccine (Lambert et al. 2020).

Viral mutations as a challenge to global immunization

Approximately, at the same time when the development of vaccine and global immunization has been progressing, the viral genome of SARS-CoV-2 has also been undergoing mutations and changes. Some of these mutations have resulted in different variants of the virus capable of causing a stealthier form of COVID infection, which may even have a higher transmissibility rate (Luo et al. 2021). SARS-CoV-2 variants were first identified in UK (B.1.1.7), South Africa (B.1.351), and Brazil (P.1) and have now been found in the USA and other parts of the globe (Pereira 2021). Although all lineages require urgent and immediate action, it is expected B.1.1.7 variant to rise rapidly in frequency in the USA over the next few weeks/months. It is now firmly established that the B.1.1.7 variant of the virus is inherently more transmissible (~50%; doubling in relative frequency ~ weekly) (Volz et al. 2021). Similar transmission patterns have been observed in UK, Denmark, Ireland, Portugal, Jordan, and other places. When a country finds this lineage, one may assume that it will become dominant quickly.

B.1.351 and P.1 variants are independent lineages with several key mutations in common. These point mutations resulting in L18F, K417N/T, E484K, and N501Y are commonly shared among the new variants. Specifically, N501Y, also known as NellY, is also shared with B.1.1.7 variant (Garcia-Beltran et al. 2021). Seeing the same mutations pop up in multiple locations (convergent evolution) may indicate the presence of a "selection" pattern. The development of new mutations in the viral genome is alarming and may reduce the effectiveness of current vaccine in the future (Garcia-Beltran et al. 2021). If these mutations

become more frequent, enough to alter the RNA-virus's/protein structures, there will be a need to update vaccines to target the key disrupted epitopes.

It is expected to see B.1.1.7 rise rapidly in the coming weeks and months, but the same may not be accurate for B.1.351 and P.1, at least not all across the USA. On a positive note, Israeli HMO Maccabi reported that even though 40–50% of Israel's COVID-19 cases were the B.1.1.7 "British" variant, just 20 coronavirus tests were positive out of 128,000 people who had their second Pfizer shot a week or more previously. None of the 20 cases was seriously ill. Most of the 20 patients were over 55 years old and about half had a preexisting condition. None had a fever over 38.5°C or required hospitalization. This is reassuring news about the vaccine's continued ability to protect from a mutated strain (Green et al. 2021). Although the development of new variants of SARS-CoV-2 increases anxiety within society, mutations can only occur in replicating virus. Therefore, global immunization that effectively controls the replication of the original form of the SARS-CoV-2 virus will prevent the development of new mutations and viral variants.

ARDS and vaccination risk

Infection with SARS-CoV-2 in humans has resulted in various medical complications and clinical manifestations that are associated with progression from asymptomatic, to moderately symptomatic, to significantly symptomatic with illness leading to death or, in others, alleviation of symptoms and full recovery (Wang et al. 2020). Approximately 80% of COVID-19 patients show no clinical signs or only minor to moderate symptoms. However, nearly 15% develop serious respiratory conditions, and 5% develop ARDS, lung collapse, shock, or multiorgan failure (Wu et al. 2020; Xu et al. 2020). In these severe cases, extreme symptomatic respiratory involvement and development of ARDS begins 8–9 days after the emergence of symptoms. This may cause death due to respiratory impairment and severe hypoxia. These complications often arise after day 14, exceeding the peak viral load (Shi et al. 2020; Tay et al. 2020). The production of viral-neutralizing antibodies, especially anti-S IgG, correlates with ARDS development and may correspond to the development of ADE (antibody-dependent enhancement). As already seen in the prior decade of SARS-CoV infections, rapid and early development of antiviral-IgG at the start of symptoms with maximal titer in about 14 days results in a higher risk of mortality and severe lung damage (Zhang et al. 2006; Zhao et al. 2020). Efficient neutralizing antibody production should dramatically inhibit viruses and keeps them from binding to target receptors, contributing to lower viral replication. However, the development of SARS-CoV-2 neutralizing antibodies may activate a heightened inflammatory response, "cytokine storm," and cause serious systemic manifestations including lung injury. ADE is believed to occur through two separate mechanisms: by enhanced antibody-mediated virus uptake into phagocytic cells leading to increased infection and viral replication, or by sub-par levels of neutralizing antibodies that mediate immune complex formation leading to greater inflammation and severe illness (Lee et al. 2020). The findings of multiple experiments using animal models vaccinated with SARS-CoV have also demonstrated a higher risk of pulmonary damage associated with elevated inflammatory pulmonary response than non-vaccinated animals (Bolles et al. 2011; Liu et al. 2019; Tseng et al. 2012). We may conclude that in previously infected and recovering patients, severe ADE complications due to the interaction of viruses with antibodies and the immune system may also result in lung damage during reinfection with SARS-CoV-2.

A variety of prototype DNA vaccines encoding different S proteins have been tested for their defensive effectiveness against intranasal and intratracheal SARS-CoV-2 threats in rhesus macaques. The vaccinated monkeys demonstrated a decrease in bronchoalveolar lavage (BAL) and nasal swab viral loads and a dramatic drop in viral replication of the upper and lower respiratory pathway. On the other hand, less immunogenic vaccines showed slight protection in BAL and no protection in nasal swabs (Yu et al. 2020). The effectiveness of antibody-related defense against SARS-CoV-2 reinfection relies on the availability and adequate amount of defensive neutralizing antibodies and the efficacy of plasma cells and memory B cells in quick reaction to viral loads (Khoshkam et al. 2021). Further research is required to explain these observations in more depth.

Conclusion

Although it seems unlikely, if the COVID-19 pandemic abruptly ends before widespread vaccine distribution is complete, the scientific community and pharmaceutical industry will continue developing vaccine options to be ready for the recurrence of a future outbreak of SARS-CoV-2 or a related virus. The outstanding efforts of the scientific community has rapidly developed multiple vaccine candidates. More than 40 clinical trials are currently ongoing, of which 10 are in Phase 3, and several have been marketed for selected demographic groups throughout the world. It is important to note that all approved vaccines have been nearly 100% effective in preventing death due to COVID-19 and are highly effective (60–95%) against symptomatic disease. It appears that it will be many months before widespread global use of vaccines leads to universal protection against COVID-19.

We have reviewed several unique concerns associated to SARS-CoV-2 and the vaccines that have been designed thus far. Public concerns about the virus and vaccines may interfere with public health measures to control COVID-19. Complications such as ADE, ARDS and cytokine storm are not fully understood, and investigators continue research to aid our understanding of this virus and its complications. Therefore, the importance of public health strategies, such as physical distancing, early detection, self-isolation, and outbreak control needs to be continually emphasized as important preventive interventions.

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