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A Review on COVID-19 and Vaccine Development: What We Have Learned in this Pandemic

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Abstract

The emergence of the Coronavirus disease (COVID-19) was initially documented in December 2019 in Wuhan, China which quickly evolving into a global pandemic. COVID-19 is caused by the Severe Acute Respiratory Syndrome coronavirus 2 (SARS-CoV-2) virus. While the majority of individuals infected experience mild to moderate respiratory symptoms and recover without specific treatment, a minority endure severe illness requiring intensive medical care.In response, scientific/academic institutions and pharmaceutical manufacturers embarked on the development of COVID-19 vaccines, rigorously gathering evidence on their safety and efficacy. Regulatory authorities meticulously assess this data prior to international distribution. This article discusses on the life cycle and host cell invasion mechanisms of SARS-CoV-2 virus, pathophysiology of COVID-19, diagnostic tests, preventive measures, and vaccines development. Overall, this review offers a thorough comprehension of the COVID-19 pandemic, providing stakeholders with the knowledge needed to effectively respond to and mitigate its impact on public health and society.

Keywords: COVID-19; vaccines; coronavirus; SARS-CoV-2 virus; immunity

Introduction

Coronavirus disease (COVID-19) is a respiratory system infection caused by the Severe Acute Respiratory Syndrome coronavirus 2 (SARS-CoV-2) virus. This virus, known for causing previous outbreaks such as Middle East Respiratory Syndrome (MERS) and Severe Acute Respiratory Syndrome (SARS), emerged in December 2019 in Wuhan, China, before spreading rapidly worldwide (1, 2). Originating in bats, it was transmitted to intermediary animals like the pangolin before crossing into humans. This intermediary animal harbored a coronavirus closely resembling COVID-19, suggesting a zoonotic transmission route, where the virus adapted and mutated as it spread among humans, acquiring characteristics conducive to rapid transmission. The COVID-19 outbreak was declared as a pandemic by World Health Organization on March 11, 2020(3). Up to date, SARS-CoV-2 stands as one of the most lethal viruses in human history, resulting in over 6.8 million deaths globally (4).

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During the initial stage of this outbreak, COVID-19 presented with mild to moderate symptoms such as bodyaches, fatigue or weakness, dry cough, breathlessness, diarrhea, nausea, difficulty with sense of smell and taste, loss of appetite and fever, with the majority of patients recovering without specific treatment(5, 6). However, a minority experienced severe symptoms necessitating intensive medical care. The elderly (aged above 60) and individuals with underlying chronic conditions such as chronic respiratory disease, chronic renal diseases, cardiovascular disease, cancer, obesity, hypertension or diabetes were at heightened risk of developing severe illness (3, 7, 8).

During the COVID-19 pandemic, scientific and academic institutions, along with pharmaceutical manufacturers, swiftly initiated the development of COVID-19 vaccines, meticulously collecting evidence on safety and efficacy to ensure their reliability. Regulatory authorities rigorously assess these vaccines before authorizing their distribution to other countries. COVID-19 vaccines are deemed safe for individuals aged 18 and above, offering protection against severe illness from COVID-19 (3).As of November 26, 2021, data from Our World in Data shows that approximately 54% of the global population has received at least one dose of a recognized COVID-19 vaccine. With 7.88 billion doses administered worldwide and an estimated 28.95 million doses administered daily, vaccination efforts have seen significant progress. However, disparities persist, particularly in less developed countries, where only 5.7% of the population has been vaccinated. While vaccines contribute to prevention, complete protection may not be guaranteed, underscoring the importance of continued research. Therefore, in addition to vaccination, it is crucial to adhere to preventive measures such as wearing masks and practicing social distancing(9).

Life Cycle and Host Cell Invasion Mechanisms of Sars-CoV-2 Virus

The virus undergoes a five-step life cycle within the host, starting with attachment, penetration, biosynthesis, maturation, and ultimately release. Initially, the virus attaches to host receptors, initiating the process. Subsequently, it either fuses with the host cell membrane or enters the host cells through the endocytosis pathway. Once inside, the virus releases its contents, such as RNA, into the nucleus of the host cells, triggering the production of viral proteins. Following biosynthesis, viral particles are formed and then released from the host cell(10).The primary mode of transmission is through person-to-person spread via respiratory droplets. Additionally, transmission via the fecal-oral route is also possible(11).

Coronaviruses possess four fundamental structural proteins: the spike protein, membrane protein, envelope protein, and nucleocapsid protein, which are essential for the assembly of maturevirions (12). During SARS-CoV-2 infection, the virus enters host cells by binding its spike protein to ACE2 receptors, primarily located in the lungs (13).The spike protein of SARS-CoV-2 consists of two functional subunits: S1, which is responsible for attaching to the host cell receptor, and S2, which facilitates membrane fusion and entry into the host cell(14).

The spike protein of SARS-CoV-2 is cleaved by cellular proteases TMPRSS2 and CTSL following attachment to host proteins. This cleavage occurs in a two-step sequential process. Initially, priming cleavage takes place at the S1/S2 site, followed by activation cleavage at the S2 site near a fusion peptide within the S2 subunit. Inspired by observations from related coronaviruses like SARS-CoV and MERS-CoV, this model suggests that the first cleavage stabilizes the S2 subunit at the attachment site, while the subsequent cleavage activates the spike protein(15). This activation leads to irreversible conformational changes essential for membrane fusion. Subsequently, the virus fuses with the host cell membrane, enters pulmonary alveolar epithelial cells, and releases its genetic material into the host cells, initiating further infectious processes(16).

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The replication process of the virus involves transcription facilitated by RNA polymerase activity. This process generates new negative-strand RNA from the original single-strand positive RNA. The newly synthesized RNA acts as a template for generating new positive-strand RNAs, which are then utilized to produce new proteins within the host cell through translation(17). Notably, the viral nucleocapsid protein dissociates from the positive-strand RNAs and are important in viral gene replication and expression(18).

Furthermore, the viral membrane protein binds to the nucleocapsid, aiding in the completion of virion assembly. These assembled virions are then encapsulated in the endoplasmic reticulum (ER) membrane and transferred to the ER lumen. The envelope protein is responsible in altering the secretory pathways, facilitating viral release. Ultimately, the newly formed virus particles are delivered to the cell membrane via Golgi vesicles and are released into the extracellular space through exocytosis(19). Once released, these newly formed virus particles have the capability to infect nearby epithelial cells and contribute to community transmission via respiratory droplets or aerosols.

Pathophysiology of COVID-19

The SARS-CoV-2 virus enters the upper respiratory tract through respiratory aerosols and airways, where it binds to nasal epithelial cells(20).Initial infection occurs in airway ciliated cells in which the cilia acid in the virus transport through PCL mucin layer, leading to local replication and proliferation(21). The immunological response is minimal during the early stage of infection, which typically lasts for a few days. Despite the relatively low viral load during this period, patients remain highly infectious (5).

Then, the virus travels to the upper respiratory tract through the conducting airways, prompting an enhanced innate immune response..Symptoms typically manifest as dry cough, fever and lethargy, reflecting the involvement of the upper airways. Virus-infected cells produce C-X-C motif chemokine ligand 10 (CXCL-10) and interferons (IFN-α and IFN-β), which stimulate a strong immune response during this phase. Most infected individuals do not advance beyond this stage, as the immune response is usually effective in controlling the infection (22).

Approximately one-fifth of all infected individuals progress to this stage of the disease, experiencing severe respiratory symptoms. The virus invades and infects type 2 alveolar epithelial cells via the host receptor ACE-2, initiating replication to produce new viral Nucleocapsids. This triggers the release of various cytokines and inflammatory markers, including interleukins (IL-1, IL-6, IL-8, IL-120, and IL-12), tumor necrosis factor (TNF-α), interferons (IFN-α and IFN-β), CXCL-10, monocyte chemoattractant protein-1 (MCP-1), and macrophage inflammatory protein-1 (MIP-1), by virus-infected pneumocytes. This inflammatory response, often termed a 'cytokine storm,' results in the accumulation of CD8 cytotoxic T cells, CD4 helper T cells and neutrophilsin the lung tissue. While these cells play a role in combating the virus, their presence also leads to cellular inflammation and tissue damage. As a result, the death of host cells leads to the release of additional virus particles, which then infect neighboring type 2 alveolar epithelial cells in a similar manner. This ongoing process of viral replication and the presence of inflammatory cells contribute to extensive damage to the alveoli. Consequently, both type 1 and type 2 pneumocytes are lost, ultimately culminating in the development of acute respiratory distress syndrome(22).

Symptoms and Transmission of COVID-19

According to the Centers for Disease Control and Prevention (CDC), the novel coronavirus primarily affects respiratory health, with symptoms ranging from mild to severe,.Approximately 35% of individuals infected with COVID-19 may be

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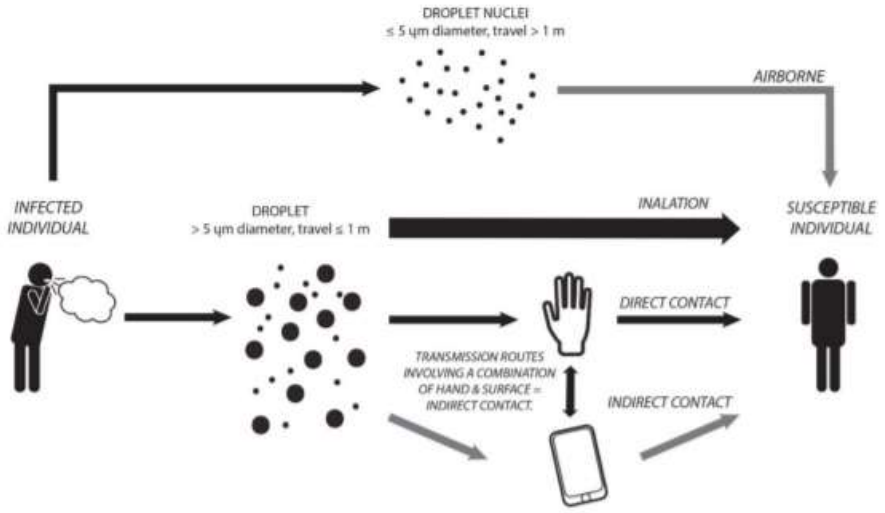

Fig. 1: Transmission of COVID-19

asymptomatic, and 40% of transmission occurs before symptom onset(23). Symptoms typically manifest within 2 to 14 days after viral infection. Less common symptoms, such as sore throat, headache, muscle aches, diarrhea, irritated eyes, skin rash, or discoloration of fingers or toes, are also reported, though cough, fever, fatigue, and loss of taste or smell are more frequently observed(24, 25). Notably, immediate medical attention should be sought by individuals experiencing serious symptoms such as shortness of breath, loss of speech or mobility, confusion, or chest pain.

Reports have indicated transmission of COVID-19 from person to person, primarily spreads among individuals in close contact within approximately 2 meters (Fig. 1). Similar modes of transmission were observed with MERS-CoV and SARS-CoV, where human-to-human transmission is believed to primarily happen through respiratory droplets generatedbyan infected person who is coughing, sneezing or talking(26).

Diagnostic Tests for COVID-19

The RT-PCR assay serves as the standard diagnostic method for detecting COVID-19 (Fig. 2). Samples are collected from various sources such as blood, stool, lower airway secretions, sputum, or throat swabs (nasopharyngeal in children)to analyze the existence of SARS-CoV-2. Majority of commercially FDA-approved SARS-CoV-2 PCR assays demonstrate specificity of nearly 100%, provided that there is no cross-contamination during specimen processing (27).

Serological tests are designed to detect the presence of antibodies in serum/plasma of individuals as a response to SARS-CoV-2 infection(28). The CDC's serological test boasts a sensitivity of 96% and a specificity of over 99%. These tests encompass Rapid Diagnostic Tests (RDTs), which typically detect patient antibodies like IgG and IgM, or viral antigen. RDTs are usually conducted using nasal swab fluid, saliva, or blood samples obtained from a finger prick, with colored lines indicating positive or negative infection results. Additionally, Enzyme-Linked Immunosorbent Assays (ELISAs) are utilized, employing serum samples, plasma, or whole blood from patients. During ELISA testing, samples are reacted with proteins to form an antibody-protein complex. Another method is the neutralization assay, which detects active antibodies against the virus (29).

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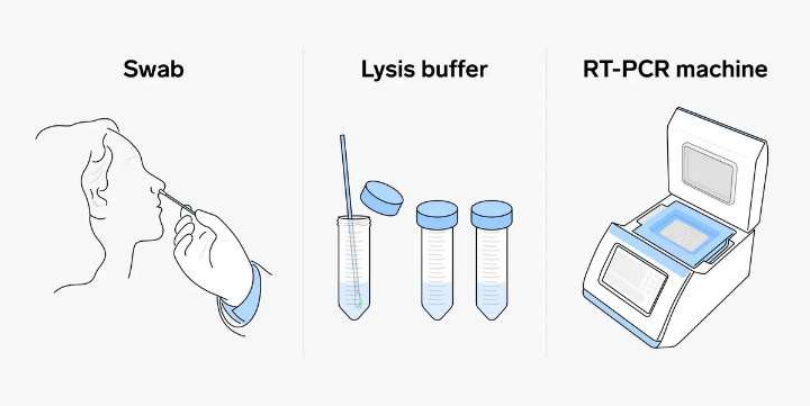

Fig. 2: RT-PCR assay

Additional laboratory tests, such as a nonspecific Complete Blood Count (CBC), are conducted to monitor leukocyte count, with counts < 1000 being associated with severe disease(30). Elevated procalcitonin levels may indicate bacterial co-infection, while increases in inflammatory markers levels such as ALT/AST, creatinine, D-dimer, CPK, lactate dehydrogenase (LDH), myohemoglobin, and ferritin may also be indicative of severe disease(31). When it comes to imaging, chest CT scans are considered more sensitive and specific than lung X-rays (CXR). While CXRs generally reveal bilateral infiltrations, they may appear normal in the early stages of the disease. In contrast, lung CT scans typically show infiltrates, ground-glass opacities, and subsegmental consolidation, features also observed in patients affected by SARS and MERS, both of which belong to the coronavirus family along with SARS-CoV-2 virus (32).

Development of COVID-19 Vaccines

Before vaccines were developed, medical practitioners explored various alternatives to treat patients with SARS syndrome. In Malaysia, some of the treatments utilized included Ivermectin, typically an animal drug, which was used as an alternative to alleviate SARS symptoms. Another drug employed was hydroxychloroquine, an antimalarial medication designed to combat malaria-causing organisms, but repurposed to mitigate symptoms and reduce mortality in SARS treatment. It's important to note that neither of these drugs was specifically developed to target SARS syndrome; rather, they were utilized as desperate alternatives. Despite claims suggesting their effectiveness, there is a lack of clinical trials supporting such assertions (33).

The development of COVID-19 vaccines has known as a primary strategy for global institutions to combat the pandemic. Typically, the process of developing a vaccine for a specific bacteria or virus can span anywhere from 5 to 10 years. However, in the case of COVID-19 vaccines, this timeline was significantly accelerated, with vaccines being fully developed and ready for use within a year. This remarkable speed can be attributed to the collaborative efforts of researchers and developers worldwide, who redirected their focus to this critical area of research. For these individuals, it became a race against time; the faster a vaccine could be developed against the COVID-19 virus, the more lives could be saved. Governments, non-governmental organizations (NGOs), and researchers alike joined forces with a singular purpose: to create a vaccine with the highest efficacy and minimal side effects, capable of being deployed globally to combat the pandemic.

Among the early players in vaccine development are Pfizer-BioNTech(31). Figure 3

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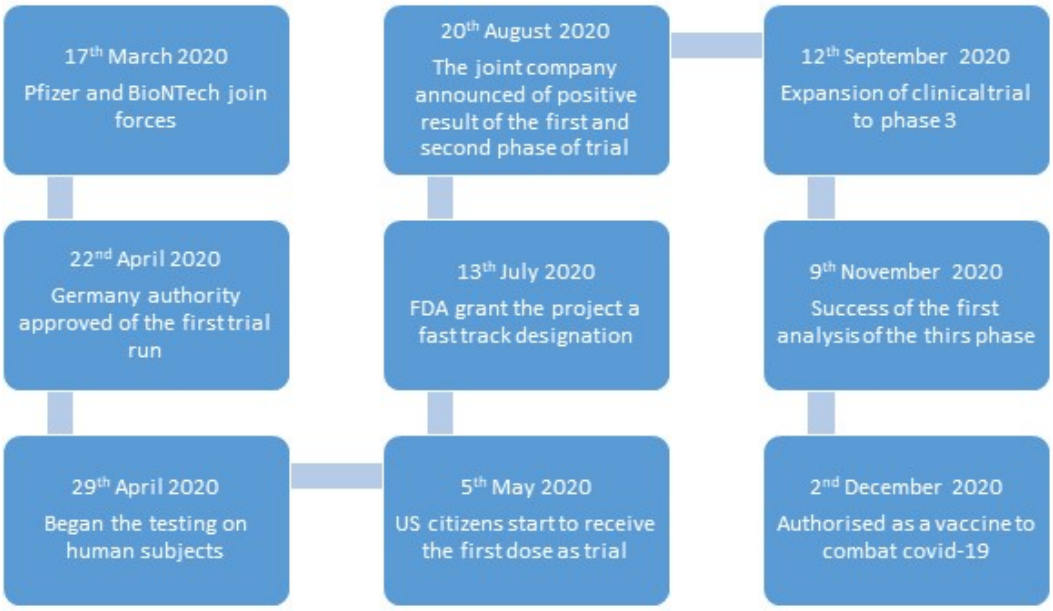

Fig. 3: Timeline of Pfizer-BioNTech vaccine development

illustrates the timeline of the Pfizer-BioNTech vaccine development. The joint venture between Pfizer and BioNTech was officially announced on March 17, 2020. Just four days prior to this, on March 13, 2020, Pfizer's CEO, Albert Boula, expressed his commitment to joining the battle against COVID-19 and outlined plans to produce vaccines. Approximately a month later, on April 22, 2020, German authorities approved their trial run, marking the beginning of testing. Human trials commenced on April 29, 2020. By May 5, 2020, the first doses of the vaccine were administered to US citizens. On July 13, 2020, the joint project received a fast-track designation from the FDA to expedite trials. Positive data from the first and second phases of the lead vaccine study were announced by Pfizer on August 20, 2020. Subsequently, on September 12, 2020, a proposal to expand clinical trials to the third phase was made. On November 9, 2020, success was achieved in the initial analysis of the third phase study. Just 11 days later, on November 20, 2020, Pfizer and BioNTech submitted an authorization request for the vaccine to be used as a COVID-19 vaccine. On December 2, 2020, authorization was granted, allowing the vaccine to be utilized in the fight against COVID-19. Finally, on February 24, 2021, the vaccine became the first to be administered in Malaysia. The vaccination program was rolled out in phases, with Phase 1 targeting 500,000 frontliners. Subsequently, Phase 2 focused on approximately 9.4 million senior citizens aged over 60 years, as well as individuals with severe diseases and disabilities (34).

Working Mechanism of COVID-19 Vaccines

The conventional understanding of vaccines as weakened versions of bacteria or viruses is evolving due to advancements in scientific research. While traditional vaccines may use weakened or inactivated pathogens, a new mechanism has emerged, particularly in mRNA vaccines, which doesn't involve the introduction of whole viruses. Alternatively, mRNA vaccines utilize messenger ribonucleic acid (mRNA), which carries instructions for protein synthesis(32).

In the protein synthesis process, RNA/DNA of viruses replicate the original

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parent strands in the nucleus before being translated by ribosomes, leading to the formation of new amino acids that constitute proteins. By focusing solely on the mRNA segment responsible for protein synthesis, scientists have developed a more efficient and effective approach, albeit one that requires a longer and more complex research process. The spike protein that surrounds viruses is also a protein, making it a target for mRNA vaccines. Through extensive efforts, researchers have harnessed mRNA vaccines to prompt the body to recognize specific viruses, essentially simulating an infection without the actual presence of the virus (29).

In vaccine development, the goal is to prime the body to produce antibodies before exposure to the pathogen, whereby three categories of vaccines have been developed for COVID-19. mRNA vaccines deliver genetic material from the COVID-19 virus into cells to produce specific viral proteins. These proteins stimulateimmune system to generate antibodies against the SARS-CoV-2 virus, enabling it to recognize and combat the virus in future infections(35). The BioNTech-Pfizer vaccine serves as an example of this type. Clinical results have demonstrated the safety and tolerability of this vaccine in children aged 5 to 11, leading to its authorization and recommendation for individuals aged 5 and above.

Viral vector vaccines, such as the AstraZeneca vaccine, transportthe genetic code of SARS-CoV-2 antigens into body cells by utilizing a modified harmless virus as carrier. Upon administration, cells produce specific viral proteins recognized by the immune system, thereby triggering an immune response(36). However, the AstraZeneca vaccine is not recommended for individuals under 18 years old. Another category, inactivated vaccines, includes examples like the Sinovac vaccine, which contain deactivated SARS-CoV-2 virus to prompt an immune response in the body. This vaccine is recommended for individuals aged 18 and above, though safety data for those over 60 is limited owing to the small sample size in clinical trials(36).

The human immune system consists of the innate immune system, which operates continuously even in the absence of infection, and the adaptive immune system, which activates upon exposure to infections(37). Natural killer (NK) cells and antigen-presenting cells (APCs) serve as links between these two immune system arms. T and B cells remain inactive on the adaptive immune system side until triggered by infections or the presentation of foreign antigens by APCs to helper T cells. Vaccination mimics an infection, prompting the body to mount an immune response without causing illness. Once the MHC-II peptide is presented to the adaptive immune system, B and T cells recognize the spike protein of COVID-19 and initiate a response by producing antibodies and engaging in T-cell cytotoxicity. Activated B and T cells retain a memory of the infection, providing long-term immunity against future exposures.

Evidence of the effectiveness

Pfizer-BioNTech conducted clinical trials involving individuals aged 16 and older, demonstrating that their vaccine exhibited 95% effectiveness in preventing COVID-19 infection after two doses in those without prior infection (38).Additionally, separate trials focusing on children and adolescents aged 5 to 15 years old revealed over 90% efficacy. These findings suggest that the immune response elicited in children aged 5–15 years old was comparable to that seen in individuals aged 16–25 years. Furthermore, the vaccine displayed consistent efficacy of over 90% across diverse demographics, including various age groups, genders, races, ethnicities, and individuals with underlying medical conditions. Data indicates that mRNA COVID-19 vaccines provide robust protection in real-world scenarios, similar to their performance in clinical trials. This high level of protection substantially reduces the risk of contracting COVID-19, including severe illness, by 90% or more among fully vaccinated individuals.

A randomized, double-blind study involving 43,548 participants aged 16 and

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above assessed the safety and efficacy of an mRNA vaccine targeting the SARS-CoV-2 spike protein. Participants received either the vaccine or a placebo via intramuscular injection on Day 0 and Day 21 and were monitored for symptomatic COVID-19 development for approximately 2 months. Vaccine recipients experienced higher rates of local and systemic reactions, including pain, erythema, fever, headache, and myalgias, compared to placebo recipients, with more pronounced reactions after the second dose. These reactions were mostly mild to moderate and resolved quickly. Efficacy analysis showed up to 95% protection against symptomatic COVID-19 following the second dose. Thus, the mRNA-based vaccine was deemed safe and provided significant protection against COVID-19 in individuals aged 16 and above(39).

Side effect of COVID -19 vaccines

Like medications, COVID-19 vaccinations can induce a range of side effects, typically ranging from mild to moderate and short-term. These effects are a normal part of the body's immune response as it builds protection against the virus. While these side effects may temporarily interfere with daily activities, they usually resolve within a few days. It's worth noting that allergic reactions are rare, and some individuals may not experience any side effects at all. Studies suggest that individuals who experience a severe allergic reaction to a specific vaccine should avoid receiving additional doses of that vaccine.

Data indicates that the majority of individuals experience mild side effects within 7 days of vaccination, which are typically common and do not interfere with daily activities. These side effects may include fever, chills, tiredness, headaches, muscle or join aches, arm soreness, redness and swelling. The intensity of side effects following the second dose is frequently reported to be higher compared to those experienced after the first dose, indicating that the vaccine is effectively stimulating the immune response (40).

There is speculation that polyethylene glycol (PEG), one of the ingredients in the Pfizer/BioNTech vaccine, may trigger anaphylaxis, a severe hypersensitive reaction of the body to an antigen. However, the association between PEG and vaccine-induced anaphylaxis remains unclear. While allergies to PEG are rare, they can result in severe and potentially fatal reactions. Although PEG has not been used in vaccines before, it is common in many drugs. Reports suggest that PEG may trigger anaphylaxis, leading to life-threatening symptoms such as rashes, a sudden decrease in blood pressure, difficulty breathing, and a rapid heartbeat. Hypersensitivity reactions to PEG may depend on its molecular weight (MW)(41). This highlights the risk for undiagnosed individuals with PEG allergies who may encounter anaphylaxis when exposed to mRNA vaccines containing PEG. Consequently, it is crucial to identify such individuals before vaccination. Patients suspected or confirmed to have a PEG allergy should refrain from receiving PEG-containing mRNA vaccines (41).

However, certain individuals may experience serious side effects, although they are extremely rare and unlikely to occur following any vaccination, including COVID-19 vaccination. Myocarditis and pericarditis are two examples of serious and rare side effects that may occur. However, most cases are mild (42-44). Myocarditis involves inflammation of the heart muscle, while pericarditis involves inflammation of the outer lining of the heart. These side effects have been reported in approximately 1 in 1 million doses of the Pfizer/BioNTech vaccine. They are more commonly observed in adolescents and young adults following completion of the two doses of the vaccine. Symptoms of myocarditis and pericarditis may include breathlessness, palpitations, and chest pain. If these symptoms occur within a week after receiving the vaccine, immediate medical assistance should be sought. The Pfizer-BioNTech COVID-19 vaccine typically requires two shots to complete the primary series, even if side effects are experienced

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after the first shot, unless advised otherwise by medical experts. However, reports indicate a significant decrease in the humoral response to vaccination within six months, highlighting the need for additional doses to maintain sufficient protection levels (45). Booster shots are recommended for individuals aged 18 years and older who completed their primary vaccination series with the Pfizer-BioNTech vaccine at least 6 months ago.

Conclusion

Vaccination emergesan important tool in combating the COVID-19 pandemic. Vaccines currently approved and authorized by the World Health Organization (WHO) have exhibited effectiveness against SARS-CoV-2 virus, effectively preventing severe disease, hospitalization, and fatalities. Moreover, the incidence of severe adverse reactions to vaccination is significantly lower than the risk of serious illness or death due to COVID-19 infection. Building public trust and confidence in COVID-19 vaccines is essential for their effective deployment. However, further scientific research and clinical trials are imperative, particularly regarding the application of vaccines in children. This ensures the safety and efficacy of vaccines across all age demographics, ultimately contributing to the end of the pandemic.

Authorship Contribution Statement

Kai Bin Liew (KBL): Conceptualization, Writing - Original draft, Supervision. Hiu Ching Phang (HCP): Writing – Original Draft. Bey Hing Goh (BHG): Writing - Review and editing. Chien Ing Yeo (CIY): Writing – Original Draft. Long Chiau Ming: Investigation, Writing - Original draft. A.B.M. Helal Uddin: Writing - Review and editing. Ashok Kumar Janakiraman (AKJ): Investigation, Writing - Original draft. Phei Er Kee: Visualization, Writing - Review and editing.

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Conflict of Interests

The authors declare no conflict of interest with regard to the work.

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