Adverse Events Profile of COVID-19 Preventative Strategies

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Definition: The COVID-19 pandemic has caused millions of deaths and has affected most people across the world, either directly or indirectly. Many preventative and therapeutic strategies have been employed since the beginning of the pandemic. With the development of the mRNA vaccine within a year of the start of the pandemic, we are entering a new era of vaccinology, and the adverse event profile of the COVID-19 vaccine is also becoming more apparent with time. While the benefits of the vaccines and other preventative strategies certainly outweigh the risk of adverse events, prospective clinical trials are urgently needed to determine whether specific populations, including those with a personal or family history of autoimmune disease, are at higher risk of developing certain adverse events, in order to minimize risk further.

Keywords: COVID-19; COVID-19 vaccine; adverse events

1. Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) COVID-19 is a novel RNA β-coronavirus that has spread globally among humans since its first appearance in Wuhan, China. SARS-CoV-2 is known to affect multiple organs in the human body, including the lungs, brain, heart, pancreas, and kidneys. With constant genetic mutation in the virus spike protein resulting in the development of new strains, rises in case numbers have been observed since the start of the pandemic in different parts of the world. Most recently, with rising case numbers caused by the South African Beta variant, many countries have again imposed travel restrictions and nationwide lockdowns. Current knowledge on the safety profile of COVID-19 vaccines is from phase 1–3 randomized controlled trials conducted during the early stage of the vaccine development, and from vaccine safety surveillance programs implemented in several countries. More extensive prospective clinical trials are needed for a complete understanding of COVID-19 vaccines’ adverse event profile. Growing evidence suggests autoimmunity is an independent risk factor for developing adverse events post-COVID-19 vaccination. More extensive prospective clinical trials are needed for a complete understanding of COVID-19 vaccines’ adverse event profile. This review article summarizes the etiopathology of COVID-19 and some of the uncommon adverse events associated with prevention strategies (primary prevention such as vaccines and secondary prevention such as monoclonal antibodies).

2. COVID-19 Etiopathology

SARS-CoV-2 belongs to the Coronavirus family and is named after the genetically similar SARS-CoV, which caused a pandemic in 2002–2003 [1]. Since the World Health Organization (WHO) declared the start of a pandemic on 11 March 2020 [2], there have been more than 250 million confirmed cases of COVID-19 worldwide, including 5 million deaths, as of 25 November 2021 [3]. Almost 48 million cases have been registered in the US alone, and more than 750,000 people have died as of 28 November 2021 [4]. Common symptoms of infection are a sore throat, dry cough, shortness of breath, fever, chills, loss of appetite, diarrhea, and loss of taste or smell. COVID-19 spreads when either droplets and particles containing the virus from an infected person are exhaled and breathed in by another
person, likely standing within six feet, or if these infected droplets and particles reach another person’s eyes, nose, or mouth through coughing or sneezing. Touching the mucous membrane lining of the eyes, nose, or mouth with hands that have a virus can also facilitate virus spread. Various reports have been published that report SARS-CoV-2 as a cause of acute respiratory distress syndrome [5], new-onset diabetes [6], cardiovascular adverse events [7], rhabdomyolysis [8,9], and various neurologic complications [10]. The effects on various organs result from direct viral toxicity or indirectly via host immune responses secondary to the infection. COVID-19 exhibits its effects in two stages. The initial stage of virus entry into host cells, by the viral spike protein binding to angiotensin-converting enzyme 2 (ACE2) receptors present on host cells [11,12]. This initial phase is followed by the late stage of hyperimmune response caused by the production of cytokines such as TNF-alpha, GM-CSF, IL-1, IL-6, and interferon-phigamma. The severity of the disease also depends on the host immunity: higher hospitalization rates and more severe symptoms and fatal outcomes have been documented in patients with weak innate immunity, such as in elderly patients and those with co-morbidities such as diabetes, hypertension, obesity, and immunosuppression.

3. Prevention Strategies

3.1. Primary Prevention

Primary prevention strategies aim to prevent the occurrence of COVID-19 in individuals and comprise of the strict usage of face masks, maintaining appropriate social distancing and proper hand hygiene, and widespread vaccination against the viral agent of this disease.

The most commonly administered vaccines in the US are two mRNA vaccines [13] with more than 94% efficacy, made by Pfizer–BioNTech (BNT162b2) and Moderna (mRNA-1273), as well as one modified adenoviral vaccine with more than 65% efficacy made by Johnson and Johnson (Janssen) [14]. The messenger RNA in the mRNA vaccines possesses the genetic information required to produce surface spike proteins. Host antigen-presenting cells enable the recognition of these spike protein antigens by lymphocytes, which produce complementary antibodies. Another means by which the vaccine produces immunity is by inducing CD4+ and CD8+ T cell immune responses. Host CD4+ T cells induce the production of cytokines, whereas CD8+ T cells remove the virus from the intracellular compartment [15,16]. The Janssen vaccine is not a live viral vaccine, but instead carries a modified adenoviral vector with the genetic code for the SARS-CoV-2 spike protein antigen, which triggers an immune response and protects the host against actual viral infection [17]. Some of the other vaccines available outside the US are ChAdOx1-nCoV (non-replicating vector vaccine manufactured by Oxford and AstraZeneca), Gam-COVID-Vac (non-replicating vector vaccine manufactured by Gamaleya Research Institute), CoronaVac (inactivated vaccine manufactured by SinoVac), and BBIBP-CorV and WBIP (inactivated vaccine manufactured by Sinopharm).

Post-Vaccination Adverse Events

In general, vaccines are safe, with common adverse effects of injection site pain, redness, swelling, myalgia, fever, chills, and fatigue. There are currently no absolute contraindications for vaccination, except for a history of allergies or anaphylaxis, which may increase the recipient’s risk of experiencing such an adverse event to COVID-19 vaccines. Because the mRNA vaccines are the first of their kind to be licensed for use in humans and have been available for less than a year, data on short- and long-term adverse events are currently limited. The Vaccine Adverse Event Reporting System (VAERS) database, published by the Centers for Disease Control (CDC), USA, aims to assess and report the real-world adverse event profile for these vaccines. Even though VAERS is the only way to assess adverse event profiles on a broad scale, this dataset also has limitations, including passive data collection and underreporting. Therefore, the occurrence of adverse events in real-world populations of vaccinated individuals maybe even higher.
Various case reports and case series of unusual adverse events from the vaccines have been published, some of which have proven fatal. One such adverse event is rhabdomyolysis [11,18–20]. Rhabdomyolysis is a potentially life-threatening clinical syndrome that typically results from a skeletal muscle injury, resulting in the release of toxic levels of myoglobin, electrolytes, enzymes such as creatinine phosphokinase (CPK), aldolase, lactate dehydrogenase, and other substances into the circulating blood [21]. Common risk factors for rhabdomyolysis include viral infections such as CMV, COVID-19, excess alcohol use, heat exhaustion, over-exercising, or genetic factors [11]. According to VAERS, at least 201 vaccine recipients have experienced this adverse event (of which 110 were male, 86 female, and 5 unknown); of these, 16 individuals (12 male and 4 female) died as of 17 December 2021 [22].

Further analysis by age group reveals that all recipients who experienced this adverse event were over the age of 50. Aggressive intravenous hydration remains the primary mode of treatment for rhabdomyolysis, but this condition often progresses despite treatment, and may lead to renal failure requiring hemodialysis. It is not entirely clear why some vaccine recipients and not others develop rhabdomyolysis post-vaccination; however, currently, the available literature suggests that the presence of autoimmune conditions such as rheumatoid arthritis and the use of medications such as statins may be independent risk factors for the development of post-vaccination rhabdomyolysis [11]. The post-vaccination CPK level should be checked in a larger clinical trial to assess whether the vaccine causes an asymptomatic rise in the CPK level post-administration in all recipients and if only those with risk factors develop the symptomatic stage (i.e., rhabdomyolysis).

Post-vaccination cardiac adverse events are also well documented. As per the VAERS dataset, 2339 vaccine recipients (1113 male, 1189 female, and 37 unknown) have experienced atrial fibrillation (AF) after vaccination, as of 17 December 2021. Of these, 144 (70 female and 74 male) died from this adverse event. Upon further analysis of VAERS data [22], pre-existing cardiac disease increases the risk of cardiac adverse events. The majority of recipients who experienced this adverse event were over the age of 50. Only 175 recipients were under 50 and experienced AF post-vaccination. Overall, Pfizer–BioNTech had the highest incidence of this particular adverse event, and all three individuals below age 50 who died from this adverse event had received the Pfizer–BioNTech vaccination. One newborn age <6 months also experienced AF post-Moderna vaccine administration. AF is usually caused by ectopic foci, single-circuit reentry, or multiple-circuit reentry. Any inflammation of cardiac muscles can make the atria more vulnerable to fibrillation [23]. Typical clinical presentation is the patient displaying chest pain, shortness of breath, chest palpitations, lightheadedness, or dizziness. There is compelling evidence that dysregulated immune systems can produce autoantibodies against specific ion channels on cardiac myocytes, thus promoting cardiac arrhythmias [24]. It is not entirely clear why some patients develop new-onset atrial fibrillation post-vaccination at this time; however, it is possible that when vaccines trigger an immune reaction, a dysregulated immune system resulting from autoimmune conditions can potentially produce autoantibodies against cardiomyocytes or cardiac ion channels, leading to cardiac myocyte inflammation and cardiac arrhythmias.

Reports of post-vaccination myocarditis, pericarditis, ventricular fibrillation, ventricular flutter, and cardiac arrest have also been documented. A total of 2444 vaccine recipients experienced myocarditis, 1916 experienced pericarditis, 254 experienced ventricular tachycardia, 205 had ventricular fibrillation, and 956 experienced cardiac arrest after vaccination. Of these, 47, 13, 28, 53, and 626 vaccine recipients, respectively, died from these adverse events. The age-wise distribution shows that 1784 individuals under the age of 50 developed myocarditis, 1189 developed pericarditis, 89 developed ventricular tachycardia, 34 developed ventricular fibrillation, and 200 vaccine recipients under age 50 developed cardiac arrest. Again, no data are available regarding personal medical history, family history, home medications use, and risk factors for further analysis. The question of why some individuals experience these adverse events remains to be answered. Table 1
summarizes the data on cardiac adverse events following vaccination against COVID-19. Table 2 describes these incidences and deaths by complication and vaccine type.

**Table 1. Cardiac adverse events post-COVID-19 vaccination.**

| Vaccine           | Sex     | Myocarditis | Pericarditis | Ventricular Tachycardia | Ventricular Fibrillation | Cardiac Arrest |
|-------------------|---------|-------------|--------------|-------------------------|-------------------------|----------------|
| JANSSEN           | Female  | 23          | 33           | 07                      | 04                      | 34             |
|                   | Male    | 28          | 47           | 11                      | 15                      | 57             |
|                   | Unknown | 7           | 8            | -                       | -                       | 1              |
| MODERNA           | Female  | 273         | 314          | 46                      | 40                      | 145            |
|                   | Male    | 521         | 374          | 59                      | 41                      | 217            |
|                   | Unknown | 15          | 14           | 1                       | -                       | 08             |
| PFIZER-BioNTech   | Female  | 460         | 422          | 63                      | 50                      | 211            |
|                   | Male    | 1090        | 694          | 66                      | 52                      | 263            |
|                   | Unknown | 27          | 10           | 1                       | 03                      | 20             |
| **Total**         |         | **2444**    | **1916**     | **254**                 | **205**                 | **956**        |
| **Deaths**        |         | **47**      | **13**       | **28**                  | **53**                  | **626**        |

**Table 2. Incidence and death from diabetes post-COVID-19 vaccination.**

| Vaccine           | Sex     | Event Reported | Deaths |
|-------------------|---------|----------------|--------|
| JANSSEN           | Female  | 268            | 12     |
|                   | Male    | 211            | 17     |
|                   | Unknown | 15             | 1      |
| MODERNA           | Female  | 1560           | 39     |
|                   | Male    | 998            | 62     |
|                   | Unknown | 24             | 1      |
| PFIZER-BioNTech   | Female  | 2625           | 41     |
|                   | Male    | 1572           | 64     |
|                   | Unknown | 69             | 3      |
| **Total**         |         | **7342**       | **240**|

VAERS data also show that 7342 individuals have so far developed post-vaccination diabetes (Table 2) as of 17 December 2021, although the type of diabetes is not specified. In addition, 1263 recipients under 50 years of age developed diabetes as an adverse event post-vaccination. No data are available on diabetes risk factors among these individuals, such as the family history of diabetes, personal history of obesity, or the presence of prediabetes. It also does not specify whether this adverse event was short-lived or whether these vaccine recipients required longer-term dietary modification, oral hypoglycemic agents, or insulin treatment. Autoimmunity has an acceptable role in the development of diabetes, among many others. Dysfunctional immune responses can trigger the production of tumor necrosis factor (TNF)-α and other pro-inflammatory cytokines, and the production of autoantibodies against the pancreas, resulting in dysregulated insulin production and sensitivity and insulin-dependent diabetes mellitus (IDDM) [25,26]. There have been reports of people who tested positive for glutamic acid decarboxylase (GAD)-65 antibody (an autoantibody against the pancreas) developing diabetes following COVID-19 infection [27]. These findings support the role of autoimmunity in the development of post-COVID-19 diabetes. The role of autoimmunity in the development of new-onset diabetes post-COVID-19 vaccination should be explored.

There have also been 673 documented cases of post-vaccination renal failure (285 females and 379 males), including 227 deaths; 6688 documented cases of stroke (3894 female, 2661 males, and 133 unknown), including 379 deaths; 2542 documented cases of respiratory failure (1153 females and 1371 males), including 806 deaths; 238 documented cases of liver failure (115 females, 117 males, and 6 unknown) including 79 deaths; 1090 documented cases of thrombocytopenia (591 females and 471 males), including 119 deaths; and
462 documented cases of hypothyroidism (425 female, 31 male, and 6 unknown) including 7 deaths after vaccination against COVID-19 [22]. Hypothyroid as an adverse event was seen to be the highest in females receiving Pfizer–BioNTech. Table 3 summarizes the complete adverse event profile. Seventy-four recipients under age 50 developed renal failure, 1413 developed stroke, 214 developed respiratory failure, 48 developed liver failure, 311 developed thrombocytopenia, and 142 recipients under age 50 developed hypothyroidism.

The role of autoimmunity has been well-documented in developing thrombocytopenia, cerebrovascular accident (CVA), hypothyroidism, and liver and renal failure [28–32]. In autoimmune conditions, the immune system, upon stimulation with the vaccine, can potentially produce autoantibodies against blood vessels resulting in vasculitis/stroke, thyroid tissue resulting in hypothyroidism, hepatocytes, or platelets resulting in liver failure and thrombocytopenia. Heme protein deposition in renal tubules from autoimmune hemolysis is a well-known cause of autoimmune renal failure [32]. Whether these adverse events are short- or long-term remains to be seen. There are no data on whether these individuals had any risk factors for these conditions, such as personal or family history of autoimmune disorders, history of hypertension, COPD (chronic obstructive pulmonary disease), tobacco use, alcohol use, antiplatelet medications, hepatitis, or fatty liver.

Table 3. Other major adverse events post-COVID-19 vaccination.

| Vaccine          | Renal Failure | CVA (Stroke) | Respiratory Failure | Liver Failure | Thrombocytopenia | Hypothyroid |
|------------------|---------------|--------------|---------------------|---------------|-----------------|-------------|
| JANSSEN          | 68            | 816          | 267                 | 31            | 177             | 28          |
| MODERNA          | 272           | 2567         | 903                 | 80            | 344             | 40          |
| PFIZER-BioNTech  | 333           | 3305         | 1372                | 127           | 569             | 389         |
| Total            | 673           | 6688         | 2542                | 238           | 1090            | 462         |
| Deaths           | 227           | 379          | 806                 | 79            | 119             | 7           |

3.2. Secondary Prevention

Secondary prevention strategies for COVID-19 aim to reduce the impact of the disease in individuals who already have it by attenuating progression to later disease stages, using passive immunotherapy with monoclonal antibodies (mAbs). For high-risk, mild-to-moderate, non-hospitalized cases of COVID-19, the US Food and Drug Administration (FDA) approved emergency use of the mAb cocktails casirivimab/imdevimab (REGN-COV2; approved in November 2020) and bamlanivimab/etesevimab (approved on February 2021) [33,34]. Additionally, dexamethasone, remdesivir, and tocilizumab have also been used as a means of secondary prevention for different indications. For example, remdesivir is an antiviral and is the only Food and Drug Administration-approved medicine used in treating hospitalized COVID-19 patients. Systemic corticosteroids such as dexamethasone are standard of care in all COVID-19 patients requiring supplemental oxygen, as it suppresses the cytokine storm induced by the hyperactive immune system [35]. Tocilizumab prevents IL-6, which is involved in the late hyper-inflammatory stage caused by COVID-19 infection [36], by antagonizing IL-6 receptors.

mAbs are particularly useful in the early stages of COVID-19 infection. They bind to the viral spike protein and block viral entry into host cells, thereby preventing viral replication and reducing viral load, which reduces the risk of disease progression to the cytokine-mediated hyperinflammatory phase [37,38]. mAbs are generally safe. The most common adverse events of REGN-COV2 are allergic reactions immediately post-infusion, such as fever/chills, dyspnea, hives, and itching. Some minor local side effects such as bruising, pain, or soreness at the injection site are commonly reported. However, one case report published recently documented life-threatening gastrointestinal (GI) bleeding after infusion with REGN-COV2, requiring admission to an intensive care unit, massive blood transfusion, and urgent hemicolectomy [39]. The pathology report for this individual did not indicate a bleeding site, but showed a viable colon and terminal ileum with diverticulosis. GI bleeding is a well-known side effect of long-term tocilizumab treatment,
primarily due to its anti-IL-6 receptor activity, as this receptor is involved in enterocyte proliferation in the GI tract [40,41]. However, the individual in this case study did not have any prior risk factors such as a history of GI bleeding or receipt of antiplatelet or anticoagulant medications. It remained unclear why this patient developed the fatal GI bleed following mAB infusion.

4. Conclusions and Prospects

The development of mRNA vaccines with more than 94% efficacy in less than one year is a highly significant medical achievement. With widespread vaccination still taking place, and the efficacy of the vaccines against new mutated strains of the virus continuously being assessed, it is vital to record and examine their associated adverse event profiles.

Based on this review, it is evident that these adverse events occur equally in both males and females and across all types of vaccines, except for the incidence rate for the development of hypothyroid, which is seen more in females than males. In addition, the older population aged >50 years is at the highest risk for developing severe adverse events for most adverse events, except for the incidence of myocarditis and pericarditis, which was seen to be slightly higher in the younger populations than in the recipients aged >50 years.

Some questions remain to be answered. Prospective clinical trials are required to determine whether the personal history of autoimmune conditions is an independent risk factor for the development of adverse events. Interestingly, the adverse events profile of vaccines is almost identical to the adverse event of actual COVID-19 infection. No other vaccines have had so much of a broad-spectrum adverse events potential in the past. Adjuvant polyethylene glycol used in mRNA vaccines has never been used before in human vaccines. The adjuvants play an essential role in enhancing the desired immune response [42,43]. Adjuvant-induced autoimmune response (ASIA) is also an equally well-known phenomenon, and the role of PEG in inducing an autoimmune reaction to vaccine certainly needs to be explored. Currently, no guidelines are available for vaccination in patients with autoimmune disorders. It is yet to be determined whether certain adverse events generally occur after the first dose itself or only after the second dose. Whether the second dose of the vaccine should be administered at the recommended interval after the first dose in those with autoimmune conditions or if the interval between two doses should be extended to minimize adverse events needs to be looked into. People with known risk factors should be advised to watch for potential adverse events. Having this understanding will also give potential vaccine recipients a chance to decide if they would like to receive the vaccine or not after understanding the risks vs. benefits. The collection of more information on risk factors from prospective studies, such as personal or family histories of autoimmune conditions, co-morbidities, and medications, will help identify patients at greater risk of developing certain adverse events, for whom measures could be taken to mitigate the risk. For example, it may be appropriate to advise short, temporary breaks from medications or substance use, such as statins or alcohol, post-vaccination against COVID-19 to minimize the risk of adverse events such as rhabdomyolysis. Vaccine recipients with risk factors such as obesity or a family history of diabetes should be educated on symptoms of new-onset diabetes such as polyuria, polydipsia, polyphagia, or weight loss, so as to prevent complications from uncontrolled blood sugar levels such as diabetic ketoacidosis. Vaccine recipients with a known underlying cardiac disorder should be advised to watch for symptoms like chest pain, palpitation, or shortness of breath and to seek immediate medical attention in such a case. Knowing about such symptoms would help vaccine recipients seek timely medical attention to minimize the risk of developing complications and further death.

While the benefits of vaccination outweigh the risks and adverse events in the global population, more work is urgently needed to help minimize potentially serious adverse events in high-risk groups.
5. Summary

- The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) COVID-19 is a novel RNA β-coronavirus that has caused millions of deaths and has affected most people across the world, either directly or indirectly.
- Primary prevention of the disease is mainly possible due to the rapid advancement of the vaccines, whereas secondary prevention mostly aims at identifying the disease in the early stages and preventing the advancement of the disease with the help of the monoclonal antibodies, or through the use of the interleukin-6 (IL-6), such as tocilizumab.
- With global mass vaccination, we are also learning more about adverse events related to vaccines and other preventative strategies.
- Vaccines and other measures to counter this deadly condition are safe in general and the benefits certainly outweigh the harms. However, growing evidence suggests autoimmunity as an independent risk factor in the development of a higher incidence of various adverse events post-COVID-19-vaccination. It is of utmost importance to develop guidelines regarding COVID-19 vaccination such as the total number of required doses including booster doses, duration between two doses, and post-vaccination monitoring in this group.

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