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CURRENT OPINION

Adverse events related to COVID-19 vaccines: the need to strengthen pharmacovigilance monitoring systems

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Abstract

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by a new species of β-coronavirus genus named severe acute respiratory syndrome coronavirus 2. The COVID-19 pandemic, which started in late 2019 and continues as at mid-2021, has caused enormous damage to health and lives globally. The urgent public health need has led to the development of vaccines against COVID-19 in record-breaking time. The COVID-19 vaccines have been widely rolled out for the masses by many countries following approval for emergency use by the World Health Organization and regulatory agencies in many countries. In addition, several COVID-19 vaccine candidates are undergoing clinical trials. However, myths, fears, rumors, and misconceptions persist, particularly in regard to adverse events. In this commentary, we describe the adverse events associated with COVID-19 vaccines and discuss why it is essential to have a functional adverse event monitoring system in this context.

Key Points

A small number of vaccines against COVID-19 have been authorized since 2020.

Pharmacovigilance systems are imperative to ensure the safety of COVID-19 vaccines.

Active pharmacovigilance monitoring involving all stakeholders of COVID-19 vaccination is needed to prevent and document possible adverse events related to COVID-19 vaccines.

Background

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by a new species of β-coronavirus named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1, 2]. It is a single-stranded RNA β-coronavirus whose genome encodes structural proteins, nonstructural proteins, and accessory proteins [3, 4]. Since its outbreak in late 2019, the virus has spread globally, creating global health, socio-economic, and humanitarian crises [5–7]. Globally, as of

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19 June 2021, more than 183 million confirmed cases of COVID-19 and almost 4 million deaths have been recorded [8, 9]. The high transmission rate of the virus means the numbers of confirmed cases are increasing exponentially, with new mutational variants also contributing. In addition, the mortality rate is higher in elderly patients and those with preexisting health conditions [10–12].

Thus far, the lack of effective treatment means vaccination, alongside other public health mitigation measures such as hand hygiene and social distancing, remains the only pathway to suppression of the virus and release from the pandemic. As a result, many governments have approved the rollout of some vaccines through emergency approval procedures, and several clinical trials are ongoing worldwide to find specific treatments and vaccines for COVID-19 [13–15]. However, fears, rumors, and misconceptions persist, particularly regarding COVID-19 vaccines. This article aims to provide information about the currently approved vaccines and the adverse events reported thus far and to discuss why excellent adverse event monitoring systems are vital.

Approved Vaccines and Ongoing Trials

As of 19 June 2021, 78 vaccine candidates are in development in 201 different ongoing trials. Among them, 12 vaccines were approved by the US FDA, the World Health Organization (WHO) and the European Medicines Agency (Table 1) [16].

As the virus is spreading widely in the population and causing infections, many new variants are emerging. Researchers believe that COVID-19 vaccines currently in development or already approved induce a broad immune response, so they are expected to give at least some protection against future viral strains. However, data are being collected to analyze the effectiveness of COVID-19 vaccines on new variants [27]. For example, in Qatar, a study was conducted to assess the effectiveness of the Pfizer–Biotech COVID-19 vaccine against the variants of concern, such as B.1.1.7 (α variant; WHO classification) and the B.1.351 (β variant; WHO classification), found that people who received two doses of the Pfizer–BioNTech vaccine were 75% less likely to develop a case of COVID-19 caused by B.1.351 (β) than were unvaccinated people [28].

Adverse Events with COVID Vaccines

Almost all vaccines for COVID-19 cause common side effects such as pain and swelling at the injection site, fever, chills, fatigue, joint pain, nausea, muscle soreness, and headache. In addition, some adverse events observed throughout the clinical trials are unique to specific vaccines, such as neutropenia with the AstraZeneca/Oxford vaccine [29], heart palpitations with Sputnik V, and vomiting with the CanSino vaccine [30]. Nevertheless, the findings from various clinical trials of COVID-19 vaccines concluded that the vaccines were well-tolerated and had a favorable safety profile. That has supported the large-scale evaluation of COVID-19 vaccines in the ongoing phase III trials and emergency use authorization by regulatory bodies in most countries [18, 26]. Table 2 summarizes the common adverse events from approved vaccines reported in clinical trials.

Post-authorization Experience

As at 14 June 2021, the Centers for Disease Control and Prevention (CDC) have recorded more than 3500 reports of side effects from people in the USA who have received COVID-19 vaccines. The CDC data also revealed hospitalizations of those receiving COVID-19 vaccines [44]. Summaries of their symptoms include heart palpitations, severe abdominal pain, seizures, and "almost stroke-like symptoms." Several people have also reported that they could not breathe after receiving the shot [46].

According to the CDC report from 14–23 December 2020, 21 cases of anaphylactic reaction out of 1,893,360 first doses of the Pfizer vaccines were detected in the USA [46]. In addition, from 21 December 2020 to 10 January 2021, ten cases of anaphylactic reaction out of 4,041,396 first doses of Moderna vaccines were detected in the USA [47]. Anaphylactic reactions were treated with epinephrine and recovered fully [46]. Additionally, few people who received the Moderna vaccine were diagnosed with Bell's palsy (facial nerve paralysis) [48]. At the same time, it is important to remember that COVID-19 caused such palsy before vaccinations started [49]. In Estonia, vaccination with Pfizer and Moderna vaccines began around December 2020 [50]. A total of 158 side effects have been reported to the medicines agency, two of which were severe. One person developed a hypersensitivity reaction 10 minutes after receiving the dose. Another vaccinated person developed a visual impairment; speech disorder; malaise; numbness of the nose, nasopharynx, and lips; and limb tenderness 2 days after receiving the second dose. Treatment was required, and the person recovered fully [50]. However, researchers are still figuring out whether these reactions are related to the core ingredients of the vaccine.

Several rare but serious adverse reactions have been reported in the postmarketing surveillance of COVID-19 vaccines. For instance, according to a retrospective descriptive study using spontaneous reports submitted to the EudraVigilance database from 17 February to 12 March 2021, of the 54,571 adverse reactions to the AstraZeneca vaccine, 28 were thrombotic events [51]. In addition, during

Table 1 List of approved COVID-19 vaccines

S.N.	Vaccine Name	Manufacturer	Vaccine Type	Efficacy	No. of Countries Approving the Vaccine	No. of Trials in No. of Countries
1	Ad5-nCoV	CanSino	Nonreplicating viral vector	65.7% [17]	1	Six trials in six countries
2	AZD1222	Oxford/AstraZeneca/ Serum Institute of India	Adenovirus vaccine	70% [18]	11	Sixteen trials in twelve countries
3	BBIBP-CorV	Sinopharm	Inactivated vaccine	86% [19]	8	Six trials in seven countries
4	BNT162b	BioNTech/Pfizer	mRNA-based vaccine	95% [20]	54	Seven trials in eight countries
5	Coronovac	Sinovac	Inactivated vaccine	Varying results in trials; 50% [21]	5	Eleven trials in five countries
6	Covaxin	Bharat Biotech	Inactivated vaccine	78% [22]	1	Five trials in one country
7	Covishield	Serum Institute of India	Adenovirus vaccine	70% [18]	4	Two trials in one country
8	EpiVac Corona	FBRI	Peptide vaccine	Not available	1	Two trials in one country
9	Verocells	Sinopharm	Inactivated vaccine	79% [23]	2	Five trials in four countries
10	mRNA-1273	Moderna, NIAID	mRNA-based vaccine	94.5% [24]	37	Five trials in one country
11	Ad26.COV2.S	Janssen	Recombinant, replication-incompetent human adenovirus type 26 vector	Severe disease: 73.1% Critical disease: 81.7% [25]	53	Eleven trials in seven countries
12	Sputnik V	Gamaleya	Adenovirus viral vector vaccine	91.6% [26]	10	Three trials in one country

mRNA messenger RNA, *NIAID* National Institute of Allergy and Infectious Diseases

postauthorization use of the Janssen COVID-19 vaccine, thrombosis involving large blood vessels, including the cerebral venous sinuses, portal vein, lower extremity veins, and pulmonary artery, combined with thrombocytopenia, have all been reported [52].

According to the CDC, since April 2021, more than 1000 cases of myocarditis and pericarditis have been reported to the Vaccine Adverse Event Reporting System after messenger RNA COVID-19 vaccination (i.e., Pfizer–BioNTech, Moderna) in the USA [53]. Moreover, on 25 June 2021, the FDA revised the patient and provider fact sheets regarding the suggested increased risks of myocarditis and pericarditis following vaccination [54]. However, data on postmarketing surveillance of other COVID vaccines are limited.

Monitoring and Reporting of Adverse Events

Monitoring the safety of vaccines is essential to improve safety profiles and enhance public trust. In Canada, the vaccine-associated adverse events surveillance program is involved in the Division of Immunization's spontaneous voluntary reporting system for adverse reactions to vaccines. Individual case reports and standardized causality assessment by the multidisciplinary expert team are critical [55]. The WHO Programme for International Drug Monitoring provides a safety surveillance manual for COVID-19 vaccines that mandates several requirements for the safety of COVID-19 vaccines to be met [56]. In addition, regional and national pharmacovigilance centers within different countries can manage the pharmacovigilance of COVID-19 vaccines [56]. A study by Soldatos et al. [57] showed that pharmacovigilance played a considerable role in improving vaccine safety [57].

Pharmacovigilance, which relates to the systematic detection, reporting, assessment, understanding, and prevention of adverse reactions [58, 59], is an essential aspect of surveillance to ensure the safety of COVID-19 vaccines. Scientists around the globe are working collaboratively to develop safe and effective vaccines to end the pandemic. However, the rapid development of COVID-19 vaccines has raised concerns about their safety, contributing to vaccine

Table 2 Examples of adverse reactions associated with COVID-19 vaccines in clinical trials

Vaccine	Dosage Regimen	Clinical Trial Phase	Adverse Events Occurrence
BNT162b2 by Pfizer [31]	10, 20, or 30 µg: two doses given 1 month apart	II–III [32]	Common: fever, fatigue, headache, injection site pain Serious: shoulder injury related to vaccine administration, right axillary lymphadenopathy, paroxysmal ventricular arrhythmia, myocarditis and right leg paresthesia, fatigue and headache [33] Rare: not reported
mRNA-1273 By Moderna [34]	25, 50, 200, or 250 µg: two doses given 28 days apart	I	Common: fever, headache, fatigue, myalgia, chills, and injection-site pain Serious: no serious adverse reaction [35] Rare: not reported
AZD1222 by Oxford/ AstraZeneca [36]	Two doses 2 months apart	I and II	Common: headache, nausea, myalgia, arthralgia, injection-site tenderness, injection-site pain, injection-site warmth, injection-site pruritus, fatigue, malaise, feverishness, chills Serious: pyrexia, transverse myelitis, hemolytic anemia [18, 37] Rare: not reported
Sputnik V by Gamaleya [38]	Two-dose regimens	II	Common: injection-site pain, fever, muscle pain, headache, asthenia Serious: no serious adverse reaction [38] Rare: not reported
Ad5-nCoV by CanSino [30]	Two-dose regimens	II	Common: injection-site pain, rash, headache, muscle soreness, and fever Serious: no serious adverse reaction [39] Rare: not reported
Covaxin	3, or 6 µg: two doses, 28 days apart	I	Common: fever, headache, fatigue, nausea, vomiting [39] Serious: not reported Rare: not reported
BBIBP-CorV [40]	4 µg: two doses, 28 days apart	I and II	Common: fever, fatigue, injection-site pain Serious: no serious adverse reaction [40] Rare: not reported
CoronaVac [41]	3 or 6 µg	I	Common: injection-site pain Severe: urticaria [42] Rare: not reported
Covishield [43]	Two doses	III	Common: fever or chills, cough, shortness of breath, fatigue, muscle or body aches, headache, new loss of taste or smell, sore throat, congestion or runny nose, nausea or vomiting, diarrhea Serious: not reported Rare: not reported
Ad26.COV2. S by Janssen [25]	Two doses	I/IIa	Common: injection-site pain, headache, myalgia, fatigue, fever Serious: hypotension, bilateral nephrolithiasis in a patient with a history of kidney stones, legionella pneumonia, worsening of multiple sclerosis, fever leading to hospitalization Rare: not reported

hesitancy [60]. For example, in a scoping review conducted to assess healthcare workers' hesitancy to receive COVID-19 vaccines, concerns about vaccine safety, efficacy, and potential side effects were the main reasons for

COVID-19 vaccination hesitancy [61]. Therefore, it is essential to address such concerns by providing evidence-based information through established public health and regulatory bodies.

Effective communication practices, positive framing of mild side effects, and addressing misinformation related to vaccine adverse effects can reduce concerns over adverse effects of vaccines [62]. Furthermore, healthcare professionals must be at the forefront, listening to the public's concerns regarding vaccination programs and responding accordingly. In addition, monitoring of vaccine safety should occur out of the media spotlight to avoid reporting exaggerated information that can decrease vaccine acceptance [63].

Summary

To date, 12 different vaccines against COVID-19 have been approved for emergency use by many countries. As there is a lack of rigorous data from long-term trials on the safety of COVID-19 vaccines, there is an urgent need to strengthen postmarketing surveillance of adverse event data, particularly in low- and middle-income countries. This will require the continuous monitoring of vaccinated patients for possible adverse reactions to COVID-19 vaccines. Adoption of safety measures, systematic strategies, and timely assessment of any adverse incidents is crucial. Active pharmacovigilance monitoring involving all stakeholders of COVID-19 vaccination is needed to prevent and document possible adverse reactions related to COVID-19 vaccines.

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