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Title Page

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

Sunil Shrestha[1], Januka Khatri[2], Sujyoti Shakya[3,4,] Krisha Danekhu[3], Asmita Priyadarshini Khatiwada[3], Ranjit Sah[5,6], Bhuvan KC[1], Vibhu Paudyal[7], Saval Khanal[8], Alfonso J. Rodriguez-Morales[9,10,11]

[1]School of Pharmacy, Monash University Malaysia, Jalan Lagoon Selatan, 47500 Bandar Sunway, Selangor Malaysia.

[2]Department of Pharmacy, School of Science, Kathmandu University, Dhulikhel, Kavre, Nepal

[3]Department of Pharmaceutical and Health Service Research, Nepal Health Research and Innovation Foundation, Lalitpur, Nepal.

[4]Department of Pharmacy, Nobel College, Sinamangal, Kathmandu, Nepal.

[5]Tribhuvan University Teaching Hospital, Institute of Medicine, Kathmandu, Nepal

[6]National Public Health Laboratory, Kathmandu, Nepal

[7]School of Pharmacy, College of Medical and Dental Sciences, University of Birmingham, Birmingham, United Kingdom

[8]Division of Health Sciences, Warwick Medical School, University of Warwick, Coventry, United Kingdom.

[9]Grupo de Investigación Biomedicina, Faculty of Medicine, Fundacion Universitaria Autonoma de Las Americas, Pereira, Risaralda, Colombia.

[10]School of Medicine, Universidad Privada Franz Tamayo (UNIFRANZ), Cochabamba, Bolivia.

[11]Universidad Cientifica del Sur, Lima, Peru.

Corresponding authors:

Sunilcresta@gmail.com; Bhuvan.KC@monash.edu

ORCID ID: Sunil Shrestha, https://orcid.org/0000-0002-9174-7120

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Conflict of interest

The authors declare that they have no conflicts of interest.

Authors Contribution

SS(a) and JK conceptualised the idea of this manuscript, did a literature review and wrote the initial draft of the manuscript. SS(b), KD and APK made substantial changes in the conception, did a literature review, contributed to the critical review of the manuscript. BKC, VP, RS, AJRM and SK provided intellectual feedback to the concept of the study, did a literature review, contributed to the critical review of the manuscript.

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Abstract

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by a new species of beta coronavirus genus, named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The COVID-19 pandemic, which started in late 2019 and continuing in mid-2021, have caused enormous damage to health and lives globally. The urgent public health need has led to developing a vaccine against COVID-19 in record-breaking time. The COVID-19 vaccines have been widely rolled out for 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, particularly in regard to adverse events `still persist. In this commentary, we aim to describe adverse events associated with COVID-19 vaccines and discuss why it is essential to have a functional adverse event monitoring system in this context.

Keywords: adverse events, COVID-19, pharmacovigilance, vaccine surveillance, vaccine.

Key Messages

- A small number of vaccines against COVID-19 have been authorised 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 beta coronavirus named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1, 2]. It is a single-stranded RNA beta-coronavirus whose genome encodes are structural proteins, non-structural proteins, and accessory proteins [3, 4]. Since its outbreak in late 2019, the virus has spread globally, setting global health, socioeconomic, and humanitarian crises [5-7]. Globally, as of June 19, 2021, more than 183 million confirmed cases of COVID-19 and almost four million deaths have been recorded [8, 9]. Due to the high transmission rate of the virus, the numbers of confirmed cases are increasing exponentially, also contributed by new mutational variants. In addition, the mortality rate is higher in elderly patients and those with pre-existing 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 suppress the virus and way out of 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 the specific treatment and vaccines for COVID-19 [13-15]. However, fears, rumours, and misconceptions, particularly regarding COVID-19 vaccines still persist. This article aims to inform about the currently approved vaccines, adverse events reported thus far, and discuss why it is vital to have an excellent adverse event monitoring system.

Approved vaccines and ongoing trials

As of June 19, 2021, there are 78 vaccine candidates in development in 201 different ongoing trials. Among them, 13 vaccines were approved by the United States Food and Drug

Administration (USFDA), World Health Organization (WHO) and European Medicines Agency (EMA) (Table 1) [16].

Table 1. List of approved COVID-19 vaccines

SN	Name of Vaccines	Manufacturer	Type of vaccine	Efficacy	No. of countries approving the vaccine	No of trials in no. of countries
1	Ad5-nCoV	CanSino	Non-Replicating Viral Vector	65.7% [17]	1	6 trials in 6 countries
2	AZD1222	Oxford/ AstraZeneca/ Serum Institute of India	Adenovirus Vaccine	70% [18]	11	16 trials in 12 countries
3	BBIBP-CorV	Sinopharm	Inactivated Vaccine	86% [19]	8	6 trials in 7 countries
4	BNT162b	BioNTech/ Pfizer	m-RNA based Vaccine	95% [20]]	54	7 trials in 8 countries
5	Coronovac	Sinovac	Inactivated Vaccine	Varying results in trials 50% [21]	5	11 trials in 5 countries
6	Covaxin	Bharat Biotech	Inactivated Vaccine	78% [22]	1	5 trials in 1 country
8	Covishield	Serum Institute of India	Adenovirus Vaccine	70% [18]	4	2 trials in 1 country
9	EpiVac Corona	FBRI	Peptide Vaccine	Not Available	1	2 trials in 1 country
10	Inactivated	Sinopharm	Inactivated Vaccine	79% [23]	2	5 trials in 4 countries

11	mRNA-1273	Moderna, NIAID	m-RNA based Vaccine	94.5% [24]	37	5 trials in 1 country
12	Ad26.COV2.S	Janssen	recombinant, replication-incompetent human adenovirus type 26 vector	Severe COVID-19: 73.1% Critical Covid-19: 81.7% [25]	53	11 trials in 7 countries
13	Sputnik V	Gamaleya	adenovirus viral vector vaccine	91.6% [26]	10	3 trials in 1 country

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 research or 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 analyse the effectiveness of COVID-19 vaccines on new variants [27]. For example, in Qatar, to assess the effectiveness of the Pfizer-Biotech Covid-19 vaccine against the variants of concern (VOC), such as B.1.1.7 (α variant, WHO classification) and the B.1.351 (β variant, WHO classification), 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 to COVID vaccines

Almost all vaccines for COVID-19 cause common side effects like pain and swelling at the injection site, fever, chills, fatigue, joint pain, nausea, muscle soreness, and headache. In addition, some adverse events are unique to individual vaccines that have been observed throughout the clinical trials, like neutropenia by AstraZeneca/Oxford vaccine [29], heart palpitations by Sputnik

V and vomiting CanSino vaccine [30]. Nevertheless, the findings from various clinical trials of COVID-19 vaccines concluded that the vaccines are well tolerated and have a favourable safety profile. That has supported the large-scale evaluation of COVID-19 vaccines in the ongoing phase 3 trials and emergency use authorisation by most countries' regulatory bodies [18, 31]. Table 2 summarises the common adverse events of approved vaccines reported in clinical trials.

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

Vaccine	**Dosage regimen**	**Clinical trial phase**	**Adverse reaction (AR) occurrence**
BNT162b2 by Pfizer [32]	(10, 20 , 30) µg two doses given one month apart	Phase 2-3 trials[33]	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 [34].Rare: Not reported
mRNA-1273 By Moderna [35]	(25, 50, 200 or 250) µg two doses given 28 days apart	Phase 1	Common: fever, headache, fatigue, myalgia, chills, and injection-site pain. Serious: No serious AR [36] Rare: Not reported
AZD1222 by Oxford/ Astrazeneca [37]	Two doses are given two months apart	Phase 1 and 2	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, Haemolyticanaemia [18, 38]. Rare: Not reported
Sputnik V by Gamaleya [39]	Two dose regimens	Phase 2	Common: injection site pain, fever, muscle pain, headache, asthenia Serious: No serious AR [39] Rare: Not reported
Ad5-nCoV by CanSino [40]	Two dose regimens	Phase 2	Common: Injection site pain, rash, headache, muscle soreness, and fever Serious: No serious AR [41]. Rare: Not reported

Covaxin	(3,6) µg two doses at 28 days apart	Phase 1	Common: Fever, headache, fatigue, nausea, vomiting [41]. Serious: Not reported Rare: Not reported
BBIBP-CorV [42]	4 µg two doses at 28 days apart	Phase 1 and 2	Common: Fever, fatigue, injection site pain Serious: No serious AR [42] Rare: Not reported
CoronaVac [43]	(3,6) µg	Phase 1	Common: Injection site pain Severe: Urticaria [44] Rare: Not reported
Covishield [45]	Two doses	Phase 3	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	Phase 1/2a	Common: Injection site pain, headache, myalgia, and fatigue, fever Serious: hypotension, bilateral nephrolithiasis in a patient with a history of kidney stones, legionella pneumonia, worsening of multiple sclerosis, and fever leading to hospitalisation. Rare: Not reported

Post authorisation experience

The Centers for Disease Control and Prevention (CDC) have recorded more than 3500 reports in the USA till June 14, 2021, of side effects from people who have received COVID-19 vaccines. The CDC data also revealed hospitalisations of those receiving COVID-19 vaccines [46]. Summaries of their symptoms include heart palpitations, severe abdominal pain, seizures, and "*almost stroke-like symptoms*." Several people also complained that they could not breathe after receiving the shot [47].

According to the CDC report on December 14–23, 2020, 21 cases of anaphylactic reaction out of 1,893,360 first doses of the Pfizer vaccines were detected in the US [48]. In addition, during December 21, 2020, to January 10, 2021, 10 cases of anaphylactic reaction out of 4,041,396 first doses of Moderna vaccines were detected in the US [49]. Anaphylactic reaction were treated with epinephrine and recovered fully [48]. Additionally, few people who received the Moderna vaccine were diagnosed with Bell's palsy condition (facial nerve paralysis) [50]. At the same time is important to remember that COVID-19 caused such palsy before vaccinations started [51]. Outside the US, in Estonia, vaccination with Pfizer and Moderna vaccines began towards December 2020 [52]. A total of 158 side effects have been reported to the Medicines Agency, two of them being severe. One person developed a hypersensitivity reaction 10 min after the dose was given. Another vaccinated person developed a visual impairment, speech disorder, malaise, numbness of the nose, nasopharynx, lips, and limb tenderness two days after receiving the second dose. Treatment was required, but the person recovered fully [53]. However, researchers are still figuring out whether these reactions are related to the core ingredients of the vaccine or not.

Several rare but serious adverse reactions have been reported in the post-marketing surveillance of COVID-19 vaccines. For instance, as according to a retrospective, descriptive study using spontaneous reports submitted to the Eudravigilance database from February 17 to March 12, 2021, 28 thrombotic events were linked to the AstraZeneca vaccine of 54,571 adverse reactions [54]. In addition, during post-authorisation 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 has been reported [55].

According to CDC, there have been more than a thousand reports to the Vaccine Adverse Event Reporting System (VAERS) of cases of myocarditis and pericarditis after mRNA COVID-19

vaccination (i.e., Pfizer-BioNTech, Moderna) in the United States since April 2021 [56]. Moreover, on June 25, 2021, the FDA revised the patient and provider fact sheets regarding the suggested increased risks of myocarditis and p following vaccination [57]. However, there is limited data on post-marketing surveillance of other COVID vaccines.

Monitoring and reporting of adverse events

Monitoring the safety of vaccines is essential to improving safety profiles and enhancing public trust. In Canada, the vaccine-associated adverse events surveillance program is involved in a spontaneous voluntary reporting system of adverse reactions of vaccines by the Division of Immunization. Individual case reports, standardised causality assessment by the multidisciplinary expert team are critical [58]. WHO Programme for International Drug Monitoring Center provides a safety surveillance manual for COVID-19 vaccines that mandates several requirements for the safety of COVID-19 vaccines to be met [59]. In addition, regional and National pharmacovigilance centres within different countries can manage the pharmacovigilance of COVID-19 vaccines [59]. A study by Soldatos, Taglang and Jackson has shown a considerable role of pharmacovigilance in improving vaccine safety [60].

Pharmacovigilance, which relates to systematic detection, reporting, assessment, understanding and prevention of adverse reactions [61, 62], is an essential aspect for 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 vaccines' safety, contributing to vaccine hesitancy [63]. For example, in a scoping review conducted to assess healthcare workers' hesitancy to COVID-19 vaccines, concerns about vaccine safety, efficacy, and potential side effects were the main reasons

for COVID-19 vaccination hesitancy [64]. 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 vaccine [65]. Furthermore, healthcare professionals must be at the forefront to listen to the public's concerns regarding vaccination programs and respond accordingly. In addition to this, monitoring vaccines safety should occur out of the media spotlight to avoid reporting exaggerated information that can decrease vaccine acceptance [66].

Summary

As of now, 13 different vaccines against COVID-19 have been approved for emergency use by many countries. As there is a lack of rigorous data on the safety of COVID-19 vaccines based on long term trials, there is an urgent need to strengthen post-marketing surveillance of adverse event data, particularly in low and middle-income countries. That necessitates the continuous monitoring of vaccinated patients for the possible adverse reactions of COVID-19 vaccines. Adoption of safety measures, systematic strategies, and timely assessment of any adverse incidence 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.

Declarations

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