Review Article

Adverse Events Following Vaccination with COVID-19 Vaccines: A Narrative Review

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ABSTRACT

Introduction: *The Covid-19 pandemic has had a devastating effect globally. The rapid development of vaccines certainly helped in mitigating the damage by controlling the transmission of infection as well as by decreasing the incidence of severe disease. The rapid development process raised concerns over vaccines' safety particularly its long-term safety. Study of AEFI of these vaccines is essential to guide choices for specific groups of population as well as to address concerns with regards to vaccine hesitancy.*

Methods: *Pubmed and Cochrane review database were used to access the literature. Data from pertinent official sources such as WHO, govt. of India and others were also used. All the relevant articles were organised using Zotero reference manager.*

Results: *The adverse reactions to various Covid 19 vaccines is mild to moderate in severity with no significant interference in daily activities of the recipient. Minor effects are similar in pregnant and non-pregnant population although some studies reported higher frequency of nausea and vomiting with Pfizer-BioNTech and Moderna vaccines. There is no unique pattern in cause of deaths among few vaccine related deaths that have been reported.*

Conclusion: *Vaccine has been the cornerstone in controlling Covid-19 pandemic and remains the key for preventing any future outbreaks. The vaccines are safe to administer and induces protection. It is vital to be aware of and keep monitoring the adverse events which shall help in better selection of vaccines for groups and subgroups of populations as well as to address the problem of vaccine hesitancy.*

Keywords: *Covid-19 vaccine, AEFI, Vaccine Hesitancy, Adverse effects*

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INTRODUCTION

COVID-19, which has been declared a global pandemic by WHO on March 11, 2020, has 774,291,287 reported cases according to WHO as on Jan 14, 2024 with maximum cases reported in USA followed by China and India. India has reported 45,021,758 confirmed cases since the virus first emerged in late 2019 from Wuhan, China. Cumulative global deaths according to the WHO data stands at 7,019,704 as of Jan 14, 2024 while the death burden in India stands at 533,414.[1]

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the causative agent of COVID-19, belonging to the Coronaviridae family in the Nidovirales order. Corona represents crown-like spikes on the outer surface of the virus; thus, it was named coronavirus. Coronaviruses are minute in size (65–125 nm in diameter) and contain a single-stranded RNA as a nucleic material.[2] The S (spike), E (envelope), M (membrane), and N (nucleocapsid) proteins are the four structural proteins of SARS-CoV-2. Type I membrane proteins and glycoproteins make up coronavirus S proteins. S1 and S2, two functional sections, comprise them. The attachment of the virion to the host cell membrane is catalyzed by the S1 subunit, whereas the S2 subunit facilitates fusion. According to studies, SARS CoV 2 is an obligatory receptor for human angiotensin-converting enzyme 2 (ACE2), for which it has a greater affinity than the original SARS virus. Basigin may also help SARS-CoV-2 enter cells. For SARS-CoV-2 to enter, transmembrane protease, serine 2 (TMPRSS2) must prime the initial spike protein. Using ACE2, the host protein neuropilin 1 (NRP1) may help the virus enter the host cell. Following the attachment of a SARS CoV 2 virion to a target cell, the host receptor ACE2 and a fusion peptide in the S2 subunit are revealed by the cell's TMPRSS2 cutting open the virus' spike protein. The virion is

isolated from the remainder of the host cell by an endosome that surrounds it upon fusion. When the endosome's pH falls or when the host cysteine protease cathepsin cleaves the virion, it escapes. Subsequently, the virion releases RNA into the cell, compelling it to replicate and spread the virus, infecting further cells.[3]

A virus mutates through the replication process, the resulting mutated version of the virus is called a variant. There are thousands of variants of SARS-CoV-2. The WHO has currently declared five variants of concern, which are Alpha, Beta, Gamma, Delta (emerged in India) and Omicron. The latest dominating variant is JN.1 which does not have sufficient studies to demonstrate its severity.[4] The SARS-CoV-2 causes acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) which leads to pulmonary failure and result in fatality. These viruses were thought to infect only animals until the world witnessed a severe acute respiratory syndrome (SARS) outbreak caused by SARS-CoV, 2002 in Guangdong, China.[5]

A variety of campaigns and actions has been undertaken to combat this pandemic, beginning with the establishment of local lockdowns and mass testing.[5,6] To restore normalcy and enable economic growth, vaccines were the best option. The first COVID-19 vaccine introduced in December 2020 has become a milestone in the fight against this pandemic. On December 2, 2020, using an Emergency Use Authorization (EUA), the UK became the first country to approve Pfizer-BioNTech's COVID-19 vaccine, BNT162. It is a lipid nanoparticle-derived, nucleoside-modified mRNA vaccine that encodes the SARS-CoV-2 glycoprotein spike.[8]

mRNA-1273 from Moderna was the second COVID-19 vaccine in the US to be authorized under EUA. mRNA-1273 is a lipid-encapsulated mRNA vaccine that encodes the SARS-CoV-2 prefusion-stabilized spike protein.[8]

Another type of vaccine was developed by Oxford/AstraZeneca, the SARS-CoV-2 structural surface spike protein gene was integrated into the ChAdOx1 nCoV-19 vaccine (AZD1222; trade name Vaxzevria), which is made from replication-deficient chimpanzee adenovirus ChAdOx1.[8]

At the beginning of New Year, 2021 India's drug regulatory agency, Central Drugs Standard Control Organisation (CDSCO) decided to approve the newly developed COVID-19 vaccines, which were undergoing clinical trials. The regulatory agency issued a restricted emergency approval for COVAXIN, besides COVISHIELD.[9] COVAXIN is developed by Hyderabad-based Company Bharat Biotech International Ltd. in collaboration with the Indian Council of Medical Research (ICMR) and the National Institute of Virology (NIV), whereas COVISHIELD is the vaccine candidate from Pune-based Serum Institute of India. COVAXIN is developed using "Whole-Virion Inactivated Vero Cell-derived platform technology" which means it contains the dead virus and they are incapable of infecting people but still able to instruct the immune system to mount a defensive reaction against an infection. COVISHIELD is developed by "Viral Vector Platform Technology". It is a recombinant, replication-deficient chimpanzee adenovirus vector encoding the SARS-CoV-2 Spike (S) glycoprotein. It was produced in genetically modified human embryonic kidney (HEK) 293 cells. This genetically modified virus is not capable of infecting the beneficiary but can very well instruct the immune system to prepare a mechanism against such viruses. The dosing interval for COVAXIN is 4-6 weeks while it is 12-16 weeks for COVISHIELD for better efficacy. Clinical efficacy for COVAXIN and COVISHIELD is 81% and 82.4% respectively.[10]

During the pandemic, vaccines against COVID-19 were developed at an unprecedented speed. These vaccines were approved for emergency use. In India, five vaccines have been approved by the Drugs Controller General of India to date. Vaccines approved in India are Covishield (ChAdOx1), COVID-19 vaccine (Covaxin) (BBV152), SputnikV, Johnson & Johnson, and Zycov-D. [11,12,13]

As of 19 June 2023, a total of1346 crores of vaccine doses has been administered worldwide[1] and according to Ministry of Health and Family welfare, total vaccine doses given in India stands at 220,67,85,749.[13] To monitor the adverse events following immunisation in India, we have Adverse Events Following Immunisation (AEFI) Program. The Immunization Division of MoHFW (Ministry of Health & Family Welfare) has taken few steps to strengthen the national AEFI surveillance system for COVID-19 vaccinations. Adverse Event is defined as an event in which medical care resulted in an undesirable clinical outcome, not caused by underlying disease-that prolonged the patient stay, caused permanent patient harm, required life-saving intervention, or contributed to death.[14]

METHODOLOGY :

The concept of interest was the challenges to discover the adverse reactions of the COVID-19 vaccines especially that using the observational studies. We included only an observational quantitative study designs as most of the review were on clinical trials and pre and post-intervention.[15,16] Observational studies has benefit for document the effects of naturally exposed outcomes, which in this case are any outcomes produced by an intervention or treatment that were not originally intended by the person who prescribed the intervention.[17]

SEARCH STRATEGY

On November 2023, we conducted initial research using all identifier keywords and relevant terms in the electronic databases PubMed, Science Direct, and Cochrane review database. In the search, keywords with Boolean operators ("OR" and "AND") related to process development and trigger tool validation were used (Table 1). Data from pertinent official sources such as WHO, Govt. of India and others were also used. We did not search the grey literature because we are only interested in studies published in peer-reviewed journals that are based on scientific methods that use evidence to develop conclusions. All the relevant articles were organised using Zotero reference manager.

TABLE 1 Search Terms

Population	Interest	Outcomes
COVID-19	Vaccine	Adverse effect
COVID-19	Vaccination	Adverse event
COVID		Adverse Reaction

RESULTS

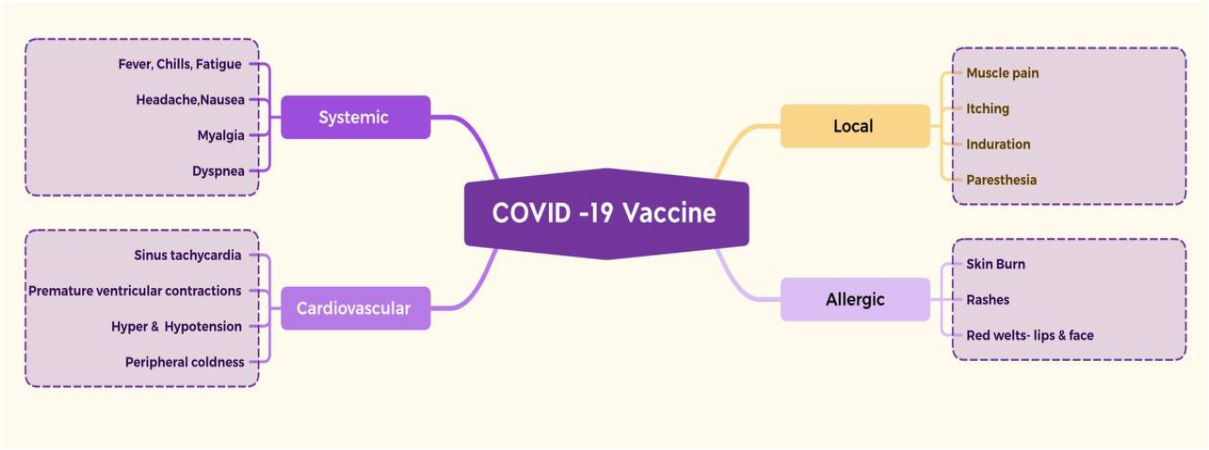

Figure 1: COVID - 19 vaccine ADRs

Adverse reactions are classified into two types: vaccine-related events and allergic reactions. The majority of research has been on negative vaccination reactions, and also no allergic reactions. The most commonly reported COVID-19 vaccine-related adverse reactions include local injection and systemic side effects. Joint or muscle pain, tenderness, itching, and paresthesia in the injection site comprised the local side effects.[18-22,25,28] Fever, chills, fatigue, headache, nausea, myalgia, pyrexia, and dyspnea are among the systemic side effects.[24–29,31–34] Some cardiovascular side effects like sinus tachycardia, premature ventricular contractions, and right bundle branch block may occur.[27] Allergic reactions included skin burn, rashes and red welts on the lips and face.

COVISHIELD

The majority of adverse events reported after the ChAdOx1 nCoV -19 vaccine (Covishield) were non-serious. Deep kamal et.al. 2021 reported 57% recipients developed non-serious AEFI rate after the first dose of vaccination; the overall rate of serious adverse events reported was approximately 0.2%. The overall rate of non- serious adverse events was approximately 14.1% after the second dose of vaccination. No serious adverse events were reported after the second dose of vaccination.[29] This supports the findings of phase 1 and phase 2/3 trial of ChAdOx1 nCoV-19 vaccines wherein the majority of recipients reported with non-serious AEFI.[30]

The majority of adverse events were noted within the first 48 h of vaccination after first and second doses. The rate of adverse events showed a declining trend after 48 h of vaccination.[29] Similarly, declining trend was observed in one study where researchers found that 89% of recipients who have logged at least one systemic adverse event after vaccination did not report any systemic adverse event after 3 days and 98.3% did not report any after one week.[18] The adverse events were reported at much lower frequencies in comparison to the Phase 2/3 trial of the ChAdOx1 nCoV19 vaccine wherein 88% of participants (18e55 years) reported adverse events.[18] However in another study 33.7% of recipients reported adverse events after the first dose of vaccine. Variation in the rate might be because some studies included active surveillance by enquiring repeatedly for AEFI whereas some studies opted for passive surveillance through the app for one week only.(Deep kamal et.al. 2021) reported that overall common adverse events included feeling unwell (20.6%), headache (18.4%), fever (13.04%), and fatigue (14.27%) after the first dose.[29] Ramaswamy MN et al. 2021 reported < 30% of users complained of injection site pain and < 25% of fatigue and headache after the first dose(30). As per the recent report submitted by The National AEFI Committee to the Union Health Ministry about the Bleeding and clotting events following COVID vaccination in India, reported more than 2300 cases through the COWIN Platform and only 700 Adverse events were reported to be severe (MoHFW, 2021). The AEFI Committee has done a deep review of all these reports, of which only 26 cases were reported to be potential thromboembolic events following the administration of the Covishield vaccine. Hence, the data shows a very minuscule but definitive risk of thromboembolic events.[27]

COVAXIN

(Swayam Pragyan Parida et al. 2022) reported AEFI among 29.8% of the Covaxin beneficiaries. Higher AEFI was reported among the beneficiaries who took the first dose (38.1%) when compared to the second dose (26.4%).[31] This finding was similar to a study conducted by (Kaur et al.) in North India; they have reported 40% and 16.6% of the AEFI among first and second-dose beneficiaries, respectively. (35). The majority of the AEFI was mild in nature. Pain at the injection site was the most common AEFI, followed by fever and myalgia. Young adults reported AEFIs more frequently than the elderlies. Females reported higher AEFI than males in (Swayam Pragyan

Parida et al. 2022)[31].This finding was similar to a study done by (Menni et al. 2021) in the United Kingdom(18). The reported AEFI in (Swayam Pragyan Parida et al. 2022) was higher than that of the Phase 2 trial of Covaxin. Ella et al.[32] However, the results of (Swayam Pragyan Parida et al. 2022) were in accordance with other published trials of viral vector vaccines[33,34]

Most of the studies reported few to none serious adverse events. The severe AEFI rate reported by Kaur et al[35] among the first dose and second dose beneficiaries was 0.3% and 0.1%, respectively. Overall, few serious adverse events were reported in the studies from ChAdOx1 in India, Korea, and Nepal(35). In most of the studies majority of the AEFI are mild-moderate in nature. These results depict the higher safety profile of the COVID-19 vaccines. Females reported higher AEFI than the male participants. A similar result was reported in studies by Kamal et al[29] and Kaur et al.[35]. The common adverse events reported in studies were injection site pain, tenderness, fever, headache, fatigue, and myalgia. These are also the common adverse events reported in the Phase 2 trial of the BBV152 vaccine.[32] Other than gender, other significant predictors for AEFI were comorbidities, history of steroid intake, history of allergy, history of medication in last 6 months, and history of acute infection in the last 3 months.[31]

SPECIFIC ADVERSE EVENTS

Thrombocytopenia with thrombosis, most notably cerebral venous sinus thrombosis or cerebral venous thrombosis (CVT) within 28 days of vaccination, have been associated with Ad26.COV2.S (Janssen) and AZD1222 (AstraZeneca), both of which use the adenovirus-vector platform. As a result of 6 reports of CVT, the FDA and CDC recommended a pause in the administration of Ad26.COV2.S vaccine in the US on April 13, 2021.[8] A CVT event occurs when the smaller draining cortical veins or the cerebral venous sinus system are completely or partially occluded. It is more likely to occur in young adults and is 3 times as common among women than men.[8] According to the CDC, more than 10,000 reports of myocarditis were reported to the VAERS after COVID-19 vaccination (Pfizer-BioNTech and Moderna) in the US. These reports, however, are infrequent compared with the hundreds of millions of vaccine doses that were administered without adverse effects.[8]

CONCLUSION

To end the pandemic crisis, the development of affordable, effective, safe, and transportable vaccines has become necessary. Some risks are associated with COVID-19 vaccinations, but no vaccination is entirely safe. The majority of the reactions were mild to moderate in nature and did not affecting daily tasks, appearing within 1–2 days following vaccination and dissipating within a few days. The most common symptoms are localized pain and swelling at the injection site, fever, headache, myalgia, and chills. Cases of thrombosis, notably CVT, are mostly seen with the adenoviral vector vaccines. Myocarditis is seen with the mRNA vaccines. Vaccine has been the cornerstone in controlling Covid-19 pandemic and remains the key for preventing any future outbreaks. The vaccines are safe to administer and induces protection. It is vital to be aware of and keep monitoring the adverse events which shall help in better selection of vaccines for groups and subgroups of populations as well as to address the problem of vaccine hesitancy. In most of the studies majority of the AEFI are mild-moderate in nature. These results depict the higher safety profile of the COVID-19 vaccines.

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