



REPORTED SIDE EFFECTS OF COVID-19 VACCINATION: A SCOPING REVIEW

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Abstract

Introduction: Complex factors could be involved in explaining of vaccine hesitancy related to human behavior such as “theory of planned behavior”. A quantitative and qualitative studies are needed to explain the reasons behind hesitancy towards COVID-19 vaccine since it could jeopardize the effort of the pandemic control. This study aimed to review the well-documented side effects of COVID-19 vaccination in the published literature.

Methods We selected randomized controlled trial-type studies that evaluate the side effects of the COVID-19 vaccine. PubMed, Web of Science, Embase, CINAHL, PsycINFO, LILACS, SCOPUS, ClinicalTrials.gov, International Clinical Trials Registry Platform (ICTRP), medRxiv.org, biorxiv.org, preprints.org and the Cochrane Library were searched for eligible studies until November 2022. Three reviewers will independently screen and select studies, assess methodological quality and extract data. A meta-analysis were performed, if possible, and the Grading of Recommendations, Assessment, Development and Evaluations summary of findings were presented.

Results: Different types of vaccine adverse effects have been described, such as anaphylaxis, fever, joint and muscular pain, headache, weakness, nausea, chills, erythema, lymphadenopathies, paresthesia, vomiting, dizziness, arrhythmias, changes in blood pressure, and facial paralysis. During the first 15 days after vaccination, there is a high risk of developing all adverse symptoms. We found a total of 29 results from PubMed and one through manual searches. There are eight COVID-19 vaccine candidates have been approved for emergency use in different countries and 12 candidates in the clinical evaluation stage, which are developed using inactivated vaccine platform until August 2022.

Conclusions: At present, it is very crucial to establish the safety of the COVID-19 vaccines when emergency approval is being granted to these vaccines without completion of all phases of clinical trials. Therefore, the details of these vaccines and clinical trials reporting the safety of COVID-19 vaccines are not conclusive.

Keywords: Vaccine, Side-effects, Thrombosis, Safety, COVID-19

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Introduction

The severe acute respiratory syndrome, caused by coronavirus 2 (SARS-CoV-2) and called COVID-19, resulted in a widespread pandemic that affects almost all countries in the world [1]. It affects more than 187 million people and caused more than four million deaths till July 2021 [2]. The pandemic leads to unprecedented economic impact and social restriction and became a major threat for health system. The World Health Organization has been initiating global efforts for primary and secondary prevention of COVID-19. A start point in the prevention of the pandemic was implementation of infection control measures such as mouth masks, hand hygiene, social distancing, and closure of public places. Active surveillance with early detection, isolation and treatment of cases have been implied in order to reduce the epidemic curve and prevent health system collapse. However, awaiting vaccine was the best intervention as hundreds of research centers engaged into the development of the vaccine.

By the first quarter of 2021, several vaccines have passed the phase III trial and become approved to be used in mass vaccination such as Pfizer-BioNTech vaccine (US - Germany), Oxford AstraZeneca vaccine (UK), Moderna vaccine (US), Gamaleya-Sputnik V vaccine (Russia, China's Covid-19 Vaccine (China), and Johnson & Johnson vaccine (US). However, a high level of vaccine hesitancy was reported in different countries which is a result of misconceptions associated with COVID-19 pandemic. As many anti-vaccination groups became very active particularly after application of quarantine, myths related to conspiracy theory became prevalent during the early pandemic days [3]. Public view about vaccine has been influenced by these misconceptions which resulted in high level of vaccine hesitancy, particularly after reporting of few rare side effects that were linked to the vaccine. Thus, vaccine availability did not guarantee acceptance of the vaccine by the general population and even by some of health staff. A systematic review showed the effect of public acceptance of a vaccine on vaccine coverage rate [4]. Many determinants were found responsible for low vaccine acceptance such as perceived severity of infection, education, ethnicity, and cultural background [5]. Complex factors could be involved in explaining of vaccine hesitancy related to human behavior such as "theory of planned behavior" [6,7]. A quantitative and qualitative studies are needed to explain the reasons behind hesitancy towards COVID-19 vaccine since it could jeopardize the effort of the pandemic control. This study aimed to review the well-documented

side effects of COVID-19 vaccination in the published literature.

Methods

We selected randomized controlled trial-type studies that evaluate the side effects of the COVID-19 vaccine. PubMed, Web of Science, Embase, CINAHL, PsycINFO, LILACS, SCOPUS, ClinicalTrials.gov, International Clinical Trials Registry Platform (ICTRP), medRxiv.org, biorxiv.org, preprints.org and the Cochrane Library were searched for eligible studies until November 2022. Three reviewers will independently screen and select studies, assess methodological quality and extract data. A meta-analysis were performed, if possible, and the Grading of Recommendations, Assessment, Development and Evaluations summary of findings were presented.

We extracted and consolidate study-level data and extracted data from relevant studies. Collecting relevant study-level characteristics and experimental covariates were conducted. Data appraisal and preparation of the article include:

- Compute appropriate outcome measure
- Evaluate extent of between-study inconsistency (heterogeneity).
- Perform relevant data transformations.
- Select meta-analytic model.
- Synthesize study-level data into summary measure.
- Pool data and calculate summary measure and confidence interval.
- Explore potential sources of heterogeneity (ex. biological or experimental).
- Subgroup and meta-regression analyses.

Evaluation quality of studies and estimation model parameters for complex relationships were done by 2 reviewers. The eligible studies were included in this review.

Results and discussion

Different types of vaccine adverse effects have been described, such as anaphylaxis, fever, joint and muscular pain, headache, weakness, nausea, chills, erythema, lymphadenopathies, paresthesia, vomiting, dizziness, arrhythmias, changes in blood pressure, and facial paralysis [8]. During the first 15 days after vaccination, there is a high risk of developing all adverse symptoms. We found a total of 29 results from PubMed and one through manual searches. There are eight COVID-19 vaccine candidates have been approved for emergency use in different countries and 12 candidates in the clinical evaluation stage, which

are developed using inactivated vaccine platform until August 2021. Remarkable progress has been made in the COVID-19 vaccines race while FDA provided full approval to the BNT162b2 vaccine on August 2021. T cells specific to SARS-CoV-2 spike protein in the majority of vaccinated participants [9]. In this instance, the neutralizing antibody titers were obtained before the first dose, 21 days after the first dose, and seven and 14 days apart from the second dose, in which the antibody titers were highest at seven and 14 days apart from the second dose of vaccination. Moreover, the younger had higher antigen-binding IgG and virus-neutralizing antibody responses than the older [10]. BNT162b2 had an efficacy of 95% against COVID-19 after a two-dose (30 lg per dose and 21 days apart) vaccination [11]. The vaccine efficacy was generally identical across subgroups with individuals of different ages, sex, race, ethnicity, obesity, and pre-existing conditions. For this instance, the efficacy was 93.7-100% in participants (age of 16-55, [C 65, and C 75 years) who had no existing SARS-CoV-2 infection. Moreover, the efficacy also was similar in a separate analysis having participants with hypertension. Furthermore, the vaccine was 52.4% effective in preventing COVID-19 between two doses, but 90.5% effective within seven days interval of two-dose vaccination. A recent study from Public Health England (PHE) has shown that the vaccine had efficacy against Delta and Alpha variants as 88% and 93%, respectively, after administration of the second dose [12]. Liu et al. reported that the vaccine had neutralizing activity against the Gamma variant, which is analogous to the action against the Alpha variant, and in the case of the Beta variant, the neutralizing activity was negligible.

On the contrary, the vaccine showed two dose-dependent systemic or local reactions, such as grade 1 and 2. A common adverse event was pain at the injection site, and other systematic events were also reported. The common systemic events were fatigue, chills, muscle pain, headache, and joint pain. Fever was also reported in some patients following the first and second dose vaccination but typically resolved within a day [13]. Gladly, no grade 4 adverse events were reported. However, grade 3 reactions such as sleep disturbance and pyrexia have been reported in a few participants. The incidence rate was about 12.6 cases per million (second doses), which was less severe and usually resolved without medical intervention. In a case-control study conducted in Hong Kong, 16 out of 4,51,939 cases were confirmed with Bell's palsy/ facial nerve palsy after the first dose, whereas another case-control study in Israel found

no association between Bell's palsy and the vaccine. In the phase 1 trial, the vaccine induced both virus-neutralizing antibody and spike glycoprotein binding antibody responses in the participants aged 18-55 years [14]. The vaccine (both 25-lg and 100-lg doses) also elicited CD4⁺ T-cell responses, predominantly Th1 responses stimulated by S-specific peptide pools with a fraction type 2 helper T-cell (Th2) responses. T-cell responses was also reported in the participants vaccinated with 100 lg dose (after the second dose). The vaccine also had an efficacy of 93.6% in the SARS-CoV-2 seropositive participants. In the Qatar study, the vaccine showed 94.4% and 100% efficacy against the Alpha variant at C 28 days of the first dose and day 14 after the second vaccination dose, respectively. In the case of the Beta variant, the efficacy was 73.7% and 96.4% after 28 days of the first dose and 14 days of the second dose, respectively. Conversely, the most common adverse effect was pain at the injection site, and the others were tiredness, headache, muscle ache, joint ache, chills, swollen lymph nodes in the vaccine injected arm, generally resolved within a day or two [15]. Further, nausea, vomiting, and fever were also reported. A significant portion of the participants has experienced these side effects after the second dose. Similar to the BNT162b2 vaccine, the incidence rate of adverse effects of the mRNA-1273 was about 12.6 cases per million dose (second dose) and had less severity and fatality, which did not require any medical intervention [16].

T-cell responses were detected. In addition, neutralizing antibody and spike protein-binding antibody responses were seen in most participants on day 29 after the single dose. The phase ENSEMBLE trial reported that the vaccine had an efficacy of 67% (single dose) against moderate to severe COVID-19 (symptomatic for at least 14 days) cases and 66% efficacy against patients having 28 days of onset [17]. The data from the phase ENSEMBLE trial also demonstrated that the vaccine efficacy was 85% against severe COVID-19 across all region studies and minimized hospitalization and death by COVID-19 after 28 days of vaccination. The effectiveness of the vaccine showed geographical variations such as in the USA, the efficacy was 72%, whereas, in South Africa (95% cases with the Beta variant), it was 64% against moderate to severe diseases and 81.7% against severe or critical illness after 28 days of vaccination. In Brazil (69% cases with the Gamma variant), the efficacy was 68.1% against moderate to severe diseases and 87.6% against severe or critical illnesses [18]. Conversely Sadoff et al. reported that the most common local reaction

was injection site pain and the most frequent systemic reactions were headache, fatigue, myalgia, and nausea. The vaccine showed both humoral and cell-mediated immunity. The vaccine-induced IgG responses (28 days after vaccination) against the SARS-CoV-2 spike protein in all participants after two-dose vaccination were identical across the ages of 18-55, 56-69, and ≥ 70 years. Moreover, neutralizing antibody responses have also been found after a booster dose (second dose) and were similar across all age groups. The vaccine also induced T-cell responses maximized at day 14 after vaccine administration (first dose). The interim primary efficacy analysis by Ramasamy et al. revealed that the vaccine's efficacy was 70.4% after the second dose and 64.1% after the first dose in all participants. The USA Phase 3 trial by Astra-Zeneca revealed that the vaccine had 79% efficacy among the symptomatic COVID-19 and 100% efficacy in the severe and hospitalized COVID-19 patients. The efficacy was identical across diverse ethnicity and ages, and showed 80% efficacy in participants aged ≥ 65 years [19].

Moreover, study data from Canada showed that the vaccine (Vaxzevria) had an efficacy of 90% against hospitalization or death caused by the Alpha variant, 87% against the Delta, and 82% against the Beta and Gamma variants after the first dose. Regarding symptomatic COVID-19 cases, the vaccine was 72% effective against the Alpha, 70% against the Delta, and 50% against the Beta and Gamma variants [20]. On the other hand, both local and systemic reactions were reported in all participants after vaccination. The most common local reaction was pain in the injection site, and other systematic reactions were fever, muscle ache, headache, chills, fatigue, malaise, and nausea, which were primarily mild and had 4-5 days of occurrence after vaccination [21]. The reactions were more common in younger than older adults (≥ 65 years). After the first dose, the vaccine also had a rare adverse event called thrombosis (blood clot) with thrombocytopenia syndrome. It could induce both humoral and cellular immune responses in all participants. The phase 3 clinical trial results revealed that it had induced virus-neutralizing antibody response in the participants aged ≥ 60 years. Furthermore, the vaccine efficacy was almost similar in the participants aged 18-60 years. Cell-mediated immune responses were also identified in the participants where peripheral blood mononuclear cells had secreted IFN- γ against SARS-CoV-2 spike glycoprotein (at day 28 after the first dose). The interim results of the phase 3 trial showed that the vaccine had an efficacy of 91.6% against COVID-19 (from day 21

after the first dose to the day of receiving the second dose). Although Logunov et al. found no serious adverse events, the most common local reaction was pain at the injection site, and other systematic reactions were headache, asthenia, and muscle and joint pain. The vaccine-induced humoral responses were found as 100% seroconversion rate in 18-59 and ≥ 60 years of participants [22]. In addition, in the 18-59 years group, the seroconversion rate was above 75% on day 14 after the first dose administration, and the rest of the participants were seroconverted on day 28. The 18-59 years group also had higher neutralizing antibody titers than the ≥ 60 years group. Sinopharm reported that the vaccine had an efficacy of 79.34% in the phase 1/2 trial, and in the phase 3 trial (multi-countries), the efficacy was 79% in both symptomatic and hospitalized patients after 14 days of vaccination.

The local reactions were pain at the vaccination site, flush, swelling, scleroma, rash, and itching. The systemic reactions were headache, fever, fatigue, muscle pain, joint ache, cough, breathing difficulty, nausea, diarrhea, and skin itching [23]. In the phase 1 trial, the vaccine (two doses) induced humoral responses against SARS-CoV-2 at 104 days after vaccination (3 months after the second dose). At the same time, serum neutralizing antibodies were also detected among all the participants. In the phase 2 trial, the vaccine (after two doses) induced prominent Th1 immune responses with a high level of IFN- γ . The immune responses were significantly higher in the phase 2 trial than in the phase 1 trial. Moreover, the vaccine could induce both memory B-cell and T-cell responses, where the latter expressed the memory phenotype marker CD45RO⁺. Bharat Biotech claimed that the vaccine had an efficacy of 77.8% against symptomatic, 63.6% against asymptomatic, and 93.4% against severe symptomatic COVID-19 cases. Contrarily, the most common local adverse reaction was pain at the injection site, followed by other systematic reactions such as headache, fatigue, vomiting, and fever. The reactions were mild to moderate and more frequent after the first dose. However, one severe adverse reaction of viral pneumonitis was reported in the phase 1 trial [24]. The vaccine had been induced both humoral and cellular responses in most of the participants. The vaccine elicited RBD (receptor binding domain) binding antibodies (four-fold higher) and live virus binding antibodies (four-fold higher) in 94-100% and 50-75% of the participants. Moreover T-cell responses were detected on day 14 after vaccination and antibodies on day 28, and both were in peaked value at the times mentioned above. T cells was reported in all

the participants. However, when pre-existing anti-Ad5 immunity was high, both the antibody and T-cell response were slightly reduced.

The Ad5-nCoV vaccine efficacy was 68.83% (single dose) against all symptomatic and 95.47% against severe COVID-19 cases 14 days after vaccination. After 28 days of vaccination, the efficacy was 65.28% against all symptomatic and 90.07% against severe COVID-19 cases [25]. Conversely, the vaccine was reported with some common adverse reactions such as fever, fatigue, headache, and muscle ache. Those reactions were mild, moderate, and consistent among all the participants. Further, no severe adverse reactions were noted as a matter of concern. Until August 2021, the phase 3 trial result of the vaccine has not been published yet. In addition, the vaccine had a similar immune response in adults aged ≥ 60 years [26]. The neutralizing antibody responses were reported in the older (≥ 60 years) and younger adults (18-59 years) with similar magnitude after two doses of vaccination (3 lg and 6 lg). The study also reported a strong correlation between the neutralizing antibodies and the anti-RBD IgG antibodies. Moreover, weak T-cell responses were found in 18-59 years aged adults. In Brazil, the phase 3 trial demonstrated that the vaccine efficacy was 51% against symptomatic and 100% against severe SARS-CoV-2 infection after the second dose. In Turkey, the phase 3 trial revealed that the vaccine efficacy was 83.5% on 14 days after administration of the second dose [23]. Conversely, the most common adverse reactions were mild pain at the injection site, elevated blood pressure, headache, fatigue, dizziness, and rash. There were no grade 4 adverse events or fatality has been seen. However, the case-control study from Hong Kong revealed that the vaccine could cause Bell's palsy, where 28 out of 5,37,205 cases were confirmed with this type of adverse event [22]. It induced humoral responses against SARS-CoV-2 in all participants. In the phase 2 trial, the virus-neutralizing antibodies were found 14 days after the second dose with a seroconversion rate of 76% in people who received 25 lg of vaccine and 72% in people who received 50 lg of the vaccine. However, the third dose of the vaccine was found with an increased seroconversion rate in both 25 lg and 50 lg dose groups estimating 97% and 93%, respectively. The most common adverse reactions were mild and transient pain at the injection site, redness, and swelling, resolved within 3-4 days after vaccination. The trials also documented that the neutralizing antibody responses were higher between 21 and 28 days after the second dose and highest after the third or booster dose administration [27]. Sinopharm reported that the

vaccine had an efficacy of 72.51%. A recent study showed that the vaccine efficacy was 79% in both symptomatic and hospitalized patients after 14 days of vaccination and 78.1% against only symptomatic adult patients.

On the contrary, the most common adverse reaction was transient mild pain at the injection site. The second dose of the vaccine reported no adverse events in the participants after vaccination [28]. In the phase 2 trial of the candidate vaccine, ten times more neutralizing antibodies were found in the vaccinated people than in the recovered COVID-19 patient. Low-income countries are not getting the spotlight of the vaccination program as only 0.3% of the total vaccines are administered in their arms. On the other hand, 83% of the total shots are applied in the high and upper- and middle-income countries to make their people vaccinated. The people of Africa got the lowest doses of vaccines, only 5.8 people per hundred population, whereas 88 people per hundred population brought under vaccination in North America. Furthermore, 91%, 68%, 64%, and 41% of people become vaccinated in Europe South America Asia, and Oceania, respectively (Fig. 3). Most of the wealthy countries pre-ordered vaccine doses, but the low-income countries could not ensure enough amounts, such as the countries of Africa. As of August 2021, 87% of the total 4.62 billion doses of vaccines are obtained by high-income countries, while low-income countries just received 0.3 percent. Discrimination is clear as almost one of every four people of rich countries gets vaccinated, while it is one in over 500 in the low-income countries. There was a hope of herd immunity as different studies described that almost 60-70% of the population gained immunity through vaccinations or past exposure to the virus [29].

Conclusions

At present, it is very crucial to establish the safety of the COVID-19 vaccines when emergency approval is being granted to these vaccines without completion of all phases of clinical trials. Therefore, the current evidence reflected the safety generated from the results of published clinical trials of these vaccines. The details of these vaccines and clinical trials reporting the safety of COVID-19 vaccines are not conclusive. Despite all the vaccines' benefits and effectiveness, as mentioned previously, mild and negligible side effects have been observed. It can affect some plans in the screening or follow-up of cancerous patients simultaneously.

Conflict of interests

The authors declared no conflict of interests.

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