Review Article

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TANAFFOS

Safety and Adverse Effects Related to COVID-19 Viral Vector Vaccines: A Systematic Review

SeyedAhmad SeyedAlinaghi [1], Ava Pashaei[2], Marcarious M. Tantuoyir [3,4], Amirali Karimi [3], Hengameh Mojdeganlou [5], Newsha Nazarian [6], Farzin Vahedi [3], Arian Afzalian [3], Parnian Shobeiri [3], Mohsen Dashti [7], Afsaneh Ghasemzadeh [7], Pegah Mirzapour [1], Sahar Nooralioghli Parikhani [3], Esmaeil Mehraeen [8]

[1] Iranian Research Center for HIV/AIDS, Iranian Institute for Reduction of High Risk Behaviors, Tehran University of Medical Sciences, Tehran, Iran, [2] School of Nursing, The British Columbia University, Vancouver, British Columbia, Canada, [3] School of Medicine, Tehran University of Medical Sciences, Tehran, Iran,[4] Biomedical Engineering Unit, University of Ghana Medical Center (UGMC), Accra, Ghana, [5] Department of Pathology, The Johns Hopkins University, School of Medicine, Baltimore, MD, USA, [6] School of Medicine, Islamic Azad University, Tehran, Iran, [7] Department of Radiology, Tabriz University of Medical Sciences, Tabriz, Iran,[8] Department of Health Information Technology, Khalkhal University of Medical Sciences, Khalkhal, Iran.

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Correspondence to: Mehraeen E
Address: Department of Health Information Technology, Khalkhal University of Medical Sciences, Khalkhal, Iran
Email address: es.mehraeen@gmail.com

Background: There have been safety concerns regarding the COVID-19 vaccines because of their unprecedented speed of development. Therefore, systematic reviews are necessary to address these concerns and reduce public hesitancy regarding COVID-19 vaccines. This study aims to systematically review the reported adverse events related to viral vector COVID-19 vaccines.

Materials and Methods: We performed a systematic search in the databases of PubMed, Scopus, Web of Science, and Cochrane on September 15th, 2021. This study adheres to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist. The records underwent two-step title/abstract and full-text screenings, and the eligible records were included in the data extraction process. We used the Newcastle-Ottawa Scale (NOS) for the Bias Assessment of included articles.

Results: The adenovirus vector-based COVID-19 vaccines, including the Janssen COVID-19 vaccine, the AstraZeneca COVID-19 vaccine, and the Sputnik V vaccine were included in this review. Among these vaccines, the AstraZeneca has presented enormous side effects with most being systemic and a few sporadic cases of life-threatening events such as thrombosis and capillary leak syndrome and even death in a few cases. Prominent systemic side effects of the adenovirus vaccines include fever, fatigue, malaise, arthralgia, myalgia, sweating, and dizziness. Erythema, swelling, tenderness, itching, and numbness at the injection site are the most common local reactions.

Conclusion: It appeared that the frequency of serious adverse events is negligible, and vaccination to prevent severe COVID-19 and mortality has greater benefits than adverse events in the general population.

Keywords: Adenovirus vector; Adverse effects; Adverse events; COVID-19; COVID-19 Vaccines; SARS-CoV-2

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a novel positive-sense and single-stranded RNA virus, first broke out in December 2019 in Wuhan, China. Since then, the Coronavirus disease 2019 (COVID-19) rapidly spread and resulted in the ongoing pandemic which was first declared by the World Health Organization (WHO) on March 11th, 2020. As of January 17th, 2022, COVID-19 has claimed the lives of more than 5.5 million people and over 326 million cases have been confirmed by WHO globally (1,2). The COVID-19 pandemic substantially burdened healthcare practitioners, hospitals, researchers,

the global economy, and social life and forced governments to develop prevention and treatment modalities to control the devastating situation. From the beginning, the most effective tool for halting extremely rapid COVID-19 transmission was the development of vaccines since there is no specific therapy for the disease. As a result, various health sectors came together to quickly develop effective vaccines to curb the number of new cases and mortality rates (3, 4).

Therefore, after the publication of the first SARS-CoV-2 genomic sequence (5), various vaccines were developed and granted emergency approval by the US Food and Drug Administration (FDA) and WHO within less than a year after the official declaration of the pandemic (6-8). Currently, WHO has granted safety approval to 10 vaccines including; two mRNA vaccines (Pfizer-BioNTech and Moderna), three adenoviral-vector vaccines (Oxford/AstraZeneca, Johnson & Johnson, and Covishield), three inactivated vaccines (Bharat Biotech, Sinopharm Beijing, and Sinovac), and two Protein Subunit vaccines (Novavax and COVOVAX). Moreover, according to the latest WHO reports on 18 January 2022, 194 vaccines were included in pre-clinical trials and there were 140 vaccines in clinical development (9, 10).

COVID-19 vaccines effectively prevent SARS-CoV-2 transmission, severe illness, hospitalization, and associated complications (11, 12). From December 2020 to January 2022, 60.3% of the global population have been vaccinated with at least one dose of COVID-19 vaccines, and approximately 9.82 billion doses have been administrated worldwide (13). However, from the beginning, there have been safety concerns regarding the COVID-19 vaccines because of their unprecedented speed of development, and currently, many clinical trials are investigating the safety of these vaccines. The most common adverse effects following vaccination comprise local reactions including pain, swelling, and redness at the injection site, and systemic reactions including fever, chills, headache, fatigue, and myalgia that mostly occur within days after vaccination and resolve shortly after (14).

Among the aforementioned vaccines, rare cases of thrombotic events in uncommon sites like cerebral venous sinus have occurred mainly among recipients of Adenovirus vector vaccines such as AstraZeneca (ChAdOx1 nCoV-19), and Johnson & Johnson (Ad26COVS1) with an incidence rate of one in 100,000 to one in 1,000,000 (15). Therefore, to reduce public hesitancy regarding COVID-19 vaccines, and provide better information about possible rare adverse events of COVID-19 adenovirus vector vaccines, we conducted a systematic review to determine the adverse events following vaccinations with Adenovirus vector vaccines from published literature.

MATERIALS AND METHODS

This study is a systematic review of scientific literature conducted on September 15th, 2021. The authors studied the safety and adverse effects related to COVID-19 viral vector vaccines. Our study adheres to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist to ensure the reliability and validity of this study and its results.

Data sources

Through the application of a systematic search and using the keywords in the online databases of PubMed, Scopus, Web of Science, and Cochrane on September 15th, 2021. We downloaded and imported all the search results into EndNote 9 application. We also looked for other sources such as other online databases and references of retrieved studies to find all the relevant studies that concern the aims of the present review. The keywords were adapted from the medical subject headings (MeSH) websites and the previous studies. Supplementary material 1 contains search terms for all the databases. The PubMed search term is mentioned below:

((((((COVID-19[Title]) OR (SARS-CoV-2[Title])) OR (SARS-CoV2[Title])) OR (2019-nCoV[Title])) OR (Novel Coronavirus[Title])) AND ((((Vaccine*[Title]) OR (Vaccination[Title])) OR (Vaccinated[Title])) OR (Immunization[Title]))) AND (((((Safety[Title]) OR (Side

effect*[Title])) OR (Adverse event*[Title])) OR (Adverse effect*[Title])) OR (Adverse reaction*[Title]))

Study selection

Three independent investigators retrieved the most relevant studies by titles and abstract screening. Subsequently, the full texts of the retrieved papers were reviewed and the most relevant papers were selected according to the eligibility criteria. Then, we extracted the appropriate data and organized them into a table. Additionally, original papers that were peer-reviewed and published in English, and fulfilled the eligibility criteria were included in the final report.

The exclusion criteria were as follows: (1) Conference abstracts or papers in which their full texts were not available; (2) non-original studies: reviews, systematic reviews, meta-analyses, and opinions; (3) non-human studies; (4) Case reports; and (5) studies on other types of vaccines.

Data extraction

After summarizing, we transferred the name of the first author, year of publication, country/ethnic group, type of study (e.g., clinical trial), manufacturer, phase, sample population, age, gender, serious adverse event (name and frequency), time from injection to the appearance of adverse events, and side effects (local and systemic) to a data extraction sheet. Four independent investigators gathered this information and subsequently organized them into the table. Finally, to ensure no duplications or overlaps exist in the content, all the selected articles were cross-checked by other authors.

Quality and Bias Risk Assessment

The PRISMA checklist was used to ensure the quality and reliability of selected articles. Two independent researchers evaluated the consistency and quality of the articles and the bias risk. In either case of discrepancy in viewpoints, a third independent researcher resolved the issue. The full texts of selected articles were fully read, and the key findings were extracted for this qualitative synthesis. Furthermore, we used the Newcastle Ottawa Scale (NOS) to evaluate the studies. This scale consists of three items: selection, comparability, and exposure/ outcome. These items have a maximum score of 4, 2, and 3 respectively. By adding these values, a top score of 9 is assigned for individual studies (Table 1).

Table 1. Newcastle-Ottawa Scale (NOS) bias risk assessment of the studies

Reference	Selection (out of 4)	Comparability (out of 2)	Exposure/ Outcome (out of 3)	Total (out of 9)
(18)	***	**	***	8
(20)	****	**	**	8
(19)	***	*	**	6
(21)	****	**	***	9
(22)	****	**	*	7
(24)	****	**	*	7
(25)	****	**	***	9
(32)	****	*	***	8
(26)	**	**	**	6
(38)	***	*	**	6
(16)	****	**	***	9
(34)	**	*	***	6
(23)	****	**	**	8
(27)	****	*	**	7
(39)	***	*	**	6
(28)	****	**	***	9
(29)	***	**	**	7
(33)	***	**	**	7
(35)	****	*	*	6
(30)	***	**	***	8
(17)	***	**	***	8
(36)	***	*	***	7
(37)	****	**	***	9
(31)	***	*	**	6

RESULTS

A total of 1064 records were retrieved from the initial search in online databases and manual searching of other sources. In the initial screening, 547 duplicates were removed. From the remaining 515 records, 171 were removed in the title and abstract screening phase and a total of 346 studies entered the full-text screening (344 from database searching and two from other sources). In full-text screening, 322 articles were excluded as they did not meet the eligibility criteria. A total of 24 studies met the inclusion criteria and were eventually used in the qualitative analyses. The PRISMA flow diagram in Figure 1 provides an extensive illustration of this process.

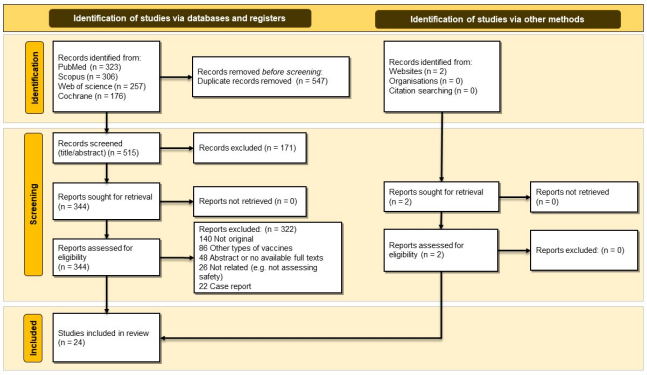

Figure 1. PRISMA 2020 flow diagram of the selection process for this systematic review.

The study design aimed to systematically review the various reports concerning the safety and adverse events specifically related to the adenovirus COVID-19 vaccines approved by the WHO. Phases 1, 2, and 3 RCTs, cohort, and cross-sectional studies that reported the adverse events of the adenovirus COVID-19 vaccines (mainly AstraZeneca, Janssen COVID vaccine, Sputnik V) were used in this synthesis. Studies with scores from 7 to 9 had high quality, 4 to 6 had high risk, and 0 to 3 had a very high risk of bias. Consequently, 17 (70 %) of the studies included had high quality and 7 (30 %) had a high risk of bias. However, there were no studies with a very high risk of bias involved in this qualitative synthesis as seen in Table 1.

Significant Adverse Effects

Janssen COVID-19 vaccine

The Janssen COVID-19 vaccine is one of the adenovirus-vector-based vaccines that has been described in this study. Few studies (16, 17) exist related to the side effects of this vaccine. Notable significant adverse events (Figure 2) include neuromuscular & skeletal: Myalgia (10% to 39%) (16), systemic: Fever (0% to 13%), local: Erythema at the injection site (0% to 9%), swelling at the injection site (0% to 7%), pain at the injection site (21% to 60%)(16, 17), gastrointestinal: Nausea (2% to 16%), and the nervous system: Fatigue (30% to 52%), headache (27% to 44%) (17). Gillian-Barre syndrome and hypersensitivity reactions such as anaphylaxis, angioedema, and urticaria were also reported in some studies (Table 2). The onset of these reactions is often within 3 weeks after injection. Local reactions that were associated with this vaccine include pain, swelling, and erythema at the injection site (17). Patients reporting local side effects are mostly between 18 to 59 years (17). The onset of these prominent local side reactions has been reported to be a few hours to about 7 days after injection. Additionally, they may persist for up to 2 days after onset (17). The Janssen COVID-19 vaccine could also be associated with some systemic reactions such as headache, myalgia, nausea, fatigue, fever, and asthenia. The onset of these reactions is a few hours to approximately 7 days after injection. Similar to the local side effects, the systemic reactions usually persist for 2 days after taking the vaccine. Sporadic adverse reactions include thrombocytopenia syndrome (TTS) (17) which could present after 2 weeks of injection.

AstraZeneca COVID-19 vaccine

The Vaxzevria (AstraZeneca) vaccine side effects have been extensively reviewed and reported in the previous literature (Figure 3). The significant adverse reactions from this vaccine could be systemic such as fever (≤12%; feverishness: 4% to 39%), sweating, nasal discharge, cough, asthenia(18-23); or local such as pain at injection site (10% to 60%), tenderness at injection site (32% to 79%), warm sensation at injection site (4% to 17%), erythema at injection site (≤3%), induration at injection site (≤3%), injection site pruritus (2% to 7%), swelling at injection site (≤3%) (16, 18-31); gastrointestinal including nausea (6% to 24%), vomiting (≤2%), diarrhea, decreased appetite (18, 19, 21, 32, 33);nervous system including chills (2% to 37%), fatigue (27% to 65%), headache (20% to 61%), malaise (10% to 48%), shortness of breath, syncope, anxiety, dizziness, and drowsiness (16, 18-26, 34-37); neuromuscular & skeletal including arthralgia (7% to 28%), bone pain, myalgia (14% to 52%); dermatologic including diaphoresis, pruritus, and skin rash (16, 19, 20, 22-31, 33). Notably, life-threatening events that occurred with this vaccine include pulmonary embolism, thrombocytopenia syndrome (TTS), high fever of 40.5°C, severe angina, anaphylaxis, acute transverse myelitis, thrombosis and capillary leak syndrome with death in few cases (18, 21, 23, 29, 32, 34-37). The presentation of these adverse effects is almost rapid, thus, a few hours to about one-week post-injection. Additionally, most of the studies indicated that people between 18 to 64 years had a higher frequency of systemic and local AEs. Further details are presented in Table 2.

Table 2. Severe adverse events, local and systemic side effects of adenovirus COVID-19 vaccines

First Author	Publication	Country/ethnic group	Type of Study	Manufacturer	Phase	Sample population	Age	Gender	Serious adverse event	Time to adverse event	Side effects	
											Local	Systemic
Abu-Hammad (18)	2021	Jordanian Healthcare Workers	cross-sectional	AstraZeneca Pfizer BioNTech Sinopharm	N/A	409(for all vaccines)	34.99 ± 12.07	M 29.3% F 70.7%	Chest pain (0.6% After AstraZeneca injection)	N/A	Numbness, pain,	Fever, fatigue, myalgia Joint pain Diarrhea Shortness of breath Bone pain Adverse events are significantly associated with AstraZeneca (97.8%first dose 98.3% second dose)
Al Khames Aga (20)	2021	Iraq and Jordan	Cross-sectional	AstraZeneca Pfizer BioNTech Sinopharm	2	696 received AstraZeneca 340 received Sinopharm	Median: 49 years	M 51.61% (of the total population) F 48.3	Severe chest pain: 1 case (with AstraZeneca) Signs and symptoms after the first AstraZeneca dose injection were more prevalent	7 days after the first dose	Pain Redness Urticarial swelling	Nasal discharge, sweating, dry cough, , dizziness Anxiety, Dry cough Abdominal pain, Arthralgia, Tachycardia, Dyspnea was mostly associated with AstraZeneca
Al Bahrani(19)	2021	Saudi Arabia	Cross-sectional study	AstraZeneca	3	1592	37.4	M 81% F 19%	N/A	7 and 21 days after the first vaccine dose.	pain	GI (abdominal pain, diarrhea, vomiting) Cardiac disorder (palpitation, chest pain) Fever Musculoskeletal (joint pain, myalgia) Respiratory (shortness of breath) Skin rash
Falsey (21)	2021	United States, Chile, and Peru	double-blind, randomized, placebo-controlled	AstraZeneca	3	21,635	50	M 55% F 44.4%	119 serious adverse events in 101 cases (0.5%) -Neurologic -Vascular -Hematologic -Pulmonary embolism -Thrombocytopenia	During 28 days after vaccination	N/A	N/A
Folegatti (22)	2020	UK	a single-blind, randomized controlled trial	AstraZeneca	1/2	543	35	M 50.2% F 49.8 %	N/A	7 days	Pain, redness	Muscle ache, malaise, chill, fever
Frater (24)	2021	UK	single-arm open-label vaccination sub-study	AstraZeneca	2/3	54	42.5	N/A	In this study of people with HIV, ChAdOx1 nCoV-19 was safe and immunogenic, supporting vaccination for those well-controlled on ART.	during the first 7 days after prime vaccination	pain	Fatigue, headache, malaise, chill, muscle ache, joint pain, nausea,

First Author	Publication	Country/ethnic group	Type of Study	Manufacturer	Phase	Sample population	Age	Gender	Serious adverse event	Time to adverse event	Side effects	
											Local	Systemic
Hatmal (25)	2021	Jordan	Cross-sectional	Sinopharm, (38.2%) AstraZeneca, (31%) Sputnik (2.98%) Johnson & Johnson (0.09%) Pfizer-BioNTech	3	2213 Participants Sinopharm:845 Astrazeneca:686 Sputnik:65 Johnson & Johnson; 2	N/A	M 39.2 % F 60.8 %	Severe side effects: AstraZeneca: 23.2% Sinopharm:2.5%	10 days	Mild to moderate side effects: AstraZeneca: 65.7% Sinopharm: 51.8% Pain, swelling,	Fatigue, chills, dizziness, fever, headache, joint pain, myalgia, tiredness,
Kim (32)	2021	South Korea/Asian	Prospective Cohort	-AstraZeneca -Pfizer	N/A	1403: AstraZeneca	Mean: As: 36 Pf:36	AstraZeneca: M 27.1 % F 72.9 %	Vomiting	1 day after the first dose	Injection site pain (Ast:78%,)	Myalgia (Ast:61%, Fatigue (Ast:51%, Headache (Ast:47%, Fever (Ast:36%,)
Kim (26)	2021	South Korea/Asian	-	-AstraZeneca -Pfizer	1	1679(AstraZeneca)	20-29: 34% 30-39: 28% >40: 38%	AstraZeneca: M 23.8% F 76.2 %	N/A	1 day after the first dose and second dose	-Local Tenderness -Local erythema/heating -Local edema	-Myalgia -Chills -Fatigue Headache -Arthralgia -Dizziness -Nausea -Vomit -Pruritus -Dyspnea -Rash
Logunov (38)	2021	Russia/White	Cohort	Sputnik	3	14,964	Mean: 45.3	M 61.1% F 38.9%	0	The first day after the second dose	-Injection site reaction	-Flu-like illness -Headache -Asthenia
Lotan (16)	2021	USA/White	Prospective Cohort	-AstraZeneca -Moderna -Pfizer -Johnson & Johnson	N/A	438	median: 51 (18-82)	M 16.4% F 83.6%	0	Neurologic: (Median:3.5 days) other SE: 1 day after injection	-Pain at the injection site -Redness at the injection site -Swelling at the injection site	-Headache -Muscle pain -Fatigue -Fever -Chills Dizziness Neurological Symptoms
Wi (31)	2021	Korea	Cohort	AstraZeneca	N/A	1440 vaccinated individuals (one dose)	35.84±11.13 Mean ±SD	M 27.1% F 38.8%	All the adverse reactions are mild to moderate	Within Seven days after vaccination	1301 adverse events: most common: pain at the injection site (77.8%) Swelling of injection site:24.9%	Fever Chills Fatigue Nausea Vomiting Headache Myalgia Arthralgia urticaria

First Author	Publication	Country/ethnic group	Type of Study	Manufacturer	Phase	Sample population	Age	Gender	Serious adverse event	Time to adverse event	Side effects	
											Local	Systemic
MacIntyre (34)	2021	Australia/White-Mixed	-	AstraZeneca	N/A	11,525,207	18-59	N/A	Thrombosis with Thrombocytopenia Syndrome (TTS incidence) (347/11525207)	4-42 days after injection		
Madhi (23)	2021	South Africa/African	Double-blind, placebo-controlled, phase 1B/2A trial	AstraZeneca	1B/2A Trial	81	Median: 36 Range: 23-45	M 39% F 61%	40.5-degree fever (1/81)	<2 days	tenderness, hardness, bruising, and itching at the injection site	Headache, joint and muscle pain, and weakness
Massoud (27)	2021	Kuwait/Arab	Cross-sectional study	-AstraZeneca -Pfizer	N/A	82	73< 55 years 9>55 years	M 41.4% F 58,6%	0	1 day after the first dose and second dose	-Pain -redness -swelling at the injection site	-Headache -Fatigue -Myalgia -Fever -Chills -Arthralgia -Nausea -Diarrhea -Sore throat -Lymphadenopathy
Mehraeen (39)	2021	Iran/ Caucasians	Observational study	Sputnik	3	30 health care workers (18 individuals with children 1-6 y)	25-45 y	M 16.6% F 83.3%	0.3% severe adverse events (Syncope 2 individuals after vaccine injection)	Within 5 days after vaccination	N/A	Fever Chills Headache Myalgia Cough (83% of children had fever 5 days after parents)
Menni (28)	2021	UK/White	prospective observational study	-AstraZeneca -Pfizer	3	345,280 (Received AstraZeneca)	Mean:50.6 years	AstraZeneca: M: 42.5% F: 57.7%	0	<8days	58.7% local reaction after AstraZeneca -Pain -Swelling -Tenderness -Itch -Swelling armpit glands -Redness -Warmth -Bruising	0.4% Allergic reaction after AstraZeneca injection -Headache -Fatigue -Chills and shivers -Diarrhea -Fever -Arthralgia -Myalgia -Nausea Rash -Skin burning -Red welts on face and lips

First Author	Publication	Country/ethnic group	Type of Study	Manufacturer	Phase	Sample population	Age	Gender	Serious adverse event	Time to adverse event	Side effects	
											Local	Systemic
Oh (29)	2021	South Korea/Asian	Cross-sectional study	-AstraZeneca -Pfizer	N/A	1,808,107 AstraZeneca doses injected	18-49 years: 24.5% 50-74 years: 26.2% >75 years: 49.3%	M 36.5% (totally for AstraZeneca and Pfizer)	383 serious adverse events after AstraZeneca (Death, anaphylaxis, others): 0.2 per 1000 doses	1 day after the first dose and second dose	Adverse events after AstraZeneca: 7.7 per 1000doses -Injection site reaction	-Myalgia -Fever -Headache Are 3 most common -Arthritis -Vomiting -Allergic reaction -Dizziness -Nausea -Chills -Diarrhea
Park (33)	2021	South Korea/Asian	Cross-sectional survey	-AstraZeneca -Pfizer	N/A	299 cases (AstraZeneca first dose) 304 cases the second dose	20-29 YEARS: 31% 30-39 Years: 20% 40-49 Years: 19% 50-59 Years: 26% >60 Years: 4%	M 25.5% F 74.4%	0	1 day after the first dose and second dose	-Local pain The incidence of adverse events was much lower after the second dose of AstraZeneca compared to the first dose)	-Fever -Chills -Myalgia -Headache -Nausea -Vomiting -Urticaria -Dyspnea -Chest pain
Roman (35)	2021	1 case report from Panama 43 ATM cases from 21 countries	Cross-sectional study	-AstraZeneca	N/A	86,000,000	Mean: 49(ATM)	M 53.4% F 46,5%	Acute Transverse Myelitis (43/86,000,000)	10 days to 6 weeks	N/A	N/A
Rotondo (30)	2021	Italy	Prospective Cohort	-AstraZeneca -Pfizer	N/A	185	Mean: 60	M 24.3% F 75.6%	N/A	<2 days	-Site injection pain	-Headache -Fever -Myalgia -Fatigue -Fever
Sadoff (17)	2021	United States/ Peru /Argentina /Chile/ South Africa /Colombia/ Brazil and Mexico	RCT	Janssen COVID vaccine (Ad26COV2.S)	3	19,630 COVID negative (vaccine) 19,691 individuals (placebo)	Median: 52 (18-100)	M 55.1 % F 44.9%	7 serious adverse events were considered to be related to vaccination	N/A	Injection site pain in the vaccine group:48.6%	Headache:38.9% Fatigue:38.2% Myalgia: 33.2% Nausea: 14.2%
Tobaiqy (36)	2021	Review the Reports submitted to the Eudra Vigilance database (17Feb-12Mar2021)	Retrospective Descriptive study	Oxford-AstraZeneca	N/A	54,571 adverse event reports	>85y: 57.1% 65-85y: 32.1% 18-64y: 10.7%	M 32.1% F 67.9%	-28 thrombotic adverse events -3 deaths (Pulmonary embolism) (females) -1 death(male): thrombosis (	N/A	N/A	N/A
Voysey (37)	2020	Brazil, South Africa, UK	RCT	AstraZeneca	1. UK: Phase:1/2 2. UK: Phase:2/3 3. Brazil: Phase:3 4. South Africa: Phase:1/2	23,848 participants	≥18 y	F 60.5%	84 serious adverse events in (79 individuals in the AstraZeneca group) 3 cases of Transverse myelitis	1 case of Transverse myelitis:14 days after the second dose 2cases of transverse myelitis 10 days after the first dose (maybe unrelated to vaccination because they have previous unrecognized multiple sclerosis,) 1 case with high fever(>400C) after 2 days	N/A	N/A

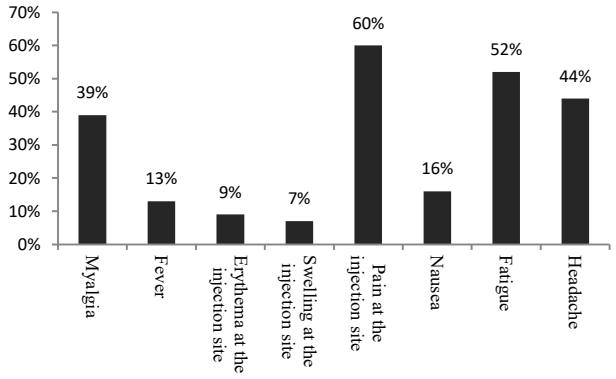

Figure 2. A bar graph illustrates common adverse effects of the Janssen COVID-19 vaccine

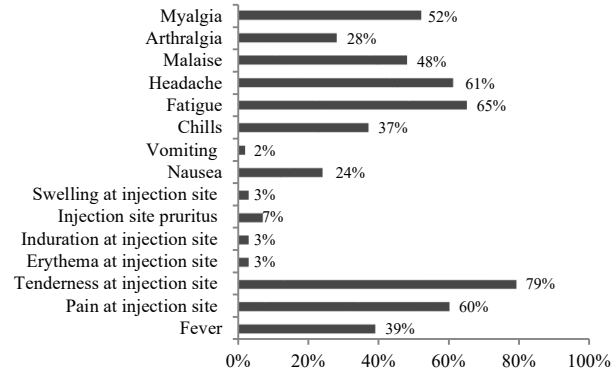

Figure 3. A graphical illustration of the common adverse effects of the AstraZeneca COVID-19 vaccine

Sputnik V COVID-19 vaccine

This type of vaccine was described by two studies included in our analysis (38, 39). The side effects associated with this vaccine are mostly mild to moderate (Figure 4). Sputnik V vaccine elicits systemic reactions such as headache, asthenia, fever, chills, myalgia, cough, and flu-like illness (38, 39). The onset of these systemic reactions is mostly seen in less than 8 days post-vaccination. Pain and erythema are the local side effects associated with this vaccine (38). Few cases (<1%) are considered severe, prominently syncope (39) is linked with the vaccine. The AEs usually resolve within 2-5 days after onset. Additionally, these side effects are frequently observed in people between 24 to 45 years (38, 39). Table 2 summarizes the AEs related to the Sputnik V, AstraZeneca, and Janssen COVID-19 vaccines.

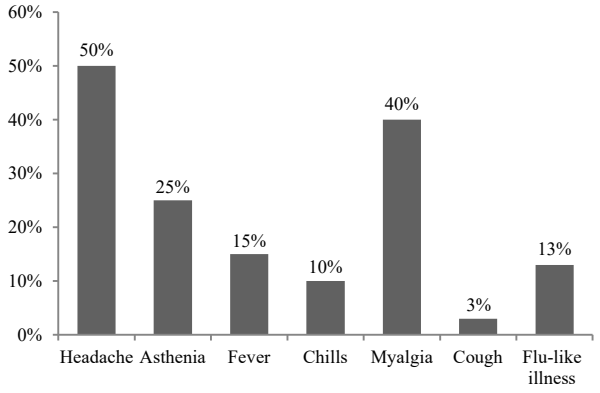

Figure 4 A bar graph showing common adverse effects of the Sputnik V COVID-19 vaccine

DISCUSSION

The safety and adverse effects related to COVID-19 viral vector vaccines, summarizing the findings from 24 published articles, were reported in this study. It appeared that serious adverse events of adenovirus vaccines are few and the side effects were often mild to moderate. In about 14 articles, at least one case of serious adverse events was reported. The AstraZeneca vaccine was investigated in most of the studies and the adverse events reported after the AstraZeneca vaccine were higher than other vaccines which could be attributed to its widespread and early usage. Cardiovascular complications and neurological events were the more frequently reported serious adverse events.

Serious Adverse Events

Serious adverse events were reported differently across studies. The synthesis of this study typically presents these SAEs as follows:

Cardiovascular Events

The studies in this analysis assessed the possible cardiovascular adverse events after vaccination. Chest pain (14,36), thrombocytopenia syndrome (30,37), pulmonary embolism (17, 21), thrombosis (34, 36), and hematologic complications (21) were reported in individuals who received AstraZeneca. In addition, syncope was reported in those who received Sputnik V(39). No significant relationship has been found between the adenovirus vector vaccines of COVID-19 and cardiovascular adverse events.

The findings of a similar systematic review were consistent with our study as cardiovascular events were reported in 0.01% of those who received the vaccine (40). Thrombosis is a challenging side effect reported by some recipients of the AstraZeneca vaccine. was mentioned by two studies with large populations in our synthesis. However, it seems that it is more probable to occur within the first month of injection (34, 36). Since cardiovascular events are serious and may be life-threatening, more research on different populations and ages is suggested to determine the relationship between cardiovascular events and COVID-19 vaccination.

Allergic

One of the studies reported allergic reactions following AstraZeneca and Pfizer receivers (0.2/per thousand doses) (29). This incidence rate was higher than the findings of a systematic review and meta-analysis that reported allergic adverse events with an incidence rate of 7.91per million cases (41).

Neurologic

The results from included studies showed that post-vaccination neurological adverse events are rare and there is no relationship between the vaccination and neurological events. In two studies, transverse myelitis was reported as one of the neurological adverse events after the vaccination with AstraZeneca with an incidence rate of 43 in 86,000,000 between 10 days to 6 weeks after vaccination (35) and 3 in 23,848 between 10-14 days after vaccination(37). Also, some neurological events were reported several days after vaccination with AstraZeneca in other studies (21). The coincidence of neurological adverse events and COVID-19 vaccination should be assessed carefully.

Mortality

There is no direct relationship between the COVID-19 vaccination and mortality and more detailed studies are needed to clarify the possible relationship. In two studies, deaths of AstraZeneca and Pfizer vaccine recipients have been reported; 3 deaths in AstraZeneca recipients (36) and one death in Pfizer recipients (29).

Local and systemic side effects

The most common local adverse reaction was injection site pain, followed by injection site swelling and injection site redness. Generally, all systemic adverse effects were substantially more prevalent among recipients of viral vector-based vaccines than mRNA-based vaccines. The EMA's safety report on the ChAdOx1 nCoV-19 vaccine revealed that 52.7% of vaccination recipients experienced headaches, followed by fatigue (53%), malaise (44.4%), muscular discomfort (43.9%), fever (41.1%), chills (32.2%), and joint pain (26.6%) (42). Our systematic review results demonstrated that headache and fatigue were the most prevalent systemic adverse events among viral vector-based vaccine users, followed by chills, muscle pain, malaise, fever, and joint pain, within 7 days after injection. The rates of adverse effects after vaccination with ChAdOx1 nCoV-19 were lower than anticipated. The phase 2–3 trial of the ChAdOx1 nCoV-19 vaccine (42) revealed systemic adverse effects in 88% of people aged 18–55 years who got the first injection. Individuals who received the ChAdOx1 nCoV-19 vaccine were more likely to experience systemic side effects than those who received the BNT162b2 vaccine.

Individuals with evidence of prior SARS-CoV-2 infection are likewise more likely to have adverse effects from both vaccinations than those without such evidence. It has to be determined if this higher reactogenicity correlates with enhanced immunogenicity. Vaccines have greater immunogenicity in persons with a history of infection, and these individuals have higher levels of antibodies than those without a history of infection (43-45).In contrast to the abovementioned studies, a cohort study in Korea by *Wi et al.* shows that all the adverse reactions following AstraZeneca injection are mild to moderate and they mostly occur during the first week after injection (31).

The 24 studies included in this systematic review were from various populations and ages. These studies revealed a variety of vaccine-related adverse effects. However, we encountered limitations in terms of populations and

studies on some specific adverse events. Some of these adverse events are more significant and require further examination, hence, future investigations should be focused on these adverse events in larger populations. Additionally, in acute situations like the COVID-19 pandemic, case reports may be included in systematic reviews to gather sufficient scientific evidence in drawing concrete consensus for clinical practice.

CONCLUSION

Some adverse events were observed among the recipients of adenovirus vector vaccines, but no reliable relationship between these adverse events and vaccination was established. The benefits of the vaccination in preventing COVID-19 progression to more severe stages and death are far greater than its adverse events, and this can be understood from the few serious adverse events and mortality reported from the vaccination as demonstrated in this study.

REFERENCES

1. SeyedAlinaghi S, Mirzapour P, Dadras O, Pashaei Z, Karimi A, MohsseniPour M, et al. Characterization of SARS-CoV-2 different variants and related morbidity and mortality: a systematic review. ***Eur J Med Res*** 2021;26(1):51.
2. Mehraeen E, Pashaei Z, Akhtaran FK, Dashti M, Afzalian A, Ghasemzadeh A, et al. Estimating Methods of the Undetected Infections in the COVID-19 Outbreak: A Systematic Review. ***Infect Disord Drug Targets*** 2023;23(4):e240123213106.
3. Mehraeen E, Salehi MA, Behnezhad F, Moghaddam HR, SeyedAlinaghi S. Transmission Modes of COVID-19: A Systematic Review. ***Infect Disord Drug Targets*** 2021;21(6):e170721187995.
4. Mehraeen E, Dadras O, Afsahi AM, Karimi A, Pour MM, Mirzapour P, et al. Vaccines for COVID-19: A Systematic Review of Feasibility and Effectiveness. ***Infect Disord Drug Targets*** 2022;22(2):e230921196758.
5. Yadav PD, Potdar VA, Choudhary ML, Nyayanit DA, Agrawal M, Jadhav SM, et al. Full-genome sequences of the first two SARS-CoV-2 viruses from India. ***Indian J Med Res*** 2020;151(2 & 3):200-209.
6. Mehraeen E, Najafi Z, Hayati B, Javaherian M, Rahimi S, Dadras O, et al. Current Treatments and Therapeutic Options for COVID-19 Patients: A Systematic Review. ***Infect Disord Drug Targets*** 2022;22(1):e260721194968.
7. Mehraeen E, Oliaei S, SeyedAlinaghi S, Karimi A, Mirzapour P, Afsahi AM, et al. COVID-19 in Pediatrics: A Systematic Review of Current Knowledge and Practice. ***Infect Disord Drug Targets*** 2022;22(5):e290921196908.
8. SeyedAlinaghi S, Karimi A, Pashaei Z, Afzalian A, Mirzapour P, Ghorbanzadeh K, et al. Safety and Adverse Events Related to COVID-19 mRNA Vaccines; a Systematic Review. ***Arch Acad Emerg Med*** 2022;10(1):e41.
9. World Health Organization. COVID-19 vaccine tracker and landscape 2022, January 18 [Available from: https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines.
10. World Health Organization. Status of COVID-19 Vaccines within WHO EUL/PQ evaluation process updated 2021, December 23 [Available from: https://extranet.who.int/pqweb/news/status-covid-19-vaccines-within-who-eulpq-evaluation-process-updated
11. McDonald I, Murray SM, Reynolds CJ, Altmann DM, Boyton RJ. Comparative systematic review and meta-analysis of reactogenicity, immunogenicity and efficacy of vaccines against SARS-CoV-2. ***NPJ Vaccines*** 2021;6(1):74.
12. Pormohammad A, Zarei M, Ghorbani S, Mohammadi M, Razizadeh MH, Turner DL, et al. Efficacy and Safety of COVID-19 Vaccines: A Systematic Review and Meta-Analysis of Randomized Clinical Trials. ***Vaccines (Basel)*** 2021;9(5):467.
13. World Health Organization. Who Coronavirus (Covid-19) Dashboard 2022, January 17 [Available from: https://covid19.who.int/.
14. Chen M, Yuan Y, Zhou Y, Deng Z, Zhao J, Feng F, et al. Safety of SARS-CoV-2 vaccines: a systematic review and meta-analysis of randomized controlled trials. ***Infect Dis Poverty*** 2021;10(1):94.
15. Hernández AF, Calina D, Poulas K, Docea AO, Tsatsakis AM. Safety of COVID-19 vaccines administered in the EU: Should we be concerned? ***Toxicol Rep*** 2021;8:871-9.

16. Lotan I, Romanow G, Levy M. Patient-reported safety and tolerability of the COVID-19 vaccines in persons with rare neuroimmunological diseases. ***Mult Scler Relat Disord*** 2021;55:103189.
17. Sadoff J, Gray G, Vandebosch A, Cárdenas V, Shukarev G, Grinsztejn B, et al. Safety and Efficacy of Single-Dose Ad26.COV2.S Vaccine against Covid-19. ***N Engl J Med*** 2021;384(23):2187-201.
18. Abu-Hammad O, Alduraidi H, Abu-Hammad S, Alnazzawi A, Babkair H, Abu-Hammad A, et al. Side Effects Reported by Jordanian Healthcare Workers Who Received COVID-19 Vaccines. ***Vaccines (Basel)*** 2021;9(6):577.
19. Al Bahrani S, Albarrak A, Alghamdi OA, Alghamdi MA, Hakami FH, Al Abaadi AK, et al. Safety and Reactogenicity of the ChAdOx1 (AZD1222) COVID-19 Vaccine in Saudi Arabia. ***Int J Infect Dis*** 2021;110:359-62.
20. Al Khames Aga QA, Alkhaffaf WH, Hatem TH, Nassir KF, Batineh Y, Dahham AT, et al. Safety of COVID-19 vaccines. ***J Med Virol*** 2021;93(12):6588-94.
21. Falsey AR, Sobieszczyk ME, Hirsch I, Sproule S, Robb ML, Corey L, et al. Phase 3 Safety and Efficacy of AZD1222 (ChAdOx1 nCoV-19) Covid-19 Vaccine. ***N Engl J Med*** 2021;385(25):2348-60.
22. Folegatti PM, Ewer KJ, Aley PK, Angus B, Becker S, Belij-Rammerstorfer S, et al. Safety and immunogenicity of the ChAdOx1 nCoV-19 vaccine against SARS-CoV-2: a preliminary report of a phase 1/2, single-blind, randomised controlled trial. ***Lancet*** 2020;396(10249):467-78.
23. Madhi SA, Koen AL, Izu A, Fairlie L, Cutland CL, Baillie V, et al. Safety and immunogenicity of the ChAdOx1 nCoV-19 (AZD1222) vaccine against SARS-CoV-2 in people living with and without HIV in South Africa: an interim analysis of a randomised, double-blind, placebo-controlled, phase 1B/2A trial. ***Lancet HIV*** 2021;8(9):e568-80.
24. Frater J, Ewer KJ, Ogbe A, Pace M, Adele S, Adland E, et al. Safety and immunogenicity of the ChAdOx1 nCoV-19 (AZD1222) vaccine against SARS-CoV-2 in HIV infection: a single-arm substudy of a phase 2/3 clinical trial. ***Lancet HIV*** 2021;8(8):e474-85.
25. Hatmal MM, Al-Hatamleh MAI, Olaimat AN, Hatmal M, Alhaj-Qasem DM, Olaimat TM, et al. Side Effects and Perceptions Following COVID-19 Vaccination in Jordan: A Randomized, Cross-Sectional Study Implementing Machine Learning for Predicting Severity of Side Effects. ***Vaccines (Basel)*** 2021;9(6):556.
26. Kim T, Park SY, Yu S, Park JW, Lee E, Jeon MH, et al. Impacts of Side Effects to BNT162b2 and the First Dose of ChAdOx1 Anti-SARS-CoV-2 Vaccination on Work Productivity, the Need for Medical Attention, and Vaccine Acceptance: A Multicenter Survey on Healthcare Workers in Referral Teaching Hospitals in the Republic of Korea. ***Vaccines (Basel)*** 2021;9(6):648.
27. Massoud F, Ahmad SF, Hassan AM, Alexander KJ, Al-Hashel J, Arabi M. Safety and tolerability of the novel 2019 coronavirus disease (COVID-19) vaccines among people with epilepsy (PwE): A cross-sectional study. ***Seizure*** 2021;92:2-9.
28. Menni C, Klaser K, May A, Polidori L, Capdevila J, Louca P, et al. Vaccine side-effects and SARS-CoV-2 infection after vaccination in users of the COVID Symptom Study app in the UK: a prospective observational study. ***Lancet Infect Dis*** 2021;21(7):939-49.
29. Oh HK, Kim EK, Hwang I, Kim TE, Lee YK, Lee E, et al. COVID-19 vaccine safety monitoring in the Republic of Korea: February 26, 2021 to April 30, 2021. ***Osong Public Health Res Perspect*** 2021;12(4):264-8.
30. Rotondo C, Cantatore FP, Fornaro M, Colia R, Busto G, Rella V, et al. Preliminary Data on Post Market Safety Profiles of COVID 19 Vaccines in Rheumatic Diseases: Assessments on Various Vaccines in Use, Different Rheumatic Disease Subtypes, and Immunosuppressive Therapies: A Two-Centers Study. ***Vaccines (Basel)*** 2021;9(7):730.
31. Wi YM, Kim SH, Peck KR. Early Adverse Events between mRNA and Adenovirus-Vectored COVID-19 Vaccines in Healthcare Workers. ***Vaccines (Basel)*** 2021;9(8):931.
32. Kim SH, Wi YM, Yun SY, Ryu JS, Shin JM, Lee EH, et al. Adverse Events in Healthcare Workers after the First Dose of ChAdOx1 nCoV-19 or BNT162b2 mRNA COVID-19 Vaccination: a Single Center Experience. ***J Korean Med Sci*** 2021;36(14):e107.
33. Park C, Sakong J, Jo S, Kim M, Baek K. Adverse Effects on Work and Daily Life Interference among Healthcare Workers

after the First and Second ChAdOx1 and BNT162b2 COVID-19 Vaccine Doses. ***Vaccines (Basel)*** 2021;9(8):926.

34. MacIntyre CR, Veness B, Berger D, Hamad N, Bari N. Thrombosis with Thrombocytopenia Syndrome (TTS) following AstraZeneca ChAdOx1 nCoV-19 (AZD1222) COVID-19 vaccination - A risk-benefit analysis for people < 60 years in Australia. ***Vaccine*** 2021;39(34):4784-7.
35. Román GC, Gracia F, Torres A, Palacios A, Gracia K, Harris D. Acute Transverse Myelitis (ATM):Clinical Review of 43 Patients With COVID-19-Associated ATM and 3 Post-Vaccination ATM Serious Adverse Events With the ChAdOx1 nCoV-19 Vaccine (AZD1222). ***Front Immunol*** 2021;12:653786.
36. Tobaiqy M, Elkout H, MacLure K. Analysis of Thrombotic Adverse Reactions of COVID-19 AstraZeneca Vaccine Reported to EudraVigilance Database. ***Vaccines (Basel)*** 2021;9(4):393.
37. Voysey M, Clemens SAC, Madhi SA, Weckx LY, Folegatti PM, Aley PK, et al. Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK. ***Lancet*** 2021;397(10269):99-111.
38. Logunov DY, Dolzhikova IV, Shcheblyakov DV, Tukhvatulin AI, Zubkova OV, Dzharullaeva AS, et al. Safety and efficacy of an rAd26 and rAd5 vector-based heterologous prime-boost COVID-19 vaccine: an interim analysis of a randomised controlled phase 3 trial in Russia. ***Lancet*** 2021;397(10275):671-81.
39. Mehraeen E, SeyedAlinaghi S, Karimi A. Can children of the Sputnik V vaccine recipients become symptomatic? ***Hum Vaccin Immunother*** 2021;17(10):3500-1.
40. Lv M, Luo X, Shen Q, Lei R, Liu X, Liu E, et al. Safety, Immunogenicity, and Efficacy of COVID-19 Vaccines in Children and Adolescents: A Systematic Review. ***Vaccines (Basel)*** 2021;9(10):1102.
41. Greenhawt M, Abrams EM, Shaker M, Chu DK, Khan D, Akin C, et al. The Risk of Allergic Reaction to SARS-CoV-2 Vaccines and Recommended Evaluation and Management: A Systematic Review, Meta-Analysis, GRADE Assessment, and International Consensus Approach. ***J Allergy Clin Immunol Pract*** 2021;9(10):3546-3567.
42. Ramasamy MN, Minassian AM, Ewer KJ, Flaxman AL, Folegatti PM, Owens DR, et al. Safety and immunogenicity of ChAdOx1 nCoV-19 vaccine administered in a prime-boost regimen in young and old adults (COV002): a single-blind, randomised, controlled, phase 2/3 trial. ***Lancet*** 2021;396(10267):1979-93.
43. Krammer F, Srivastava K, PARIS team, Simon V. Robust spike antibody responses and increased reactogenicity in seropositive individuals after a single dose of SARS-CoV-2 mRNA vaccine. ***MedRxiv*** 2021:2021-01.
44. Wise J. Covid-19: People who have had infection might only need one dose of mRNA vaccine. BMJ. 2021 Feb 2;372:n308.
45. Manisty C, Otter AD, Treibel TA, McKnight Á, Altmann DM, Brooks T, et al. Antibody response to first BNT162b2 dose in previously SARS-CoV-2-infected individuals. ***Lancet*** 2021;397(10279):1057-8.