



ORIGINAL: Is there an Association between Side Effects of AstraZeneca, Sputnik, Covaxin and Sinopharm COVID-19 vaccines and Breakthrough Infections?

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ABSTRACT

Introduction: Safe and efficacious vaccines against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), would contribute to contain the COVID-19 pandemic. In this study, we examined this question that if there is an association between the incidence of side effects and the COVID-19 breakthrough infections.

Material and Methods: This descriptive-analytical cross-sectional study was conducted for two months from June 22 to August 22, 2021. The study method was complete enumeration and 1474 healthcare workers who were medical staff of seven hospitals in Tehran and were vaccinated with one of the AstraZeneca, Covaxin, Sputnik V, and Sinopharm vaccines. Two main questions of this questionnaire were the occurrence or non-occurrence of any side effects after receiving the vaccines and the presence or absence of COVID-19 infection after vaccination.

Results: According to the results obtained, in recipients vaccinated with Sinopharm vaccine, the group that reported at least one side effects after receiving the vaccine had a significantly higher COVID-19 infection than the group reported no side effects after vaccination ($P<0.001$) ($RR=4.55$). Also in whole sample study Participants who have reported one or more side effect after COVID-19 vaccination, had 3.7 times higher risk of breakthrough infection than others ($P<0.001$); However Among those vaccinated with AstraZeneca, Covaxin and Sputnik vaccines, no significant difference was observed between the groups with and without side effects after vaccination in terms of later COVID-19 infection.

Conclusion: It seems that participants who have reported one or more side effect after COVID-19 vaccination, had times higher risk of breakthrough infection than others.

Introduction

Throughout history, infectious diseases have been a serious public health threat worldwide. From the plague (1)

in very distant past, Spanish flu in 1918 (2), HIV pandemic from 1981 to the present (3), the outbreak of severe acute respiratory

syndrome (SARS) in 2002 (4), the H1N1 flu in 2009 (5), Middle East Respiratory Syndrome (MERS) in 2012 (6) and Ebola in 2013 (7) to the latest viral disease threatening public health which is the novel coronavirus that spread from China to the world and was officially named COVID-19 (SARS-CoV-2) by World Health Organization on February 11, 2020. On January 30, 2020, WHO declared it a pandemic and a significant international public health emergency. As of September 21, 2021, more than 228 million cases of COVID-19 have been reported to WHO, including more than 4.6 million deaths. A few months after the beginning of pandemic, several vaccines against COVID-19 were developed, including mRNA-based vaccines such as BNT162b2 (Pfizer-BioNTech) and mRNA-1273 (Moderna), viral-vector vaccines such as AZD1222 (Oxford–AstraZeneca) (8) and Gam-COVID-Vac (Sputnik V) and inactivated virus vaccines such as BBV152 (Covaxin) (9) and BBIBP-CorV (Sinopharm) (10). Extensive use of safe and effective vaccines for acute COVID-19 infection, especially in combination with concomitant prevention strategies such as social distancing and hand hygiene, are able to prevent this disease (11, 12). Vaccination against COVID-19 is also the most cost-effective public health intervention. In addition to individual immunization, achieving herd immunity, especially to protect vulnerable groups is also highly suggested in society. (13) Due to the diversity of vaccines produced against COVID-19, there may be doubts as to which of the vaccines is more appropriate and effective. (14).

Severe immune reactions to vaccines are usually rare (8). However, these events can cause general fear and a loss of confidence in vaccine safety among societies (15). Millions of people vaccinated with a variety of COVID-19 vaccines have experienced side effects, including fever, headache, fatigue, muscle aches, chills, nausea, swelling, redness, and pain at the injection site (16, 17). However, not everyone responds equally to vaccines. Many people have not reported side

effects after vaccination (18). Does this mean that they are not protected against SARS-CoV-2? One of the common misconceptions especially among society, is that a vaccine that does not trigger side effects would not induce much immunity (19). In this study, we examined how close this notion is to reality. The aim of this study was to compare Sputnik, Covaxin, AstraZeneca, and Sinopharm vaccines based on possible association between the incidence of adverse events and occurrence of COVID-19 after vaccination among university staff and personnel working in selected hospitals, Tehran, Iran.

Methods

Study population

This descriptive-analytical cross-sectional study was performed on 1474 university staff and medical care personnel of seven hospitals in Tehran, Iran. All of these individuals were enrolled in the study for two months between June and August 2021 and were all vaccinated (one or two doses) with one of four vaccines (Sputnik, Covaxin, AstraZeneca, or Sinopharm) and at least ten days had elapsed since the first dose of the vaccine was received.

Study design

Study method was complete enumeration and the data were collected through a researcher-made questionnaire. After obtaining the necessary permits from Aja University of Medical Sciences, the researcher entered medical centers and distributed a questionnaire among individuals after coordination with hospital officials. Inclusion criteria were being employed in these centers and receiving one or both doses of vaccine with one of the 4 available vaccines and Exclusion criteria were non-answer to all questionnaire questions. Before distributing the questionnaire, the objectives of the study were explained to participants and were assured that all information would remain confidential and informed consent forms were received.

Survey questionnaire

The questionnaire included demographic information such as age, sex, height, weight, and questions about underlying conditions such as hypertension, hyperthyroidism or hypothyroidism, kidney, heart, lung and skin disease and diabetes. Additionally, items such as the type of vaccine and number of doses received and also about occurrence of any side effects after receiving the vaccine for up to three days such as fever, chills, fatigue, muscle pain, dizziness or headache, gastrointestinal symptoms and local symptoms such as swelling or pain in the injection site. Furthermore, COVID-19 occurrence after receiving first or second dose was questioned. The questionnaire was based on studies and was composed of valid documents of WHO, CDC and other credible articles. Afterwards, it was carefully studied by 10 faculty members and infectious disease specialists and the necessary corrections were made based on their opinions. In order to ensure the validity of the designed questionnaire, the questions were evaluated with the Content Validity Index. In order to ensure the reliability of the questionnaire, using Cronbach's alpha coefficient, the internal consistency of the questions was evaluated, which had acceptable reliability ($\alpha=0.86$).

Descriptive analysis

After completing and collecting all the questionnaires, the data were analyzed using SPSS software version 22. In order to describe the data, central indicators and dispersion such as mean and standard deviation were used. Relative risk was calculated and In order to perform analytical studies, Chi-squared test and Fisher Exact test were used and the significance level was considered less than 0.05.

Results

Study population characteristics

Participants in this study included 1040 males (70.6%) and 434 females (29.4%) and 123 patients had received one dose (8.2%) and 1351 (91.8%) both doses of the vaccine

and 91.9% of the samples had no coexisting conditions, although about 1.8% of the samples had hypothyroidism or hyperthyroidism, 1.4% high blood pressure and 0.9% diabetes and 35.9% (531 people) had a history of COVID-19, of which 17.4% (255 people) had been infected for more than 6 months before the study. Furthermore, 64.7% (953 people) were in the age range of 20-29 years old 11.3% (166 people) were under 20 years old and only 3% (42 people) were more than 50 years old. The mean BMI was 23.5 ± 3.4 and 69.2% of the subjects (1024 subjects) had normal BMI and 27% (399 subjects) were overweight and obese. Out of 1474 participants, 890 participants (60.4%) had received Sinopharm vaccine, 309 participants (21%) AstraZeneca vaccine, 214 participants (14.5%) Sputnik vaccine and 61 participants (4.1%) had received Covaxin vaccine (*Table 1*).

Association between the incidence of side effects and the COVID-19 breakthrough infections

In this study, we compared the relationship between the incidence of side effects and the COVID-19 infection after receiving the second dose of the studied vaccines (Sputnik, Covaxin, AstraZeneca and Sinopharm). In the whole study population, COVID-19 infection rate was relatively higher in the group that had at least one side effect after receiving the vaccines ($P>0.001$) and, the relative risk was 3.7 (2.1-6.51). Therefore COVID-19 infection was higher among persons who had at least one side effect than in those who did not (*Table 2*). we found out there was no significant relationship between the incidence of side effects and the COVID-19 infection after receiving Sputnik, AstraZeneca and Covaxin vaccines, ($P=0.605$), ($P=0.179$), ($P=0.678$) respectively, but among people vaccinated with Sinopharm vaccine, the group who reported at least one adverse event after vaccination, had a significantly higher chance of COVID-19 occurrence than the group which did not report any side effects ($P<0.001$) (*Table 3*).

Table 1. Characteristics of study population (n=1474)

Variable		No. of respondents (%)
Sex	Male	1040 (70.6)
	Female	434 (29.4)
Marital status	Single	1121 (76.1)
	Married	353 (23.9)
Age group	<20 years	166 (11.3)
	20-29 years	958 (64.8)
	30-39 years	171 (11.6)
	40-49 years	137 (9.3)
	50-59 years	37 (2.5)
	≥60 years	5 (3.8)
Body-Mass-Index	Underweight	56 (3.8)
	Normal	1020 (69.2)
	Overweight	325 (22)
	Obese	74 (5)
Past medical history	No underlying disease	1353 (91.9)
	Hypertension	21 (1.4)
	Hypothyroidism or hyperthyroidism	27 (1.8)
	Allergies	16 (1.1)
	Diabetes Mellitus	13 (0.9)
	Chronic neurological disease	3 (0.2)
	Chronic kidney disease	2 (0.1)
	Chronic respiratory disease	3 (0.2)
	Chronic Dermatologic disease	8 (0.5)
	Chronic cardiac disease	4 (0.3)
	Chronic liver disease	3 (0.2)
	Addiction	8 (0.5)
	Others	13 (0.9)
Time of COVID-19 infection prior to vaccination	No prior COVID-19 infection	944 (64)
	1 month before vaccination	26 (1.8)
	2 to 3 months before vaccination	99 (6.7)
	4 to 6 months before vaccination	150 (10.1)
	More than 6 months before vaccination	255 (17.4)
Vaccine type	Sinopharm	890 (60.3)
	AstraZeneca	309 (20.9)
	Sputnik V	214 (14.7)
	Covaxin	61 (4.1)
No. of received vaccine doses	One dose	123 (8.3)
	Two doses	1351 (91.7)

Table 2. Frequency of COVID-19 infection after vaccination in terms of side effects after vaccines

Vaccine side effects	COVID-19 infection number (%)	Without infection number (%)	P-value	Relative Risk
No side effects	14 (2.2)	611 (97.8)	<0.001	3.7
At least one side effect	71 (8.3)	781 (91.7)		

In this study, the occurrence of COVID-19 after receiving the second dose of Sinopharm vaccine was 1.8% among participants who did not have any side effects after vaccination (first or second dose) and 8.2% among those who had adverse events. There was a significant difference between the incidence of side

effects after injection of Sinopharm vaccine and occurrence of COVID-19 after receiving the second dose of vaccine ($P<0.001$). The relative risk for Sinopharm vaccine was 4.55 (2.23-9.29). Thus, people who developed at least one complication after the Sinopharm vaccine were 4.55 times more likely to develop COVID-19 after receiving the

second dose of the vaccine than those who had no side effects.

Table 3. Frequency of COVID-19 infection after vaccination in terms of side effects after receiving each vaccine

Vaccine	Side effects	COVID-19 infection number (%)	Without infection number (%)	P-value	Relative Risk
Sputnik V	No side effects	2 (6.7)	28 (93.3)	0.605	1.1
	At least one side effect	14 (7.6)	170 (92.4)		
Covaxin	No side effects	1 (7.1)	13 (92.9)	0.678	1.2
	At least one side effect	4 (8.5)	43 (91.5)		
AstraZeneca	No side effects	0 (0)	19 (100)	0.179	3.6
	At least one side effect	26 (9)	264 (91)		
Sinopharm	No side effects	10 (1.8)	549 (98.2)	<0.001	4.5
	At least one side effect	27 (8.2)	304 (91.8)		

Discussion

This study is one of the few studies since the beginning of the COVID-19 pandemic that compares the occurrence of COVID-19 after receiving the vaccines in two groups with or without side effects incidence. Participants vaccinated with one of four vaccines (Sputnik, Covaxin, Sinopharm or AstraZeneca) have been studied. According to previous studies, many people had reported side effects after receiving the vaccines, and the most commonly reported adverse events of COVID-19 vaccines were fatigue, headache, local tenderness, and pain around the injection site, and less common side effects such as allergic reactions and skin conditions such as irritation, rash and red pimples (20). However, many people would not experience any side effects after receiving the vaccines (18). Given the general belief in the necessity of side effects of vaccines after their injection for high efficacy against COVID-19 (21), we decided to address this issue, which has always been discussed. The results of our study indicated that recipients of AstraZeneca, Covaxin and Sputnik vaccines, not a significant difference in the occurrence of COVID-19 after vaccination between the two groups who reported at least one side effect after vaccination and Those who did not, had not observed This result is in accordance with the results and the statement of Dr. William Schaffner, Professor of Infectious Diseases at

Vanderbilt University, as well as the results of Dr. Aaron Milstone of Johns Hopkins University (21), who stated that there is no direct link between the incidence and safety of the vaccine (22). Among persons received Sinopharm vaccine, the occurrence of COVID-19 after injection was significantly higher in the group that reported at least one side effect after vaccination than in the other group. The case of the Sinopharm vaccine was almost inconsistent with the study of the Pfizer vaccine, which examined the relationship between adverse events and immunogenicity of the BNT162b2 (Pfizer-BioNTech) vaccine and concluded that there was a link between adverse reactions and antibody response. Individuals with more side effects had higher IgG SARS-CoV-2 titers and more neutralizing activity than asymptomatic individuals (23). However, according to previous studies, the Sinopharm vaccine showed a lower incidence of side effects compared to the AstraZeneca vaccine after the first and second dose injections (24), which may indicate that this association may be due to fewer adverse events. An inverse relationship was observed between side effects and vaccine efficacy. One of the limitations of this study was the lack of study on association between the side effects of vaccines and the level of antibodies against COVID-19, which could have provided a more accurate and comprehensive assessment of this ambiguous association (23).

Gender plays an important role in the immune

response to foreign antigens. Women are more prone to autoimmune diseases and vaccine side effects and their antibody titers are higher after vaccination. These differences can be attributed to the influence of environmental factors, sex chromosome genes and sex hormones on immune responses (25). We utilized self-reported data that could including incorrect classification, some participants are also more likely to report symptoms more or less or with varying severity than others, and participants may have underestimated or even forgotten their side effects. This was an observational study and our research design and data taken over a specific period of time could not allow causality Inference.

Finally, the systemic side effects collected from the reports cannot rule out the possibility that these effects may not be related to the vaccine. We also did not have enough evidence to make different assessments based on different ethnic and racial groups. According to previous studies, factors such as age, sex and previous COVID-19 infection, could affect the frequency of side effects after vaccination (20) as well as genetic factors (26), increasing age (27), male sex (28), and many diseases. Underlying conditions such as diabetes (29), hypertension and various heart diseases and cancers, impaired lung function, heart, blood circulation, renal system as well as immunocompromised individuals, chronic obstructive pulmonary disease (COPD), chronic kidney disease, immunodeficiency, asthma, autoimmune diseases such as MS, rheumatoid arthritis and lupus, cerebrovascular disease and chronic liver disease (30-33) are risk factors for COVID-19 infection, so factors studied in this study are very influential to confirm the results. This study requires several clinical trial studies to be confirmed. The advantages and strengths of this article were the high statistical population, the study of AstraZeneca, Sputnik, Covaxin, and Sinopharm vaccines and this study was one of the first studies since the beginning of the COVID-19 pandemic to examine this particular idea.

During the current pandemic, which is still in progress, globally approved vaccines, along with other public health measures, can be very helpful and beneficial in reducing the devastating health and social crisis and economic welfare losses caused by the global outbreak of COVID-19. Raising public awareness about the safety and efficacy of vaccines and addressing misinformation among community about the side effects of these vaccines can be effective in counteracting the hesitancy in vaccination among people. Given the worrying reports of waning immunity of vaccines over time (34,35), now is the time for more extensive studies in various areas such as evaluation of rare and common adverse events and long-term immunogenicity of vaccines and on the effectiveness and side effects of the third dose or booster vaccines.

Conclusion

Ultimately, according to a study, persons vaccinated with Sinopharm vaccine, the group that reported at least one side effect after vaccination had 4.5 times higher risk of breakthrough infection than the group with no side effects reported ($P < 0.001$). However, in recipients vaccinated with AstraZeneca, Covaxin and Sputnik vaccines, there was no significant difference between the groups with and without side effects after receiving the vaccines in terms of COVID-19 occurrence. Due to the fact that the parameters measured in this study are influenced by many factors, it is necessary to conduct more extensive studies with more factors.

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Ethical standards statement

This study was approved by Aja university medical science (IR.AJAUMS.REC.1400.163). The study was performed in accordance with the principles of the Declaration of

Helsinki.

Conflicts of interest

The authors declare no conflict of interest.

Authors' contributions

Conceptualization: IN and AA; Methodology: MK, IN, and FK; Investigation: AA, FK, MN, and MFY; Supervision: IN and MY; Project administration: IN and MY; Data curation: AA, MK, and MFY; Validation: MK, IN, and FK; Writing the original draft: AA and MFR; Writing review and editing: FK and MK; Formal analysis: MK; Visualization: MN and MFR. All of the authors approved the final version of the manuscript.

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