Mix-and-Match Vaccines to Boost a Better Immunity against Covid-19 in Jazan region

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Abstract

Background: Several European countries are recommending that some people who were given the first dose of the Oxford-AstraZeneca vaccine, get another vaccine for their second dose because of safety concerns. Researchers expected that such mix–and–match vaccination regimens will trigger stronger more robust immune responses than will two doses of a single vaccine. **Purpose of the research is to** evaluate the effect of mix-and-match vaccines to boost a better immunity against Covid-19 in Jazan Area. **Design**: A retrospective study was utilized using an online questionnaire among COVID-19 vaccine recipients in Jazan area, Saudi Arabia. **Data collection tool:** Infection rates were determined after receiving COVID-19 among both recipient's groups (one-type and different type vaccine). **Results**: Out of 924 participants, 528 received one type of COVID-19 vaccine and 396 had been vaccinated with different types of vaccines. Both groups showed low infection rates after receiving the second dose of vaccination, but in the case of receiving the same type of vaccination, the percentage of injuries after the third dose doubled (40%), while the infection rates remained the same (31%) after receiving the third dose in the case of receiving different types of vaccinations. **Conclusions:** the study revealed that, both types of vaccines showed a positive effect to reduce the incidence of infections after two vaccination doses. However, the impact of the mixed vaccines in the booster doses appears after the second dose.

Keywords: Vaccines, COVID-19, Boosting immunity, Infection rate.

Introduction

With the prevalence of the Corona pandemic around the world, which is caused by the SARS-CoV-2 virus, it spread rapidly causing significant death rates. Thus there was a desperate need to find an urgent treatment for the infected cases, as well as to produce a safe and efficient vaccine to reduce the spread of the disease among uninfected people. But some important problems identified as, producing the right vaccine for the right people at the right time, **Borobia et al., 2021**. The most important problem is the inappropriateness of the vaccines for all groups of people. Some international health authorities announced various vaccine candidates for emergency use, Pfizer-BioNTech mRNA (BNT162b2) and Oxford-AstraZeneca vaccine (ChAdOx1 nCoV-19) all were the first vaccines that were approved and introduced to Saudi Arabia population. The authorization for these vaccines was attained for vulnerable and some high-risk groups, such as old people with chronic diseases and healthcare workers, then they became widely available for the whole population, **Algaissi et al., 2022**.

Saudi Arabia started an early vaccination campaign as a continuation of its intelligible efforts and actions to control the spread of the COVID-19 virus **Algaissi et al., 2022**. The ultimate aim of the ministry of health in Saudi Arabia is to vaccinate 70% of the population. Most of the current vaccination system includes a second homologous booster dose following a primary dose at a one-month interval.

The recent interest in mixing COVID-19 vaccines born from the necessity stems aim to increase protection and simplifying

immunization efforts for countries facing fluctuating supplies of the various vaccines and their judicious utilization but has a risk of increasing side effects, **Borobia et al., 2021**. The concept of mixing the vaccine is not new but had been used previously for multiple illnesses including influenza, HIV, and malaria, **Groß and Seidel, 2021**. 'Heterologous vaccination' involves the delivery of the same or similar antigens of the disease agent through different types of vaccine with the first dosage being used to prime the immune system while in the following dosages using different types of vaccine to boost the immune response. This aims to increase the effect of protection and reduce the usage of the available vaccines. Mixing different types of vaccines could also elicit long-lasting and strong immune responses as compared with a single vaccine, **Shaw et al., 2021**.

American Food and Drug Administration recently authorized a mix-and-match booster shot strategy that allows fully vaccinated of Americans people to choose a booster shot of one of three Covid-19 vaccines: Johnson & Johnson, Pfizer-BioNTech, or Moderna, even if it's different from the one they initially received. A mix-and-match option not only makes it more appropriate for American people. In order to access its effect boosters—studies showed benefits from switching to another brand, especially for those who initially received the Johnson and Johnson Covid-19 vaccine, **Daniel, 2021**.

Public health officials don't recommend one type of vaccine over the other, instead, they are allowing individuals to weigh personal benefits and risks. Some studies illustrated that mixed vaccines boosted a strong antibody response regardless of the combination of brands and provides efficient protection against the Delta variant infection, **Sameeki, 2022**. Germany and Spain are offering the Moderna or Pfizer mRNA vaccines as a second dose to young people who had received a first dose of the AstraZeneca vaccine. Following concerns about serious blood clots, rather than about efficacy, (**CDC**, Global COVID-19 Vaccinations, 2021). Two doses should be given for perfect protection and direct the body to make antibodies and kill coronavirus. Therefore, this study aims to figure out if mixed vaccination regimens will trigger more robust immune responses than will the doses of a single vaccine among the population in Jazan Region, Kingdom of Saudi Arabia.

The significant of the study: With the prevalence of the Corona pandemic around the world, which spread rapidly causing significant death rates, therefore, there was a need to find an immediate and effective treatment to treat infected cases and prevent the spread of the disease, **Borobia et al., 2021**. Some international health authorities announced various vaccine candidates for emergency use. Saudi Arabia started an early vaccination campaign as a continuation of its intelligible efforts and actions to control the spread of the COVID-19 virus **Algaissi et al., 2022**. Some studies illustrated that mixed vaccines boosted a strong antibody response and provides efficient protection against the infection, **Sameeki, 2022**. Therefore, this study was conducted in a sample of populations residing in Jazan region, those who were vaccinated with two or three doses of coronavirus vaccines in order to detect the effect of mixed vaccination on boosting a better immunity against Covid-19.

The aim of the work: the present study aimed to evaluate the effect of mix-and-match vaccines to boost a better immunity against Covid-19 in Jazan Area.

Methods and subjects

Study design and population

A cross-sectional retrospective. The current study was conducted to compare the effect of receiving mix and match vaccines of Covid-19 vaccines on enhancing immunity by comparing the incidence rates among vaccine recipients after the second and third doses and examining the severity of infection symptoms.

Online survey that was conducted over a period of 3 weeks between the begging of April and first of May 2022, in Jazan region, Saudi Arabia. All populations residing in Jazan region, those who were vaccinated with two or three doses of coronavirus vaccines, are invited to share the survey also to distribute the survey to

all of their contacts on social media with the same condition.

Data collection

Data were collected using a structured closed-ended online questionnaire that was designed by the researcher. The questionnaire was launched in Arabic and English with the clarification that, this questionnaire is used for research purposes and no personal information will be publicly disclosed. Participants under the age of 18 years old could be asked for help from a trusted person or answer on their behalf. Start answering the questionnaire is an implicit consent to participate in the study. Participants from different age groups, gender, and governorates were asked to participate and to distribute the questionnaire to their contacts. The questionnaire consists of three sections. Section I: included participants' demographic data such as age, gender, educational level, and occupation. Section II: included questions about vaccination types, number of doses, and the associated side effects for each vaccine. Section III: Consists of two lists containing the same questions, one list presented to people who received mixed vaccines and the other one for those who received one vaccine type. Also, data were collected about infection after receiving vaccine doses, the severity of infection symptoms, how long the symptoms lasted, and if diagnosed with any kind of clotting, platelet deficiency, or abnormal heart symptoms.

The third part of the questionnaire was divided into two lists of questions, the first addressed recipients of the same vaccination type (Group A), and the second list addressed to recipients of different vaccination types (Group B). The questions were around whether an actual infection with the Coronavirus occurred after the second dose of vaccination, and how severe the infection was. Also, if an infection occurred after the third dose of vaccination, how severe was the infection? Also, in the third part of the questionnaire, the participants were asked about how long the infection symptoms lasted and if they were diagnosed with any of the following, blood clotting, platelet deficiency, swelling of lymph nodes, or any abnormal heart symptoms.

Content validity and reliability:

Validity and Reliability: To ensure face and content validity, the researchers sought the input of seven experts. These experts included five from the paediatric nursing department and two from the community health nursing department, in Ain Shams University in Egypt. Through their expertise, the necessary adjustments were made to various statements within the tools. This included the removal of unnecessary phrases, as well as rephrasing. The goal was to enhance the relevance and clarity of the content, ensuring that it effectively covered all aspects of mothers' knowledge and practices concerning their children's screen viewing, as well as promoting healthy developmental activities for the children. The reliability of the developed tools was evaluated by using Cronbach's alpha test.

Ethical consideration:

Ethical considerations: Ethical approval for the study was secured from the Scientific and Ethical Committee of the Faculty of Nursing at Jazan University. The participant were given information about the study's goals and anticipated results during the initial appointment. Participants were assured of the study's safety and their ability to discontinue participation at any time without providing a justification. Each individual provided an informal verbal consent before starting the data collection. The researchers assured participants that their involvement in the study was completely voluntarily, and the collected data treated confidentially.

Pilot study: A pilot study was conducted at (10%) of the total study sample. The goal of the pilot study was to evaluate the feasibility, clarity and applicability of the study tools as well to estimate time needed to fill in the study tools. Necessary modifications were done. The participated in the pilot study were excluded from the main study sample. The goal of the pilot study was to evaluate the feasibility, clarity and applicability of the study tools as well to estimate time needed to fill in the study tools. Necessary modifications were done.

Statistical analysis

Data were collected online through a Google Forms questionnaire and then interpreted and analyzed by SPSS v.23 (IBM corp., Armonk, NY, USA) with a significance level of $p \leq 0.05$, 95% confidence intervals. Then the data analysis was presented by tables and diagrams. The sample size was determined using the sample size calculator raosoft.com.

Results

Table (1), illustrated the demographic data; which showed that, 650 participants out of 924 were females (71%). Also the largest group of participants were aged from 20 to 29 years old (485= 52%), then the age category less than 20 years old which were (254 participants; 27%). Also, undergraduate students were the most participating category in the study (669 = 73%) participants. About 45% of the participants without work which was the majority percentage of the participants, followed by the workers in the education sector (27%).

Figure (1), illustrated that out of total subjects (924) who participated in the study, who had vaccinated by the second and third doses of covid-19 vaccines, (71 %) were females (± 6.07).

Figure (2), indicated that 27% of the participants are working in the educational sector, compared to the majority of participants that are not working (45% of participants), while 19 % are working in the health sector.

Table (2): illustrated that most of the participants had received three doses of the vaccine, (660 = 71%), while 528 (57%) out of the total participants received all doses of the same vaccine. The most vaccine type that the participants had received Pfizer/Biotech, the one that 836 of the participants (90%) had received, compared to those who had received AstraZeneca/Oxford (319) while only (127) participants received the Moderna vaccine. The majority of participants monitor their vital signs after vaccinations only when they feel sick (385 = 42%), while 15% of them always monitor their vital signs after vaccinations. Regarding the side effects after vaccination, the most common ones were numbness and tingling in the limbs, pain or swelling at the injection site, fever, joint pain, and acceleration or arrhythmia.

Figure (3): illustrated that 39% of the participants reported the onset of symptoms after vaccination within five to eight hours. While a smaller percentage of the participants (24%) had symptoms during a period ranging from 9 to 12 hours, approximately equal to the number of participants (242 = 26%), who had symptoms after no more than four hours.

Table 3 & Figure 4: showed that out of the 528 participants, in group A, those who received two doses of the same vaccine, only 22 % of them were infected with the Coronavirus. The majority of them about 64% (μ = 3.18) were infected without any symptoms, while infection symptoms were moderate for 17% of the participants, and severe for 6 % of them (μ = 0.32). The infection ratio, for the same group, (recipients of the same type of vaccine), after receiving three doses of vaccination, was 40% (μ = 1.9). Further, 362 participants (69%) of them had no infection symptoms. Symptoms of infection lasted for a period ranging from one to three days with 350 of the participants (66%), and for less than one day with 112 of the participants. When asking the participants about what they did to relieve the symptoms that occurred after infection, the largest proportion of the participants (42%), answered "I took painkillers while resting at home ", while 33 % of them only took rest at home (μ=1.6). Regarding the questions about whether any of the individuals in the study were diagnosed with any of the symptoms mentioned in the questionnaire, 12 out of 528 were diagnosed with clotting, 87 were diagnosed with platelet deficiency, 9 were diagnosed with swelling of the lymph nodes and 24 were diagnosed with abnormal heart symptoms.

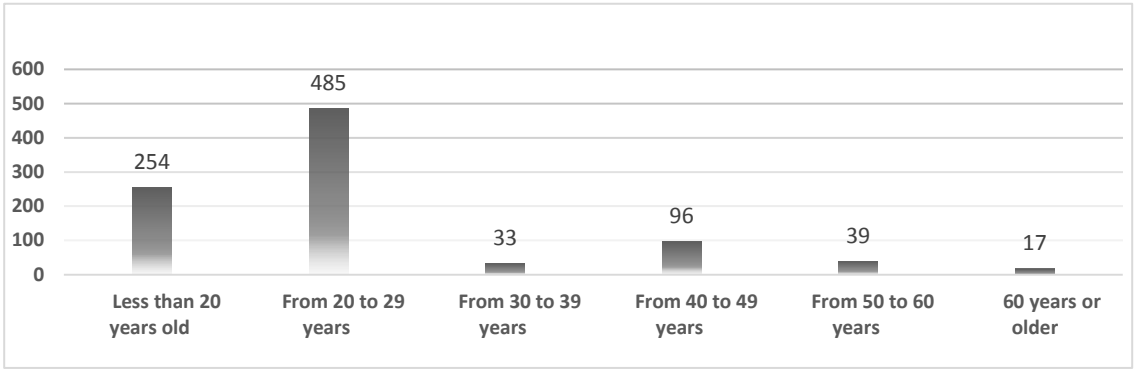

Figure 1: Participants Age Distribution

Table (1): Demographic data of the participants.

Characteristics		N = 924	Mean value (μ)
Gender	Male	274 (29%)	2.56
	Female	650 (71%)	6.07
Age	Less than 20 years	254	2.37
	From 20 to < 30 years	485 (52%)	4.53
	From 30 to < 40 years	33	0.30
	From 40 to < 50 years	96	0.89
	From 50 to < 60 years	39	0.36
	60 years or older	17	0.16
Educational level	Secondary school	41	0.38
	University Student	669 (72%)	6.25
	Bachelor's degree	152	1.42
	Higher education	62	0.58
Occupation	No work	416 (45%)	3.88
	Private sector	79	0.73
	Education Sector	254(27%)	2.37
	Health Sector	175	1.63

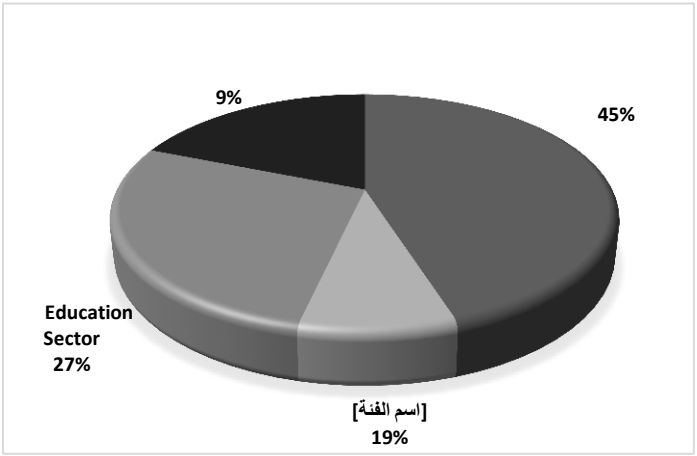

Figure 2: Occupation

Table (2): Data on receiving COVID-19 vaccines and the associated side effects.

Characteristics		N = 924	Mean value (μ)
Number of vaccine doses received against Covid -19	Two doses	264	2.46
	Three doses	660	6.1
In case if all doses of the same vaccine type	Yes	528	4.93
	No	396	3.70
Kind/s of COVID-19 vaccines received.	AstraZeneca/Oxford	319	2.9
	Pfizer/Biontech	836	7.81
	Moderna	127	1.18
Distance between receiving doses	3 months	220	2.05
	6 months	583	5.44
	More than 6 months	121	1.13
Monitoring the vital signs regularly after vaccination	always	143	1.33
	sometimes	165	1.54
	often	231	2.15
	only of I feel sick	385	3.59
Common side effects after vaccination	Numbness and tingling in the limbs	704	
	Pain or swelling at the injection site	572	
	Joint pain	484	
	Fever	495	
	Acceleration or arrhythmia	473	
	Chill	253	
	Shortness of breath	229	
	Fatigue	209	
	sore throat or dehydration	209	
Symptoms appear after the covid-19 injection	Up to 4 hours	242	2.26
	From 5 to 8 hours	357	3.33
	From 9 to 12 hours	223	2.08

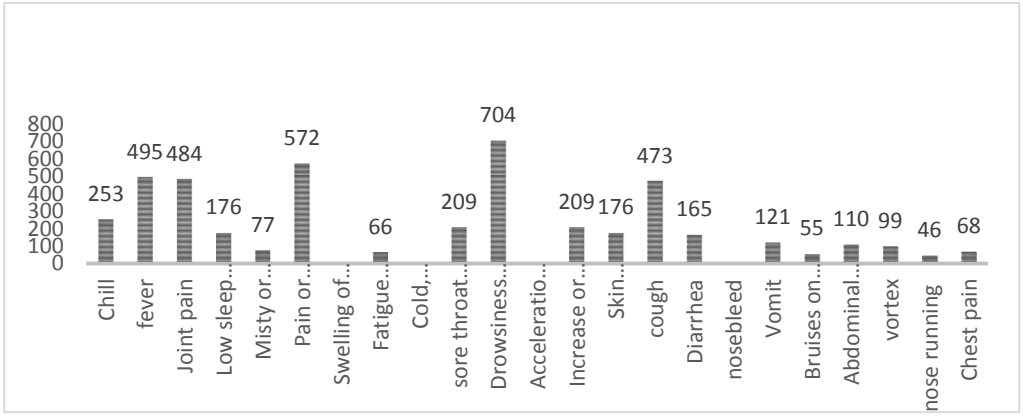

Figure 3: Common Side Effects after vaccination

Table (3): Infection after receiving Covid 19 vaccine doses.

		Group A (Receiving one type of vaccine) n=528 (57%)	Mean value µ	Group B (receiving different types of vaccine) n=396 (43%)	Mean value µ
Get Infection of COVID-19 after reviving the second dose?	**Yes**	**117**	**1.09**	**128**	**1.19**
	No	**411**	**3.84**	**268**	**2.50**
Severity of infection	**Minor**	**64**	**0.59**	**77**	**0.71**
	Moderate	**88**	**0.82**	**45**	**0.42**
	Sever	**34**	**0.32**	**24**	**0.22**
	No symptoms	**340**	**3.18**	**250**	**2.33**
Get infection of COVID-19 after the third dose.	**Yes**	**210**	**1.9**	**124**	**1.15**
	No	**318**	**3.9**	**272**	**2.54**
Severity of infection	**Minor**	**30**	**0.28**	**87**	**0.81**
	Moderate	**122**	**1.14**	**45**	**0.42**
	Sever	**14**	**0.13**	**26**	**0.24**
	No symptoms	**362**	**3.38**	**238**	**3.06**
lasting of the symptoms	**Less than one day**	**112**	**1.04**	**118**	**1.10**
	From 1 to 3 days	**350**	**3.27**	**235**	**2.19**
	From 4 to 7 days	**32**	**0.29**	**28**	**0.26**
	More than 7 days.	**34**	**0.31**	**15**	**0.14**
Procedures to relieve symptoms that occur after infection	**I took rest at home**	**172**	**1.6**	**135**	**1.26**
	I took painkillers while resting at home	**224**	**2.09**	**233**	**2.17**
	I went to the doctor's clinic	**24**	**0.22**	**22**	**0.20**
	I was admitted, and I received the required health care services	**8**	**0.07**	**6**	**0.05**
Diagnosis of infection by:					
Clotting	**Yes**	**12**	**0.11**	**24**	**0.22**
	No	**516**	**4.82**	**372**	**3.47**
platelet deficiency	**Yes**	**87**	**0.81**	**62**	**0.57**
	No	**441**	**4.12**	**334**	**3.12**
Swelling of the lymph nodes	**Yes**	**9**	**0.08**	**7**	**0.96**
	No	**519**	**4.85**	**389**	**3.63**
Abnormal heart symptoms	**Yes**	**24**	**0.22**	**16**	**0.14**
	No	**504**	**4.71**	**380**	**3.55**
Total mean		**44.25**		**34.03**	

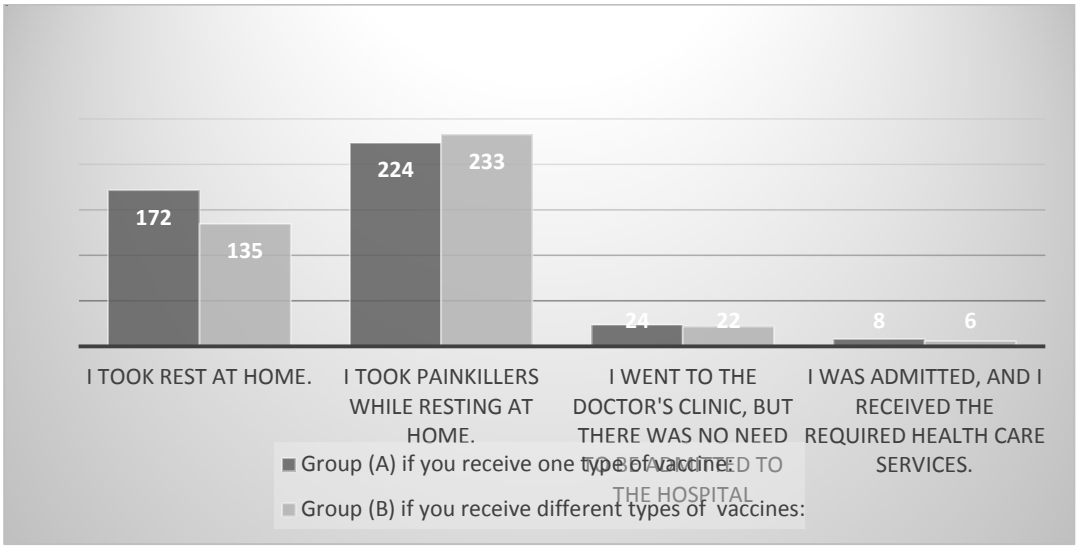

Figure 4: What did participant do to relieve the symptoms that occur after vaccination

Discussion

At the beginning of COVID-19 pandemic, many searches had been done for developing effective vaccines against SARS-CoV-2. The first dose of the vaccine was applied at the end of 2020. Nowadays, full doses of the vaccination of most of the world's population are considered the means to overcome the COVID-19 pandemic. To date, more than three billion people had received at least one dose of the available COVID-19 vaccines, and about two billion people are fully vaccinated worldwide, which accounts for roughly 27% of the world's population **(Borobia et al., 2021 & Algaissi et al., 2022)**. AstraZeneca vaccine is the most used worldwide, as it administered in 182 countries, followed by Pfizer —BioNTech, Moderna, and Sinopharm vaccine, administered in 115, 68, and 66 countries, respectively, **Kardani et al., 2016**.

Vaccination had been associated with various struggles, as some adverse reactions resulted in the discontinuation of the use of specific vaccines in some poor countries that had faced difficulties supplying enough vaccine doses, and the emergence of new variants of concern which had resulted in reduced the effectiveness of available vaccines against COVID-19. The mix-and-match strategy, using different vaccines in the first and second doses, which may successfully solve these struggles. Moreover, this strategy associated with higher cellular and humeral immune responses without significantly increasing the adverse reactions. Hence, this strategy could help to improve the effectiveness of the vaccines and act as a solution to vaccine shortages in poor regions, **Borobia et al., 2021**.

Mixing the vaccine is not a new concept but had been previously used for many diseases. As a result, there are multiple types of COVID-19 vaccines including inactivated virus, virtual vector-based, and RNA-based vaccines. The potential risks involved in mixing the vaccine include increased side effects reported as adverse events following immunization (AEFI). Increased fever, headache, joint pain, and malaise which had been reported among elderly population receiving mixed vaccination [**WHO, 2021& Alhazmi et al., 2021**]. It is supposed that this increase in side effects may even be greater among the young population due to the great systemic reactogenicity. For several reasons it is desirable to use different types of vaccines as it may lead to stronger immunity which known as heterologous prime boosting [**Sesa et al., 2021; Deming& Lyk2, 2021 and Polack et al.,2020**].

Previous studies on using heterologous vaccines in prime-boost immunization strategy shown great success. Studies suggest that by evoking both cellular and humoral immune responses, heterologous vaccines could result in 4–10 times higher T-cell responses **(Hillus et al., 2021)**.

In the current study, the infection rates, symptoms, and adverse effects after receiving Covid-19 vaccines that are in use in Jazan province, KSA, were investigated, as a means of comparing the use of similar or mixed vaccines to boost a better immunity against Covid-19. The research findings are based on an analysis of the data collected from the participants through a set of questions that were directed to the category of recipients of the same type of vaccine and the category of recipients of different types of vaccines.

The majority of the participants were women, with an age from 20 to 29 years old and university students. The number of participants who received three doses was three times more than the recipients who received two doses. Additionally, the number of recipients of vaccine doses of the same type exceeded half of the total number of participants. Moreover, the vast majority of Pfizer vaccine recipients had intervals between vaccinations ranging from 3 to 6 months. Furthermore, the most common side effects among the participants were numbness and tingling in the limbs, fever, joint pain, pain, and swelling at the injection site. Symptoms of side effects appeared less than eight hours post vaccination.

Concerning the incidence of Covid-19 infection after receiving the second dose of vaccinations, the current study results showed that the infection rate among the cases of receiving the same type of vaccine was ten percent less than in the case of receiving the vaccine from different types, which enhances the preference of similar vaccines in emphasizing protection against infection with Covid-19. In the case of receiving the third dose of the vaccine, the percentage of infections increased among the cases of receiving the same type of vaccine to almost double, while the infection rates after receiving the different types of vaccination remained the same.

From the previous results, it is inferred that if the same type of vaccine is received, the immunity against Covid-19 is enhanced to a better degree after receiving the second dose only, while the importance of different vaccines appears when receiving the booster doses after the second dose. In agreement with the results obtained from the finding of a study done by Callaway, 2021 who stated that vaccinating people with both the Oxford-AstraZeneca and the Pfizer-BioN Tech COVID-19 vaccines produces a potent immune response against SARS-Cov-2 **(Callaway, 2021)**. Similarly Daniel Altman, 2022 says, "Giving people two doses of different types of vaccines probably makes sense", **(Altman and Bayton, 2022)**. But also, wondering what will happen if people need a third dose to prolong immunity or protect against emerging coronavirus variants. This is what researchers hoped for and expected from mixing different vaccines, a strategy known as a heterologous prime and boost, which had been deployed for vaccines against other diseases, such as Ebola **(Shaw et al., 2021)**.

Furthermore, the majority of infection cases without appearing symptoms were apparent in both types of similar and different vaccinations, this confirms the idea that vaccinations reduce the symptoms of infection as well as reduce the incidence of the infection itself. The continuity of infection symptoms, if any, is less than three days for the vast majority of vaccine recipients in both cases, which were dealt with by taking painkillers and resting at home. In addition, the number of cases diagnosed with any kind of clotting, platelet deficiency, swelling of the lymph nodes, or abnormal heart symptoms, was small, most of them were platelet deficiency 16 % in both cases.

Conclusions

To sum up, the study represents that, both types of vaccines showed efficacy to reduce the incidence of infections after two vaccination doses. However, the importance of the mixed vaccines in the booster doses appears after the second dose. This shows that mix and match COVID-19 vaccines are better at boosting immunity in the long term, especially when receiving booster doses after the second dose.

The conclusion is to use the first and second doses of the same or different vaccination types, provided that the third and subsequent doses are of a different type.

Recommendations

Continuous health education program for about safety and importance of Covied 19 vacation and receiving all dose.

Statements and Declarations

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