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REVIEW ARTICLE

COVID-19 Vaccines' Protection Over Time and the Need for Booster Doses; a Systematic Review

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Abstract: **Introduction:** Controversies existed regarding the duration of COVID-19 vaccines' protection and whether receiving the usual vaccine doses would be sufficient for long-term immunity. Therefore, we aimed to systematically review the studies regarding the COVID-19 vaccines' protection three months after getting fully vaccinated and assess the need for vaccine booster doses. **Methods:** The relevant literature was searched using a combination of keywords on the online databases of PubMed, Scopus, Web of Science, and Cochrane on September 17th, 2021. The records were downloaded and the duplicates were removed. Then, the records were evaluated in a two-step process, consisting of title/abstract and full-text screening processes, and the eligible records were selected for the qualitative synthesis. We only included original studies that evaluated the efficacy and immunity of COVID-19 vaccines three months after full vaccination.This review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement to ensure the reliability of results. **Results:** Out of the 797 retrieved records, 12 studies were included, 10 on mRNA-based vaccines and two on inactivated vaccines. The majority of included studies observed acceptable antibody titers in most of the participants even after 6 months; however,it appeared that the titers could also decrease in a considerable portion of people. Due to the reduction in antibody titers and vaccine protection, several studies suggested administering the booster dose, especially for older patients and those with underlying conditions, such as patients with immunodeficiencies. **Conclusion:** Studies indicated that vaccine immunity decreases over time, making people more susceptible to contracting the disease. Besides, new variants are emerging, and the omicron variant is continuing to spread and escape from the immune system, indicating the importance of a booster dose.

Keywords: COVID-19;COVID-19 vaccines; Immunity; SARS-CoV-2; Vaccines; Vaccine-preventable diseases

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1. Introduction

Since the coronavirus disease 2019 (COVID-19) pandemic spread all over the globe, it has been posing a considerable healthcare crisis by affecting more than 250 million individuals and leading to more than 5 million deaths up until now (1). It has also influenced other aspects of life, including economic, technological, and social aspects. Since COVID-19 is highly contagious,substantial effort is required to curtail the pandemic(2). In this regard, vaccines offer a promising opportunity for fighting the pandemic and have shown considerable efficacy against severe COVID-19 infection, hospitalization, and death (3). Despite the emergence of new variants, the most effective approach to curb the pandemic seems to be mass vaccination and reaching herd immunity against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)(4).

The duration of immunity that most vaccines generate against various common infections is limited and developing strong immunity often requires booster doses. The generation of long-term immunity by COVID-19 vaccines and the necessity to administer booster doses for different COVID-19 vaccines is still a matter of debate. Considering this, it is of great importance to define the duration in which the humoral immune responses are efficient enough against COVID-19 infection (3, 5).

Some studies have demonstrated that a few months after the injection of the second dose, the effectiveness of COVID-19 vaccines wanes as antibody levels drop (6, 7). Thus, an additional booster dose may be needed to restore the high level of immunity, especially against new variants, and maintain the equilibrium of the protective humoral immunity and COVID-19 viral load during exposure. Some groups, including the elderly, are at higher risk of profound IgG decrease over time and thus increased probability of being infected with COVID-19(8). However, it is intriguing that even after a few months, the effectiveness against severe disease course and hospitalization is rather sustained (6). In a retrospective cohort study conducted by Tartof et al., participants who were fully vaccinated showed high immunity against all variants of COVID-19 up until six months after vaccination, but the immunity had been decreasing over that time (6). However, they reported no decreased effectiveness against hospital admissions in any age group during the study period.

Thomas et al. found 91% protection from Pfizer/BioNTech vaccine after six months, silencing the concerns and showing its sufficient protection during this time (9). On September 17th, 2021, the United States food and drug administration (FDA) refuted the need for a booster dose six months after the second dose of the Pfizer/BioNTech vaccine for the general population, and only recommended it for people above 65 years of age and some specific groups, but later booster doses were recommended for all the people (10, 11).

Concerns still exist regarding vaccines' duration of immunity and the need for booster doses, especially for other types of vaccines (12). Considering that new variants of COVID-19 may continue to emerge all around the world and disrupt the efforts that have been done so far to control the pandemic, it is of great importance to determine which vaccines require a booster dose for maintaining immunity against COVID-19. A systematic evaluation of this matter elucidates the path for designing new vaccination strategies. Therefore, we aimed to systematically review the studies regarding the COVID-19 vaccines' protection three or more months after getting fully vaccinated and assess if vaccine booster doses are required.

2. Methods

This study is a comprehensive review of the literature to describe COVID-19 vaccines' protection over time. We also investigated the need for booster doses. In order to ensure solidity and reliability of the outcomes, this review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.

2.1. Data sources

We executed a comprehensive and systematic search in the online databases of PubMed, Scopus, Web of Science, and Cochrane on September 17th, 2021. Keywords were selected using the medical subject headings (MeSH) and previous studies. We provided the search terms for all the databases in Supplementary material 1. The search terms for PubMed were as follows:

A. "COVID-19" OR "SARS-CoV-2" OR "SARS-CoV2" OR "2019-nCoV" OR "Novel Coronavirus" [Title/ Abstract]

B. "Vaccine" OR "Vaccination" OR "Vaccinated" OR "Immunization" [Title/ Abstract]

C. "Immunity duration" OR "Immunity period" OR "Protection duration" OR "Duration"OR"Month" OR "Year"[Title/ Abstract]

D. [A] AND [B] AND [C]

2.2. Study selection

The retrieved records were imported to an EndNote file and the duplicates were removed. In a biphasic approach, three-independent researchers screened and selected eligible studies. Inthe first phase, the retrieved records were reviewed and screened based on the relevancy of titles and abstracts. The full texts of the remaining articles were assessed based on eligibility criteria in the second phase to select the most appropriate articles. Original articles discussing the efficacy of COVID-19 vaccines at least three months after full vaccination (second dose in most cases, first dose in case of single-dose vaccines) were included in our study.

Publications subject to one or more of the following exclusion criteria were excluded from our study:
– Non-original studies, such as review articles
– Case reports and case series
– Abstract papers, conference abstracts, and other studies without available full texts
– Ongoing clinical trials without yet published results
– Preclinical studies and studies on subjectsother than humans, such as pure laboratory or animal studies
– Studies evaluating vaccine effectiveness in periods shorter than three months after becoming fully vaccinated against COVID-19. Three months was chosen as the cut-off point because full vaccinations usually provide adequate protection in the first three months (13-15).

2.3. Data extraction

Two researchers extracted the following information from the eligible studies included in the review (each recorded the data of half of the studies):first author (reference) ID, country and year of study,type of study, study population, sex percentage and mean age of the population, vaccine type, time passing from vaccination,changes in antibody levels, vaccine efficacy against infection, and disease severity parameters as well as mortality, authors' opinion about booster dose, and summary of other notable findings. These data were transferred into a word table, and then another independent researcher reviewed the extracted results to re-check and verify them.

2.4. Quality/risk of bias assessment

We utilized the Newcastle-Ottawa Scale (NOS) risk assessment tool to evaluate bias risk of the included studies. This scale adds up to a total score of nine in three categories. These categories consist of selection, comparability, and exposure/outcome and receive maximum scores of four, two, and three, respectively (Table 2).

3. Results

In this study, by applying systematic search strategies, 797 relevant records were identified and retrieved from PubMed, Scopus, Web of Science, and Cochrane. After a primary review of retrieved articles, 380 duplicates were removed, and the title and abstract of the remaining 417 articles were evaluated. By applying the selection criteria, 388 articles were excluded, and only 29 articles were screened by their full texts. After the review of full texts, 17 articles were excluded. Finally, 12 articles met the inclusion criteria and were included in the final review (Figure 1).

Table 1 summarizes the results of the studies. The studies were conducted in various countries with 15 countries involved overall; one study was multinational and included six countries (USA, Turkey, Germany, South Africa, Brazil, and Argentina), and the other studies were conducted in Belgium (n=2), USA, China, Estonia, France, Spain, Israel, Greece, Italy, and Kazakhstan (each n=1).The vaccine types in included studies were mRNA-based (n=10), and inactivated virus (n=2)vaccines. The interval between the administration of the second dose of the vaccine and the antibody titer assessment varied between 4 weeks to 6 months. The majority of included studies observed acceptable antibody titers in most of the participants even after 6 months (16, 17); however, the titers decreased in a considerable portion of the people(18). Due to the reduction in the antibody titer over time, several studies suggested administering the booster dose, especially for older patients and those with underlying conditions, such as patients with immunodeficiencies(17-19).Table 2 demonstrates the results of the quality assessment. All the studies had acceptable quality assessment scores, but they mostly lacked adequate matching for confounders.

4. Discussion

COVID-19 pandemic is a serious global challenge due to its high prevalence and the emergence of new variants.Vaccination is one of the best solutions to mitigate the immense burden of the virus, in addition to the social distancing, using face masks, and observing health protocols.We reviewed 12 articles concerning COVID-19 vaccination, elicited antibody response, duration of triggered immunity, and the necessity of the booster dose. In 10 studies, the vaccine type was mRNA-based, and in two studies, it was inactivated vaccine. In seven studies, participants were healthcare workers, adults, and individuals with cancer. The majority of articles mainly discussed the importance of booster doses, since antibody titers decline over time.

Favresse et al. reported that antibody titers significantly decreased three months after vaccination with BNT162b2 in seronegative and seropositive healthcare workers (20).Consistently, the study by Erice et al. showed a reduction in anti-SARS-CoV-2 receptor-binding domain antibody (anti-RBD antibody) titers in healthy individuals three months after the second dose; indicating that a booster dose could be beneficial(19).Terpos et al. also reported a decline in effective antibody titers (anti-S-RBD antibody and neutralizing antibody) six months after vaccination(18). These findings emphasize the beneficial effects of a booster dose against COVID-19; particularly, in reducing the rate of hospitalization and mortality, which are specifically important in the elderly and people with underlying diseases.

A study by Gou et al. on efficacy of inactivated vaccines evaluated 2 age groups, one of which mostly consisted of the elderly. This study demonstrated the value of a booster dose,

as there is always concern over elderly people's morbidity and mortality (21),yet more studies are required in order to assess the antibody alteration in elderly population.

In addition, a study by Waldhorn et al. showed a significant decrease in antibody titer over time. Since the study population was cancer patients with an average age of 66, it is possible that immunodeficiency and advanced age are both to blame for the considerable drop (22). However, more studies for assessment of antibody alterations in each group, separately, could be useful in determining the effect of each change in factor on antibody titer over time.

In recent months,the COVID-19 wave attracted global attention due to its new variant (Omicron B.1.1.529). Although this new variant has lower mortality, it is more contagious, spreads faster, and can even result in severe illness. This global issue could be best resolved by the enhancement of the immune system; therefore, the third dose of vaccine is beneficial to accentuate antibody response(23).

Concerning the immune response, Hedges et al. found that vaccination causes higher levels of antibody in comparison with previous COVID-19 infection. This showed the necessity of vaccination even in individuals with previous COVID-19 infection(24). Besides, it has been shown that a booster dose of the COVID-19 vaccine can elicit a strong antibody response that could protect the individuals from acquiring the disease and severe disease, and subsequently reduce the mortality and morbidity of the disease (11).

Studies suggest that age plays an important role in vaccination. The study of Naaber et al. reported that older people may have a weaker response to COVID-19 vaccines and also may have fewer side effects (16). Terpos et al. also showed that antibody titers decrease more slowly in younger persons; therefore, younger individuals had higher antibody titers compared to older people with the same number of days passing from vaccination (18). Likewise, Erice et al. observed that younger individuals (especially those aged 21 to 30) had higher antibody titers following COVID-19 vaccination(19). Compared to other included studies, Zakaria et al. evaluated the younger study population (mean age: 28) and discovered that antibody titer decreased over time (25). Considering this finding and based on the study by Terpos et al. (18), booster doses continue to play an important role.

Terpos et al. also showed that underlying diseases such as diabetes or autoimmune diseases may affect the antibody titers, leading to lower neutralizing antibody titers(18). These findings showed that the efficacy of vaccines can be influenced by different factors, including age and underlying disease. Therefore, a booster dose would be most beneficial in these vulnerable groups. However, it has been recently recommended for all age groups from all backgrounds (11).

5. Limitations

This study has several limitations. First, the number of included studies was limited and they did not encompass all types of vaccines, and the publications existed only on mRNA-based and inactivated vaccines. We also could not conduct a meta-analysis due to the limited number of studies and their heterogeneity. Regarding the study populations, 7 out of 12 studies were performed on healthcare workers, an important group vulnerable to the COVID-19. This can be considered both a strength and a limitation, as healthcare workers are a special and vulnerable group and require specific attention, but this means that the number of population-based studies on the general population were limited. On the other hand, only one study targeted another important group, the immunocompromised patients, and further specific studies on this group are required. Furthermore, although the studies had acceptable quality assessment scores, many of them lacked adequate matching for confounders. A strength of the present review was that included studies were conducted in 15 countries, making the results more reliable worldwide. Overall, we could deduce the benefits of booster doses using the existing evidence.

6. Conclusion

Studies have shown that the immunity due to COVID-19 vaccines diminishes over time. Such decrease is more evident in older people and those with specific underlying diseases, such as immunodeficiencies. Furthermore, new COVID-19 variants, particularly Omicron, are on the rise and it has been documented that they may evade the immunity rendered by vaccines; therefore, immediate efforts are required to refurbish the vaccines to trigger the appropriate antibody responses against these new variants. Moreover, booster doses are recommended to enhance the overall immunity of the general population against COVID-19.

7. Declarations

7.1. Acknowledgments

The present study was conducted in collaboration with Khalkhal University of Medical Sciences, Iranian Research Center for HIV/AIDS, Tehran University of Medical Sciences, and Walailak University.

7.2. Availability of data and materials

All data generated or analyzed during this study are included in this published article.

7.3. Authors' contributions

(1) The conception and design of the study:Esmaeil Mehraeen, SeyedAhmad SeyedAlinaghi

(2) Acquisition of data: Amirali Karimi, Alireza Shojaei
(3) Analysis and interpretation of data: Ava Amiri, Sara Mahdiabadi
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(5) Revising it critically for important intellectual content: SeyedAhmad SeyedAlinaghi, Omid Dadras, Esmaeil Mehraeen
(6) Final approval of the version to be submitted: all authors

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7.5. Competing interests

The authors declare that there is no conflict of interest regarding the publication of this manuscript.

7.6. Ethics approval and consent to participate

Not applicable.

7.7. Consent to publication

Not applicable.

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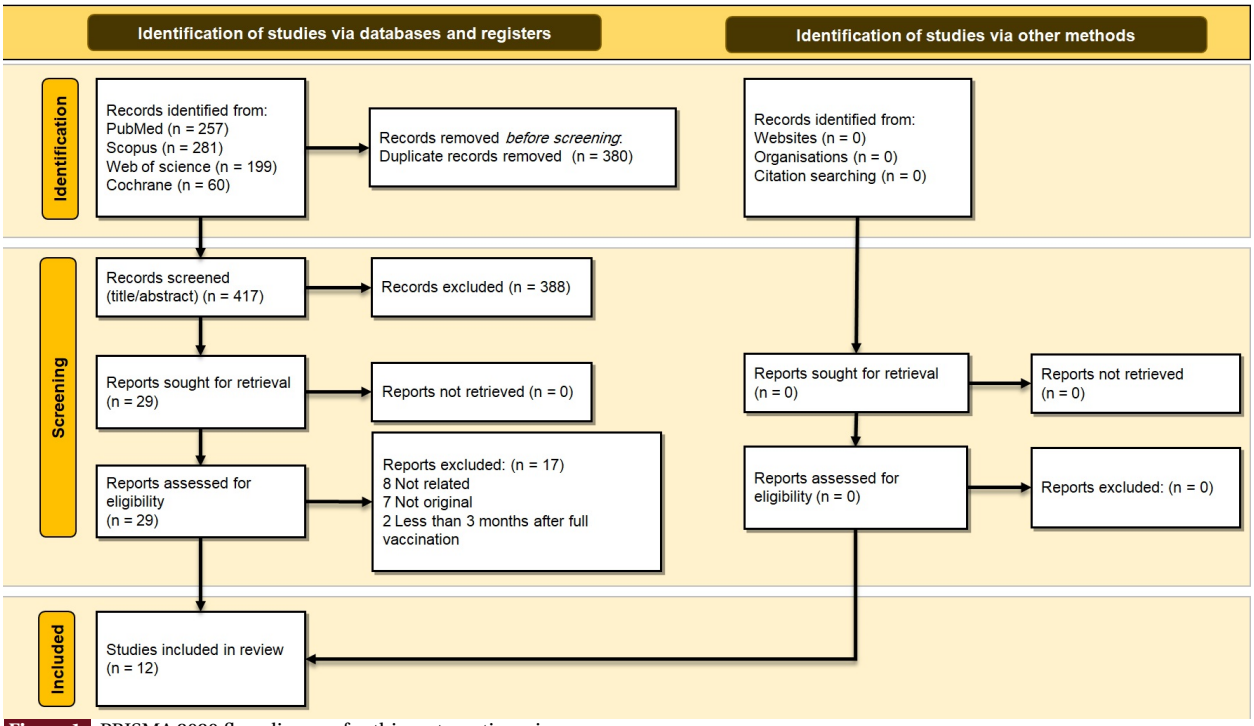

Figure 1: PRISMA 2020 flow diagram for this systematic review.

Table 1: Summary of findings based on each study

First author (reference)	Type of study	Study population (N)	Male (%)	Mean age (SD)	Type	Time after vaccination	Changes in antibody levels	Vaccine efficacy against			Author's opinion about booster dose	Summary of findings
								Infection	Disease severity	Mortality		
A.Erice (19) Spain, 2021	Observational study	Adults	62%	46.0 years (SD 11.4 years)	mRNA vaccine	Serum samples were obtained a mean of 40.1 days (SD 2.8 days) and 88.8 days (SD 2.8 days) after the second dose of BNT162b2	Median [IQR] anti-RBD titres 1.5 months after vaccination were 9,356 [5,844 - 16,876] AU/mL; three months after vaccination, median anti-RBD titres had declined to 3,952 [2,190 - 8,561] AU/mL (p <0.001)	Advanced severe COVID-19 has been reported in fully vaccinated individuals a median of 39.5 days after the second dose of BNT162b2				A low anti-RBD antibody titer is one aspect related tothe advanced SARS-CoV-2 infection after complete vaccination with BNT162b2
J.Favresse (20) Belgium, 2021	Ongoing multicenter, prospective, and interventional study	Healthcare professionals	22.5	43	mRNA COVID-19 vaccine	3 months	The maximal antibody response was reached between days 28 and 42 (2204 versus 1,863; P=0.20), with a 48.8–57.7-fold increase compared to day 14 (i.e. 38.2 U/mL)					As calculated by the one-compartmental model, the estimated half-life of antibodies observed from data collected until 90 days after vaccination for seronegative members was 55 days (95% CI: 37–107 days)
W.Gou (21) China, 2021	Clinical trial	Healthy adults aged ≥18	41.1 and 59.5 in twoage groups	The mean (standard deviation) age was 43.1 (9.6) years in participants aged 18–59 years and 66.7 (4.3) in those aged ≥60 years (79.2% aged 60–69 years)	Inactivated	90 days	Geometric mean titerof neutralizing antibody on day 90 after the third injection ranged from 87 to 129, respectively, among participants receiving three doses of vaccines					The initial results of the Phase 1/2 trial among adults, including those aged 60 years or older, showed that the inactivated vaccine against SARS-CoV-2 was safe and immunogenic.
J.F. Hedges (24) USA, 2021	Cohort			41.8	mRNA	6 months	The neutralization titers had declined 6 months after vaccination,similar to 6 months after natural infection.					The antibody responses induced by vaccination were significantly higher than those induced by natural infection. Therefore, the study suggests that vaccination is still vital, even for those naturally infected or diagnosed with COVID-19.

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First author (reference)	Type of study	Study population (N)	Male (%)	Mean age (SD)	Type	Time after vaccination	Changes in antibody levels	Vaccine efficacy against			Author's opinion about booster dose	Summary of findings
								Infection	Disease severity	Mortality		
P.Naaber (16) Estonia, 2021	Longitudinal observational	Healthcare workers	42	42.5	mRNA	6 months	In the first serum sample, the median anti-S-RBD IgG reached 540.0 AU/mL (IQR 64.5-1102.0). In the following tests, a progressive decay of antibodies was seen, up to the value of 55.7 AU/mL (IQR 26.2-84.7) at the 6-month follow-up				This study may allow to define a protective antibody threshold, below which the risk of break-through infections significantly increases and which could, hence, guide the time point when to offer a booster dose.	The study approves the persistence of anti-S-RBD neutralizing antibodies through 6 months after the vaccination.
M.Pouquet (26) France, 2021	Longitudinal survey	Health care workers			RNA-based vaccines	6 months						
E. Terpos (18)	Prospective study	Health care workers	32.9	48	mRNA	3 months	Three months after the second vaccination (i.e., on D111), the decline in NAb titers was even more prominent with a median inhibition of 92.7% (SD 11.8)				The longitudinal study is continuing in order to determine the time point of NAbs decrease below the positivity threshold, and the fading of protective immunity against COVID-19; when a booster vaccine dose might be necessary.	Both NAbs and anti-S-RBD antibodies, the maximum levels are seen at day 36. A statistically significant decrease in both types of antibodies was observed after day36 up to day111
S. J. Thomas (9) 6 countries, USA, Turkey, Germany, South Africa, Brazil, Argentina; 2021	Clinical trial	Adolescents and adults	50.9	51	mRNA	6 months		Vaccine efficacy of 91.1%				BNT162b2 effectively prevents COVID-19 for up to 6 months after the second dose across various populations, despite the emergence of

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First author (reference)	Type of study	Study population (N)	Male (%)	Mean age (SD)	Type	Time after vaccination	Changes in antibody levels	Vaccine efficacy against			Author's opinion about booster dose	Summary of findings
								Infection	Disease severity	Mortality		
												SARS-CoV-2 variants, including the beta variant, and the vaccine continues to show a promising safety profile.
M. Tré-Hardy(17) Belgium, 2021	Prospective study	Health care workers	25.4	50.1	mRNA	5 months	Antibody values went from 400 [400-400] AU/mL at 3 months after first injection to 221.0 [202.3-241.2] AU/mL at 6 months after first injection, and from 400 [400-400] AU/mL at to 400 [365.0-400] AU/mL at				Introducing a booster dose, under certain circumstances, could have a significant impact in terms of public health	All applicants still had detectable SARS-CoV-2 IgG antibodies up to 5 months after complete vaccination.
I.Vicenti(27) Italy, 2021	Longitudinal study	Health care workers (HCWs)	39.1		mRNA	3 months	Previously infected vaccinated HCWs (n=23): 546 Uninfected vaccinated HCWs (n=13): 20				In uninfected HCWs completing the two-dose vaccine program, a third mRNA vaccine dose is a sensible option to counteract the substantial NtAb decline occurring at a significantly higher rate compared with previously infected, vaccinated HCWs	Median NtAb at V2_90 (90±2 days after the second dose) was still significantly higher than median NtAb at V_0 (before receiving the first dose) both in HCWs with past mild disease (p=0.01) and in those experiencing asymptomatic infection (p=0.001).

Table 1: Summary of findings based on each study

First author (reference)	Type of study	Study population (N)	Male (%)	Mean age (SD)	Type	Time after vaccination	Changes in antibody levels	Vaccine efficacy against			Author's opinion about booster dose	Summary of findings
								Infection	Disease severity	Mortality		
I.Waldhorn(22) Israel, 2021	Prospective follow-up report of the primary study	Cancer patients with solid tumors	55	66	mRNA	166 ± 29 days	Both cohorts depicted a drastic decline in serology titer over time,but the titer remained above the threshold value					There was no notable difference in the median absolute serology titer between the seropositive individuals within the two cohorts (patients vs. controls).
K. Zakaria(25) Kazakhstan, 2021	Clinical trial	Adults aged 18 years and older	77.3	28	Inactivated whole-virion	6 months	An increase in the titers of neutralizing antibody was statistically significant, reaching Geometric Mean Titer of 5.1 (95% CI 3·5–7·6) on day 21 and Geometric Mean Titer of 100 (95% CI 77–129) on day 42. On day180 after the first immunization, the Geometric Mean Titer dropped to 7 (95% CI 5–7)					In both trials, specific antibodies were detected in MNA and ELISA on study day 180, but the titers dropped in comparison today 42.

SD: standard deviation; IQR: interquartile range; CI: confidence interval; S-RBD: spike protein receptor-binding domain; Ig: Immunoglobulin; NAb/NtAb: neutralizing antibody; MNA:microneutralization assay; ELISA:enzyme-linked immunosorbent assay.

Table 2: The results of Newcastle-Ottawa scale (NOS) risk of bias assessment

The first author (Reference)	Selection (out of 4)	Comparability (out of 2)	Exposure/ Outcome (out of 3)	Total score (out of 9)
A.Erice(19)	***	-	**	5
J.Favresse(20)	***	*	**	6
W.Gou(21)	***	-	***	6
J.F. Hedges(24)	****	*	**	7
P.Naaber(16)	****	*	**	7
M.Pouquet(26)	***	*	***	7
E. Terpos(18)	****	*	*	6
S. J. Thomas(9)	****	*	**	7
M. Tré-Hardy(17)	***	*	***	7
I.Vicenti(27)	****	*	***	8
I.Waldhorn(22)	****	*	***	8
K. Zakaria(25)	****	*	**	7