Medical Research Archives

ESMED
European Society of Medicine

OPEN ACCESS

Published: March 31, 2023

Citation: Dashti M, Azimi N, et al., 2023. Effectiveness of Covid-19 Vaccination on BA.4/BA.5 Variant: A Review of Current Literature, Medical Research Archives, [online] 11(3). https://doi.org/10.18103/mra.v11i3.3583

DOI
https://doi.org/10.18103/mra.v11i3.3583

ISSN: 2375-1924

REVIEW ARTICLE

Effectiveness of Covid-19 Vaccination on BA.4/BA.5 Variant: A Review of Current Literature

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ABSTRACT

The B.1.1.529 (Omicron) variant of SARS-CoV-2 has rapidly spread with many variants like BA.1, BA.2, BA3., BA4., and BA5. With sublineages as well. It (Omicron) was first discovered in November 2021 and has become the predominant variant in several nations. Due to the sensitivity of infection and various other limitations like no particular real-time data for different age groups, there is a lack of information on the actual efficacy of vaccines against this variant. Limitations of data and reviews and the incidence of emergence rather than hospitalized people would result in an underestimation of the efficacy of vaccines against severe diseases. This systematic review was conducted by following PRISMA guidelines. Specific inclusion and exclusion parameters were strictly followed. Our studies show that a substantial number of people have received mRNA COVID-19 vaccine doses. The booster dose must be administered and obtained immediately before all efforts to stop the pandemic go to waste. Focusing on the primary vaccination is no longer sufficient.

Keywords: COVID-19 vaccines, Efficacy, Booster dose, Omicron variation

Introduction

Recently, Omicron variants with multiple lineages have been spreading globally. Several new sublineages, such as BA.1 and BA.2, the related sublineages BA.2.12.1 and BA.3 (relatively rare), and the more recent sublineages BA.4 and BA.5, have emerged. BA.2.12.1 was predominantly found in the United States, and BA.4 and BA.5 were mainly detected in South Africa, with a combined frequency of more than 88%[1]. These new Omicron variants have demonstrated considerable neutralizing escape. Thus, there is a crucial challenge of whether COVID-19 vaccines have the essential efficacy to prevent infection[2].

Strains gradually emerge and carry multiple mutations, especially in the spike gene sequence. Therefore, unique mutations in the spike proteins on BA.4 and BA.5, including L452R and F486V (near the ACE2 receptor of the host cell attachment spot), are known to be a potential reason for their ability to evade neutralizing antibodies and induce some immune responses[3]. Overall, 30 mutations with 15 amino acid substitutions on the viral spike for the Omicron variant have delayed the resolution of the pandemic and are a matter of concern for the efficacy of the existing vaccine[4].

Many studies have been conducted to approach the question of antibody escape of BA.2.12.1, BA.4, and BA.5 sub-lineages by exposing them to blood samples of vaccinated people or patients already infected with SARS-CoV-2; however, the effectiveness of the existing vaccines has not been entirely ideal thus far[5]. The efficiency of neutralizing antibodies against BA.4 and BA.5 was compared in a study between vaccinated and unvaccinated groups, and a considerable drop (>7-fold) in neutralizing antibody titres was found for these sublineages compared to that of BA.1[3]. An efficacious vaccine is needed to prevent infection and control the pandemic.

In this study, we aimed to review the effectiveness of prior vaccination and boosters in BA.4 and BA.5 variant-positive COVID-19 patients and investigate the effectiveness of the booster dose.

Methods and materials

We followed the PRISMA guidelines for conducting this systematic review.

PICO Question

Patient: BA.4 and BA.5 variant-positive COVID-19 patients

Intervention: Prior vaccination

Comparison: Type of vaccination and number of doses

Outcome: Effectiveness of vaccination

Search Strategy

The literature was systematically searched (July 2022) for relevant materials in PubMed/Medline, Embase, Web of Science, and Scopus, up to and including July 2022, with no time restrictions, and only publications in English were included in the study. The reference lists of the included studies were searched manually for potential materials. The following search strategies were used for each database and are shown in Table 01:

Table 01: Keywords designed for each database.

Database	Keyword	Result
PubMed/Medline	((("Vaccines"[Mesh]) OR "Vaccine Potency"[Mesh] OR Vaccine OR Vacc* OR Vaccination) AND (Covid-19 OR Covid OR Sars-Cov-2)) AND (BA.5 OR BA.4)	13 papers
Embase	('vaccines':ab,ti,kw OR 'vaccine potency':ab,ti,kw OR 'vaccine':ab,ti,kw OR 'vaccination':ab,ti,kw) AND ('covid-19':ab,ti,kw OR 'covid':ab,ti,kw OR 'sars-cov-2':ab,ti,kw) AND ('ba.5':ab,ti,kw OR 'ba.4':ab,ti,kw)	18 papers
Web of Science	((ALL=(Vaccines OR Vaccine Potency OR Vaccine OR Vaccination)) AND ALL=(Covid-19 OR Covid OR Sars-Cov-2)) AND ALL=(BA.5 OR BA.4)	Four papers
Scopus	(TITLE-ABS-KEY (vaccines) OR TITLE-ABS-KEY ("Vaccine Potency") OR TITLE-ABS-KEY (vaccine) OR TITLE-ABS-KEY (vaccination)) AND (TITLE-ABS-KEY (covid-19) OR TITLE-ABS-KEY (covid) OR TITLE-ABS-KEY (sars-cov-2)) AND (TITLE-ABS-KEY (ba.5) OR TITLE-ABS-KEY (ba.4))	7 papers
Scopus secondary document	(TITLE-ABS-KEY (vaccines) OR TITLE-ABS-KEY ("Vaccine Potency") OR TITLE-ABS-KEY (vaccine) OR TITLE-ABS-KEY (vaccination)) AND (TITLE-ABS-KEY (covid-19) OR TITLE-ABS-KEY (covid) OR TITLE-ABS-KEY (sars-cov-2)) AND (TITLE-ABS-KEY (ba.5) OR TITLE-ABS-KEY (ba.4))	0 papers

Inclusion and Exclusion Criteria

The inclusion criteria of the current review were as follows:

1. Randomized clinical trials (RCTs), controlled clinical trials (CCTs), prospective and retrospective cohort studies, case series, and in vitro studies on the effectiveness of Covid-19 vaccination against Omicron variants BA.4 and BA.5
2. Only English language.

The exclusion criteria were as follows (the reasons for excluding articles are also recorded in Table 1):

1. Any other types of variants
2. Systematic reviews and meta-analyses.
3. Publication in any language other than English.

Study Selection Process

Two independent reviewers (M.D. and N.A.) conducted a duplicate search to determine accurate reports using the inclusion and exclusion criteria. Instances of divergence of opinion were resolved by consulting a third investigator (M. D.). The full-text version of papers was obtained for all titles that appeared to meet the inclusion criteria or in case of any hesitancy. After that, one author studied each paper at least twice (M. D.).

Data Extraction

Whenever applicable, the following data were retrieved from the finally included studies by an author (M.D.) based on a predefined checklist worksheet and reviewed by two other authors for accuracy (M.D. and N.A.). In case of missing data or any hesitancy, the corresponding author of the study was contacted via emails, up to two emails, as the poorly reported outcomes of included materials could thread the validity of our work. The following data were extracted: first author, year of publication, country of origin, number of cases, case description, age, sex, type of variant, type of vaccination, and effectiveness.

Results

Study Selection

The PRISMA flow diagram for the study selection process through different stages is shown in Figure 1. The initial search yielded 42 results. Twenty studies remained after duplication removal. Of the remaining materials, 4 were excluded based on the content of the title and abstract (if necessary). Full texts were retrieved for the remaining 16 papers. Four papers were excluded after reading the full text. Finally, 12 papers were included in the systematic review.

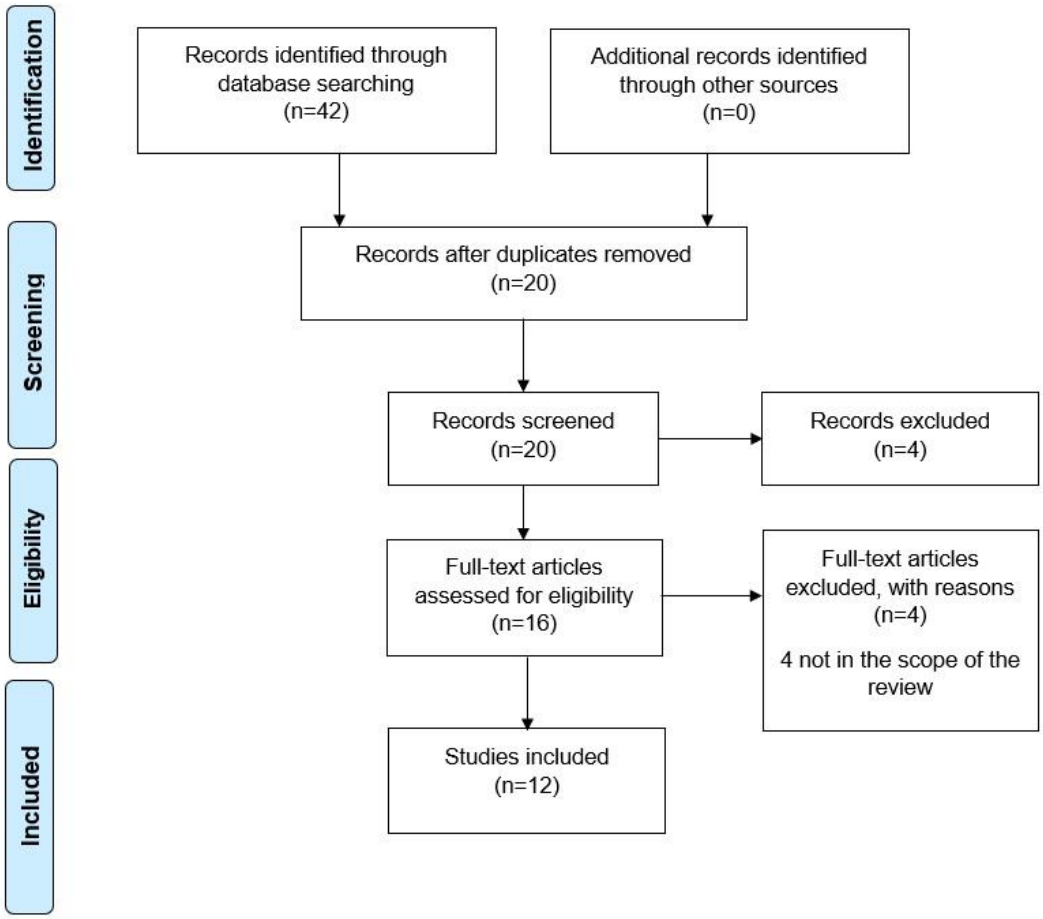

Fig. 01: PRISMA flowchart.

Statistical analysis:

Of the 796 individuals included in this review, 291 were women, 211 were men, and 294, the gender was not specified. The age range of the patients was 20-80 years. Of these, 577 people had received three doses of the vaccine, 111 people had received two doses of the vaccine, 74 people had been vaccinated without the mention of doses, and 34 people had not been vaccinated.

In general, the effectiveness of BA.4 and BA.5 variants was reduced by 3.91 times compared to that of BA.1. In individuals who received 3 doses of vaccination, the effectiveness of BA.4 and BA.5 was reduced by 1.95 times compared to that of BA.1. In those who received 2 doses of vaccination, the effectiveness of BA.4 and BA.5 was 4.75 times lower than that of BA1. Additionally, for those who received two or three doses of vaccination, the effectiveness of BA.4 and BA.5 was 4.2 times lower than that of BA.2.

In these studies, only in individuals who received three doses of vaccination were changes in the effects of BA.4 and BA.5 compared to the reported D614G variant. In people who received 3 doses of vaccination, the effectiveness of BA.4 and BA.5 was 11.3 times lower than that of D614G.

Discussion:

The rates of infection of the subvariants BA.4/5 and BA.2.12.1 of SARS-CoV-2 Omicron have risen radically, especially in South Africa and the United States. These new subvariants have additional mutations among their spike proteins, which raises questions and concerns that they might escape antibodies through neutralization thus further lowering the effectiveness of therapeutic monoclonal drugs and COVID-19 vaccines. The recent detection and dramatic expansion of three new Omicron subvariants have raised concerns[6].

In early February, a subvariant BA.2.12.1 emerged in the U.S. and expanded significantly to almost 55% of the SARS-CoV-2 variants in the country and almost worldwide. In South Africa, the subvariants BA.5 and BA.4 prevailed in January and swiftly became dominant with a percentage of 88%. These novel subvariants of Omicron have been perceived around the globe, with a total ratio of approximately 50% and even more in the past few weeks. Their growth curves in South Africa and the United States specify a significant transmission benefit that will have a probable effect in the next SARS-CoV-2 upsurges, as is being perceived in the United States and the U.K., phylogeny analysis of these novel types of COVID showed that they progressed autonomously from BA.2[7].

It has been indicated clearly from epidemiological data that the BA.4/5 and BA.2.12.1 subvariants of SARS are highly infectious; nevertheless, further mutations in the subvariants at the top of receptor-binding domain (RBD) boost the likelihood of a significant loss of affinity for the receptors of viruses, such as hACE2 (an enzyme in humans named a human angiotensin-converting enzyme). Researchers have identified the binding affinity of refined spike proteins of major Omicron subvariants and D614G to dimeric hACE2 using SPR (surface plasmon resonance)[8].

Whole-genome sequencing (WGS) is the benchmark for characterizing accurate novel viral variants and genome designations. For WGS of SARS-CoV-2, the Sanger technique has been used in many instances. Two sequencing methods, next-generation sequencing (NGS) and Sanger sequencing were used to identify the first SARS-CoV-2 WGS from a patient infected with 2019-nCoV. However, NGS, which can make thousands of equivalent reads per sequence, is speedily modified in SARS-CoV-2 sequencing identifications[9].

In many areas and countries worldwide, reagent facilities, bioinformatics support, lack of instrumentation, time requirements, and data storage issues limit the practice of WGS for surveillance or routine clinical use. After the WGS of a novel variant is characterized, Sanger sequencing based on a single amplicon of a selected viral genome section is a quick and cost-effective substitute for variant tracking[10].

The Sanger sequencing method can offer a better read (1.2 kb) to count an amplicon ranging in size from 0.5-1 kb; however, samples, for example, nasal swabs, saliva, or even wastewater, frequently lack a whole segment of RNA, making it difficult to produce larger amplicons in PCR (RT–qPCR) reverse transcriptase quantitative methods.

Consequently, overall variant surveillance and early discovery of viral mutations are essential as a countermeasure; for example, they could aid in therapeutic drug developments and precautionary vaccine modification. Presently, WGS is primarily used to characterize the SARS-CoV-2 genome and to identify variants. Nevertheless, this method has many limits, as it requires reagent resources, significant equipment, and personnel time and has a higher cost. With NGS development, it is possible to decrease the time and cost of sequencing[11].

Original screening of viral presence in nasal and saliva swabs in VTM (viral transport medium) speeds up the process of sequencing. It might also be utilized for other samples, including urine, water, and body fluids[12].

Researchers have identified that a single-stranded RNA of 30 kb of SARS-CoV-2 codes for approximately 16 nonstructural proteins (1-16), which are generated from 4 structural proteins: the membrane (M), spike (S), nucleocapsid, and envelope (E) proteins[13]. The receptor-binding domain, which is a segment of 194 amino acid residues in the spike protein at the S1 subunit, adheres to the host cell receptor to initiate S2 subunit membrane fusion and removal[14]. The receptor-binding motif (RBM) and RBD contain 69 amino acid residues (from amino acids 438 to 506). Overlying the ACE2 binding position is immunodominant and comprises the mainstream counteracting epitopes.

Nineteen of the 20 most influential (MAbs) counteracting monoclonal antibodies have been identified to bind to the binding site of ACE2. The RBM segment has great amino acid variability among SARS-CoV and SARS-CoV-2. Mutational variations in the RBM segment might influence virus antigenicity, vaccine efficacy, and viral transmissibility[15], Higdon, et. al., showed that the Omicron variant beginning late 2021, has shown reductions in vaccine efficacy[16]. Consequently, the region of the SARS-CoV-2 RBD surrounding the RBM section was used for Sanger sequencing and PCR amplification. The initial primer pair was intended to magnify a 246-bp section (522 to 440 aa) of the spike protein of SARS-CoV-2 (319 to 541 aa) and was utilized to distinguish alpha from BV1[17].

According to experts and data available, we can assume there are many gaps and a lack of information about whether persons immunized with the vaccine of COVID-19 have immunity against Omicron BA.4 and BA.5 compared with other strains or not[18].

Typically, it has been revealed that heterologous booster schedules were immunogenically higher than boosters with the same COVID-19 vaccines/homologous prime[19].

Given the resource limitation and cost involved in WGS worldwide, the Sanger RBM-targeted sequencing strategy was accepted in various studies for rapid molecular surveillance of variants when identifying SARS-CoV-2. Vaccine modification and therapeutic development of genomic surveillance of the SARS-CoV-2 variant are essential to combat the COVID-19 pandemic. Single amplicon-based Sanger sequencing is a quicker and more cost-effective alternative for variant surveillance than whole-genome sequencing.

Conclusion

Variants BA.4 and BA.5 showed higher infection rates than former variants, and individuals with booster doses showed fewer infection rates than those with only two vaccine doses, regardless of the vaccine type. This indicates that the booster dose must be administered before all efforts to stop the pandemic go to waste.

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Table 02: Data extraction table.

Author/Year	Country	Number of cases	Description of the cases	Age (Years)	Sex	Variant Type	Vaccination Type	Effectiveness
Qian Wang[1]/2022	USA	N= 16	Three doses of the mRNA-1273 or BNT162b2 vaccine	26-78	F= 7 M= 9	BA.2.12.1 BA.4 BA.5 D614G	mRNA-1273 BNT162b2	Neutralization titers of BA.4/5 were remarkably lower (19.2-fold) for the three doses vaccinated, compared to D614G, and by 4.2-fold compared to BA.2. Moreover, similar results were found for sera neutralization of the other cohorts, with the lowest titers against BA.4/5, followed by BA.2.12.1. Patients with both mRNA vaccination and SARS-CoV-2 infection showed 4.3 greater resistance to neutralization compared to BA.4/5 in their sera.
		N= 22	Infected by non-Omicron variants of SARS-CoV-2 before or after vaccination	22-67	F= 14 M= 8			
		N= 13	Patients with either BA.1 breakthrough infection after vaccination	35-78	F= 2 M= 4 UNK = 7			
		N= 12	Patients with either BA.2 breakthrough infection after vaccination	28-69	F=7 M= 5			
Nicole P. Hachmann[2]/2022	USA	N= 27	Vaccinated and boosted with the mRNA vaccine BNT162b2 (3 doses)	35 (23-67)	F= 24 M= 3	BA.1 BA.2, BA.2.12.1, BA.4 BA.5	BNT162b2 (3 doses) (Pfizer-BioNTech)	Group 1: Median nAb titers for BA.4/5 were 3.3-fold lower than median BA.1. Group 2: For the Omicron infection, the data show a 2.9 reduction fold comparing BA.4/5 to BA.1. BA.4/5 considerably escaped nAb elicited by vaccination and infection, and the SARS-CoV-2 Omicron variant kept evolving with increasing neutralization escape.
		N= 27	Infected with Omicron BA.1 or BA.2 Days from last vaccine dose to positive PCR test, 83 (37-153)	34 (27-41)	F=21 M=6		BNT162b2 (3 doses) = 8 BNT162b2 (2 doses)/mRNA-1273 (1 dose)= 2 mRNA-1273 (3 doses)= 7 mRNA-1273 (2 doses)/BNT-1273 (1 dose)= 2 mRNA-1273 (2 doses)/Ad26.COV2.S (1 dose)= 1 BNT162b2 (2 doses)= 4 Ad26.COV2.S (1 dose)/mRNA-1273 (1 dose)= 1	

							Ad5/Ad26 (2 doses)/mRNA-1273 (1 dose)= 1 Unvaccinated= 1	
Panke Qu[5]/2022	USA	N= 4	Vaccinated with 2-doses of the Moderna mRNA-1273 vaccine	37 (31-56) years	F=7 M=8	BA.4 BA.5 D614G	Moderna mRNA-1273 Pfizer/BioNTech mRNA-1273	BA.4/5 showed potent nAb resistance similar to the BA.1 and BA.2, with nAb titers nearly 20-fold lower than ancestral D614G. NT50 is 4-fold lower than ancestral D614G and 31% (p=0.08) lower than BA.2.
		N= 11	Vaccinated with 2-doses of the Pfizer/BioNTech mRNA-1273 vaccine					
Prerna Arora[6]/2022	Germany	N= 10	Nonvaccinated and infected with Omicron wave	20-71 years	F=5 M=5	BA.2.12.1 BA.4 BA.5	BNT162b2 (Pfizer-BioNTech)	BA.4/5 neutralization was notably decreased compared with BA.2 and BA.2.12.1 for the unvaccinated group. For triple BNT162b2 vaccination, BA.4/5 evaded neutralization of antibodies with 8.1-times lower neutralization compared to B.1.
		N= 10	Vaccinated with three doses without breakthrough infection 13-47 days since the last vaccination	25-64 Years	F=8 M=2			
		N= 10	Vaccinated with three doses with breakthrough infection of Omicron wave 99-187 days since the last vaccination	25-44 years	F=7 M=3			
Yunlong Cao[7]/2022	China	N= 40	3 doses of CoronaVac			BA.1 BA.2.12.1, BA.4 BA.5	CoronaVac	BA.2.12.1, BA.4, and BA.5 showed higher neutralization evasion than BA.2 in sera from patients with triple-vaccination and infection with BA.1. BA.1-derived vaccine boosters may not reach sufficient immunity against BA.4/5. The plasma NT50 of BA.1 convalescents against BA.4/5, compared to that against BA.1, was reduced 8.0x fold.
		N= 39	2 doses of CoronaVac and 1 booster dose of ZF2001				CoronaVac ZF2001	
		N= 54	BA.1 convalescents + 3 doses of CoronaVac before BA.1 infection				CoronaVac	
Mary-Ann Davies[8]/2022	SOUTH AFRICA	N=3,793	None vaccinated Single dose vaccinated Double dose vaccinated Triple dose vaccinated	20-39 years 1,783 (47.0%)	F= 2466 M= 1327	BA.4 BA.5	None 1,535 (40.5%) Single dose Ad26.COV2.S 488 (12.9%)	Both BA.4/5 waves showed lower severe hospitalization hazards or death, similar to BA.1 but lower than previous waves.

				40-49 years 767 (20.2%) 50-59 years 623 (16.4%) 60-69 years 333 (8.8%) ≥70 years 287 (7.6%)			single dose BNT162b2 147 (3.9%) 2 doses Ad26.COV2.S 298 (7.9%) 2 doses BNT162b2 1,067 (28.1%) 2 doses Ad26.COV2.S + BNT162b2 5 (0.1%) ≥3 doses Ad26.COV2.S 38 (1.0%) ≥3 doses of BNT162b2 192 (5.1%) ≥3 doses Ad26.COV2.S + BNT162b2 23 (0.6%)	The previous infection was highly protective against severe hospitalization or death, similar to vaccination for boosted, two, and single doses, respectively.
Khadija Khan[9]/2022	South Africa	N= 24	Unvaccinated	31.5 (26-49) years	F=16 M=8	BA.4 BA.5	BNT162b2 (Pfizer-BioNTech) Ad26.CoV.2S (Johnson and Johnson)	$FRNT_{50}$ in unvaccinated participants declined 7.6-fold, 95% CI 4.9-12.0 for BA.4, and 7.5-fold, 95% CI 4.4-12.5 for BA.5. In the vaccinated group, $FRNT_{50}$ reduced 3.2-fold, 95% CI 2.3-4.4 for BA.4, and 2.6-fold, 95% CI 1.8-3.7 BA.5. In the vaccinated group, the neutralization level was 5-times fold higher than the unvaccinated group; a similar escape was found for BA.4 and BA.5, comparing each other.
		N= 15	Vaccinated + BA.1 infection	37 (32-60) years	F=9 M=6			
Chaitanya Kurhade[10]/2022	USA	N= 22	Vaccinated with three doses	26-75 years	F=14 M= 8	WA1/2020 BA.4 BA.5	BNT162b2 (Pfizer-BioNTech)	For vaccinated people, immune sera of those who received 3 doses of BNT162b2 were neutralized. The geometric mean titres (GMTs) of WA1/2020 and BA.4/5 were 1335 and 103, respectively. These findings suggest that the BA.4/5 variant had the highest susceptibility to evade neutralization compared to the original variants.

Lyke[11]/ 2022	USA	N= 50	mRNA-1273 vaccine boosted with 100 **mg** mRNA-1273.	50% age 18–55 50% older than 56 In each group	F= 50% M= 50%	BA.1 BA.2 BA.3 BA.4 BA.5 D614G	mRNA-1273	Boosted Omicron neutralization titers are substantially higher for homologous mRNA vaccine boosting and for heterologous mRNA and Ad26.COV2.S vaccine boosting, compared with homologous Ad26.COV2.S boosting. Homologous mRNA vaccine boosting generates nearly equivalent neutralizing activity against Omicron sublineages BA.1, BA.2, and BA.3 but modestly reduced neutralizing activity against BA.2.12.1 and BA.4/BA.5 compared with BA.1. For Omicron sublineages, neutralizing antibodies after 90 days of homologous mRNA-1273 vaccine and booster dose declined by 5.6-14.2x fold compared to D614G linage.
		N= 50	Ad26.COV2.S vaccine boosted with Ad26.COV2.S.				mRNA-1273, Ad26.COV2.S	
		N= 50	BNT162b2 vaccine boosted with BNT162b2.				BNT162b2	
		N= 50	mRNA-1273 vaccine boosted with 50 **mg** mRNA-1273.				mRNA-1273	
		N= 50	Ad26.COV2.S vaccine boosted with BNT162b2.				Ad26.COV2.S, BNT162b2	
		N= 50	BNT162b2 vaccine boosted with Ad26.COV2.S.				BNT162b2, Ad26.COV2.S	
Jasmin Quandt[12]/2022	Germany	N= 23	Double vaccinated	52 (23-80)		BA.1 BA.2 BA.4 BA.5	BNT162b2 (Pfizer-BioNTech)	The pVN50 GMT of double-vaccinated individuals with Omicron BA.4/5 infection was 15-fold higher than the GMTs of Omicron-naïve double-vaccinated individuals. In contrast, Omicron BA.1 infection exhibited a slight boost effect on neutralization of BA.4/5, with pVN50 GMTs significantly lower than COVID-19 (GMT 135 vs. 740). Considering SARS-CoV-2 variants and SARS-CoV-1 pVN50 GMTs compared to Wuhan, breakthrough infection with Omicron BA.1 does not elicit sufficient cross-neutralization of Omicron BA.4/5 in double and triple vaccinated patients in comparison with triple-vaccinated Omicron-naïve patients.
		N= 24	Triple vaccinated	38 (20-69)				
		N= 8	Double vaccinated + prior Omicron infection	39 (27-60)				
		N= 10	Triple vaccinated + prior Omicron infection	32 (23-60)				
Aekkachai Tuekprakhon[13]/2022	UK		(n = 41): 28 days after the third dose of the Oxford AstraZeneca (AZD1222) vaccine	37 (22-66)		BA.1 BA.2 BA.4 BA.5	AZD1222 (AstraZeneca) BNT162b2 (Pfizer-BioNTech)	For AZD1222, neutralization titres for BA.4/5 were decreased 2.1-fold and 1.8-fold compared to BA.1 and BA.2, respectively.

			(n =19): 28 days after the third dose of the Pfizer-BioNTech (BNT162b2) vaccine					Additionally, in the BNT162b2 group, neutralization titres were reduced 3.1-fold compared to both BA.1 and BA.2. These reductions in titre may decrease vaccine effectiveness, especially in the long term, as antibody titres wane.
Brian J. Willett[14]/2022	UK	N= 7	2 doses of the Pfizer/BioNTech (BNT162b2) vaccine followed by a third dose of the Pfizer/BioNTech (BNT162b2) vaccine			BA.1 BA.2 BA.4 BA.5	AZD1222 (AstraZeneca) BNT162b2 (Pfizer-BioNTech)	Sera from postvaccination have the same ability to neutralize BA.1, BA.2, and BA.4/BA.5. Triple-vaccinated sera exhibited a similar drop in neutralizing titre for all Omicron lineages, such as an 8- to 10-fold drop against BA.4/BA.5. Using an older vaccinated cohort, it was found that for both three doses of BNT162b2 and two dose ChAdOx1 + BNT162b2 boost vaccine, the booster dose improved BA.4 neutralizing titres by ≥10-fold.
		N= 8	2 doses of the Oxford/AstraZeneca ChAdOx1 (nCoV-10/AZD1222) vaccine followed by a third dose of the Pfizer/BioNTech (BNT162b2) vaccine					

nAb: Neutralizing antibodies
$FRNT_{50}$: Focus reduction neutralization test
NT_{50}: Neutralization titre
pVN_{50}: 50% pseudovirus neutralization
GMTs: Geometric mean titres