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REVIEW

Potency of BNT162b2 and mRNA-1273 vaccine-induced neutralizing antibodies against severe acute respiratory syndrome-CoV-2 variants of concern: A systematic review of in vitro studies

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Summary

BNT162b2 and mRNA-1273 are two types of mRNA-based vaccine platforms that have received emergency use authorization. The emergence of novel severe acute respiratory syndrome (SARS-CoV-2) variants has raised concerns of reduced sensitivity to neutralization by their elicited antibodies. We aimed to systematically review the most recent in vitro studies evaluating the effectiveness of BNT162b2 and mRNA-1273 induced neutralizing antibodies against SARS-CoV-2 variants of concern. We searched PubMed, Scopus, and Web of Science in addition to bioRxiv and medRxiv with terms including 'SARS-CoV-2', 'BNT162b2', 'mRNA-1273', and 'neutralizing antibody' up to June 29, 2021. A modified version of the Consolidated Standards of Reporting Trials (CONSORT) checklist was used for assessing included study quality. A total 36 in vitro studies meeting the eligibility criteria were included in this systematic review. B.1.1.7 (Alpha), B.1.351 (Beta), P.1 (Gamma), and B.1.617.2 (Delta) are four SARS-CoV-2 variants that have recently been identified as variants of concern. Included studies implemented different methods regarding pseudovirus or live virus neutralization assays for measuring neutralization titres against utilized

Abbreviations: ACE2, angiotensin-converting enzyme 2; CONSORT, Consolidated Standards of Reporting Trials; COVID-19, coronavirus disease 2019; GISAID, Global Influenza Surveillance and Response System; NTD, N-terminal domain; PRISMA, Preferred Reporting Items for Systematic reviews and Meta-Analyses; PROSPERO, Prospective Register of Systematic Reviews; RBD, receptor binding domain; S1, spike 1; S2, spike 2; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; WHO, World Health Organization.

viruses. After two dose vaccination by BNT162b2 or mRNA-1273, the B.1.351 variant had the least sensitivity to neutralizing antibodies, while B.1.1.7 variant had the most sensitivity; that is, it was better neutralized relative to the comparator strain. P.1 and B.1.617.2 variants had an intermediate level of impaired naturalization activity of antibodies elicited by prior vaccination. Our review suggests that immune sera derived from vaccinated individuals might show reduced protection of individuals immunized with mRNA vaccines against more recent SARS-CoV-2 variants of concern.

KEYWORDS
BNT162b2, mRNA-1273, neutralizing antibody, SARS-CoV-2, variants of concern

1 | INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), caused the global pandemic of coronavirus disease 2019 (COVID-19), which infected more than 181 million and killed 3.9 million people across the world as of June 29, 2021.[1] Since the emergence of COVID-19, several drastic public health measures such as draconian lockdowns have been imposed to contain the virus spread and end the pandemic. Understandably, substantial focus has been given to the rapid manufacture and distribution of vaccines that would enable herd immunity for some countries as early as the second half of 2021. This is exemplified by early authorization for emergency use of Pfizer-BioNtech (BNT162b2)[2] and Moderna (mRNA-1273)[3] vaccines, knowing to be the first mRNA based platform vaccines rolled out on a global scale.

SARS-CoV-2 is a positive-stranded RNA virus. The spike protein of the virus consists of two fragments: The spike 1 (S1) subunit, consisting of N-terminal domain (NTD) and receptor binding domain (RBD), is responsible for viral attachment to the host cell through angiotensin-converting enzyme 2 (ACE2), whereas the spike 2 (S2) subunit completes membrane fusion.[4] Because the spike protein is an important mechanism of viral cell entry, it has been a potential target for vaccine development.[5]

Due to the great numbers of viral genome replications that occur in infected individuals and the error-prone nature of RNA dependent RNA polymerase,[6] progressive accrual mutations do and will continue to occur. Despite ineffectiveness of most mutations to viral fitness, a few may provide beneficial features that could give the virus an opportunity to transmit more efficiently and evade host immune response.[7] As a result, efficient mutations could be the subject of natural selection and lead to emergence of novel SARS-CoV-2 variants that are able to expand rapidly across countries and overcome public health efforts to restrict the infection. However, as vaccines currently in circulation have been designed based on the spike sequence of the ancestral SARS-CoV-2 strain, outbreaks of novel variants could be a potential threat for compromising immunogenicity of these vaccines.[8–10]

In recent months, several mutations have appeared in the spike protein, leading to identification of novel variants with several substitutions or deletions in the spike protein. The variants, which have potential to increase transmissibility, virulence, or evade available diagnostics, vaccines, and therapeutics, have been denoted as variants of concern. According to the World Health Organization (WHO), these variants which named Alpha (Lineage B.1.1.7), Beta (Lineage B.1.351), Gamma (Lineage P.1), and Delta (Lineage B.1.617.2) were first emerged in the United Kingdom, South Africa, Brazil, and India, respectively, where they have rapidly become dominant and are currently spreading across the globe (Figure S1 and S2).[11]

Serum neutralization activity is a common predictor of protection against SARS-CoV-2 following natural infection or vaccination.[12,13] Due to variations observed in the spike genome, effective protection from SARS-CoV-2 infection requires a sufficient breadth of neutralizing antibodies rather than potency alone.[14] Preliminary studies have shown that mutant viruses increase the affinity of binding to host cell receptors and diminish the susceptibility of neutralization by pre-existing antibodies raised through either prior infection or vaccination.[15–18]

In the present study, effectiveness of neutralizing antibodies elicited by two doses of mRNA based vaccine platforms, including BNT162b2 and mRNA-1273, was systematically evaluated according to variants of concern using data from in vitro studies.

2 | METHODS

The guideline of Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement was followed for review reporting.[19] As the evaluation was on in vitro studies, the pre-specified protocol could not be published on the International Prospective Register of Systematic Reviews (PROSPERO). However, the protocol was pre-specified and no alterations to the proposed evaluation methods (including design and outcomes) occurred literature retrieval.

2.1 | Search strategy

Three online databases (PubMed, Scopus and Web of Science) and two preprint servers (bioRxiv and medRxiv) were screened for

relevant records up to June 29, 2021. Search terms included 'SARS-CoV-2', 'COVID-19', 'B.1.1.7', 'B.1.351', 'P.1', 'B.1.617.2', 'BNT162b2', 'mRNA-1273', and 'neutralizing antibody'. No search filters were applied to any fields, including study type, publication date, or language. Details on the search strategy for each database are represented in Table S1. Several journals were screened directly from the associated portal, including the New England Journal of Medicine, Science, Nature, and Cell journals, while grey literature included manual screening of results from the first 100 pages of the Google Scholar search engine as well as forward and backward citation searching of reference lists from included studies to find further eligible publications.

2.2 | Study selection

Search results were exported to EndNote X8.0 (Clarivate Analytics, Philadelphia, PA, USA) reference manager software. Following removal of duplicates, titles and abstracts from remaining articles were screened against inclusion and exclusion criteria by two independent review authors. Studies requiring full-text review were again screened by two independent review authors, with discrepancies resolved through consensus, and where required a third author as arbiter. We contacted the corresponding authors for retrieving full-text of articles that we could not access to their full-texts.

Studies meeting the following criteria were included: (1) In vitro studies comparing 50% neutralization titre against SARS-CoV-2 variants of concern and a reference strain for samples obtained from vaccine recipients, (2) Studies reporting fold change of neutralization titre or displayed it in high resolution images, (3) Studies recruiting samples from individuals who received two doses of 30 μg BNT162b2 vaccine or 100 μg mRNA-1273 vaccine, (4) Studies utilizing viruses with at least one set of mutations as reported by WHO for each variant of concern,[20] and (5) Studies reporting the exact mutation in the spike protein of utilized viruses or reporting the strain name and Global Influenza Surveillance and Response System (GISAID; https://www.gisaid.org/hcov19-mutation-dashboard/)-ID. Exclusion criteria were as follows: (1) Samples were collected from convalescent individuals who were not vaccinated, (2) The vaccine type was not clearly determined, (3) Recruited individuals received only one dose of vaccine, (4) Studies were conducted on samples from vaccinated mice or non-human primates, (5) Neutralization titre was measured for viruses with only a specific subset of mutations, and (6) Study types other than in vitro (e.g., clinical trials, animal studies, and systematic reviews).

2.3 | Data extraction

Two independent reviewers extracted the following characteristics from identified studies using standardized templates: first author's name, title, publication date, country of origin, sample size, gender and age of vaccine recipients, type of vaccine, history of previous SARS-CoV-2 infection, and days passed from the second vaccine dose that samples were obtained. Variant of concern type and its spike protein mutation profiles, type of reference virus, stain name or GISAID-ID for variants and reference viruses were also extracted. Where the mutation profile of spike protein was not reported, an additional source, that is the GISAID webpage were was searched.[21] Laboratory methods, including type of neutralization assay and source of the utilized viruses, fold changes in 50% neutralization titre, and relevant *p*-values were also recorded. If fold changes were not reported, neutralization titres were digitized from figures in papers with a digital extraction tool.[22] Disagreements between review authors were resolved by discussion and consensus, or where required consultation with a third reviewer.

2.4 | Risk of bias assessment

Given that no established guidelines currently exist for quality assessment of in vitro studies, two independent review authors used a modified version of the Consolidated Standards of Reporting Trials (CONSORT) tool, which was developed to appraise the quality of studies in dentistry.[23] Discrepancies were resolved through discussion and consultation with a third reviewer. The checklist contains 15 items enabling assessment of methodological quality for included studies, taking into account evidence presented in the abstract, introduction, methods, results, discussion, and other information sections. Each item is answered as a Yes (1 point) or a No (0 point) based on reporting the relevant information. Therefore, a maximum of 15 points and a minimum of 0 point could be assigned to each study for evaluating quality.

2.5 | Data synthesis

Data analysis was performed using qualitative methodology with narrative synthesis. Included studies were categorized based on the variant of interest and type of vaccine. Tables summarizing outcome measures and related findings from each type of vaccine were made. Meta-analysis was not possible due to substantial differences across investigation methods, which was a pre-specified decision, therefore, no test for assessment of publication bias was performed.

3 | RESULTS

The systematic search identified 782 records of which 120 were duplicates and excluded. Following title and abstract screening of the remaining 662 records, 69 full text publications were screened for eligibility. Eighteen studies evaluated the effects of single mutations,[24–41] six studies evaluated the effects of other variants which were not variants of concern,[42–47] three were review

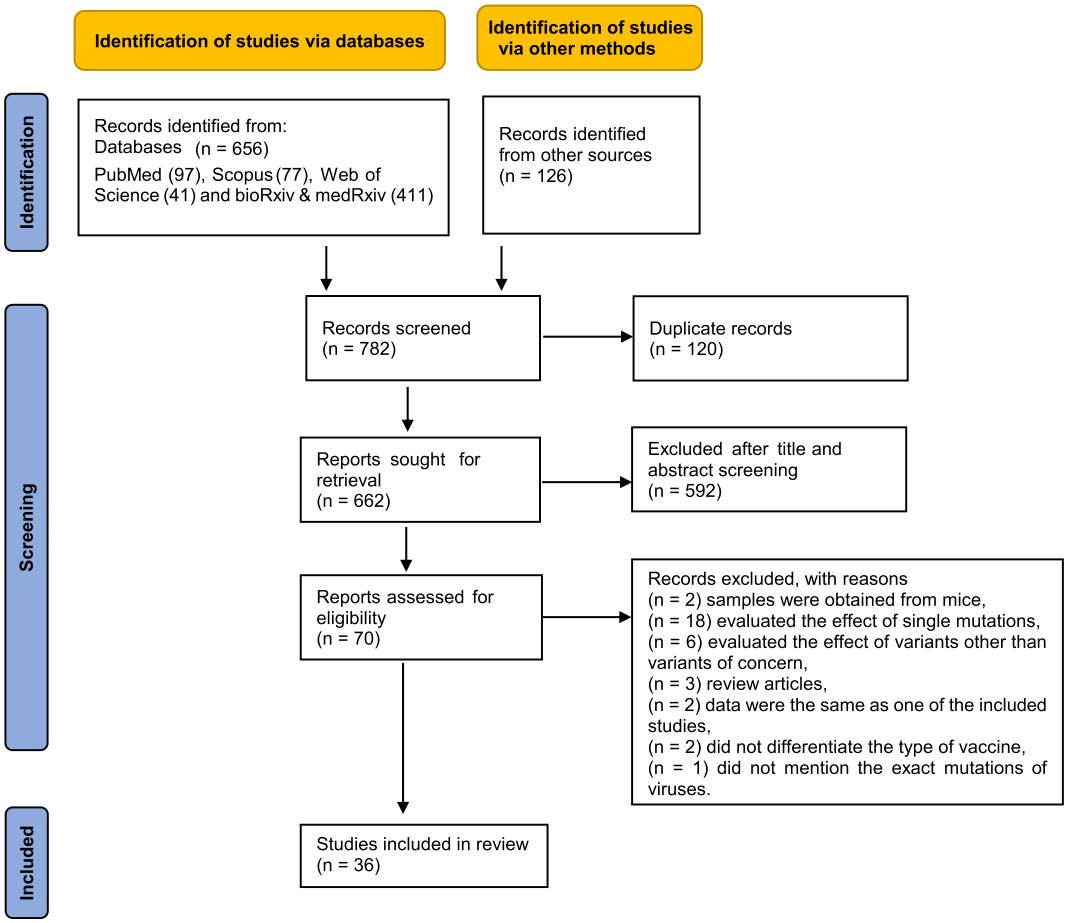

FIGURE 1 Study selection process

articles,[48–50] two studies were re-analysis of previously published articles,[51,52] two studies did not differentiate type of vaccines,[53,54] two studies were conducted on animal subjects,[55,56] and one did not mention the exact mutations of viruses.[57] Finally, 36 publications met the inclusion criteria and were included in this systematic review (Figure 1).

3.1 | Study characteristics

3.1.1 | B.1.1.7 variant

BNT162b2 vaccine

Twenty-two studies[15,16,58–77] with a total of 968 samples evaluated the effect of B.1.1.7 variant on antibody neutralization activity elicited by BNT162b2 vaccine. Samples were obtained at least seven days and up to 91 days after the second dose of vaccine. The reference strain was a virus with D614G mutation in 10 studies,[60–62,66–68,70,72,73,77] a virus with no functional mutation in 11 studies,[15,16,58,59,63–65,69,71,74,75] and both types of viruses were used as comparator strains in one study.[76] Fourteen studies utilized live virus neutralization assays,[15,16,58,59,61,63,64,66,68,70,72,73,75,77] seven used pseudovirus neutralization assays,[60,62,65,67,69,71,74] and one used both types of assays.[76] Fifty percent neutralization titre was decreased as little a s2.6 fold or increased up to 3.8 fold in studies utilizing live virus neutralization assays, and decreased as little as 6.7 fold or increased up to 1.69 fold in studies utilizing pseudovirus neutralization assays, as compared with reference strain (Table 1).

mRNA-1273 vaccine

Eight studies[18,65,69,76,78–81] with a total of 295 samples evaluated the effect of B.1.1.7 variant on antibody neutralization activity elicited by mRNA-1273 vaccine. Samples were obtained at least seven days and up to 180 days after second dose of vaccine. The reference strain was a virus with D614G mutation in four studies,[18,78,79,81] a virus with no functional mutation in three studies,[65,69,80] and both types of viruses were used as a comparator strain in one study.[76] Two studies utilized live virus neutralization assays,[79,80] while four used pseudovirus neutralization assays,[18,65,69,81] and two used both type of assays.[76,78] Fifty percent neutralization titre was decreased as little as 1.77 fold or increased up to 1.6 fold in studies utilizing live virus neutralization assays and it was decreased as little as 3.1 fold in studies utilizing pseudovirus neutralization assays, as compared with reference strain (Table 1).

TABLE 1 Summary of included studies evaluating the neutralization activity of samples against B.1.1.7 variant obtained from vaccine recipients

Vaccine type	Serological assay	Sample size	Days post second vaccine dose	Reference strain	Fold change in 50% neutralization titre	*p*-value of change	History of previous SARS-CoV-2 infection	Age	Sex (number of female)	Country	Study ID
BNT162b2	Live virus neutralization test (FRNT)	51	14–15 days	WT	−2.6	<0.0001	NA	50 (21–82)	28	USA	Bates et al. 2021[b] [59]
	Live virus neutralization test (FRNT)	24	7 days	D614G	−2.03	<0.0001	NA	45 (26–64)	15	USA	Chen et al. 2021[61]
	Live virus neutralization test (FRNT)	25	7–17 days	WT	−3.3	<0.0001	No	43 (25–63)	14	UK	Dejnirattisai et al. 2021[63]
	Live virus neutralization test (PRNT)	20	14–28 days	WT	1.25	0.02	No	51 (23–69)	14	USA	Liu et al. 2021[15]
	Live virus neutralization test (PRNT)	20	14–28 days	WT	1.15	0.04	No	51 (23–69)	14	USA	Liu et al. 2021[a] [16]
	Live virus neutralization test (PRNT)	13	21–28 days	D614G	2.17	<0.0001	Yes	42 (34–56)	10	Netherlands	Geers et al. 2021[66]
	Live virus neutralization test (PRNT)	12	21–28 days	D614G	1.99	<0.01	No	47 (34–55)	11	Netherlands	Geers et al. 2021[66]
	Live virus neutralization test (MN)	159	21–37 days	WT	−2.6	NA	No	43	99	UK	Wall et al. 2021[75]
	Live virus neutralization test (MN)	25	7–17 days	WT	−2.4	<0.0001	No	NA	NA	UK	Skelly et al. 2021[b] [64]
	Live virus neutralization test (MN)	180	13–33 days	D614G	1	NS	NA	43 (20–65)	149	Finland	Jalkanen et al. 2021[b] [68]
	Live virus neutralization test (MN)	60	30 days	WT	−1.1	NS	No	45 (25–65)	38	Italy	Anichini et al. 2021[58]

(Continues)

TABLE 1 (Continued)

Vaccine type	Serological assay	Sample size	Days post second vaccine dose	Reference strain	Fold change in 50% neutralization titre	*p*-value of change	History of previous SARS-CoV-2 infection	Age	Sex (number of female)	Country	Study ID
	Live virus neutralization test (microplate neutralization assay)	10	7 days	WT	1.3	NS	NA	42 (29–64)	5	USA	Wang et al. 2021[76]
	Live virus neutralization test (S-Fuse neutralization assay)	10	7 days	D614G	1.45	NS	NA	NA	NA	France	Planas et al. 2021[72]
	Live virus neutralization test (S-Fuse neutralization assay)	15	21 days	D614G	3.8	<0.05	NA	NA	NA	France	Planas et al. 2021[72]
	Live virus neutralization test (S-Fuse neutralization assay)	16	35 days	D614G	1.87	NS	No	60 (37–75)	5	France	Planas et al. 2021[b 73]
	Live virus neutralization test (S-Fuse neutralization assay)	13	91 days	D614G	1.31	NS	No	NA	NA	France	Planas et al. 2021[b 73]
	Live virus neutralization test (whole virus replication assay)	29	7 days	D614G	−2.5	<0.0001	No	55 (38–65)	20	France	Marot et al. 2021[b 70]
	Live virus neutralization test (cytopathic effect [CPE]-based assay)	37	10–20 days	D614G	2.27	<0.0001	No	46 (23–67)	21	Italy	Zani et al. 2021[77]
	Lentivirus-vector pseudovirus neutralization test	50	28 days	D614G	−1.6	0.0035	No	>60–<35	31	Netherlands	Caniels et al. 2021[b 60]
	Lentivirus-vector pseudovirus neutralization test	21	21 days	D614G	−1.9	<0.001	NA	NA	NA	UK	Collier et al. 2021[62]
	Lentivirus-vector pseudovirus neutralization test	21	21 days	D614G	−6.7	<0.0001	NA	NA	NA	UK	Collier et al. 2021[a 62]

TABLE 1 (Continued)

Vaccine type	Serological assay	Sample size	Days post second vaccine dose	Reference strain	Fold change in 50% neutralization titre	*p*-value of change	History of previous SARS-CoV-2 infection	Age	Sex (number of female)	Country	Study ID
	Lentivirus-vector pseudovirus neutralization test	30	7–32 days	WT	−2.1	NS	No (except one suspected case)	35 (26–66)	18	USA	Garcia-Beltran et al. 2021[65]
	Lentivirus-vector pseudovirus neutralization test	16	14 days	WT	1.69	NS	Yes	39 (29–44)	11	Spain	Trinité et al. 2021[b 74]
	Lentivirus-vector pseudovirus neutralization test	16	14 days	WT	−2.38	NS	No	45 (30–61)	12	Spain	Trinité et al. 2021[b 74]
	VSV-vector pseudovirus neutralization test	40	7–21 days	WT	−1.25	<0.01	No	23–73	NA	USA	Muik et al. 2021[71]
	VSV-vector pseudovirus neutralization test	10	7 days	D614G	−2	0.004	NA	42 (29–64)	5	USA	Wang et al. 2021[76]
	VSV-vector pseudovirus neutralization test	15	13–15 days	D614G	−1.77	<0.01	NA	42 (25–65)	4	Germany	Hoffmann et al. 2021[67]
	VSV-vector pseudovirus neutralization test	30	22–68 days	WT	−2.2	<0.0001	NA	36 (21–73)	19	USA	Liu et al. 2021[b 69]
mRNA-1273	Live virus neutralization test (FRNT)	24	14 days	D614G	−1.2	NA	No	18–>71	NA	USA	Pegu et al. 2021[b 78]
	Live virus neutralization test (FRNT)	24	90 days	D614G	−1.3	NA	No	18–>71	NA	USA	Pegu et al. 2021[b 78]
	Live virus neutralization test (FRNT)	24	180 days	D614G	−1.3	NA	No	18–>71	NA	USA	Pegu et al. 2021[b 78]
	Live virus neutralization test (FRNT)	14	14 days	D614G	1.2	0.04	No	18–55	8	USA	Edara et al. 2021[b 79]
	Live virus neutralization test (FRNT)	14	14 days	WT	−1.77	0.02	No	18–55	8	USA	Edara et al. 2021[80]

(Continues)

TABLE 1 (Continued)

Vaccine type	Serological assay	Sample size	Days post second vaccine dose	Reference strain	Fold change in 50% neutralization titre	*p*-value of change	History of previous SARS-CoV-2 infection	Age	Sex (number of female)	Country	Study ID
	Live virus neutralization test (microplate neutralization assay)	12	15 days	WT	1.6	NS	No	18–>70	NA	USA	Wang et al. 2021[76]
	Lentivirus-vector pseudovirus neutralization test	35	7–177 days	WT	−2.3	NS	No (except one suspected case)	47.3 (25–67)	25	USA	Garcia-Beltran et al. 2021[65]
	Lentivirus-vector pseudovirus neutralization test	24	14 days	D614G	−1.5	NA	No	18–>71	NA	USA	Pegu et al. 2021[b 78]
	Lentivirus-vector pseudovirus neutralization test	24	90 days	D614G	−1.6	NA	No	18–>71	NA	USA	Pegu et al. 2021[b 78]
	Lentivirus-vector pseudovirus neutralization test	24	180 days	D614G	−1.6	NA	No	18–>71	NA	USA	Pegu et al. 2021[b 78]
	Lentivirus-vector pseudovirus neutralization test	29	28 days	D614G	−2	<0.0001	No	18–>71	18	USA	Shen et al. 2021[81]
	VSV-vector pseudovirus neutralization test	19	24–49 days	WT	−1.48	NS	NA	39 (20–65)	12	USA	Liu et al. 2021[b 69]
	VSV-vector pseudovirus neutralization test	12	15 days	D614G	−1.8	0.003	No	18–>70	NA	USA	Wang et al. 2021[76]
	VSV-vector pseudovirus neutralization test	8	7 days	D614G	−1.2	NS	No	NA	NA	USA	Wu et al. 2021[18]
	VSV-vector pseudovirus neutralization test	8	7 days	D614G	−3.1	0.008	No	NA	NA	USA	Wu et al. 2021[a 18]

Abbreviations: FRNT, focus reduction neutralization test; MN, microneutralization assay; NA, Not available; NS, Not significant; PRNT, plaque reduction neutralization test; VSV, vesicular stomatitis virus; WT, wild type (Wuhan strain).

[a]The utilized B.1.1.7 mutant viruses had an additional E484K substitution.

[b]Preprint article.

3.1.2 | B.1.351 variant

BNT162b2 vaccine

Twenty-one studies[15,58–61,63–70,72,73,75–77,82–84] with a total of 891 samples evaluated the effect of B.1.351 variant on antibody neutralization activity elicited by the BNT162b2 vaccine. Samples were obtained at least seven days and up to 91 days after second dose of vaccine. The reference strain was a virus with D614G mutation in 12 studies,[60,61,66–68,70,72,73,77,82–84] a virus with no functional mutation in eight studies,[15,58,59,63–65,69,75] and both types of viruses were used as a comparator strain in one study.[76] Fourteen studies utilized live virus neutralization assays,[15,58,59,61,63,64,66,68,70,72,73,75,77,82] while six used pseudovirus neutralization assays,[60,65,67,69,83,84] and one used both types of assays.[76] Fifty percent neutralization titre was decreased up to 22.83 fold in studies utilizing live virus neutralization assays and up to 41.2 fold in studies utilizing pseudovirus neutralization assays, as compared with reference strains (Table 2).

mRNA-1273 vaccine

Seven studies[17,18,65,69,76,78,85] with a total of 310 samples evaluated the effect of the B.1.351 variant on antibody neutralization activity elicited by the mRNA-1273 vaccine. Samples were obtained at least seven days and up to 180 days after second dose of vaccine. The reference strain was a virus with D614G mutation in four studies,[17,18,78,85] a virus with no functional mutation in two studies,[65,69] and both types of viruses were used as comparator strains in one study.[76] One study utilized live virus neutralization assays,[85] while four used pseudovirus neutralization assays,[17,18,65,69] and two used both types of assays.[76,78] Fifty percent neutralization titre was decreased up to 12.4 fold in studies utilizing live virus neutralization assays and up to 27.7 fold in studies utilizing pseudovirus neutralization assays, as compared with reference strains (Table 2).

3.1.3 | P.1 variant

BNT162b2 vaccine

Nine studies[15,58,60,61,63,65,67,77,86] with 272 samples evaluated the effect of the P.1 variant on antibody neutralization activity elicited by the BNT162b2 vaccine. Samples were obtained at least seven days and up to 32 days after the second dose of vaccine. The reference strain was a virus with D614G mutation in four studies,[60,61,67,77] a virus with no functional mutation in four studies,[15,58,63,65] and both types of viruses were used as comparator strains in one study.[86] Five studies utilized live virus neutralization assays,[15,58,61,63,77] while three used pseudovirus neutralization assays,[60,65,67] and one used both types of assays.[86] Fifty percent neutralization titre was decreased up to 2.99 fold in studies utilizing live virus neutralization assays and it up to 6.7 fold in studies utilizing pseudovirus neutralization assays, as compared with reference strain (Table 3).

mRNA-1273 vaccine

Four studies[18,65,78,86] with 115 samples evaluated the effect of P.1 variant on antibody neutralization activity elicited by mRNA-1273 vaccine. Samples were obtained at least seven days and up to 180 days after second dose of vaccine. The reference strain was a virus with D614G mutation in one study,[18] a virus with no functional mutation in one study,[65] and both types of viruses were used as comparator strains in two studies.[78,86] Three studies utilized pseudovirus neutralization assays,[18,65,78] while one used both types of assays.[86] Fifty percent neutralization titre was decreased to 4.8 fold in a study utilizing live virus neutralization assays and up to 4.5 fold in studies utilizing pseudovirus neutralization assays, as compared with reference strain (Table 3).

3.1.4 | B.1.617.2 variant

Five studies[73,75,87–89] with 275 samples evaluated the effect of the B.1.617.2 variant on antibody neutralization activity elicited by BNT162b2 vaccine. Samples were obtained at least seven days and up to 91 days after the second dose of vaccine. The reference strain was a virus with D614G mutation in two studies[73,89] and a virus with no functional mutation in three studies.[75,87,88] All of the included studies utilized live virus neutralization assays except one study that used both pseudovirus and live virus assays.[89] Fifty percent neutralization titre was decreased up to 8.4 fold as compared with the reference strain (Table 4). No investigation assessed the effect of B.1.617.2 variant on neutralization activity of antibodies elicited by the mRNA-1273 vaccine.

3.2 | Quality assessment

Quality of included studies ranged from 4 to 9, using the modified version of the CONSORT checklist (Table S2). The average score was 7.8 points, reflecting 52% of the possible total score of 15. Potential sources of bias were primarily attributed to issues concerning sample size estimation and randomization methods, including sequence generation, allocation concealment mechanism, implementation, and blinding. In addition, a registered pre-specified protocol was not provided for any of the included studies. Furthermore, limitations were discussed in only half of the eligible studies. Figure 2 illustrates a summary of the modified CONSORT checklist per item.

4 | DISCUSSION

This systematic review found that the B.1.351 variant had the most reduced sensitivity against antibody neutralization induced by vaccination with BNT162b2 or mRNA-1273, while the B.1.1.7 variant had the least, and P.1 and B.1.617.2 variants had an intermediate phenotype, using either live virus or pseudovirus

TABLE 2 Summary of included studies evaluating the neutralization activity of samples against B.1.351 variant obtained from vaccine recipients

Vaccine type	Serological assay	Sample size	Days post second vaccine dose	Reference strain	Fold change in 50% neutralization titre	p-value of change	History of previous SARS-CoV-2 infection	Age	Sex (number of female)	Country	Study ID
BNT162b2	Live virus neutralization test (FRNT)	24	7 days	D614G	−10.2	<0.0001	NA	45 (26–64)	15	USA	Chen et al. 2021[61]
	Live virus neutralization test (FRNT)	51	14–15 days	WT	−8.8	<0.0001	NA	50 (21–82)	28	USA	Bates et al. 2021[b 59]
	Live virus neutralization test (FRNT)	25	7–17 days	WT	−7.6	<0.0001	No	43 (25–63)	14	UK	Dejnirattisai et al. 2021[a 63]
	Live virus neutralization test (PRNT)	20	14–28 days	WT	−2.74	<0.001	No	51 (23–69)	14	USA	Liu et al. 2021[15]
	Live virus neutralization test (PRNT)	13	21–28 days	D614G	−3.34	<0.0001	Yes	42 (34–56)	10	Netherlands	Geers et al. 2021[a 66]
	Live virus neutralization test (PRNT)	12	21–28 days	D614G	−3.07	NA	No	48 (34–55)	11	Netherlands	Geers et al. 2021[a 66]
	Live virus neutralization test (MN)	159	21–37 days	WT	−4.9	NA	No	43	99	UK	Wall et al. 2021[a 75]
	Live virus neutralization test (MN)	25	7–17 days	WT	−4.49	0.000001	No	NA	NA	UK	Skelly et al. 2021[a b 64]
	Live virus neutralization test (MN)	180	13–33 days	D614G	−4.57	<0.0001	NA	43 (20–65)	149	Finland	Jalkanen et al. 2021[a b 68]
	Live virus neutralization test (MN)	60	30 days	WT	−4.2	<0.001	No	45 (25–65)	38	Italy	Anichini et al. 2021[a 58]
	Live virus neutralization test (microplate neutralization assay)	10	7 days	WT	−10.3	0.002	NA	42 (29–64)	5	USA	Wang et al. 2021[76]

TABLE 2 (Continued)

Vaccine type	Serological assay	Sample size	Days post second vaccine dose	Reference strain	Fold change in 50% neutralization titre	p-value of change	History of previous SARS-CoV-2 infection	Age	Sex (number of female)	Country	Study ID
	Live virus neutralization test (S-Fuse neutralization assay)	10	7 days	D614G	−4.66	<0.01	NA	NA	NA	France	Planas et al. 2021[a] [72]
	Live virus neutralization test (S-Fuse neutralization assay)	15	21 days	D614G	−14.23	<0.05	NA	NA	NA	France	Planas et al. 2021[a] [72]
	Live virus neutralization test (S-Fuse neutralization assay)	16	35 days	D614G	−8.83	<0.001	No	60 (37–75)	5	France	Planas et al. 2021[b] [73]
	Live virus neutralization test (S-Fuse neutralization assay)	13	91 days	D614G	−22.83	<0.0001	No	NA	NA	France	Planas et al. 2021[b] [73]
	Live virus neutralization test (virus neutralization test)	7	12 days	D614G	−5.1	NA	NA	NA	NA	Germany	Becker et al. 2021[a] [82]
	Virus neutralization test (whole virus replication assay)	29	7 days	D614G	−4.8	<0.0001	No	55 (38–65)	20	France	Marot et al. 2021[a b] [70]
	Live virus neutralization test (cytopathic effect [CPE]-based assay)	37	20–10 days	D614G	−1.73	<0.0001	No	46 (23–67)	21	Italy	Zani et al. 2021[77]
	Lentivirus-vector pseudovirus neutralization test	50	28 days	D614G	−5.1	<0.0001	No	>60–<35	31	Netherlands	Caniels et al. 2021[a b] [60]
	Lentivirus-vector pseudovirus neutralization test	30	7–32 days	WT	−34.5	<0.0001	No (except one suspected case)	35 (26–66)	18	USA	Garcia-Beltran et al. 2021[65]
	Lentivirus-vector pseudovirus neutralization test	30	7–32 days	WT	−41.2	<0.0001	No (except one suspected case)	35 (26–66)	18	USA	Garcia-Beltran et al. 2021[a] [65]

(Continues)

TABLE 2 (Continued)

Vaccine type	Serological assay	Sample size	Days post second vaccine dose	Reference strain	Fold change in 50% neutralization titre	p-value of change	History of previous SARS-CoV-2 infection	Age	Sex (number of female)	Country	Study ID
	Lentivirus-vector pseudovirus neutralization test	5	7 days	D614G	−3.1	≤0.01	No	NA	NA	USA	Tada et al. 2021[a] [83]
	VSV-vector pseudovirus neutralization test	10	7 days	D614G	−6.5	0.002	NA	42 (29–64)	5	USA	Wang et al. 2021[a] [76]
	VSV-vector pseudovirus neutralization test	15	13–15 days	D614G	−7.85	<0.05	NA	42 (25–65)	4	Germany	Hoffmann et al. 2021[67]
	VSV-vector pseudovirus neutralization test	15	24–31 days	D614G	−11.13	<0.001	NA	43 (26–58)	12	Germany	Hoffmann et al. 2021[84]
	VSV-vector pseudovirus neutralization test	30	22–68 days	WT	−10.46	<0.0001	NA	36 (21–73)	19	USA	Liu et al. 2021[a] [b] [69]
mRNA-1273	Live virus neutralization test (FRNT)	24	14 days	D614G	−5	NA	No	18–>71	NA	USA	Pegu et al. 2021[a] [b] [78]
	Live virus neutralization test (FRNT)	24	90 days	D614G	−6.1	NA	No	18–>71	NA	USA	Pegu et al. 2021[a] [b] [78]
	Live virus neutralization test (FRNT)	24	180 days	D614G	−4.3	NA	No	18->71	NA	USA	Pegu et al. 2021[a] [b] [78]
	Live virus neutralization test (FRNT)	19	14 days	D614G	−3.8	<0.0001	No	>56	NA	USA	Edara et al. 2021[a] [85]
	Live virus neutralization test (microplate neutralization assay)	12	15 days	WT	−12.4	0.002	No	18–>70	NA	USA	Wang et al. 2021[76]
	Lentivirus-vector pseudovirus neutralization test	35	7-177 days	WT	−27.7	<0.0001	No (except one suspected case)	47 (25–67)	25	USA	Garcia-Beltran et al. 2021[65]

TABLE 2 (Continued)

Vaccine type	Serological assay	Sample size	Days post second vaccine dose	Reference strain	Fold change in 50% neutralization titre	p-value of change	History of previous SARS-CoV-2 infection	Age	Sex (number of female)	Country	Study ID
	Lentivirus-vector pseudovirus neutralization test	35	7-177 days	WT	−20.8	<0.0001	No (except one suspected case)	35 (26–66)	25	USA	Garcia-Beltran et al. 2021[a] [65]
	Lentivirus-vector pseudovirus neutralization test	26	28 days	D614G	−9.7	<0.001	No	18–>71	17	USA	Shen et al. 2021[a] [17]
	Lentivirus-vector pseudovirus neutralization test	24	14 days	D614G	−9.1	NA	No	18–>71	NA	USA	Pegu et al. 2021[a b] [78]
	Lentivirus-vector pseudovirus neutralization test	24	90 days	D614G	−9.7	NA	No	18–>71	NA	USA	Pegu et al. 2021[a b] [78]
	Lentivirus-vector pseudovirus neutralization test	24	180 days	D614G	−7	NA	No	18–>71	NA	USA	Pegu et al. 2021[a b] [78]
	VSV-vector pseudovirus neutralization test	12	15 days	D614G	−8.6	0.0005	No	18–>70	NA	USA	Wang et al. 2021[a] [76]
	VSV-vector pseudovirus neutralization test	8	7 days	D614G	−6.4	0.008	No	NA	NA	USA	Wu et al. 2021[a] [18]
	VSV-vector pseudovirus neutralization test	19	24–49 days	WT	−7.56	<0.0001	NA	39 (20–65)	12	USA	Liu et al. 2021[a b] [69]

Abbreviations: FRNT, focus reduction neutralization test; MN, microneutralization assay; NA, not available; NS, not significant; PRNT, plaque reduction neutralization test; VSV, vesicular stomatitis virus; WT, wild type (Wuhan strain).

[a]The utilized B.1.351 mutant viruses had an additional L18f substitution.

[b]Preprint article.

TABLE 3 Summary of included studies evaluating the neutralization activity of samples against P.1 variant obtained from vaccine recipients

Vaccine type	Serological assay	Sample size	Days post second vaccine dose	Reference strain	Fold change in 50% neutralization titre	p-value of change	History of previous SARS-CoV-2 infection	Age	Sex (number of female)	Country	Study ID
BNT162b2	Live virus neutralization test (FRNT)	15	7 day	D614G	−2.23	0.002	NA	NA	NA	USA	Chen et al. 2021[61]
	Live virus neutralization test (FRNT)	25	7–17 days	WT	−2.6	<0.0001	No	43 (25–63)	14	UK	Dejnirattis et al. 2021[63]
	Live virus neutralization test (PRNT)	20	14–28 days	WT	−2.99	NS	No	51 (23–69)	14	USA	Liu et al. 2021[15]
	Live virus neutralization test (MN)	60	30 days	WT	−1.2	0.03	No	45 (25–65)	38	Italy	Anichini et al. 2021[58]
	Live virus neutralization test (microplate neutralization assay)	10	7 days	WT	−3.8	0.002	NA	42 (29–64)	5	USA	Wang et al. 2021[86]
	Live virus neutralization test (cytopathic effect [CPE]-based assay)	37	20–10 days	D614G	−1.38	0.0002	No	46 (23–67)	21	Italy	Zani et al. 2021[77]
	Lentivirus-vector pseudovirus neutralization test	50	28 days	D614G	−2	<0.0001	No	>60–<35	31	Netherlands	Caniels et al. 2021[a] [60]
	Lentivirus-vector pseudovirus neutralization test	30	7–32 days	WT	−6.7	<0.0001	No (except one suspected case)	35 (26–66)	18	USA	Garcia-Beltran et al. 2021[65]
	VSV-vector pseudovirus neutralization test	15	13–15 days	D614G	−5.12	<0.01	NA	42 (25–65)	4	Germany	Hoffmann et al. 2021[67]
	VSV-vector pseudovirus neutralization test	10	7 days	D614G	−2.2	0.002	NA	42 (29–64)	5	USA	Wang et al. 2021[86]

TABLE 3 (Continued)

Vaccine type	Serological assay	Sample size	Days post second vaccine dose	Reference strain	Fold change in 50% neutralization titre	p-value of change	History of previous SARS-CoV-2 infection	Age	Sex (number of female)	Country	Study ID
mRNA-1273	Live virus neutralization test (microplate neutralization assay)	12	15 days	WT	−4.8	0.0005	No	18–>70	NA	USA	Wang et al. 2021[86]
	VSV-vector pseudovirus neutralization test	8	7 days	D614G	−3.5	0.008	No	NA	NA	USA	Wu et al. 2021[18]
	VSV-vector pseudovirus neutralization test	12	15 days	D614G	−2.8	0.0005	No	18–>70	NA	USA	Wang et al. 2021[86]
	Lentivirus-vector pseudovirus neutralization test	24	14 days	D614G	−2.8	NA	No	18–>71	NA	USA	Pegu et al. 2021[a] [78]
	Lentivirus-vector pseudovirus neutralization test	35	7–117 days	WT	−4.5	<0.001	No (except one suspected case)	47 (25–67)	25	USA	Garcia-Beltran et al. 2021[65]
	Lentivirus-vector pseudovirus neutralization test	24	180 days	D614G	−3.8	NA	No	18–>71	NA	USA	Pegu et al. 2021[a] [78]

Abbreviations: FRNT, focus reduction neutralization test; MN, microneutralization assay; NA, not available; NS, not significant; PRNT, plaque reduction neutralization test; VSV, vesicular stomatitis virus; WT, wild type (Wuhan strain).

[a]Preprint article.

TABLE 4 Summary of included studies evaluating the neutralization activity of samples against B.1.617.2 variant obtained from BNT162b2 vaccine recipients

Serological assay	Sample size	Days post second vaccine dose	Reference strain	Fold change in 50% neutralization titre	*p*-value of change	History of previous SARS-CoV-2 infection	Age	Sex (number of female)	Country	Study ID
Live virus neutralization test (MN)	159	21–37 days	WT	−5.8	NA	No	43	99	UK	Wall et al. 2021[a] [75]
Live virus neutralization test (S-Fuse neutralization assay)	16	35 days	D614G	−1.54	NS	No	60 (37–75)	5	France	Planas et al. 2021[c] [73]
Live virus neutralization test (S-Fuse neutralization assay)	13	91 days	D614G	−2.36	<0.05	No	NA	NA	France	Planas et al. 2021[c] [73]
Live virus neutralization test (PRNT)	20	14–28 days	WT	−1.46	0.004	No	51 (23–69)	14	USA	Liu et al. 2021[88]
Live virus neutralization test (FRNT)	25	7–17 days	WT	−2.5	<0.0001	No	43 (25–63)	14	UK	Liu et al. 2021[b] [89]
Live virus neutralization test	10	24–29 days	D614G	−8.4	<0.01	NA	NA	NA	UK	Mlcochova et al. 2021[c] [90]
Lentivirus-vector pseudovirus neutralization test	32	24–29 days	D614G	−2.9	<0.0001	NA	71 (46–83)	13	UK	Mlcochova et al. 2021[c] [90]

Abbreviations: FRNT, focus reduction neutralization test; MN, microneutralization assay; NA, not available; NS, not significant; PRNT, plaque reduction neutralization test; VSV, vesicular stomatitis virus; WT, wild type (Wuhan strain).

[a]The utilized B.1.617.2 mutant virus had additional K77R and A222V substitution.

[b]The utilized B.1.617.2 mutant virus had additional A222V substitution.

[c]Preprint article.

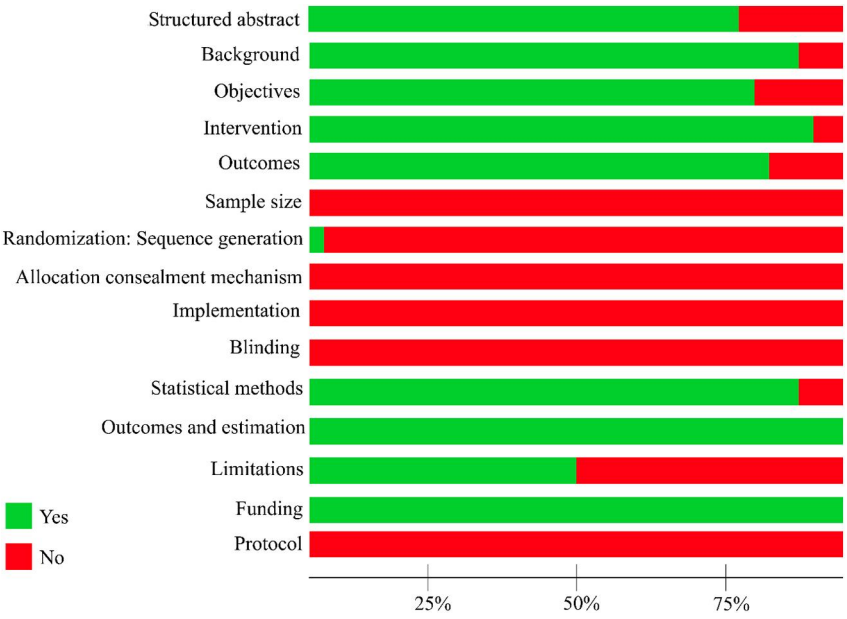

FIGURE 2 Percentage of modified Consolidated Standards of Reporting Trials (CONSORT) scores for included studies per item

neutralization assays. In line with a recent review, the emergence of ongoing SARS-CoV-2 variants may potentially compromise current monoclonal antibodies and vaccine effectiveness.[90] These findings are of great importance since the immune escape of SARS-CoV-2 variants could confer an unpredictable threat to the whole world vaccination program, which could increase the risk of infection with mutant viruses, particularly later post decline of antibody titres.

4.1 | RBD mutations as potential threat against vaccine efficacy

Vaccination is a key component of a long lasting strategy to bring the COVID-19 pandemic under control. Pfizer-BioNTech and Moderna vaccines are two lipid nanoparticled-mRNA encoding perfusion stabilized forms of the full-length SARS-CoV-2 spike protein, with more than 94% efficacy at preventing disease.[13,91] How previously vaccinated individuals with either BNT162b2 or mRNA-1273 have responded to novel SARS-CoV-2 variants has been the subject of intense scrutiny over recent months. All of the variants of concern have mutations in the RBD region, which is the main target for neutralizing antibodies,[92,93] resulting in ineffectiveness of immune protection provided by natural infection or vaccination. Given that the RBD has functional plasticity,[93,94] ongoing mutations in this region would be feasible as the pandemic continues to evolve potentially compromising efficacy of current vaccines. The impact of changes in neutralization titres is challenging to predict, since it remains difficult to estimate precisely to what extent the reduction in neutralizing antibodies will affect vaccine efficacy leading to increase the risk of breakthrough infections or higher COVID-19 severity in vaccinated populations.

4.2 | Mutations in variants of concern that are responsible for escaping from neutralizing antibodies

Mutations that occur in the RBD region of spike protein are of the greatest concern due to their potential to promote escape from the vaccine induced neutralizing antibody response, which predominantly targets this region. N501Y substitution is shared among the RBD region of B.1.1.7, B.1.351, and P.1 spike genome. Although this mutation has been suggested to enhance the ACE2 binding affinity,[95] it has no pronounced effect on neutralizing activity of sera from vaccinated individuals.[31,39,76,79,96,97] While both B.1.351 and P.1 have mutations at 417 residue, studies have reported that this mutation has no potential impact on reduced sensitivity to neutralizing antibodies.[36,61] It appears that E484K substitution in B.1.351 and P.1 variants likely plays a crucial role in reducing the susceptibility of being neutralized by sera from vaccinated individuals. The E484 residue importantly is critical for binding of highly potent neutralizing antibodies.[98] This significant effect on serum neutralization can be elucidated by the dominance of RBD neutralizing antibodies, corroborated by studies indicating reduced neutralization titres mediated by the E484K mutation alone.[27,36,39,41,76,97,99,100] In addition, the original B.1.1.7 variant did not have E484K substitution in RBD, but there have been some reports that it recently poses E484[101] and it vitro studies have shown that while B.1.1.7 has minimal impact on serum neutralization, B.1.1.7 mutations alongside E484K could significantly reduce efficacy of neutralizing antibodies.[18,62] Therefore, E484K mutation located in the RBD would become a serious threat to the protection efficacy of mRNA-based SARS-CoV-2 vaccines.

It is worth noting that the RBD of spike has the major impact on responding to neutralizing antibodies, however, despite the same encoded mutations in RBD of P.1 and B.1.351 (E484K, K417N/T and

N501Y), neutralization of the P.1 variant is not compromised as severely as neutralization of B.1.351 when using vaccine sera immunized by earlier SARS-CoV-2 variants. This could be presumably justified by other distinct sets of mutations or deletions, particularly those introduced in NTD of viral spike.[102–104]

Despite the great number of investigations on the efficacy of current vaccines for B.1.1.7, B.1.351, and P.1 variants, there is a lack of studies for the B.1.617.2 variant, which has recently been identified as variant of concern by WHO. B.1.617.2 harbours two mutations at 452 and 478 residues. In vitro experiments have demonstrated that L452R could compromise the neutralization titres,[105,106] while there were no studies evaluating the impact of the T478K mutation.

4.3 | An urgent need for standardization of methodology of in vitro studies

In recent decades, several high throughput methods have been developed for quantification of neutralizing antibodies and the COVID-19 pandemic has provided a beneficial opportunity for expediting research on upgrading neutralization assays.[107] It is noteworthy that included studies in this present review used different methods, including pseudovirus assays or live virus assays for testing neutralization activity of antibodies, that make comparability and therefore reliability of results challenging. Using authentic viruses or pseudovirus particles may have different impacts on neutralization due to the additional mutations outside of the spike region or differences in the density of spike protein per virion, which may alter sensitivity to neutralizing antibodies. However, recent studies have reported a high degree of concordance between pseudovirus and live virus neutralization assays, evaluating antibody response to SARS-CoV-2.[108–111] Furthermore, D614G mutation is one of the earliest substitutions that emerged and rapidly became globally dominant. Thereafter, in vitro studies aiming to make a comparison on neutralization activity of sera between an emerging variant and a reference strain utilized either virus bearing the D614G mutation or Wuhan strain with no functional mutations as comparator strain. It has been revealed that viruses with mutation in 614 residue may be neutralized better than the Wuhan strain by sera from vaccinated individuals.[18,37,112] Consequently, the reduction fold of neutralization titres against a certain variant may be potentially dependent on the comparator strain. Taken together, despite the questionable scientific relevance of distinct methods, there is an urgent need for standardization of neutralization assays and methods that in vitro studies utilize for comparing vaccine elicited immune effectors between different viruses to avoid diverse interpretations of final results.

Moreover, the status of individuals who received vaccines for previous SARS-CoV-2 infection was not clear in several included studies, which may impact the potency of antibodies to neutralize emerging variants. It has been demonstrated that sera from individuals who had recovered from SARS-CoV-2 infection prior to vaccination could not only neutralize B.1.351 more effectively than those who had been SARS-CoV-2 naïve, but there were also no significant reductions in neutralization titres against B.1.351 as compared to wild type strain after two dose vaccination.[53]

4.4 | Cellular immunity as another predictor of protection against novel variants

While the effect of humoural immunity on protection against mutant viruses for mRNA vaccine platforms has been extensively investigated, there is a need to study how the cellular immunity could contribute to protecting vaccinated individuals against novel variants. However, recent studies have suggested that T cell responses raised to early SARS-CoV-2 strains might be minimally impacted by emerging variants.[66,113,114]

4.5 | Real-world effectiveness of mRNA vaccines over the expansion of variants of concern

During the second and third wave of SARS-COV-2 infection in Qatar, the B.1.1.7 and B.1.351 variants became dominant and nearly all of the infected cases were caused by these two variants. At the same time period, several individuals have been vaccinated with at least one dose of BNT162b2. Comparing the infection rate between vaccinated and unvaccinated individuals, two dose vaccination was effective at 89.5% and 75.0% in reducing the risk of infection by B.1.1.7 and B.1.351, respectively. Interestingly, the vaccine reaches 100% effectiveness in preventing severe, critical, or fatal disease for both variants.[115] Another study evaluating the effectiveness of BNT162b2 vaccine against B.1.617.2 variant reported that while two dose vaccination was effective at 93.4% in preventing B.1.1.7 infection, it reduces minimally to 87.9% against B.1.617.2 variant.[116] Therefore, confirming the results of in vitro investigation, the B.1.351 would be responsible for greatest rate of breakthrough infections.

4.6 | Potent neutralization of variants of concern by single dose vaccination in convalescent individuals

For previously SARS-CoV-2 infected cases, a single dose of vaccines may act as booster dose following natural infection. Indeed, single dose vaccination post infection achieves similar levels of neutralizing antibodies to two doses in naïve vaccinated cases and second dose vaccination following the first dose in previously infected individuals offers no additional enhancement.[117–120] It has been reported that SARS-CoV-2 naïve immune cases were not capable of making detectable neutralizing antibody response against B.1.1.7 and

B.1.351 variants after single dose vaccination. In contrast, vaccinated post infection individuals showed a strong neutralizing antibody response against B.1.1.7 and B.1.351 variants after single dose vaccination.[53,54,121] Consequently, the robust boosting of neutralizing antibodies in these subjects after one dose may have implications in settings where supply is limited.

4.7 | Development of next generation vaccines with spike sequence of emerging variants

Given the ongoing emergence of SARS-CoV-2 variants, designing next generation vaccines as booster doses with diverse mutated spike sequences appears to be the only countermeasure strategy for combating the pandemic. Indeed, multiple vaccine companies have announced that they already initiated working on reformulating current vaccines with variants of concern. In this regard, Moderna has recently started the evaluation of booster dose containing the B.1.351 spike sequence in a phase 1 clinical trial.[122] However, efficacy of reformulated vaccines incorporating new viral strains may be challenging for individuals with pre-existing immunity to ancestral strains. Whether the modified areas in spike protein will be capable of eliciting the unique antibody response, rather than boosting memory response against early strains is yet to be determined.[123] Therefore, intensive studies are needed to examine efficacy of booster doses for novel SARS-CoV-2 variants. Furthermore, based on our review, B.1.351 is the variant of greatest concern since it results in the largest reduction in neutralization titres, thus, despite the individuals who have already been vaccinated against SARS-CoV-2 globally, new variants such as B.1.351 may lead to a significant reinfection risk and it would be reasonable that developing booster vaccines constructs to B.1.351 should be prioritized.

4.8 | Overview and future outlook

The emergence of variants of concern highlights the beginning of viral antigenic drift, which may be going in a direction that eventually leads to escape from our current prophylactic interventions against the spike protein. It is therefore imperative to closely monitor the emergence of novel SARS-CoV-2 variants and functional impacts that their mutations may have on vaccine efficacy. While viral sequence surveillance for detecting novel mutations in the SARS-CoV-2 genome has been established in several countries, global coverage is still insufficient. Consequently, suppression of viral replication by multiplying mitigation measures and expediting vaccine deployment is critical in reducing the risk of a new generation of SARS-CoV-2 variants. Finally, worldwide research on development of a general SARS-CoV-2 vaccine and challenges that mutations pose on vaccine program development, would offer a unique period in human history that can be studied and used to outline strategies for future infectious disease outbreaks.

5 | LIMITATIONS

Our study relies on in vitro investigations, therefore, reduction in neutralization titres of antibodies against novel variants may not be generalizable to in vivo environments. In addition, the time period for collecting specimens following the second vaccination dose ranged from a few days to one month across studies, therefore, it is possible that antibody titres would have decreased over time to levels no longer able to provide adequate protection against mutant viruses. For instance, it was shown that almost half of vaccinated individuals with mRNA-1273 were unable to neutralize the B.1.351 variant after three months.[78] Thus, long-term evaluation of neutralizing antibody titres in vaccinated individuals is required to assess durability of protection against emerging SARS-CoV-2 variants. Although serum neutralizing antibody titre is a potent predictor of protection, mRNA vaccines could also elicit other immune effectors such as CD4+ and CD8+ T cells, complement deposition, and non-neutralizing antibodies[124] that induce antibody-dependent cytotoxicity. As a result, mechanisms other than neutralization by antibodies could confer further substantial vaccine-mediated protection necessitating the need for further investigations. Considering the methodology of present systematic review, we cannot rule out the probability of missing some studies that our searching process might have failed to find. Additionally, there is no approved guideline for apprising the quality of in vitro studies, so we used the modified version of CONSORT checklist that have not been evaluated for its measurement properties. Finally, there is potential for publication and reporting bias, which has not been quantified as part of this review. Despite these limitations, to the best of our knowledge, this is the first article systematically reviewing the effectiveness of current mRNA vaccines against novel SARS-CoV-2 variants by eliciting neutralizing antibodies.

6 | CONCLUSION

The recent emergence of multiple SARS-CoV-2 variants has disrupted confidence in the current generation of vaccines to provide adequate protection against COVID-19. Our review suggests that immune sera derived from vaccinated individuals might fail to protect people immunized by mRNA vaccines against more recent SARS-CoV-2 variants of concern; mutations present in B.1.351 were found to have the most impact on impairing antibody naturalization activity, with B.1.1.7 showing minimal impact, and P.1 and B.1.617.2 showing an intermediate effect. With the emergence of ongoing mutations, it is likely that SARS-CoV-2 vaccines will require updating in the near future, with immunity monitored to compensate for viral evolution.

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CONFLICT OF INTEREST

The authors declare no competing interests.

ETHICS STATEMENT

No ethical approval required for this article.

AUTHORS CONTRIBUTION

Maryam Noori and Seyed Aria Nejadghaderi designed and wrote the first draft of the manuscript; Shahnam Arshi, Kristin Carson-Chahhoud, Khalil Ansarin, Ali-Asghar Kolahi and Saeid Safiri critically revised the manuscript. All authors reviewed and approved the final version of the manuscript.

DATA AVAILABILITY STATEMENT

Data supporting findings from this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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