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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Funding information
National Institute for Medical Research Development, Tabriz University of Medical Sciences; Shahid Beheshti University of Medical Sciences

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...
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 neutralization 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, 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 was searched. 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. 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. 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; six studies evaluated the effects of other variants which were not variants of concern; three were review
articles,\textsuperscript{48–50} two studies were re-analysis of previously published articles,\textsuperscript{51,52} two studies did not differentiate type of vaccines,\textsuperscript{53,54} two studies were conducted on animal subjects,\textsuperscript{55,56} and one did not mention the exact mutations of viruses.\textsuperscript{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\textsuperscript{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,\textsuperscript{60–62,64,68,70,72,73,77} a virus with no functional mutation in 11 studies,\textsuperscript{15,16,58,59,63–65,69,71,74,75} and both types of viruses were used as comparator strains in one study.\textsuperscript{76} Fourteen studies utilized live virus neutralization assays,\textsuperscript{15,16,58,59,61,63,64,66,68,70,72,73,75,77} seven used pseudovirus neutralization assays,\textsuperscript{60,62,65,67,69,71,74} and one used both types of assays.\textsuperscript{76} Fifty percent neutralization titre was decreased as little as 2.6 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\textsuperscript{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,\textsuperscript{18,78,79,81} a virus with no functional mutation in three studies,\textsuperscript{55,69,80} and both types of viruses were used as a comparator strain in one study.\textsuperscript{76} Two studies utilized live virus neutralization assays,\textsuperscript{79,80} while four used pseudovirus neutralization assays,\textsuperscript{18,65,69,81} and two used both type of assays.\textsuperscript{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).
| 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 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   |
|              | Live virus neutralization test (FRNT) | 24          | 7 days                        | D614G            | −2.03                                  | <0.0001           | NA                          | 45 (26–64) | 15                     | USA     | Chen et al. 2021    |
|              | Live virus neutralization test (FRNT) | 25          | 7–17 days                     | WT               | −3.3                                   | <0.0001           | No                          | 43 (25–63) | 14                     | UK      | Dejnirattisai et al. 2021 |
|              | Live virus neutralization test (PRNT) | 20          | 14–28 days                    | WT               | 1.25                                   | 0.02              | No                          | 51 (23–69) | 14                     | USA     | Liu et al. 2021      |
|              | Live virus neutralization test (PRNT) | 20          | 14–28 days                    | WT               | 1.15                                   | 0.04              | No                          | 51 (23–69) | 14                     | USA     | Liu et al. 2021      |
|              | Live virus neutralization test (PRNT) | 13          | 21–28 days                    | D614G            | 2.17                                   | <0.0001           | Yes                         | 42 (34–56) | 10                     | Netherlands | Geers et al. 2021 |
|              | Live virus neutralization test (PRNT) | 12          | 21–28 days                    | D614G            | 1.99                                   | <0.01             | No                          | 47 (34–55) | 11                     | Netherlands | Geers et al. 2021 |
|              | Live virus neutralization test (MN) | 159         | 21–37 days                    | WT               | −2.6                                   | NA                | NA                          | 43          | 99                     | UK      | Wall et al. 2021     |
|              | Live virus neutralization test (MN) | 25          | 7–17 days                     | WT               | −2.4                                   | <0.0001           | No                          | NA          | NA                    | UK      | Skelly et al. 2021   |
|              | Live virus neutralization test (MN) | 180         | 13–33 days                    | D614G            | 1                                      | NS                | NA                          | 43 (20–65) | 149                    | Finland | Jalkanen et al. 2021 |
|              | Live virus neutralization test (MN) | 60          | 30 days                       | WT               | −1.1                                   | NS                | No                          | 45 (25–65) | 38                     | Italy   | Anichini et al. 2021 |
| 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 |
| Live virus neutralization test (S-Fuse neutralization assay) | 10 | 7 days | D614G | 1.45 | NS | NA | NA | NA | France | Planas et al. 2021 |
| Live virus neutralization test (S-Fuse neutralization assay) | 15 | 21 days | D614G | 3.8 | <0.05 | NA | NA | NA | France | Planas et al. 2021 |
| 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 |
| Live virus neutralization test (S-Fuse neutralization assay) | 13 | 91 days | D614G | 1.31 | NS | No | NA | NA | France | Planas et al. 2021 |
| 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 |
| 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 |
| Lentivirus-vector pseudovirus neutralization test | 50 | 28 days | D614G | −1.6 | 0.0035 | No | >60–<35 | 31 | Netherlands | Caniels et al. 2021 |
| Lentivirus-vector pseudovirus neutralization test | 21 | 21 days | D614G | −1.9 | <0.001 | NA | NA | NA | UK | Collier et al. 2021 |
| Lentivirus-vector pseudovirus neutralization test | 21 | 21 days | D614G | −6.7 | <0.0001 | NA | NA | NA | UK | Collier et al. 2021 |
| 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 |
| Lentivirus-vector pseudovirus    | neutralization test                | 16          | 14 days                       | WT               | 1.69                                   | NS                 | Yes                                      | 39 (29–44)| 11                      | Spain   | Trinité et al. 2021      |
| Lentivirus-vector pseudovirus    | neutralization test                | 16          | 14 days                       | WT               | −2.38                                  | NS                 | No                                       | 45 (30–61)| 12                      | Spain   | Trinité et al. 2021      |
| VSV-vector pseudovirus neutralization test |                      | 40          | 7–21 days                     | WT               | −1.25                                  | <0.01              | No                                       | 23–73    | NA                      | USA     | Muik et al. 2021          |
| VSV-vector pseudovirus neutralization test |                      | 10          | 7 days                        | D614G            | −2                                     | 0.004              | NA                                       | 42 (29–64)| 5                       | USA     | Wang et al. 2021          |
| VSV-vector pseudovirus neutralization test |                      | 15          | 13–15 days                    | D614G            | −1.77                                  | <0.01              | NA                                       | 42 (25–65)| 4                       | Germany | Hoffmann et al. 2021     |
| VSV-vector pseudovirus neutralization test |                      | 30          | 22–68 days                    | WT               | −2.2                                   | <0.0001            | NA                                       | 36 (21–73)| 19                      | USA     | Liu et al. 2021b 69      |
| mRNA-1273                        | Live virus neutralization test (FRNT) | 24          | 14 days                       | D614G            | −1.2                                   | NA                 | No                                       | 18–71    | NA                      | USA     | Pegu et al. 2021b 78     |
| mRNA-1273                        | Live virus neutralization test (FRNT) | 24          | 90 days                       | D614G            | −1.3                                   | NA                 | No                                       | 18–71    | NA                      | USA     | Pegu et al. 2021b 78     |
| mRNA-1273                        | Live virus neutralization test (FRNT) | 24          | 180 days                      | D614G            | −1.3                                   | NA                 | No                                       | 18–71    | NA                      | USA     | Pegu et al. 2021b 78     |
| mRNA-1273                        | Live virus neutralization test (FRNT) | 14          | 14 days                       | D614G            | 1.2                                    | 0.04               | No                                       | 18–55    | 8                       | USA     | Edara et al. 2021b 79    |
| mRNA-1273                        | Live virus neutralization test (FRNT) | 14          | 14 days                       | WT               | −1.77                                  | 0.02               | No                                       | 18–55    | 8                       | USA     | Edara et al. 2021b 80    |

(Continues)
| 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. 2021^6   |
| 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. 2021^78  |
| Lentivirus-vector pseudovirus    | neutralization test                            | 24          | 90 days                     | D614G            | −1.6                                   | NA                | No                                       | 18–>71 | NA                   | USA      | Pegu et al. 2021^78  |
| Lentivirus-vector pseudovirus    | neutralization test                            | 24          | 180 days                    | D614G            | −1.6                                   | NA                | No                                       | 18–>71 | NA                   | USA      | Pegu et al. 2021^78  |
| 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. 2021^69   |
| VSV-vector pseudovirus neutralization test |                                  | 12          | 15 days                     | D614G            | −1.8                                   | 0.003             | No                                       | 18–>70 | NA                   | USA      | Wang et al. 2021^6   |
| 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. 2021^18    |

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).

^aThe utilized B.1.1.7 mutant viruses had an additional E484K substitution.

^bPreprint article.
### 3.1.3  B.1.351 variant

**BNT162b2 vaccine**

Twenty-one studies 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, a virus with no functional mutation in eight studies, and both types of viruses were used as a comparator strain in one study. Fourteen studies utilized live virus neutralization assays, while six used pseudovirus neutralization assays, and one used both types of assays. 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 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, a virus with no functional mutation in two studies, and both types of viruses were used as comparator strains in one study. One study utilized live virus neutralization assays, while four used pseudovirus neutralization assays, and two used both types of assays. 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).

### 3.1.4  B.1.617.2 variant

**BNT162b2 vaccine**

Four studies 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, a virus with no functional mutation in one study, and both types of viruses were used as comparator strains in two studies. Three studies utilized pseudovirus neutralization assays, while one used both types of assays. 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).

### 3.2  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
| 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 |
|              | Live virus neutralization test (FRNT) | 51 | 14–15 days | WT | −8.8 | <0.0001 | NA | 50 (21–82) | 28 | USA | Bates et al. 2021 |
|              | Live virus neutralization test (FRNT) | 25 | 7–17 days | WT | −7.6 | <0.0001 | No | 43 (25–63) | 14 | UK | Dejnirattisai et al. 2021 |
|              | Live virus neutralization test (PRNT) | 20 | 14–28 days | WT | −2.74 | <0.001 | No | 51 (23–69) | 14 | USA | Liu et al. 2021 |
|              | Live virus neutralization test (PRNT) | 13 | 21–28 days | D614G | −3.34 | <0.0001 | Yes | 42 (34–56) | 10 | Netherlands | Geers et al. 2021 |
|              | Live virus neutralization test (PRNT) | 12 | 21–28 days | D614G | −3.07 | NA | No | 48 (34–55) | 11 | Netherlands | Geers et al. 2021 |
|              | Live virus neutralization test (MN) | 159 | 21–37 days | WT | −4.9 | NA | No | 43 | 99 | UK | Wall et al. 2021 |
|              | Live virus neutralization test (MN) | 25 | 7–17 days | WT | −4.49 | 0.000001 | No | NA | NA | UK | Skelly et al. 2021 |
|              | Live virus neutralization test (MN) | 180 | 13–33 days | D614G | −4.57 | <0.0001 | NA | 43 (20–65) | 149 | Finland | Jalkanen et al. 2021 |
|              | Live virus neutralization test (MN) | 60 | 30 days | WT | −4.2 | <0.001 | No | 45 (25–65) | 38 | Italy | Anichini et al. 2021 |
|              | 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 |
| 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. 2021a 72         |
| Live virus neutralization test       | (S-Fuse neutralization assay)                                                     | 15          | 21 days                        | D614G            | −14.23                                  | <0.05            | NA                                       | NA   | NA                     | France   | Planas et al. 2021a 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. 2021b 73         |
| Live virus neutralization test       | (S-Fuse neutralization assay)                                                     | 13          | 91 days                        | D614G            | −22.83                                  | <0.0001          | No                                       | NA   | NA                     | France   | Planas et al. 2021b 73         |
| Live virus neutralization test       | (virus neutralization test)                                                       | 7           | 12 days                        | D614G            | −5.1                                    | NA               | NA                                       | NA   | NA                     | Germany  | Becker et al. 2021a 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. 2021a 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. 2021a 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 65 |

(Continues)
| 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        | NA                     | USA     | Tada et al. 2021a      |
| VSV-vector pseudovirus neutralization test | 10                                       | 7 days      | D614G                       | −6.5             | 0.002                                  | NA               | 42 (29–64)                             | 5         | USA                    | Wang et al. 2021a |
| VSV-vector pseudovirus neutralization test | 15                                       | 13–15 days | D614G                       | −7.85            | <0.05                                  | NA               | 42 (25–65)                             | 4         | Germany                | Hoffmann et al. 2021a |
| VSV-vector pseudovirus neutralization test | 15                                       | 24–31 days | D614G                       | −11.13           | <0.001                                 | NA               | 43 (26–58)                             | 12        | Germany                | Hoffmann et al. 2021a |
| VSV-vector pseudovirus neutralization test | 30                                       | 22–68 days | WT                         | −10.46           | <0.0001                                | NA               | 36 (21–73)                             | 19        | USA                    | Liu et al. 2021b |
| mRNA-1273                          | Live virus neutralization test (FRNT)    | 24          | 14 days                    | D614G            | −5                                     | NA               | No                                     | 18–>71   | NA                     | USA     | Pegu et al. 2021a      |
| mRNA-1273                          | Live virus neutralization test (FRNT)    | 24          | 90 days                    | D614G            | −6.1                                   | NA               | No                                     | 18–>71   | NA                     | USA     | Pegu et al. 2021a      |
| mRNA-1273                          | Live virus neutralization test (FRNT)    | 24          | 180 days                   | D614G            | −4.3                                   | NA               | No                                     | 18–>71   | NA                     | USA     | Pegu et al. 2021a      |
| mRNA-1273                          | Live virus neutralization test (FRNT)    | 19          | 14 days                    | D614G            | −3.8                                   | <0.0001          | No                                     | >56       | NA                     | USA     | Edara et al. 2021a     |
| mRNA-1273                          | Live virus neutralization test (microplate neutralization assay) | 12          | 15 days                    | WT               | −12.4                                  | 0.002            | No                                     | 18–>70   | NA                     | USA     | Wang et al. 2021       |
| mRNA-1273                          | 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. 2021a |
| 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 (number of female) | Sex | 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 |
| Lentivirus-vector pseudovirus neutralization test | 26 | 28 days | D614G | −9.7 | <0.001 | No | 18–>71 | 17 | USA | Shen et al. 2021 |
| Lentivirus-vector pseudovirus neutralization test | 24 | 14 days | D614G | −9.1 | NA | No | 18–>71 | NA | USA | Pegu et al. 2021 |
| Lentivirus-vector pseudovirus neutralization test | 24 | 90 days | D614G | −9.7 | NA | No | 18–>71 | NA | USA | Pegu et al. 2021 |
| Lentivirus-vector pseudovirus neutralization test | 24 | 180 days | D614G | −7 | NA | No | 18–>71 | NA | USA | Pegu et al. 2021 |
| VSV-vector pseudovirus neutralization test | 12 | 15 days | D614G | −8.6 | 0.0005 | No | 18–>70 | NA | USA | Wang et al. 2021 |
| VSV-vector pseudovirus neutralization test | 8 | 7 days | D614G | −6.4 | 0.008 | No | NA | NA | USA | Wu et al. 2021 |
| VSV-vector pseudovirus neutralization test | 19 | 24–49 days | WT | −7.56 | <0.0001 | NA | 39 (20–65) | 12 | USA | Liu et al. 2021 |

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).

*The utilized B.1.351 mutant viruses had an additional L18f substitution.

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| Vaccine type | Serological assay | Sample size | Days post second vaccine dose | Reference strain | Fold change in 50% neutralization titre | 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                                | No                                    | NA   | NA                 | USA      | Chen et al. 2021 |
|             | Live virus neutralization test (FRNT) | 25          | 7–17 days                     | WT              | −2.6                                 | <0.0001                               | No   | 43 (25–63)        | UK       | Dejnirattis et al. 2021 |
|             | Live virus neutralization test (PRNT) | 20          | 14–28 days                    | WT              | −2.99                                | NS                                    | No   | 51 (23–69)        | USA      | Liu et al. 2021 |
|             | Live virus neutralization test (MN) | 60          | 30 days                       | WT              | −1.2                                 | 0.03                                  | No   | 45 (25–65)        | Italy    | Anichini et al. 2021 |
|             | Live virus neutralization test (microplate neutralization assay) | 10          | 7 days                        | WT              | −3.8                                 | 0.002                                 | No   | 42 (29–64)        | USA      | Wang et al. 2021 |
|             | Live virus neutralization test (cytopathic effect [CPE]-based assay) | 37          | 20–10 days                    | D614G           | −1.38                                | 0.0002                                | No   | 46 (23–67)        | Italy    | Zani et al. 2021 |
|             | Lentivirus-vector pseudovirus neutralization test | 50          | 28 days                       | D614G           | −2                                   | <0.0001                               | No   | >60–<35          | Netherlands | Caniels et al. 2021 |
|             | 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 |
|             | VSV-vector pseudovirus neutralization test | 15          | 13–15 days                    | D614G           | −5.12                                | <0.01                                 | NA   | 42 (25–65)        | Germany  | Hoffmann et al. 2021 |
|             | VSV-vector pseudovirus neutralization test | 10          | 7 days                        | D614G           | −2.2                                 | 0.002                                 | NA   | 42 (29–64)        | USA      | Wang et al. 2021 |
| 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 |
| VSV-vector pseudovirus neutralization test | 8              | 7 days       | D614G                         | −3.5             | 0.008                                  | No              | NA                                       | NA   | NA                  | USA     | Wu et al. 2021 |
| VSV-vector pseudovirus neutralization test | 12             | 15 days      | D614G                         | −2.8             | 0.0005                                 | No              | 18–>70                                   | NA   | NA                  | USA     | Wang et al. 2021 |
| Lentivirus-vector pseudovirus neutralization test | 24             | 14 days      | D614G                         | −2.8             | NA                                     | No              | 18–>71                                   | NA   | NA                  | USA     | Pegu et al. 2021 |
| 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 |
| Lentivirus-vector pseudovirus neutralization test | 24             | 180 days     | D614G                         | −3.8             | NA                                     | No              | 18–>71                                   | NA   | NA                  | USA     | Pegu et al. 2021 |

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).

*Preprint article.
| 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<sup>a</sup> 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<sup>c</sup> 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<sup>c</sup> 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<sup>b</sup> 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<sup>b</sup> 89  |
| Live virus neutralization test                             | 10          | 24–29 days                    | D614G            | −8.4                                     | <0.01             | NA                                       | NA  | NA                    | NA      | Mlcochova et al. 2021<sup>c</sup> 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<sup>c</sup> 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).

<sup>a</sup>The utilized B.1.617.2 mutant virus had additional K77R and A222V substitution.

<sup>b</sup>The utilized B.1.617.2 mutant virus had additional A222V substitution.

<sup>c</sup>Preprint article.
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. 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 nanoparticle-mRNA encoding perfusion stabilized forms of the full-length SARS-CoV-2 spike protein, with more than 94% efficacy at preventing disease. 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, resulting in ineffectiveness of immune protection provided by natural infection or vaccination. Given that the RBD has functional plasticity, 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, it has no pronounced effect on neutralizing activity of sera from vaccinated individuals. 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. 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. 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. 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 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. 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
NS01Y), 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.\textsuperscript{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,\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{53}

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

While the effect of humoral 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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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. 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. 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. 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. 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 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.

ACKNOWLEDGEMENTS

We would like to acknowledge the support of the National Institutes for Medical Research Development (NIMAD), Tabriz University of Medical Sciences and Shahid Beheshti University of
Medical Sciences. The present study was funded by NIMAD and Tabriz University of Medical Sciences (grant number: 68009). In addition, the present study was partially supported by Shahid Beheshti University of Medical Sciences, Tehran, Iran (grant number: 28935). Registration and protocol: Since in vitro studies were the focus of this review, the pre-specified protocol could not be published on the International Prospective Register of Systematic Reviews (PROSPERO).

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-Ashgar 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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REFERENCES
1. WHO Coronavirus (COVID-19) Dashboard. https://covid19.who.int/
2. EUA AT, Agnihotram S. Emergency Use Authorization (EUA) for an unapproved product review memorandum identifying information.
3. WHO lists Moderna vaccine for emergency use. https://www.who.int/news/item/30-04-2021-who-lists-moderna-vaccine-for-emergency-use
4. Huang Y, Yang C, Xu X-f, Xu W, Liu S-w. Structural and functional properties of SARS-CoV-2 spike protein: potential antivirus drug development for COVID-19. Acta Pharmacol Sin. 2020;41:1141-1149. https://doi.org/10.1038/s41401-020-0485-4
5. Du L, He Y, Zhou Y, Liu S, Zheng B-J, Jiang S. The spike protein of SARS-CoV—a target for vaccine and therapeutic development. Not Rev Microbiol. 2009;7:226-236.
6. Denison MR, Graham RL, Donaldson EF, Eckerle LD, Baric RS. Coronavirus: an RNA proofreading machine regulates replication fidelity and diversity. RNA Biol. 2011;8:270-279. https://doi.org/10.4161/rna.8.2.15013
7. Volz E, Hill V, McCrone JT, et al. Evaluating the effects of SARS-CoV-2 spike mutation D614G on transmissibility and pathogenicity. Cell. 2021;184:64-75. e11. https://doi.org/10.1016/j.cell.2020.11.020
8. Moore JP. Approaches for optimal use of different COVID-19 vaccines: issues of viral variants and vaccine efficacy. J Am Med Assoc. 2021;325:1251-1252. https://doi.org/10.1001/jama.2021.3465
9. Williams TC, Burgers WA. SARS-CoV-2 evolution and vaccines: cause for concern? Lancet Respir Med. 2021;9:333-335.
10. Karim SSA. Vaccines and SARS-CoV-2 variants: the urgent need for a correlate of protection. Lancet. 2021;397:1263-1264.
11. Tracking SARS-CoV-2 variants. 2021.
12. McMahan K, Yu J, Mercado NB, et al. Correlates of protection against SARS-CoV-2 in rhesus macaques. Nature. 2021;590:630-634. https://doi.org/10.1038/s41586-020-03041-6
13. Polack FP, Thomas SJ, Kitchin N, et al. Safety and efficacy of the BNT162b2 mRNA covid-19 vaccine. N. Engl J Med. 2020;383:2603-2615. https://doi.org/10.1056/NEJMoa2034577
14. Burton DR, Poignard P, Stanfield RL, Wilson IA. Broadly neutralizing antibodies present new prospects to counter highly antigenically diverse viruses. Science. 2012;337:183-186. https://doi.org/10.1126/science.1225416
15. Liu Y, Liu J, Xia H, et al. Neutralizing activity of BNT162b2-elicted serum. N. Engl J Med. 2021;384:1466-1468. https://doi.org/10.1056/NEJMoa2102017
16. Liu Y, Liu J, Xia H, et al. BNT162b2-Elicited neutralization against new SARS-CoV-2 spike variants [Online ahead of print] 2021. N. Engl J Med. https://doi.org/10.1056/NEJMoa2106083
17. Shen X, Tang H, Pajon R, et al. Neutralization of SARS-CoV-2 variants B.1.429 and B.1.351. N. Engl J Med. 2021;384:2352-2354. https://doi.org/10.1056/NEJMoa2103740
18. Wu K, Werner AP, Koch M, et al. Serum neutralizing activity elicited by mRNA-1273 vaccine. N. Engl J Med. 2021;384:1468-1470. https://doi.org/10.1056/NEJMoa2102179
19. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71. https://doi.org/10.1136/bmj.n71
20. World Health Organization. COVID-19 weekly epidemiological update. https://www.who.int/publications/m/item/weekly-epidemiological-update-on-covid-19---11-may-2021
21. Global influenza surveillance and response system (GISAIID). https://www.gisaid.org/
22. Get data graph digitizer version 2.26.0.20. http://getdata-graph-digitizer.com/
23. Faggion CM, Jr. Guidelines for reporting pre-clinical in vitro studies on dental materials. J Evid Base Dent Pract. 2012;12:182-189. https://doi.org/10.1016/j.jebdp.2012.10.001
24. Amanat F, Thapa M, Lei T, et al. The plasmablast response to SARS-CoV-2 mRNA vaccination is dominated by non-neutralizing antibodies and targets both the NTD and the RBD. medRxiv. 2021.
25. Cherian S, Potdar V, JadHAV S, et al. Convergent evolution of SARS-CoV-2 spike mutations, L452R, E484Q and P681R, in the second wave of COVID-19 in Maharashtra, India. BioRxiv. 2021.
26. Deng X, Garcia-Knight MA, Khalid MM, et al. Transmission, infectivity, and neutralization of a spike L452R SARS-CoV-2 variant. Cell. 2021;184(13):3426-3437.
27. Jangra S, Ye C, Rathnasinghe R, et al. SARS-CoV-2 spike e484K mutation reduces antibody neutralisation. Lancet Microbe. 2021;2:e283-e284. https://doi.org/10.1016/S2666-5247(21)00068-9
28. Jangra S, Ye C, Rathnasinghe R, et al. The E484K mutation in the SARS-CoV-2 spike protein reduces but does not abolish neutralizing activity of human convalescent and post-vaccination sera. MedRxiv. 2021.
29. Kuzmina A, Khalaila Y, Voloshin O, et al. SARS-CoV-2 spike variants exhibit differential infectivity and neutralization resistance to convalescent or post-vaccination sera. Cell Host microbe. 2021;29:522-528, e522.
30. Kuzmina A, Khalaila Y, Voloshin O, et al. SARS-CoV-2 escape variants exhibit differential infectivity and neutralization sensitivity to convalescent or post-vaccination sera. Available at SSRN 3789258 2021.
31. Rathnasinghe R, Jangra S, Cupic A, et al. The N501Y mutation in SARS-CoV-2 spike leads to morbidity in obese and aged mice and is
neutralized by convalescent and post-vaccination human sera. medRxiv. 2021. https://doi.org/10.1101/2021.01.19.21249592
32. Rees-Spear C, Muir L, Griffith SA, et al. The effect of spike mutations on SARS-CoV-2 neutralization. Cell Rep. 2021;34:108890.
33. Sahin U, Muik A, Derhovanessian E, et al. COVID-19 vaccine BNT162b1 elicits human antibody and TH 1 T cell responses. Nature. 2020;586:594-599.
34. Shi P-Y, Xie X, Zou J, et al. Neutralization of N501Y mutant SARS-CoV-2 by BNT162b2 vaccine-elicited sera. bioRxiv. 2021.
35. Strengert M, Becker M, Ramos GM, et al. Cellular and humoral immunogenicity of a SARS-CoV-2 mRNA vaccine in patients on hemodialysis. medRxiv. 2021. https://doi.org/10.1101/2021.05.26.21257860
36. Wang Z, Schmidt F, Weisblum Y, et al. mRNA vaccine-elicited antibodies to SARS-CoV-2 and circulating variants. Nature. 2021;592:616-622. https://doi.org/10.1038/s41586-021-03324-6
37. Weissman D, Alameh MG, deSilva T, et al. D614G spike mutation increases SARS-CoV-2 susceptibility to neutralization. Cell Host Microbe. 2021;29:23-31. e24. https://doi.org/10.1016/j.chom.2020.11.012
38. Widera M, Wilhelm A, Hoehl S, et al. Bamclanivimab does not neutralize two SARS-CoV-2 variants carrying E484K in vitro. medRxiv. 2021. https://doi.org/10.1101/2021.02.24.21252372
39. Xie X, Liu Y, Liu J, et al. Neutralization of SARS-CoV-2 spike 69/70 deletion, E484K and N501Y variants by BNT162b2 vaccine-elicited sera. Nat Med. 2021;27:620-621. https://doi.org/10.1038/s41591-021-01270-4
40. Zhou J, Xie X, Fontes-Garfias CR, et al. The effect of SARS-CoV-2 D614G mutation on BNT162b2 vaccine-elicited neutralization. NPJ Vaccines. 2021;6:1-4.
41. Chang X, Augusto GS, Liu X, et al. BNT162b2 mRNA COVID-19 vaccine induces antibodies of broader cross-reactivity than natural infection, but recognition of mutant viruses is up to 10-fold reduced [Online ahead of print] 2021. Allergy. https://doi.org/10.1111/all.14893
42. McCallum M, Bassi J, DeMarco A, et al. SARS-CoV-2 immune evasion by the B.1.427/B.1.429 variant of concern [Online ahead of print]. Science. https://doi.org/10.1126/science.abi7994
43. Tada T, Zhou H, Ocsta BM, Samanovic MI, Mulligan MJ, Landau NR. The spike proteins of SARS-CoV-2 B.1.617 and B.1.618 variants identified in India provide partial resistance to vaccine-elicited and therapeutic monoclonal antibodies. BioRxiv. 2021.
44. West AP, Jr, Wertheim JO, Wang JC, et al. Detection and characterization of the SARS-CoV-2 lineage B.1.526. bioRxiv; 2021.
45. Zhou H, Ocsta BM, Samanovic MI, Mulligan MJ, Landau NR, Tada TB. B.1.526 SARS-CoV-2 variants identified in New York City are neutralized by vaccine-elicited and therapeutic monoclonal antibodies. bioRxiv. 2021.
46. Bayarri-Olmos R, Rosbjerg A, Johnsen LB, et al. The SARS-CoV-2 Y453F mink variant displays a pronounced increase in ACE-2 affinity but does not challenge antibody neutralization. J Biol Chem. 2021;296:100536.
47. Pei-Yong S, Jianying L, Yang L, et al. Neutralization of SARS-CoV-2 variants B.1.617.1 and B.1.525 by BNT162b2-elicited sera. Nature Portfolio. 2021. https://doi.org/10.1038/s41550-021-04721-v
48. Bian L, Gao F, Zhang J, et al. Effects of SARS-CoV-2 variants on vaccine efficacy and response strategies. Expt Rev Vaccine. 2021;20(4):365-373.
49. Focosi D, Maggi F. Neutralising antibody escape of SARS-CoV-2 spike protein: risk assessment for antibody-based Covid-19 therapeutics and vaccines [Online ahead of print]. Rev Med Virol. https://doi.org/10.1002/rmv.2231
50. Abdool Karim SS, deOliveira T. New SARS-CoV-2 variants—clinical, public health, and vaccine implications. N. Engl J Med. 2021;384:1866-1868.
51. Zhou D, Deijnertissai W, Supasa P, et al. Evidence of escape of SARS-CoV-2 variant B.1.351 from natural and vaccine-induced sera. Cell. 2021;184:2348-2361. e2346. https://doi.org/10.1016/j.cell.2021.02.037
52. Supasa P, Zhou D, Deijnertissai W, et al. Reduced neutralization of SARS-CoV-2 B.1.1.7 variant by convalescent and vaccine sera. Cell. 2021;184:2201-2211. e2207. https://doi.org/10.1016/j.cell.2021.02.033
53. Goel RR, Apostolidis SA, Painter MM, et al. Distinct antibody and memory B cell responses in SARS-CoV-2 naïve and recovered individuals following mRNA vaccination. Sci Immunol. 2021;6:6. https://doi.org/10.1126/sciimmunol.abi6950
54. Stamatakos L, Czartoski J, Wan Y-H, et al. mRNA vaccination boosts cross-variant neutralizing antibodies elicited by SARS-CoV-2 infection. Science. 2021;372:eabg9175. https://doi.org/10.1126/science.abg9175
55. Yang Y, Zang J, Xu S, et al. Efficiency of ancestral receptor-binding domain, S1 and trimeric spike protein vaccines against SARS-CoV-2 variants B.1.1.7, B.1.351, and B.1.617. 1. bioRxiv. 2021.
56. Corbett KS, Edwards DK, Leist SR, et al. SARS-CoV-2 mRNA vaccine design enabled by prototype pathogen preparedness. Nature. 2020;586:567-571.
57. Stankov MV, Coissmann A, Bonifacius A, et al. Humoral and cellular immune responses against SARS-CoV-2 variants and human coronaviruses after single BNT162b2 vaccination. medRxiv. 2021. https://doi.org/10.1101/2021.04.16.21255412
58. Anichini G, Terrosi C, Gori Savellini G, Gandolfo C, Franchi F, Cusi MG. Neutralizing antibody response of vaccinees to SARS-CoV-2 variants. Vaccines. 2021;9:517.
59. Bates TA, Leier HC, Lyski ZL, et al. Neutralization of SARS-CoV-2 variants by convalescent and vaccinated serum. medRxiv. 2021. https://doi.org/10.1101/2021.04.04.21254881
60. Caniels TG, Bontjer I, vander Straten K, et al. Emerging SARS-CoV-2 variants of concern evade humoral immune responses from infection and vaccination. medRxiv. 2021. https://doi.org/10.1101/2021.05.26.21257441
61. Chen RE, Zhang X, Case JB, et al. Resistance of SARS-CoV-2 variants to neutralization by monoclonal and serum-derived polyclonal antibodies. Nat Med. 2021;27:717-726. https://doi.org/10.1038/s41591-021-01294-w
62. Collier DA, De Marco A, Ferreira IATM, et al. Sensitivity of SARS-CoV-2 B.1.1.7 to mRNA vaccine-elicited antibodies. Nature. 2021;593:136-141. https://doi.org/10.1038/s41586-021-03412-7
63. Deijnertissai W, Zhou D, Supasa P, et al. Antibody evasion by the P.1 strain of SARS-CoV-2. Cell. 2021;184:2939-2954. e2939. https://doi.org/10.1016/j.cell.2021.03.055
64. Donal TS, Adam CH, Javier G-J, et al. Two doses of SARS-CoV-2 vaccination induce more robust immune responses to emerging SARS-CoV-2 variants of concern than does natural infection. Research Square. 2021. https://doi.org/10.21203/rs.3.rs-226857/v2
65. Garcia-Beltran WF, Lam EC, Denis St.K, et al. Multiple SARS-CoV-2 variants escape neutralization by vaccine-induced humoral immunity. Cell. 2021;184:2372-2383. e2379. https://doi.org/10.1016/j.cell.2021.03.013
66. Geers D, Shamier MC, Bogers S, et al. SARS-CoV-2 variants of concern partially escape humoral but not T cell responses in COVID-19 convalescent donors and vaccines. Science Immunology. 2021;6:eabj1750. https://doi.org/10.1126/sciimmunol.abj1750
67. Hoffmann M, Arora P, Groß R, et al. SARS-CoV-2 variants B.1.351 and P.1 escape from neutralizing antibodies. Cell. 2021;184:2384-2393. e2312. https://doi.org/10.1016/j.cell.2021.03.036

68. Jalkanen P, Kolehmainen P, Häkkinen H, et al. COVID-19 mRNA vaccine induced antibody responses and neutralizing antibodies against three SARS-CoV-2 variants; 2021.

69. Liu J, Bodnar BH, Wang X, et al. Correlation of vaccine-elicted antibody levels and neutralizing activities against SARS-CoV-2 and its variants. bioRxiv. 2021. https://doi.org/10.1101/2021.05.31.445871

70. Marot S, Malet I, Leducq V, et al. Neutralization heterogeneity of United Kingdom and South-African SARS-CoV-2 variants in BNT162b2-vaccinated or convalescent COVID-19 healthcare workers. Clin Infect Dis [Online ahead of print]. https://doi.org/10.1093/cid/cia492

71. Muik A, Wallisch A-K, Sänger B, et al. Neutralization of SARS-CoV-2 lineage B.1.1.7 pseudovirus by BNT162b2 vaccine-elicted human sera. Science. 2021;371:1152-1153. https://doi.org/10.1126/science.abg6105

72. Planas D, Bruel T, Grzelak L, et al. Sensitivity of infectious SARS-CoV-2 B.1.1.7 and B.1.351 variants to neutralizing antibodies. Nat Med. 2021;27:917-924. https://doi.org/10.1038/s41591-021-01318-5

73. Planas D, Veyer D, Baidaliuk A, et al. Reduced sensitivity of infectious SARS-CoV-2 variant B.1.617.2 to monoclonal antibodies and sera from convalescent and vaccinated individuals. bioRxiv. 2021. https://doi.org/10.1101/2021.05.26.445838

74. Trinité B, Pradenas E, Marfil S, et al. Previous SARS-CoV-2 Infection Increases B.1.1.7 Cross-Neutralization by Vaccinated Individuals. Viruses. 2021;13(6):1-12. https://doi.org/10.3390/v13061135

75. Wall EC, Wu M, Harvey R, et al. Neutralising antibody activity against SARS-CoV-2 VOCs B.1.617.2 and B.1.351 by BNT162b2 vaccination. Lancet. 2021;397(10292):2331-2333. https://doi.org/10.1016/S0140-6736(21)0290-3

76. Wang P, Nair MS, Liu L, et al. Antibody resistance of SARS-CoV-2 variants B.1.351 and B.1.1.7. Nature. 2021;593:130-135. https://doi.org/10.1038/s41586-021-03398-2

77. Zani A, Caccuri F, Messali S, Bonfanti C, Caruso A. Serosurvey in BNT162b2 vaccine-elicted neutralizing antibodies against authentic B.1, B.1.1.7, B.1.351, B.1.525 and P.1 SARS-CoV-2 variants. Emerg Microb Infect. 2021;10:1-1243. https://doi.org/10.1080/22221751.2021.1940305

78. Pegu A, O’Connell S, Schmidt SD, et al. Durability of mRNA-1273-induced antibodies against SARS-CoV-2 variants. bioRxiv. 2021. https://doi.org/10.1101/2021.05.13.444010

79. Edara VV, Norwood C, Floyd K, et al. Infection- and vaccine-induced antibody binding and neutralization of the B.1.351 SARS-CoV-2 variant. Cell Host Microbe. 2021;29:516-521. e513. https://doi.org/10.1016/j.chom.2021.03.009

80. Edara VV, Norwood C, Floyd K, et al. Increased resistance of SARS-CoV-2 variant P.1 to antibody neutralization. Cell Host Microbe. 2021;29:747-751. e744. https://doi.org/10.1016/j.chom.2021.04.007

81. Liu J, Liu Y, Xia H, et al. BNT162b2-elicted neutralization of B.1.617 and other SARS-CoV-2 variants [Online ahead of print] 2021. Nature. https://doi.org/10.1038/s41586-021-03693-y

82. Liu C, Ginn HM, Dejnirattisai W, et al. Reduced neutralization of SARS-CoV-2 B.1.617.2 by vaccine and convalescent serum [Online ahead of print] 2021. Cell. https://doi.org/10.1016/j.cell.2021.06.020

83. Miclochova P, Kemp SA, Shanker Dhar M, et al. SARS-CoV-2 B.1.617.2 Delta variant emergence and vaccine breakthrough. bioRxiv. 2021. https://doi.org/10.1101/2021.05.08.443253

84. Focosi D, Tucciari M, Baj A, Maggi F. SARS-CoV-2 variants: a synopsis of in vitro efficacy data of convalescent plasma, currently marketed vaccines, and monoclonal antibodies. Viruses. 2021;13(7):1211.

85. Baden LR, El Sahly HM, Essink B, et al. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. N Engl J Med. 2020;384:403-416. https://doi.org/10.1056/NEJMoa2035389

86. Cerutti G, Guo Y, Zhou T, et al. Potent SARS-CoV-2 neutralizing antibodies directed against spike N-terminal domain target a single supersite. Cell Host Microbe. 2021;29:819-833. e817. https://doi.org/10.1016/j.chom.2021.03.005

87. Piccoli L, Park YJ, Tortorici MA, et al. Mapping neutralizing and immunodominant sites on the SARS-CoV-2 spike receptor-binding domain by structure-guided high-resolution serology. Cell. 2020;183:1024-1042. e1021. https://doi.org/10.1016/j.cell.2020.09.037

88. Greaney AJ, Starr TN, Gilchuk P, et al. Complete mapping of mutations to the SARS-CoV-2 spike receptor-binding domain that escape antibody recognition. Cell Host Microbe. 2021;29:44-57. e49. https://doi.org/10.1016/j.chom.2020.11.007

89. Ali F, Kasry A, Amin M. The new SARS-CoV-2 strain shows a stronger binding affinity to ACE2 due to N501Y mutant. Medicine in Drug Discovery. 2021;10:100086. https://doi.org/10.1016/j.medid.2021.100086

90. Wu K, Werner AP, Moliva JL, et al. mRNA-1273 vaccine induces neutralizing antibodies against spike mutants from global SARS-CoV-2 variants. bioRxiv. 2021. https://doi.org/10.1101/2021.01.25.427948

91. Kuzmina A, Khalaila Y, Voloshin O, et al. SARS-CoV-2 spike variants exhibit differential infectivity and neutralization resistance to convalescent or post-vaccination sera. Cell Host Microbe. 2021;29(4):522-528. https://doi.org/10.1016/j.chom.2021.03.008

92. Barnes CO, Jette CA, Abernathy ME, et al. SARS-CoV-2 neutralizing antibody structures inform therapeutic strategies. Nature. 2020;585:682-687. https://doi.org/10.1038/s41586-020-2852-1

93. Tada T, Dcosta BM, Samanovic-Golden M, et al. Neutralization of viruses with European, South African, and United States SARS-CoV-2 variant spike proteins by convalescent sera and
