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Immunogenicity of SARS-CoV-2 vaccines in patients with multiple myeloma: a systematic review and meta-analysis

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Running title: COVID-19 vaccine responses in patients with MM

Keywords: Antibody response; COVID-19; COVID-19 vaccines; humoral immune response; mRNA vaccines; multiple myeloma

Word count: abstract 250 words, manuscript 2775 words

Data availability statement: The data for our systematic review and meta-analysis are publicly available based on the study design.

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Abbreviations

Ab: antibodies

CHARMS: the checklist for critical appraisal and data extraction for systematic reviews of prediction modelling studies

CDC: Centers for Disease Control and Prevention

CI: confidence interval

COVID-19: coronavirus disease 2019

EUA: emergency use authorization

FDA: the Food and Drug Administration

IQR: interquartile range

mAb: monoclonal antibodies

MM: multiple myeloma

ORs: odds ratios

pORs: pooled odds ratios

PRISMA: Preferred Reporting Items for Systematic reviews and Meta-Analyses

PROSPERO: the International Prospective Register of Systematic Reviews

SARS-CoV-2: severe acute respiratory syndrome coronavirus 2

SD: standard deviation

SE: standard error

U.S.: the United States of America

Abstract

Patients with multiple myeloma (MM) have diminished immune response to COVID-19 vaccines. Risk factors for an impaired immune response are yet to be determined. We aimed to summarize the COVID-19 vaccine immunogenicity, and to identify factors that influence the humoral immune response in patients with MM. Two reviewers independently conducted a literature search in MEDLINE, Embase, ISI Web of Science, Cochrane library, and Clinicaltrials.gov from existence through May 24th, 2022. (PROSPERO: CRD42021277005). Fifteen and five studies were included in the systematic review and meta-analysis, respectively. The average rate (range) of positive functional T-lymphocyte response was 44.2% (34.2% - 48.5%) after 2 doses of mRNA COVID-19 vaccines. The average anti-spike antibody response rates (range) were 42.7% (20.8% - 88.5%) and 78.2% (55.8% - 94.2%) after 1 and 2 doses of mRNA COVID-19 vaccines, respectively. The average neutralizing antibody response rates (range) were 25% (1 study) and 62.7% (53.3% - 68.6%) after 1 and 2 doses of mRNA COVID-19 vaccines, respectively. Patients with high-risk cytogenetics or receiving anti-CD38 therapy were less likely to have a humoral immune response with pORs of 0.36 (0.18, 0.69), I^2=0% and 0.42 (0.22, 0.79), I^2=14%, respectively. Patients who were not on active MM treatment were more likely to respond with pOR of 2.42 (1.10, 5.33), I^2=7%. Patients with MM had low rates of humoral and cellular immune response to the mRNA COVID-19 vaccines. Further studies are needed to determine the optimal doses of vaccines and evaluate the utilization of monoclonal antibodies for pre-exposure prophylaxis in this population.

Introduction

Patients with multiple myeloma (MM) have an increased risk of severe coronavirus disease 2019 (COVID-19), with a mortality rate of 34% - 37%.[1-3] Several vaccine platforms have been shown to reduce disease transmission, severity, and mortality in the general population.[4-6] However, many immunocompromised patient populations including people with MM were not included in clinical trials of COVID-19 vaccines.[5,7,8] Multiple myeloma, caused by the abnormal proliferation of clonal plasma cells producing monoclonal immunoglobulin, is the second most common hematologic malignancy in the United States (U.S.) and accounts for 10% of total hematologic malignancies.[9,10] Patients with MM are known to have diminished humoral and cellular immune response to influenza, pneumococcal, and *Haemophilus influenzae* type B vaccines.[11] Unfortunately, recent studies have also shown that patients with MM had inferior immune response to COVID-19 vaccines compared to the general population.[12-14] The impaired immune response of MM patients has raised concerns for breakthrough infections and the ineffective protection against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[15] This systematic review and meta-analysis were conducted to summarize the current information regarding the immunogenicity of COVID-19 vaccines and identify the factors that contribute to low rates of humoral response to COVID-19 vaccines in patients with MM.

Methods

2.1 Data Sources and Searches

Two authors (N.C. and K.M.) independently conducted the systematic search in MEDLINE, Embase, ISI Web of Science, Cochrane library, and Clinicaltrials.gov databases from the beginning of the pandemic until May 24th, 2022. SARS-CoV-2 vaccine, COVID-19 vaccine,

BNT162b2, Pfizer, mRNA-1273, AZD1222, Janssen, CoronaVac, and multiple myeloma were used as search terms. Full search terms are available in the supplementary material (Method S). Duplicate studies were excluded. We did not limit our search by language. Google Translate was used to translate non-English studies during title and abstract screening. We conducted the study according to the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) guidelines.[16] The International Prospective Register of Systematic Reviews (PROSPERO) registration number is CRD42021277005.

2.2 Study selection

All studies were reviewed independently by two authors (N.C. and K.M.). We included clinical trials and observational studies consisting of prospective cohort, retrospective cohort, and case-control studies. Studies were selected if they reported the immune response to COVID-19 vaccines in patients with MM. Studies of subjects with prior COVID-19 were excluded to prevent the confounding effects of immune responses from natural infection of SARS-CoV-2. If needed, we contacted corresponding authors for additional information regarding antibody testing. Conflicts were resolved by mutual consensus among reviewers.

2.3 Data Extraction and Quality Assessment

The checklist for critical appraisal and data extraction for systematic reviews of prediction modelling studies (CHARMS) was employed to guide comprehensive data extraction from included studies.[17] We extracted study design, country, center, study year, study period, type of SARS-CoV-2 vaccine, immunogenicity tests, study limitations, and other important comments. Our primary outcome was the humoral and cellular immune response rates to the COVID-19

vaccines. The seroconversion rates were calculated from the number of responders and total participants. We defined responders as subjects who tested positive for humoral or cellular response according to the study's cutoffs and definitions.

Our secondary outcome was factors that affected the humoral immune response to COVID-19 vaccines. We collected the number of responders, total participants, and odds ratios (ORs) with 95% confidence interval (CI) of the factors that were tested for an association with vaccine response. If ORs were not available, we used crude number of responders, non-responders, and total participants for the OR calculation. We used the Newcastle-Ottawa scale for assessing the risk of bias of the studies (Supplementary Table S1).[18]

2.4 Data Synthesis and Analysis

We used descriptive statistics to summarize the humoral and cellular immune response data from each COVID-19 platform and dosage. We used the weighted means for the positive humoral and cellular immune response rates. Comprehensive Meta-Analysis 3.3 software from Biostat, Inc. (Englewood, NJ, USA) was used to perform a meta-analysis and Egger's regression to identify risk factors associated with poor humoral immune response. We performed the meta-analysis with the random-effects model to obtain the pooled ORs with 95% CI, for binary or categorical variables, of factors that affected the immunogenicity. Adjusted ORs were used if the study provided both adjusted and unadjusted ORs. We used raw data to calculate unadjusted ORs if the study did not provide ORs. We performed sensitivity analyses using a leave-one-out method.[19] Publication bias was assessed by Funnel plot and Egger's regression.[20] If the p-value of Egger's regression was below 0.05, the publication bias was considered significant.[21] If there were

concerns for publication bias, data were further adjusted by the Duval and Tweedie trim-and-fill method.[22] The I^2 statistic was used to assess the heterogeneity of effect size estimates of each study. The I^2 statistic value was from 0% to 100% (I^2<25%, low heterogeneity; I^2=25%–60%, moderate heterogeneity; and I^2>60%, substantial heterogeneity).

3. Results

3.1 Study and patient characteristics

Our initial search generated 809 studies; 98 were removed due to duplicate study and 630 were excluded by screening through the titles and abstracts. We performed a full-paper review with 81 articles. Sixty-six articles were subsequently excluded due to being a review article, case report, wrong population, duplicate cohort, or different outcome of interest. A total of 15 studies were included in the systematic review and five studies were included in the meta-analysis (Figure 1). The characteristics of the 15 studies[23-37] are described in Table 1. There were 1,210 patients with MM and 38 patients with smoldering MM. Grading of recommendation assessment, development, and evaluation (GRADE) for factors influencing the seroconversion was described in the supplementary material (Supplementary Table S2).[38]

3.2 Humoral immune responses

3.2.1 mRNA vaccines

A total of 15 studies of immunogenicity of the mRNA COVID-19 vaccines were identified. There were seven studies reporting the antibody response after 1 dose of the mRNA COVID-19 vaccines. The average positive antibody response rates after 1 dose of mRNA vaccine were

42.7% (range 20.8% - 88.5%; 6 studies[24,29-32,34]) for anti-spike antibodies and 25% (1 study[36]) for neutralizing antibodies (Figure 2). The mean time to antibody testing was 28 (range 21-33) days.

Twelve studies reported the antibody response rates after 2 doses of mRNA COVID-19 vaccine. The average positive antibody response rates were 78.2% (range 55.8% - 94.3%; 10 studies[23,25,26,28-31,33-35]) for anti-spikes antibodies, and 62.7% (range 53.3% - 68.6%; 3 studies[26,27,37]) for neutralizing antibodies (Figure 2, Table 2). The mean antibody testing time was 27.3 (range 14-56) days after the second dose of mRNA vaccines. We then calculated the average positive antibody response rates by vaccine type. The average rates of positive antibody response of the BNT162b2 vaccine were 77.7% (range 55.8% - 87.4%; 7 studies[23,25,26,29,31,33,35]) for anti-spike antibodies and 62.7% (range 53.3% - 68.6%; 3 studies[26,27,37]) for neutralizing antibodies. Terpos et al. reported an increase of humoral response with the seropositivity of 85% for neutralizing antibodies after 3 doses of the BNT162b2 vaccine.[37] There is no data regarding mRNA-1273 alone for analysis.

3.2.2 Other vaccine platforms

The average positive antibody response rate was 55.9% (range 50% - 57.8%; 2 studies[24,32]) for anti-spike antibodies after 1 dose of AZD1222. At the time of our search, no data related to inactivated, or protein subunit vaccine platforms were available.

3.2.3 Risk factors for reduced humoral immune responses after 2 doses of mRNA vaccines

We included studies reporting factors that influenced the humoral immune response after 2 doses of mRNA vaccines among patients with MM or smoldering MM to ensure an analysis of a

similar disease spectrum. We reviewed host characteristics (age, sex, immunoglobulin levels, neutrophil count, lymphocyte count, previous hematopoietic cell transplantation, high-risk cytogenetics, and treatment response according to the International Myeloma Working Group definitions[39]) and treatment-related factors [anti-directed-CD38 therapy, anti-SLAM family member 7 (SLAMF7) antibody, B-cell-maturation-antigen-targeted therapy, proteasome inhibitors, immunomodulatory agents, systemic corticosteroids, ≥3 lines of treatment, and no active treatment] that could potentially impact humoral immune response after 2 doses of mRNA vaccines. However, meta-analysis could only be performed with the factors below due to lack of data or different cut-off levels in each primary study (Supplementary Table S3).

Male sex was not associated with antibody response rates. The pOR for male sex from five studies was 0.97 (0.58, 1.61), p=0.90, I^2=0 % (Figure 3).[23,25,26,28,31] High-risk cytogenetics, defined as having at least one of the following cytogenetic abnormalities: t(4;14), t(14;16), t(14;20), del(17p), or gain(1q) by fluorescence in situ hybridization[40], were associated with lower antibody response rates. The pOR for high-risk cytogenetics in two studies was 0.36 (0.18, 0.69), p=0.002, I^2=0% (Figure 3).[23,26]

We found that patients with higher antibody response rates were not receiving active treatment. The pOR for no active treatment from four studies was 2.42 (1.10, 5.33), p=0.029, I^2=7% (Figure 3).[23,25,26,28] Treatment with daratumumab (anti-CD38 antibody) was associated with lower antibody response rates, with the pOR from five studies of 0.42 (0.22, 0.79), p=0.007, I^2=14% (Figure 3).[23,25,26,28,31] Treatment with immunomodulatory agents (lenalidomide, pomalidomide, thalidomide), and proteasome inhibitors (bortezomib, carfilzomib, ixazomib) were not associated

with lower antibody response rates. The pORs of immunomodulatory agents (3 studies[23,26,28]) and proteasome inhibitors (3 studies[23,26,28]) were 0.76 (0.25, 2.31), p=0.63, I^2=64% and 0.51 (0.21, 1.24), p=0.14, I^2=29%, respectively (Figure 3).

Treatment response to MM therapy was not associated with antibody response rates. The pOR for patients with partial, very good partial, and complete response (partial-to-complete response) to treatment from four cohorts in two studies was 1.40 (0.73, 2.68), p=0.310, I^2=57% (Figure 3).[23,26] The pOR for patients with less-than-partial response from three cohorts in two studies was 0.38 (0.10, 1.42), p=0.15, I^2=35 (Figure 3).[25,26] Receiving ≥ 3 lines of treatment was not associated with lower antibody response rates, with a pOR from two studies of 0.38 (0.07, 1.97), p=0.250, I^2=71 (Figure 3).[23,26]

3.4 Cellular immune response

Three studies reported cellular immune response after 2 doses of mRNA COVID-19 vaccines among patients with MM (Table 2). The cellular immune response was evaluated by two main methods: functional T-lymphocyte response by enzyme-linked immunospot assay (ELISpot) and *in vitro* T-helper cell type 1-associated cytokine release using ELISA.[26,29,30] The average rate of positive functional T-lymphocyte response was 44.2% (range 34.2% - 48.5%).[26,29,30] Enßle *et al*. reported significantly lower median of CD19+ B-lymphocytes among antibody non-responders, compared to responders.[26]

3.5 Sensitivity analysis and publication bias

The pORs for male sex, less-than-partial response to treatment, and immunomodulatory agents (no significant association with antibody response rates) remained consistent by sensitivity analyses. The pOR for high-risk cytogenetics became insignificant after removing Avivi et al. 2021[23]. The pOR for daratumumab became insignificant when removing Enßle et al[26]. from the analysis. The pOR for proteasome inhibitors became significantly associated with lower antibody response rates after removing Avivi et al. 2021[23], with a pOR of 0.24 (0.07, 0.85), p=0.027. The pOR for no active treatment became insignificant after removing Enßle et al. 2021[26] or Greenberg et al. 2021[28]. The pOR for partial-to-complete treatment response became significantly associated with higher immune response rates when removing the partial response cohort of Enßle et al. 2021[26], with a pOR of 1.90 (1.11, 3.25), p=0.019. The pOR for receiving ≥3 lines of treatment became significantly associated with lower antibody response rates after removing Enßle et al. 2021[26], with a pOR of 0.16 (0.04, 0.61), p=0.007.

We did not find evidence of publication bias by the Egger's test and inspection of the funnel plots in following factors: male sex, partial-to-complete response to treatment, less-than-partial response to treatment, and use of proteasome inhibitors. We cannot evaluate publication bias in high-risk cytogenetics and patients receiving ≥ 3 lines of treatment due to limited numbers of included studies.

4. Discussion

This is the systematic review and meta-analysis summarizing the accumulating data regarding the cellular and humoral immune response of COVID-19 vaccines and risk factors contributing to the poor humoral antibody response in patients with MM. The average antibody response rates

increased from 43% to 78% after the second dose of mRNA COVID-19 vaccines but were still lower than rates reported in the general population[41]. One study reported the humoral immune response of 85% after 3 doses of mRNA vaccines.[37] The average cellular response rate after 2 doses of mRNA COVID-19 vaccines was 44%, which was significantly lower than rates reported for healthy controls.[30] However, interpretation of the cellular response needs to be cautious as some therapies might interfere with T-cell function assays.[42,43] This study underscores the importance of subsequent doses of the COVID-19 vaccine and adhering to the safety precautions among patients with MM regardless of vaccine status. As of July, 2022, the U.S. Centers for Disease Control and Prevention (CDC) has recommended that immunocompromised patients, including patients with MM, should receive 2 booster doses after the primary 3-dose mRNA vaccine series (BNT162b2 or mRNA-1273) or a total 4 doses of Ad26.COV2.S vaccine (the primary series, additional dose, and 2 booster doses).[44]

In this study, we identified patients with high-risk cytogenetics and patients receiving daratumumab as less likely to have an antibody response after 2 doses of mRNA COVID-19 vaccines. It is known that high-risk cytogenetics are associated with high-risk disease characteristics and have poor prognosis due to rapid disease progression, often necessitating more aggressive treatment.[40,45] Patients with high-risk cytogenetics tend to be treated with multiple anti-myeloma agents, which can potentially lead to further diminished humoral immune response. The exact mechanism linking high-risk cytogenetics and poor humoral immune response may relate to disease or treatment factors. Daratumumab targets CD38 on both cancerous and normal plasma cells, which is expected to interfere with antibody response. The finding of lower antibody response rates after treatment with daratumumab is consistent with

other studies that were excluded from this analysis due to mixed patient populations with previous COVID-19 infection or other plasma cell disorders other than MM and smoldering MM.[46-48] High-risk cytogenetics and treatment with anti-CD38 antibody could be related and confounded as patients with high-risk cytogenetics are likely to receive more aggressive treatment regimen including anti-CD38 antibody.[49] However, the primary studies do not provide sufficient information for further analyses. Patients with MM who were not on active treatment had a more favorable immune response.

Patients with MM suffer from immune dysregulation, and MM treatment can lead to further reduced immune response and increased risk of breakthrough SARS-CoV-2 infections despite being vaccinated.[15] Wang et al. reported 15.4% of patients with MM who were vaccinated with 2 doses of mRNA vaccines or 1 dose of Ad26.COV2.S developed breakthrough COVID-19 from December 1, 2020 to October 8, 2021.[50] The Omicron SARS-CoV-2 variants have raised concerns about breakthrough infections in both healthy and immunocompromised individuals, with and without boosters.[51,52] Our results demonstrate a low humoral immune response of 77% in patients with MM after 2 doses of mRNA vaccines with an increase of humoral immune response to 85% after 3 doses of mRNA vaccines.

The Food and Drug Administration (FDA) issued an emergency use authorization for tixagevimab/cilgavimab, a long-acting monoclonal antibody (mAb) cocktail, for the pre-exposure prevention against SARS-CoV-2 in moderate to severe immunocompromised patients, including those with MM based on the data from a phase III trial that a single dose of tixagevimab/cilgavimab had efficacy for COVID-19 prevention.[53,54] The FDA stated that

COVID-19 vaccines are the best prevention against SARS-CoV-2 infection; however, some patients with MM are unable to produce an adequate antibody response after receiving the vaccines.[53,55] Given the globally limited availability of tixagevimab/cilgavimab, additional questions arise as to who should be prioritized to receive mAb for pre-exposure prophylaxis, even with the patient populations identified in the emergency use authorization. Does the passive immunization from tixagevimab/cilgavimab make up for the low rates of immune response in patients with MM? The risk factors identified in this study may inform healthcare professionals on time-sensitive decisions about active versus passive immunization, by weighing the likelihood of benefit from vaccination compared to the likelihood of benefit from mAbs.

Limitations of our study include the small numbers of studies used in the meta-analysis due to mixed vaccine platforms and mixed patient populations. The majority of available data is from the mRNA platform; however, many countries use other vaccine platforms due to limited mRNA vaccine supply globally. There are very limited studies reporting immune response to three or more doses COVID-19 vaccines as of August 2022. Included studies used differing SARS-CoV-2 antibody testing techniques, and there was no gold standard for antibody testing. Lastly, the clinical significance of measured humoral and cellular immune responses in patients with MM is uncertain.

In conclusion, patients with MM had impaired immune response after COVID-19 vaccinations. Anti-CD38 directed therapy and high-risk cytogenetics were associated with lower antibody response rates, whereas patients receiving no active treatment had higher antibody response rates. Further studies are needed to determine the optimal schedule for each COVID-19 vaccine

platform, the efficacy of mAb for pre-exposure prophylaxis, and clinical outcomes in patients with MM who develop breakthrough COVID-19.

Acknowledgements/Funding

We would like to extend our gratitude to librarians at Chulalongkorn University and Johns Hopkins University School of Medicine for their contribution of retrieving full papers of studies that were not available on the databases. No funding to be disclosed for the study.

Disclosure

Dr. Nematollahi reported receiving a grant from the Fisher Center Discovery Program, Johns Hopkins University. Drs. Worasilchai, Plongla, and Chindamporn reported receiving grants from the Health Systems Research Institute (Thailand) and Rachadapiseksompotch Fund, Chulalongkorn University outside the submitted work. Dr. Permpalung reported receiving grants and salary support from the Health Systems Research Institute (Thailand), the Fisher Center Discovery Program, Johns Hopkins University, the Cystic Fibrosis Foundation, NIH, Immune Tolerance Network, and Merck outside the submitted work. Dr. Permpalung has served on the Advisory Board for Shionogi Inc and the Data Review Committee for Pulmocide Ltd. No other conflict of interest to declare.

Contributors

NC, KM, NP: study design, literature search, data extraction, quality assessment of the studies, data analysis, manuscript writing and critical review

CM: study design, literature search, manuscript writing and critical review

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Figure legends

Figure 1. PRISMA Diagram

Figure 2. Humoral immune response rates of mRNA vaccines

Figure 3. The pooled odds ratios of humoral immune responses after 2 doses of mRNA vaccines

Table 1. Study characteristics

Study	Vaccine	Country	Study period (mm/yy)	Study design	Number of patients	Subgroup of patients (numbers)	Age
Avivi 2021	BNT162b2	Israel	12/20 - 03/21	Prospective	171	MM (159); SMM (12)	Median (range) 70 (38-94)
Bird 2021	BNT162b2 or AZD1222	UK	Until 03/21	Retrospective	93	MM (93)	Not reported
Bitoun 2021	BNT162b2	France	01/21 - 03/21	Prospective	27	MM (27)	Not reported
Enßle 2021	BNT162b2	Germany	09/20 - 06/21	Prospective	77	MM (73); SMM (4)	Median (IQR) 67 (60-72)
Gavriatopoulou 2021	BNT162b2	Greece	01/21 - 05/21	Prospective	35	MM (29); SMM (6)	Median (IQR) 66 (74)
Greenberg 2021	BNT162b2 or mRNA-1273	US	12/20 - 03/21	Prospective	44	MM (44)	Median (IQR) 64 (57-69)
Henriquez 2021	BNT162b2	France	01/21 - 06/21	Prospective	60	MM (60)	Mean (range) 70 (41-92)
Marasco 2021	BNT162b2 or mRNA-1273	Italy	03/21 - 05/21	Prospective	263	MM (52)	Median (range) 73 (47-78)
Pimpinelli 2021	BNT162b2	Italy	Not reported	Prospective	42	MM (42)	Median (range) 73 (47-78)
Ramasamy 2021	BNT162b2 or AZD1222	UK	02/21 - 03/21	Prospective	23	MM (23)	Mean (SD) 62.9 (9.9)
Rehav 2021	BNT162b2	Israel	Not reported	Prospective	187	MM (187)	Median (IQR) 66 (59-73)
Stampfer 2021	BNT162b2 or mRNA-1273	US	Not reported	Prospective	96	MM (96); SMM (7)	Median 68 (35- 88)
Šušol 2022	BNT162b2	Czech Republic	Not reported	Prospective	119	MM (119)	Not reported
Terpos 2021	BNT162b2	Greece	Not reported	Prospective	48	MM (39); SMM (9)	Median (IQR) 74 (62-80)
Terpos 2022	BNT162b2	Greece	09/21 – 10/21	Prospective	167	MM (167)	Median (IQR) 68 (60-75)

IQR: interquartile range; MM: multiple myeloma; SD: standard deviation; SMM: smoldering multiple myeloma; UK: United Kingdom; US: United States

Table 2. Humoral and cellular immune response after 2 doses of mRNA COVID-19 vaccines

Study	Vaccine (dose)	Antibody measurement	Methods	Timing to Ab testing	Responders/Total (Seroconversion rate)	Cellular immune response measurement	Timing to cellular immune response testing	Responders/Total (rate)
Avivi 2021	BNT162b2 (2 doses)	Anti-spike Ab	Elecsys anti-SARS-CoV-2 (Roche)	14-21 days	121/159 (76.10%)			
Bird 2021	BNT162b2 (1 dose)	Anti-spike Ab	Ortho Clinical Diagnostics	Median (IQR) 33 (28-38) days	26/45 (57.78%)			
	AZD1222 (1 dose)				26/48 (54.17%)			
Bitoun 2021	BNT162b2 (2 doses)	Anti-spike Ab	Elecsys anti-SARS-CoV-2 (Roche)	56 days	20/27 (74.07%)			
Enßle 2021	BNT162b2 (2 doses)	Anti-spike Ab	ARCHITECT SARS-CoV-2 IgG II Quant assay (Abbott)	Median 21 days	43/77 (55.84%)	IFN-γ ELISpot	28 days	13/38 (34.21%)
Gavriatopoulou 2021	BNT162b2 (2 doses)	Neutralizing Ab	SARS-CoV-2 Surrogate Virus Neutralization Test (GenScript)	4 weeks	24/35 (68.57%)			
Greenberg 2021	BNT162b2 or mRNA-1273 (2 doses)	Anti-spike Ab	Elecsys anti-SARS-CoV-2 (Roche)	1 month	41/44 (93.18%)			
Henriquez 2021	BNT162b2 (1 dose)	Anti-spike Ab	Not reported	30 days	26/60 (43.33%)			
	BNT162b2 (2 doses)			1-2 months	51/60 (85.00%)	IFN-γ ELISpot	2 months	11/26 (42.31%)
Marasco 2021	BNT162b2 or mRNA-1273 (1 dose)	Anti-spike Ab	Elecsys anti-SARS-CoV-2 (Roche)	4 weeks	46/52 (88.46%)	Measurement of *in vitro* T-helper cell type 1-associated cytokine release using ELISA		
	BNT162b2 or mRNA-1273 (2 doses)			2 weeks	49/52 (94.23%)		2 weeks	48/99 (48.48%)
Pimpinelli 2021	BNT162b2 (1 dose)	Anti-spike Ab	LIAISON SARS-CoV-2 S1/S2 IgG chemiluminescent assay (DiaSorin)	21 days after first dose	9/42 (21.43%)			
	BNT162b2 (2 doses)			35 days after first dose	33/42 (78.57%)			

Ramasamy 2021	AZD1222 (1 dose)	Anti-spike Ab	ARCHITECT SARS-CoV-2 IgG II Quant assay (Abbott)	>3 weeks	7/14 (50.00%)
	BNT162b2 (1 dose)			>3 weeks	4/9 (44.44%)
Rehav 2021	BNT162b2 (2 doses)	Anti-spike Ab	In house ELISA	Median (IQR) 18 (15-23) days	149/187 (79.68%)
Stampfer 2021	BNT162b2 or mRNA-1273 (1 dose)	Anti-spike Ab	In house ELISA	14-21 days	20/96 (20.83%)
	BNT162b2 or mRNA-1273 (2 doses)			14-21 days	64/96 (66.67%)
Šušol 2022	BNT162b2 (2 doses)	Anti-spike Ab	EUROIMMUN SARS-CoV-2 ELISA assay	Not reported	104/119 (87.39%)
Terpos 2021	BNT162b2 (1 dose)	Neutralizing Ab	SARS-CoV-2 Surrogate Virus Neutralization Test (GenScript)	21 days	12/48 (25.00%)
Terpos 2022	BNT162b2 (2 doses)	Neutralizing Ab	SARS-CoV-2 Surrogate Virus Neutralization Test (GenScript)	1 month	110/167 (65.87%)
	BNT162b2 (3 doses)			1 month	142/167 (85.03%)

Ab: antibody; ELISA: enzyme-linked immunosorbent assay; ELISpot: enzyme-linked immune absorbent spot; IFN: interferon; IQR: interquartile range; SD: standard deviation