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ARTICLE

Epidemiology

Antibody response to a third booster dose of SARS-CoV-2 vaccination in adults with haematological and solid cancer: a systematic review

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BACKGROUND: Patients living with cancer are at a significantly increased risk of morbidity and mortality after infection with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). This systematic review aims to investigate the current available evidence about the immunogenicity of SARS-CoV-2 booster vaccines in patients living with cancer.
METHODS: A systematic search was undertaken for studies published until March 1, 2022. A systematic narrative review was undertaken to include all studies that evaluated the efficacy of booster vaccines against SARS-CoV-2 in patients with cancer.
RESULTS: Fifteen studies encompassing 1205 patients with cancer were included. We found that a booster vaccine dose induced a higher response in patients with solid cancer as compared to haematological malignancies. Recent systemic anticancer therapy does not appear to affect seroconversion in solid organ malignancies, however, there is an association between B-cell depleting therapies and poor seroconversion in haematological patients.
CONCLUSIONS: Third booster vaccination induces an improved antibody response to SARS-CoV-2 in adults with haematological and solid cancer, relative to patients who only receive two doses. Access to vaccination boosters should be made available to patients at risk of poor immunological responses, and the provision of fourth doses may be of benefit to this vulnerable population.
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INTRODUCTION

Patients living with cancer have been disproportionately affected by the Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) pandemic, with higher morbidity and mortality than the general population [1–9]. It can differ by cancer type with patients with haematological cancer at increased risk [2, 10, 11]. Therefore, the timely development and delivery of an effective vaccine was of the utmost importance for this patient group. Several vaccines have now been licensed for use worldwide, including the Pfizer-BNT162b2 (Pfizer) and Moderna-mRNA-1273 (Moderna) mRNA vaccines and the AZ-ChAdOx1 (Oxford-AstraZeneca) adenovirus-vectored vaccine. Such vaccines have been shown to be efficacious in mounting a strong immune response against SARS-Cov-2 in healthy individuals; with differences in immune response and effectiveness against COVID-19 outcomes vaccine type [12–14]. Patients with cancer have been identified to have a diminished response to vaccination in comparison to the general population and have thus been considered for additional doses [15–17]. In addition, booster vaccination campaigns have since been launched based on evidence that a third vaccine dose may further reduce infection rates in the general population [18].

Patients with cancer have been prioritised for booster doses by the Joint Committee on Vaccination and Immunisation in the United Kingdom and the Centres for Disease Control and Prevention in the United States [19, 20]. Previously reported systematic reviews and meta-analyses comparing immunogenicity between immunocompromised and immunocompetent populations have identified that patients with cancer have significantly lower immune responses after a second dose [15–17, 21]. However, further investigation of third booster vaccine immunogenicity is needed. This review aims to investigate the currently available evidence regarding the efficacy of third booster SARS-CoV-2 vaccinations in patients with cancer. The interplay between seroconversion rates and immunosuppressive therapies, cancer type and booster regimens will also be described.

METHODS

This review is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [22].

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Inclusion criteria
Assess immune response rate in people with cancer using anti-S SARS-CoV-2 IgG
Patients 18 years or older
Report original findings
English language

Exclusion criteria
Vaccine against COVID-19 not administered and/or assessed
No patients with cancer
No efficacy data
Trial protocols
Case reports
Review articles
Overlapping results
Studies <10 patients
Non-original findings

Fig. 1 Inclusion and exclusion criteria. Inclusion and exclusion criteria for selection of studies to be included in the systematic review.

Search strategy

A search of the literature was carried out on for articles with original findings published between July 1, 2020 to March 1, 2022, restricted to articles in the English language. The studies were searched through PubMed, Cochrane and medRxiv using the search terms (neoplasm* OR oncolog* OR cancer OR malign* OR immunocomp* OR immunodef*) AND (COVID-19 OR SARS-CoV-2 OR coronavirus) AND (vaccin*) AND (immun* OR sero* OR humoral OR immunogen* OR efficacy OR antibody). Preprints were included in the search to improve the breath of data, and one preprint was included [23]. Two reviewers double-screened titles and abstracts independently (YA and HT) and disagreements were discussed with a third reviewer (MT). This ensured studies were thoroughly screened with given rationale, and maximised rigour in the data collection stage, as well as reducing possible selection bias.

Study selection

Eligible studies were restricted to retrospective studies, observational studies and clinical trials that reported data on three or more doses in human participants aged eighteen years or older, with references of these studies also being screened for other possible studies for inclusion (Fig. 1). Primary outcomes were serum IgG antibody titres post third dose administration and efficacy of third booster vaccination in patients with cancer. The National Institute of Health (NIH) Quality Assessment Tool for Observational Cohort and Cross-Sectional studies was used to assess the internal validity of our selected studies (Supplementary Table 1) before proceeding with analysis [24]. This was done independently by the two reviewers (YA and HT).

Data extraction

Data was extracted independently by the two reviewers (YA and HT) according to a predetermined proforma in Microsoft Excel Version 16.45. Information extracted included type of study, year, study size, number of patients receiving each dose with a particular focus on the third dose, timing of the three doses, proportion of haematological responders and solid cancer responders for each dose, the threshold used to define vaccine responders as well as the days post-dose that the immunoassay was done. The primary outcome of immunogenicity measured as anti-spike IgG antibodies was reported in every study before and after the third dose. Other reported outcomes were treatment regimens and their effect on seropositivity. All data extracted was quality checked and reviewed once the data extraction was completed by the same two reviewers.

Summary measures and synthesis

We undertook a narrative review of the included studies, reporting their characteristics including study population, outcome measures and results described. The results were described by cancer type, cancer treatment received, booster vaccination regimen reported and if T-cell results were reported. Quantitative measures rather than qualitative seroconversion were used as the validated correlates of protection. Meta-analyses or any other statistical analyses were not possible due to the heterogeneity of study designs and outcome measures.

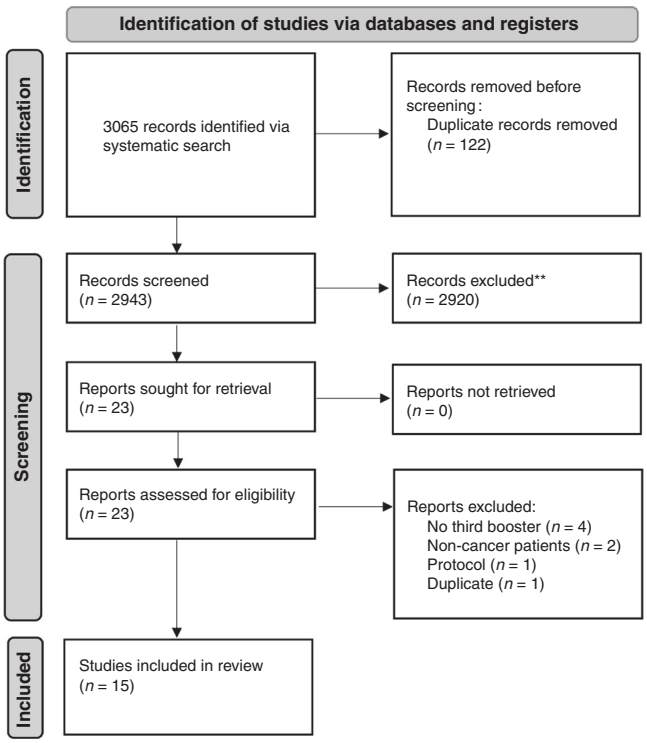

Fig. 2 PRISMA flow diagram of the study. Flowchart of study selection** – studies not meeting the inclusion criteria.

RESULTS

Figure 2 summarises the search results, and 15 studies were found to be suitable for the review, encompassing 1205 patients with cancer who had a third coronavirus vaccination (see Table 1).

Cancer type

Comparing haematological and solid malignancies. Booster vaccine responses differed greatly between patients with solid compared with haematological cancers (Fig. 3). All four studies directly comparing these patient groups found that a booster vaccine dose induced a higher response in patients with solid cancer as compared to haematological malignancies. Yang et al. [23] assessed the booster response in patients with cancer compared with healthy controls. They found that in patients with solid cancers, 88% ($n = 21$) responded after the second dose and 100% ($n = 2$) responded after the booster dose. In patients with

Table 1. General characteristics of included studies which measured vaccine efficacy in patients with solid and haematological cancer after the third dose of vaccination.

First author	Year	Study design	Title	Country	Median age	Number of patients given 3 doses	Number of controls	Humoral response definition	Data collection endpoint	Primary outcome
Bagacean et al.	2021	Prospective cohort	Humoral response to mRNA anti-COVID-19 vaccines BNT162b2 and mRNA-1273 in patients with chronic lymphocytic leukaemia	France	71 (37–93) years	95	0	≥6.8 AU/mL	28 days	SARS-CoV-2 anti-spike IgG
Di Noia et al.	2022	Prospective cohort	Potentiation of humoral response to BNT162b2 vaccine after the third dose in patients with solid cancer	Italy	67 (24–89)	407	0		28 days	Anti-spike IgG titre
Fendler et al.	2021	Prospective longitudinal cohort	Immune responses following third COVID-19 vaccination are reduced in patients with haematological malignancies compared to patients with solid cancer	UK	60 (19–84) years	199	0	IC50 titres >40	11–47 days	anti-SARS-CoV-2 IgG against beta and delta variants
Fenioux et al.	2021	Prospective observational cohort	SARS-CoV-2 Antibody Response to 2 or 3 Doses of the BNT162b2 Vaccine in Patients Treated With Anticancer Agents	France	66 (27–89) years	36	0	>1000 arbitrary units (AU)/mL to neutralise less-sensitive COVID-19 variants.	28 days and 3 months	anti-SARS-CoV-2 spike protein antibody levels
Gounant et al.	2021	Prospective cohort	Efficacy of Severe Acute Respiratory Syndrome Coronavirus-2 Vaccine in Patients With Thoracic Cancer: A Prospective Study Supporting a Third Dose in Patients With Minimal Serologic Response After Two Vaccine Doses	France	67 (27–92) years	30 (serological ?results only available for 26 of 30 vaccinated)	18	>300 AU/mL	28 days	SARS-CoV-2 anti-spike IgG
Greenberger et al.	2021	Prospective cohort	Anti-spike antibody response to SARS-CoV-2 booster vaccination in patients with B-cell-derived haematologic malignancies	USA	66 (31–80) years	49	0	>100 AU/mL	28 days	SARS-CoV-2 anti-spike IgG
Herishanu et al.	2021	Prospective Cohort	Efficacy of a third BNT162b2 mRNA COVID-19 vaccine dose in patients with CLL who failed standard 2-dose vaccination	Israel	72.1 (IQR: 68.1–77.7) years	172	0	>50 AU/mL	21 days	anti-SARS-CoV-2 S-RBD IgG titres

Table 1. continued

First author	Year	Study design	Title	Country	Median age	Number of patients given 3 doses	Number of controls	Humoral response definition	Data collection endpoint	Primary outcome
Marlet et al.	2021	Retrospective cohort	Antibody Responses after a Third Dose of COVID-19 Vaccine in Kidney Transplant Recipients and Patients Treated for Chronic Lymphocytic Leukaemia	France	70% over 65 years, 0% under 50 years	20	160 (transplant patients)	> = 30 BAU/mL (associated with 50% vaccine effectiveness against symptomatic COVID-19) (BAU = AU/mL x 0.142)	42 days	SARS-CoV-2 anti-spike IgG
Naranbhai et al.i	2022	Prospective cohort	Neutralisation breadth of SARS-CoV-2 viral variants following primary series and booster SARS-CoV-2 vaccines in patients with cancer	USA	68 (61–72) years	13	165 (cancer patients)	>1,000 U/mL (surrogate of breadth of response against multiple Covid variants)	≥14 days	breadth of responses against SARS-CoV-2 variants(alpha, gamma and delta) after booster vaccine
Reimann et al.	2021	Prospective cohort	Efficacy and safety of heterologous booster vaccination with Ad26.COV-2.S after BNT162b2 mRNA COVID-19 vaccine in haemato-oncological patients with no antibody response	Austria	72 (IQR: 60–78) years	29 (non-responders to 2 doses)	0	> = 550 mg/dl [>0.82 BAU/ml (Elecsys) and >50 AU/ml (Abbott, 7.1BAU/ml)]	28 days (except 1 patient at 40 days)	antibody to the SARS-CoV-2 spike protein receptor binding domain
Rottenberg et al.	2021	Prospective cohort study	Assessment of Response to a Third Dose of the SARS-CoV-2 BNT162b2 mRNA Vaccine in Patients With Solid Tumours Undergoing Active Treatment	USA	67 (43–88) years	37	0	>19 AU/ml	86 days	SARS-CoV-2 S1/S2 IgG
Shapiro et al.	2021	Prospective cohort	Efficacy of booster doses in augmenting waning immune responses to COVID-19 vaccine in patients with cancer	USA	69 (30–91) years	88	0	>50 AU/mL	28 days	SARS-CoV-2 spike IgG titres
Shroff et al.	2021	Cohort control	Immune responses to two and three doses of the BNT162b2 mRNA vaccine in adults with solid tumours	USA	64 years	20 (53 given 2 doses)	50 (2 doses only)	Unspecified	5–11 days	RBD-specific antibodies and virus-neutralising antibodies
Yang et al.	2022	Retrospective observational cohort	Cell-mediated and humoral immune response to SARS-CoV-2 vaccination and booster dose in immunosuppressed patients	USA	50 years	13	18	> = 1.1 (OD ratio)	≥7 days	anti-S1 IgG and SARS-CoV-2 IGRA

Table 1. continued

First author	Year	Study design	Title	Country	Median age	Number of patients given 3 doses	Number of controls	Humoral response definition	Data collection endpoint	Primary outcome
Zeng et al.	2021	Prospective Cohort	COVID-19 mRNA booster vaccines elicit strong protection against SARS-CoV-2 Omicron variant in patients with cancer	USA	58 (IQR: 51–64) years	27	23 (cancer patients, 2 doses only)	NT50 > = 80	2–112 days	nAb titres against the Omicron, D614G, and Delta variants

haematological malignancies, 50% ($n = 14$) responded after the second dose and 50% ($n = 5$) responded after the booster dose. This was in comparison to healthy controls who all responded to both second ($n = 18$) and booster ($n = 6$) doses. This suggests that booster doses may provide extra protection for patients with both solid and haematological cancers.

Three studies also compared booster efficacy in haematological versus solid cancers and analysed the effect of the booster vaccine administration in patients who did not respond to two doses of vaccine [23–25]. Fendler et al. [25] looked at two cohorts. The first was a larger cohort of 353 patients with cancer who received two doses. They found positive antibody responses in 96% ($n = 260$) of patients with solid cancer and in 70% ($n = 56$) of patients with haematological cancers. The second cohort analysed included 199 patients with cancer who received a third vaccine dose. This included 115 patients with solid cancers and 84 patients with haematological cancers. They divided this cohort according to their antibody response against the Delta variant after the second dose, with 51% ($n = 102$) patients being labelled as 'non-responders'. They found that most patients with solid cancers were in the 'responder' group (57%, $n = 65$), whilst the 'non-responder' group included a higher percentage of patients with haematological cancer (62%, $n = 52$). The third dose was administered to the 'non-responder' group, which included 50 patients with solid cancer and 52 patients with haematological cancer. They found that 94% ($n = 47$) of patients with solid cancers were responders to Delta, and 88% ($n = 44$) were responders to Beta. In patients with haematological cancers this response was significantly lower, with 54% ($n = 28$) being responders to both Beta and Delta. This suggests that the third dose can generate increased antibody responses in patients with cancer who do not initially respond to 'full' vaccination.

Shapiro et al. [26] assessed antibody responses in a cohort of 88 patients with cancer, of which 65% had solid cancers and 35% had haematological malignancies. They found that all 57% ($n = 32$) of the non-responders to the second vaccine dose had haematological malignancies except one. Booster doses were administered to these patients 168 days after the second dose and found that 100% ($n = 1$) of the patients with solid cancer responded and 55% ($n = 17$) of the patients with haematological cancer responded. Notably, all of the seronegative patients were diagnosed with a B-cell malignancy, including chronic lymphocytic leukaemia (CLL) and multiple myeloma (MM). Reimann et al. [27] found that 33% ($n = 1$) of patients with solid cancers and 31% ($n = 8$) of patients with haematological cancers responded to a third dose, given 124 days after the second dose. Importantly, they also found that patients with CLL or lymphoma were significantly less likely to develop a serological response compared to patients with other haematological cancers ($P = 0.048$), a phenomenon which has been found elsewhere [28].

CLL and other haematological malignancies. Four studies focused on booster efficacy in patients with haematological cancers only [29–32]. All of the studies found that the third booster vaccine increases the antibody response after the second dose in patients with haematological malignancies. Bagacean [29] investigated a cohort of 530 CLL patients. They found that 27% ($n = 143$) responded after the first dose, and 52% ($n = 265$) responded after the second dose. Patients who were non-responders after the second dose went on to receive a third ($n = 95$), of which 35% responded. Likewise, Herishanu [32] reported that of 172 CLL patients who had failed to respond to two-dose vaccination, 24% seroconverted after the third dose. Moreover, Greenberger and colleagues [30] found that in a cohort of patients with B-cell malignancies (including 25 patients with CLL and 18 with non-Hodgkin Lymphoma (NHL), 55% of patients without a serological

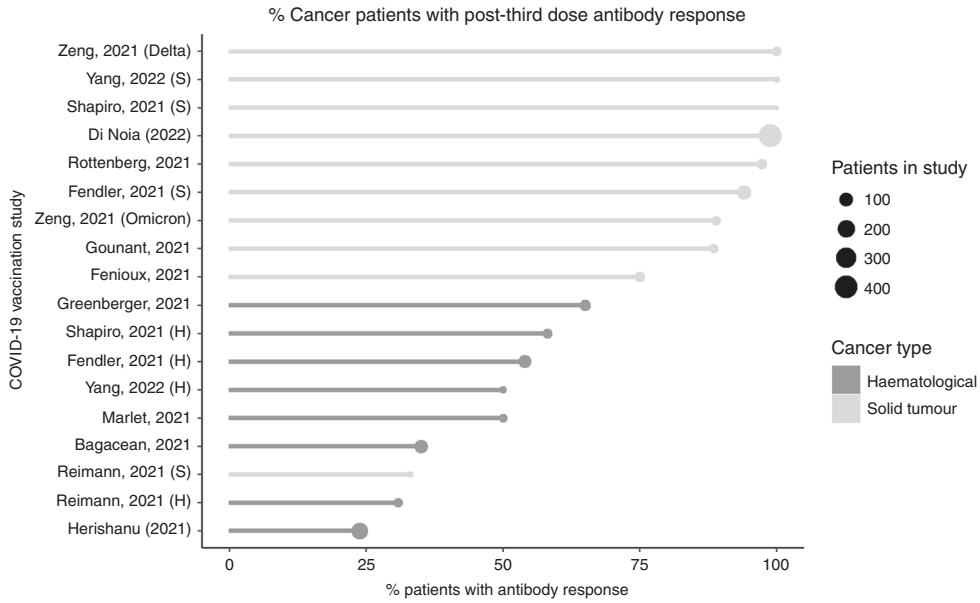

Fig. 3 The proportion of patients with cancer demonstrating post-3rd dose antibody response. Data extracted and for some studies split by patients with haematological cancer (H) and patients with solid cancer (S). Zeng et al. [35] used a neutralisation assay to assess antibody response against Delta and Omicron which is presented separately.

response after two vaccines then seroconverted after the booster vaccine. Marlet et al. [31] revealed similar findings, albeit in a smaller cohort of CLL patients. After two doses, 57% ($n = 29$) of patients initially responded. Of the 20 patients who were then vaccinated with a third dose, 50% responded with a significant increase in the proportion of patients reaching clinically beneficial levels of anti-spike IgG between the second and third doses (from 5 to 45%, $P = 0.008$). These findings demonstrate that even in patients with haematological cancer where seroconversion is thought to be particularly limited, a third booster dose can induce an extra level of much-needed protection from SARS-CoV-2.

Solid malignancies. Six studies focused on booster efficacy in patients with solid cancers only [33–38]. Most of these studies concluded that the booster dose induces an extra level of serological protection compared with having the second dose alone. Di Noia reported a 98.8% seropositive rate of 407 patients with solid tumours [38]. Of note, one study looked at how the booster affected the breadth of protection against different strains of SARS-CoV-2 in patients with solid cancers [35]. They found that after the second dose, there was a response rate of 91% for D614G, 87% for Delta and 48% for Omicron. The antibody response was increased after the third dose, with response rates of 100% for D614G, 100% for Delta and 88.9% for Omicron. This shows that the booster vaccine could confer significant extra protection for patients with solid cancer against a variety of strains of SARS-CoV-2. Two of these studies [36, 37] used healthy participants as a control group. They found that although booster vaccines do increase the antibody response in patients with solid cancers, the response is significantly lower than the response induced in the general population.

Cancer therapy

Systemic anticancer therapy (SACT), encompassing cytotoxic drugs (chemotherapy), targeted, immune or hormonal treatments have been associated with different responses. All studies reported a difference in immune response in patients on anticancer therapies, however, there was some distinction between those which had a greater effect on immune response than others. All studies included data relating to anticancer therapy that participants were actively on at time of vaccination, or treatment prior to vaccination

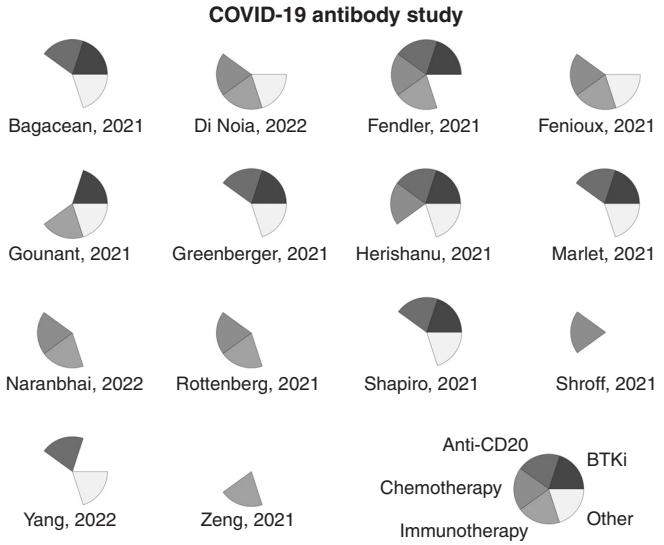

Fig. 4 Star plot illustrating the distribution of treatment regimens across the included studies. BTKi Bruton Tyrosine Kinase Inhibitor, Anti-CD20 CD20 targetted therapy.

(see Fig. 4). Treatment type varied between studies but commonly included chemotherapy, Bruton Tyrosine Kinase inhibitory therapy (BTKi), anti-CD20 antibody therapy and immunotherapy. Heterogeneity was observed regarding cancer therapies across the included studies and the proportion of patients receiving active treatment, as well as the interval between last treatment and immunisation. This makes it difficult to draw robust conclusions regarding the effect of different therapies on vaccine efficacies; however, there were some notable similarities across some studies. 42.9% ($n = 6$) of studies explored the effect of BTKi therapy on immunogenicity, and all found that BTKi therapy is a robust predictor of seronegativity; this corresponds to existing literature which analysed the effect of BTKi therapy on vaccine efficacy [33, 34] and is therefore unsurprising. Bagacean et al. [29] reported a poor positive seroconversion rate of 13% (13 of 46) for patients receiving BTKi-only therapy. Similarly, Herishanu et al. [32] reveal a

poor seroconversion of only 15.3% (9 of 59) in patients actively receiving BTKi therapy. Moreover, two participants that stopped BTKi therapy at least four months prior to vaccination demonstrated marked seroconversion [32], further suggesting that BTKi is a significant contributor to poor humoral response. The remaining study by Fenioux et al. [33] reported no difference in humoral response in patients treated with BTKi therapy and chemotherapy, however, this is limited by their small sample size.

Anti-CD20 monoclonal antibodies (mAbs) were also significantly associated with poor seroconversion and again was evaluated in 38.5% ($n = 5$) of studies. Yang et al. [23] identified anti-CD20 mAb as a treatment associated with decreased humoral response in HSCT patients, of which 80.8% ($n = 42$) are patients with haematological cancer. This was statistically significant, alongside systemic steroids. Conversely, anti-CD20 mAbs, specifically ocrelizumab was indeed associated with a high cellular response; however, the mechanism for this remains unknown. Participants who were not receiving treatment at the time of vaccination but had received treatment prior to vaccination also had significantly lower rates of response; Shapiro [26] report those remaining seronegative after the third dose had received anti-CD20 therapy at a median time of 3.9 months prior to vaccination and report the complete loss of detectable neutralising antibodies in patients with haematological cancer and those on anti-CD20 or an BTKi therapy as time progressed.

Greenberger et al. [30] also report a statistically significant correlation with patients receiving anti-CD20 mAbs or had received it within 6 months of receiving their booster dose and low anti-S antibody titres. This is in line with previous studies that have reported reduced Influenza vaccine efficacy after exposure to B-cell depleting therapies such as anti-CD20 mAbs [39]. Such a finding is likely due to the time required for B-cell reconstitution to occur after completion of anti-CD20 mAbs therapy which has been suggested to begin between 6 and 9 months after rituximab therapy [40, 41]. Of note, Yang [23] reported that patients with a poor humoral response due to the effects of their therapy, in this case anti-CD20 therapy, were more likely to mount an anamnestic response after booster vaccination than those with poor seroconversion due to the primary disease itself. This is important to note as it provides a means of partially overcoming the immunosuppressive effects of anticancer therapies with a booster.

Chemotherapy-based treatment has also been associated with negative or low anti-spike IgG neutralising antibody levels, but to a lesser extent than B-cell depleting therapies. Fenioux et al. [33] report patients receiving chemotherapy or targeted therapy to have a poorer rate of seroconversion than those treated with immunotherapy, however it appears that there is no association between intensity of humoral response and the timing of the last chemotherapy treatment. This is in contrast to the findings by Gounant [36] who showed that chemotherapy within 3 months of dose 2 was independently associated with very low antibody titres. Immunotherapy appears to induce a better immune response in comparison to chemotherapy as was reported by Fenioux [33].

Two studies considered vaccine efficacy in treatment-naïve patients. Bagacean [29] reports a response rate of 56% (18 of 32) after a third dose in treatment-naive patients that remained seronegative after standard two-dose vaccination. This is in comparison to a response rate of 24% (15 of 63) in patients receiving various anticancer therapies. This is in line with Herishanu [32] where vaccination rate approached 40% in treatment-naive and previously treated patients but was significantly lower at only 12% in patients on active anticancer therapy.

Booster vaccine regimens

All studies used a combination of BNT162b2 (BNT), mRNA-1273 (MD) and ChAdOx1 (OxA) vaccines, with variations in the specific regimens. Studies either used a homologous regime for all three doses, using exclusively BNT or Moderna or a homologous vaccine for the primary (2-dose) vaccination and a heterologous booster vaccine. The interval between the second and third dose varied significantly between studies (range 27–214 days), as did the timing of serum collection after the third dose (range 11–86 days). This should be considered when interpreting the results. One of these studies suggested that a heterologous vaccination regime could provide extra serological protection for patients with cancer [25]. They assessed a cohort of patients with solid and haematological cancers who had either BNT or OxA for the primary vaccination and a BNT booster. Through multivariable analysis of patients with haematological malignancies, they found that primary vaccination with OxA was associated with a better neutralising antibody response against both Beta and Delta variants of SARS-CoV-2.

Three studies revealed differences between the serological responses to the BNT compared with the MDN vaccination regimens. Bagacean and colleagues [29] used a homologous regime of either BNT or MDN primary and booster vaccines in a cohort of CLL patients. They found that the BNT regime was significantly negatively associated with seroconversion in univariable analysis (OR = 0.49, $P = 0.001$) and that the MDN regime has a higher seroconversion rate than BNT. In addition, in a subcohort of 32 patients with cancer who were seronegative prior to homologous booster vaccination, Shapiro [26] found that initial MDN and OxA vaccination induced a quantitatively higher antibody response (25,523 and 23,141 AU/mL, respectively) relative to the BNT vaccination (14,829 AU/mL). They also found that the MDN booster was associated with a higher antibody response relative to the BNT booster (23,948 and 15,858 AU/mL, respectively). Zeng et al. [35] also found that MDN-vaccinated patients showed a higher serological response against Omicron compared to BNT-vaccinated patients after two doses. However, they found that patients who received the BNT booster had a higher serological response compared to those who received MDN. Confidence in these conclusions should be tentative, however, as this study was small ($n = 50$) and not statistically significant and not powered to assess the difference in vaccine regimens. Several studies found no associations between booster vaccine type and outcome for patients with cancer [27, 30, 42].

T-cell responses

Three studies assessed T-cell activity and response to the booster vaccine in addition to antibody response assessment [25–27]. Fendler and colleagues [25] found that 33% ($n = 11$) of patients with solid cancer and 40% ($n = 6$) of patients with haematological malignancies had detectable T-cell responses after the second dose. After the booster dose, this rose to 73% in both groups ($n = 24$, $n = 11$), suggesting that the third vaccination induces stronger anti-SARS-CoV-2 T-cell immunity. Shapiro [26] found that the booster vaccine could stimulate anti-SARS-CoV-2 T-cell activity in patients with cancer with initially limited serological response to two vaccines. They found that 63% ($n = 20$) of patients who were seronegative prior to the booster vaccine had detectable anti-SARS-CoV-2 T-cell responses (median 577 mIU/mL, range 133 to >1800). Of the patients who remained seronegative after the booster ($n = 14$), 57% had detectable T-cell responses which were higher on average than prior to the booster (median = 1146 mIU/mL, range 1193 to >1800). One of these patients did not have a detectable pre-booster baseline T-cell response. Moreover, Reiman et al. [27] looked at whether T-cell count could be a predictive biomarker for response to booster vaccination. They investigated a cohort of 29 patients with cancer who had not responded to the second vaccine dose. Although the CD4 + and CD8 + T-cell counts just prior to booster vaccination were slightly higher in responders compared to non-responders, the difference was not statistically significant.

Time to serum collection

High levels of heterogeneity in the interval between third dose administration and serum collection were demonstrated across all studies. Some studies demonstrated waning of immunity with time, and this could account for apparent non-responders who only had their serum collected up to 100- and 12-days post third dose (see Table 1). On the contrary, some studies collected serum samples quite early on (2–7 days) post vaccination, and thus there was an observed increase in antibody titres immediately before administration of the final booster dose, thereby giving a false suboptimal antibody titre. It is difficult to conclude the optimal time for serum collection, but most studies performed immunoassay testing 28 days after each dose.

DISCUSSION

Key findings

This review has described that a third booster vaccine dose induces an increased antibody response in patients with cancer compared to primary (2 doses) vaccination. This is reassuring as healthcare systems worldwide have embarked on comprehensive booster vaccination campaigns for the general population and those at risk from increased morbidity and mortality from SARS-CoV-2 infection. However, this review has highlighted some important differences in response depending on cancer type, cancer treatment received, and vaccine regimen used.

A booster vaccine dose induced a higher response in patients with solid cancer as compared to haematological malignancies and could confer extra protection for patients with cancer who do not initially respond to primary vaccination. Further research is required in patients with haematological cancers who appear to have lower detectable antibody or cellular responses following vaccination to identify other interventions that might increase protection.

Differences have also been identified in serological responses depending on the type of cancer treatment received. SACT for solid organ malignancies does not appear to affect vaccine responses, however poor seroconversion has been associated with B-cell depleting therapies such as Bruton Tyrosine Kinase inhibitor therapy and anti-CD20 therapy. A greater interval between last treatment dose and booster vaccination was also noted to increase the chance of seropositivity. Treatment-naive patients mounted a detectable immune response in most cases. Several studies reported seroconversion rates that were substantially less in patients receiving BTKi therapy and anti-CD20 mAbs in comparison to treatment-naive patients or those on chemotherapy [25, 29, 30, 32]. This has been reflected in previous studies that have reported reduced Influenza vaccine efficacy after exposure to B-cell depleting therapies such as anti-CD20 mAbs [39]. Importantly, it has been noted that patients demonstrating poor seroconversion due to immunosuppressive therapies are more likely to mount an anamnestic response post booster vaccination than those showing poor seroconversion due to primary effects of the disease [23]. The data analysed in this review may suggest a preference for booster mRNA vaccines as opposed to traditional viral vectored vaccines in patients with cancer.

Strengths and limitations

To our knowledge, this is the first study to systematically review and critically appraise studies exploring antibody response and immunogenicity after a third SARS-CoV-2 booster vaccination in patients with cancer. This study has several limitations which must be accounted for. Firstly, the fast-paced nature of this research means that it is inevitable that we will have missed data published since our search and unpublished data which may potentially impact the findings of this review. However, we have attempted to mitigate this by including preprint servers in our search.

Secondly, most studies included were of variable quality and design. Patient populations used also varied greatly with some studies using numbers too small to allow for any strong conclusions to be drawn and making them prone to bias. The types of vaccines used were variable, although this may not have significantly impacted the data as the different vaccines have been shown to have similar efficacy [43]. Immunoassay testing methods also varied. A high level of heterogeneity was observed across included studies in relation to measures that have been correlated with immunogenicity. Many studies used neutralising antibodies as surrogate measure for immunogenicity; this is reasonable given the emerging evidence demonstrating that neutralising antibodies are indeed a reliable predictor of protection against symptomatic infection with SARS-CoV-2. Other surrogate measures that have been used include receptor binding domain proteins, SARS-CoV-2 anti-spike proteins and anti-SARS-CoV-2 T cells. Further, even amongst studies which utilised neutralising antibodies as their main measure of immunogenicity, there was much variation in the cut off threshold value of what constituted a detectable immune response. Lastly, most studies consisted of elderly patients in which immune response is already attenuated due to age which not all studies adjusted for ref. [44].

Implications for practice, policy and future research

Evidence of waning immunity with time, especially in clinically vulnerable populations on immunosuppressive therapies is of particular concern and further brings into question the extent of protection patients with cancer have even after the third booster dose [45, 46]. This highlights the importance of prioritising further booster doses for this vulnerable population, not only to possibly induce a stronger immune response than that seen with the third dose but also to restore anti-SARS-CoV-2 immunity to titres seen post booster vaccination.

Our findings indicate that MDN boosters should be prioritised for patients with cancer; this is reflected in other recent reports, which highlight the enhanced effect of MDN vaccines occurs, specifically in patients with haematological malignancies, whilst BNT and MDN have equal efficacy in the general population [30, 35]. It is important to point out that the timing of the booster dose varied significantly between these three studies, from 28 days to 168 days [26, 29]. It is yet unclear the extent to which this could affect the results. Although, in most cases, this was due to small sample sizes leading to the studies being underpowered, or simply due to a lack of multivariable analysis. Currently, there is evidence to suggest that homologous or heterologous vaccine boosters are safe, but further research is needed specifically for patients with cancer to explore the efficacy of homologous and heterologous vaccine regimens and the timing post previous dose [47].

CONCLUSION

Patients with cancer are at increased risk from adverse outcomes from SARS-Cov-19 infection compared to the general population, and vaccination has played a key role in preventing morbidity and mortality in the pandemic. The role of antibody responses is not clearly defined, and our review has demonstrated that immunogenicity, measured as antibody titres and seroconversion rates, remains significantly diminished in patients with cancer relative to the general population after a third dose. Patients with haematological malignancy have been identified as being more likely to have poorer seroconversion rates and in particular patients on B-cell-depleting therapies. All studies reported a significant improvement in vaccine efficacy in patients with solid and haematological cancer following a third booster dose. This includes those patients who did not elicit any humoral immune response after receiving the previous two doses. This highlights the need for further research into the role of boosters for patients

with cancer and other vulnerable groups to severe disease and the role of antibody status or titre as a biomarker of vulnerability. Further, the maintenance of infection prevention measures such as social distancing, wearing masks and prophylactic antibody therapies as vaccine adjuncts when cases are high is vital considering the uncertainty around vaccine efficacy in this immunocompromised population.

DATA AVAILABILITY

All data are publicly available. No additional data are available.

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YA and HT are joint first authors. All authors contributed equally to the protocol development, selection of studies, interpretation of data and decision to submit the final manuscript. YA and HT undertook the literature searches, extracted the data and quality assessments. MT confirmed the data extraction and quality assessments.

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