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Review

SARS-CoV-2 vaccine safety and immunogenicity in patients with hematologic malignancies, transplantation, and cellular therapies

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ABSTRACT

Individuals with hematological malignancies and hematopoietic stem cell transplant (HCT) recipients are immunologically heterogenous groups with varying degrees of immunosuppression at increased risk of severe disease and mortality from SARS-CoV-2 infection. SARS-CoV-2 vaccines are key interventions to preventing severe COVID-19 and its complications. While these individuals were excluded from initial vaccine trials, there is now a growing body of acceptable safety and immunogenicity data among these individuals. A consistent signal for new or worsening graft versus host disease in allogeneic HCT recipients has not been demonstrated post-vaccination. Immunogenicity in these populations is variable depending on disease and treatment factors. However, serological responses may not accurately reflect vaccine protection as correlates of protection within these populations are not yet established. Large-scale studies powered to identify rare serious events, resolve differences in vaccine responses between different vaccination strategies, and identify immune correlates of protection within these populations are needed.

1. Introduction

The severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) pandemic has caused over 450 million infections and 6 million deaths globally as of April 2022 [1]. The pandemic disproportionately impacts patients with hematologic malignancies who have increased odds of SARS-CoV-2 infection [2] and higher rates of severe disease and mortality from coronavirus disease 2019 (COVID-19) [3,4]. The introduction of effective SARS-CoV-2 vaccines has been instrumental in attenuating the impact of disease at a population level. However, COVID-19 remains a serious risk for individuals with hematologic malignancies. These patients have variable vaccine immune responses due to heterogeneous patterns of primary pathology impairing their immune system. This is further compounded by therapies that can result in profound and prolonged immune dysfunction; therefore, worsening their immunocompromised state. Furthermore, the prevalence of hematologic malignancies rises with increasing age, which is independently associated with worse COVID-19 outcomes and diminished vaccine responses [5–7], as well as with a greater number of comorbidities that may contribute additional COVID-19 risk [7,8].

COVID-19 is especially hazardous in the setting of hematopoietic stem cell transplantation (HCT) for treatment of both malignant and non-malignant conditions and chimeric antigen receptor T-cell (CAR-T) therapy for treatment of leukemia, lymphoma, and multiple myeloma [9,10]. Data from the Center of International Blood and Marrow Transplant Research revealed that 42% of allogeneic HCT (alloHCT) and 33% of autologous HCT (autoHCT) recipients experienced moderate or severe COVID-19 disease after infection with 30-day survival after COVID-19 diagnosis being 68% and 67%, respectively [9]. In another analysis of data from the European Society for Blood and Marrow Transplantation and Spanish Group of Hematopoietic Stem Cell Transplantation, 83.5% of HCT recipients diagnosed with COVID-19 experienced lower respiratory tract disease and 22.5% required ICU admission [10]. These advanced therapies can be further complicated by immune

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suppression lasting months to years due to the use of cytotoxic conditioning regimens, T- or B-cell depleting therapies, and ongoing therapeutic immunosuppression for complications such as graft versus host disease (GVHD), resulting in greater risk for infectious complications and poor vaccine responses.

Despite the pressing need for data on SARS-CoV-2 vaccine safety and efficacy in these particularly vulnerable patient populations, these and other immunosuppressed patients (with the exception of stably controlled HIV-positive patients) were excluded from the initial pre-licensure SARS-CoV-2 vaccine trials [11]. It is widely presumed that patients with hematologic malignancies and HCT recipients will have suboptimal vaccine immune responses compared to healthy individuals based on prior experiences with other vaccines. In a study of influenza vaccine responses in patients with hematologic malignancies, two doses of influenza vaccine did not improve antibody responses compared to one dose of influenza vaccine [12]. AlloHCT recipients also demonstrated poor antibody responses following vaccination with the H1N1 influenza vaccine with only 30.8% achieving seroconversion compared to 88.7% of healthy controls at 28 days, which was slightly increased to 36.4% at 50 days after vaccination compared to 89.8% of healthy controls [13]. Despite receiving SARS-COV-2 vaccines, patients with hematologic malignancy have experienced significantly higher rates of breakthrough COVD-19 infections (13.4%) than individuals without cancer (4.5%) after primary vaccine series [14].

The SARS-CoV-2 vaccines in widespread use at this time are BNT162b2 (Pfizer) and mRNA-1273 (Moderna), both novel mRNA-based vaccines and initially planned as two-dose primary series, as well as the adenovirus vector-based vaccines Ad26.COV2.S (Janssen) and ChAdOx1 (AstraZeneca); ChAdOx1 was initially planned as a two-dose primary series while Ad26.COV2.S was a one-dose primary series. Since initial Emergency Use Authorization (EUA) approval, the Centers for Disease Control (CDC) has updated primary series recommendations for immunocompromised individuals to three doses of mRNA vaccines or two doses of heterologous vaccines following initial Ad26.COV2.S (ChAdOx1 is not approved for use in the US). In this review we will evaluate currently available data through December 2021 on SARS-CoV-2 vaccines in individuals with hematologic malignancy as well as those who have undergone autoHCT, alloHCT, and CAR-T therapy with an emphasis on vaccine strategies, safety, and immunogenicity.

2. SARS-CoV-2 vaccines in patients with hematologic malignancies

Suboptimal serological responses have been observed in previous vaccination studies of individuals with hematologic malignancies compared to healthy controls [12,15]. Moreover, there may be wide variation in vaccine responses depending on the immunogen, dosing strategy, and timing of vaccination, as well as differences in type of underlying malignancy and chemotherapy. Infection risk are greater for individuals with B-cell neoplasms such as multiple myeloma or chronic lymphocytic leukemia (CLL) due to inherent impaired antibody production from the disease and its treatment, which serve to further compound the poor immune responses following vaccination [15–18].

2.1. Safety and reactogenicity

Reactogenicity encompasses the set of common or "expected" adverse reactions following vaccination due to the inflammatory response elicited by the vaccine. A subset of the published studies evaluating SARS-CoV-2 vaccine responses in patients with hematologic malignancies assessed vaccine safety and reactogenicity. These reports addressed predominantly mRNA vaccines. A single study included subjects who received either an adenovirus vector vaccine or an mRNA-based vaccine [19], while all others assessed safety responses following one or two doses of the BNT162b2 mRNA vaccine [20–26]. No serious adverse events were observed among >1000 patients with malignancy followed for up to three months after vaccination [19,20,22–26]. While no long-term safety data specific to patients with hematologic malignancies are yet available, a meta-analysis on the safety of globally available SARS-CoV-2 vaccines found that viral vector vaccines had higher adverse event rates than mRNA vaccines and inactivated vaccines, but that SARS-CoV-2 vaccines generally have an acceptable safety profile regardless of design [27].

Short-term reactogenicity among hematologic malignancy patients appears to be like that of healthy controls. Avivi et al. found that 53% of multiple myeloma patients reported adverse events within seven days of receiving a vaccine dose, which was similar to the frequency of healthy controls reporting adverse events in the same period (55%) [23]. Most of the symptoms reported were mild or moderate grade events and consisted of both local and systemic symptoms such as injection site pain (22–44%), fever (3–6%), weakness/fatigue (3–20%), and headache (2–14%) [19,20,22–25]. In a report that also included patients with solid tumors, both patients with solid tumor and hematologic malignancies reported fewer moderate symptoms than did healthy controls [21]. Most studies revealed a similar degree of symptoms between the first and second doses of vaccine. Exceptions to this similarity include Herishanu et al., who found a greater number of adverse events after the second dose of a two-dose vaccine series (local responses after dose 1 were 31% while after dose 2 were 34%, systemic responses after dose 1 were 13% while after dose 2 were 23%) [25] and Malard et al., who reported a greater number of adverse events after dose one (57.1% vs 34.4%), but increased frequency of severe events after dose two (0% grade 3 adverse events after dose 1, 8.4% with grade 3 adverse events after dose 2, no grade 4 adverse events after either vaccine dose) [20]. A statistically significant correlation between reactogenicity and serological responses was not observed [25].

2.2. Immunogenicity

Immunogenicity is the ability of a vaccine to elicit immune responses, which can be measured in many ways [28]. Immunogenicity has been assessed in patients with hematologic malignancies by seroconversion, presence of neutralizing antibodies, and T-cell responses to SARS-CoV-2. Most reports evaluated seropositivity, the presence of an antigen-specific antibody, through detection of SARS-CoV-2 spike protein-specific antibodies following vaccination. Highly inconsistent seropositivity rates were observed following vaccination, but in general, suboptimal vaccine responses were observed in hematologic malignancy patients when compared to healthy controls. These differences manifested as both decreased rates of seropositivity as well as reduced antibody levels when compared to healthy controls (Table 1).

Chowdhury et al. observed a low rate of seropositivity (58%) in patients with myeloid malignancies following the first dose of an mRNA or adenovirus vector two-dose vaccine series when compared to healthy controls who demonstrated 97% seropositivity after a single dose of BNT162b2 or ChAdOx1 [29]. Similar findings were reported by Bird et al. in a cohort of patients with multiple myeloma, among whom only 56% demonstrated seropositivity following a single dose of BNT162b2 or ChAdOx1 [30]. In comparison, 88% of patients with CML were seropositive following a single dose of BNT162b2 [26], albeit this study included 16 patients.

Individuals with hematologic malignancies had variable rates of seropositivity following two doses of mRNA SARS-CoV-2 vaccine ranging from 40 to 96% (Fig. 1) [19–21,31–36]. Overall, there was decreased seropositivity and lower anti-spike antibody levels observed after two doses of mRNA-based or at least one dose of adenovirus vector-based vaccine in patients with hematologic malignancies compared to patients with solid tumor malignancies, who in turn mounted lower vaccine responses than healthy controls [19,21,22,35,37].

However, individuals with myeloid neoplasms may have better vaccine antibody responses than those with lymphoid neoplasms.

Table 1
Summary of studies evaluating SARS-CoV-2 vaccine responses in patients with hematologic malignancies.

Year, citation	Vaccination type, # of doses	# of subjects (# and type of Heme malignancy)	Test groups	Age at immunization	Spike IgG or NAb test	Seropositivity, days after completion of vaccine	SARS-CoV-2 IgG antibody titer or NAb inhibition titer	Safety & Reactogenicity
2021 Chowdhury et al.	BNT162b2 or ChAdOx1 1 dose	$N = 59$	HM (myeloid neoplasm only) Healthy controls ($N = 232$)	Median years: Myeloid malignancy: 62 Controls: 62	Abbott IgG II Quant Assay	HM: 34/59 (58%) Controls: 224/232 (97%) >14 days	Median (AU/mL) HM: 75 Controls: 630	No significant events reported
2021 Addeo et al.	BNT162b2 or mRNA-1273 2 doses 3–4 weeks apart	$N = 131$ (HM = 25)	HM Solid tumor	Median years: 63	Roche Elecsys SARS-CoV-2 anti-S RBD IgG	After dose 1: HM: 18/25 (72%) Solid: 80/96 (83%) After dose 2: HM: 17/22 (77%) Solid: 99/101 (98%) 21–28 days after each vaccine dose	Median (AU/mL) After dose 1: HM: 6 Solid: 44 After dose 2: HM: 832 Solid: 2500	Not reported
2021 Agha et al.	BNT162b2 or mRNA-1273 2 doses 3–4 weeks apart	$N = 67$	HM	Median years: 71	Beckman Coulter (semi-quantitative)	36/67 (54%) Median days after 2nd dose: 23 (IQR 16–31 days)	Median (extinction coefficient): 14.42	Not reported
2021 Greenberger et al.	BNT162b2 or mRNA-1273 2 doses 3–4 weeks apart	$N = 1445$	HM	Median years: 68	Roche Elecsys SARS-CoV-2 anti-S RBD IgG	1088/1445 (75%) >14 days (median 41 or 42 depending on vaccine type)	Not reported	Not reported
2021 Herzog Tzarfati et al.	BNT162b2 2 doses 3 weeks apart	$N = 315$	HM Non-malignancy controls ($N = 108$)	Median years: HM: 71 Controls: 69	Diasorin Liaison SARS-CoV-2 S1/S2 IgG	HM: 235 (75%) Controls: 107 (99%) 30–60 days	Median (AU/mL) HM: 85 Controls: 157	Not reported
2021 Malard et al.	BNT162b2 2 doses 3–4 weeks apart	$N = 195$	HM	Median years: 69	Abbott IgG II Quant Assay	Based on study-specific cutoff derived from NAb association After dose 1: 1.5% After dose 2: 46.7% 14 days	Not reported	After 1st dose 57.1% had grade 1–2 adverse effects After 2nd dose 34.4% had grade 1–2 adverse effects, 8.4% with grade 3
2021 Monin et al.	BNT162b2 2 doses 3 weeks apart	$N = 151$ (HM = 56)	HM Solid tumor Healthy controls ($N = 54$)	Median years Cancer: 73 Controls: 41	ELISA for anti-spike IgG	21 days after dose 1: HM: 8/44 (18%) Solid: 21/56 (38%) Controls: 32/34 (94%) 14 days after dose 2: HM: 3/5 (60%) Solid: 18/19 (95%) Controls: 12/12 (100%)	Numerical value not reported	After 1st dose: Local: 36% Systemic: 25% After 2nd dose: Local: 23% Systemic: 14% Majority were grade 1–2 events
2021 Peeters et al.	BNT162b2 2 doses 3 weeks apart	$N = 240$ (HM = 30 SCT = 11)	HM (receiving rituximab)	Median years: Cohort: 61	Wantai ELISA for anti-S RBD IgG	Not reported 28 days	GMT (IU/mL) HM (includes SCT): 17.61	For entire cohort: 1–3% with severe reactogenicity. Local symptoms

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Table 1 (*continued*)

Year, citation	Vaccination type, # of doses	# of subjects (# and type of Heme malignancy)	Test groups	Age at immunization	Spike IgG or NAb test	Seropositivity, days after completion of vaccine	SARS-CoV-2 IgG antibody titer or NAb inhibition titer	Safety & Reactogenicity
			SCT Solid tumor	HM and SCT: 61 Controls not reported			Rituximab: 4.12 SCT: 610.67 Healthy controls: 2955.04	were more common after 2nd dose than 1st dose while systemic reactions appeared equally after both doses.
2021 Re et al.	BNT162b2 or mRNA-1273 2 doses 3–4 weeks apart	$N = 102$	HM	Median years: 75.5	Not reported	63/102 (61.8%) 6–8 weeks after vaccine dose 1	Median (UI/mL) 16.8	Not reported
2021 Thakkar et al.	BNT162b2 or mRNA-1273 2 doses 3–4 weeks apart or Ad26.COV2.S 1 dose	$N = 185$ (HM = 59)	HM Solid tumor Non-malignancy controls ($N = 26$)	Median years: Malignancy: 67 Controls: 64	Abbott IgG II Quant Assay	HM: 56 (85%) Solid: 131 (98%) Controls: not reported >7 days (Median 31.5 for solid and 28.5 for HM)	Median (AU/mL) HM: 2528 Solid: 7858 Controls: value not reported	26–37% with mild to moderate adverse effects after 1 or 2 doses of vaccine 1–3% with severe adverse effects after 1 or 2 doses of vaccine
2021 Bird et al.	BNT162b2 or ChAdOx1 1 dose	$N = 93$	MM	Median years: 67	Ortho Clinical Diagnostic	52/93 (56%) >21 days	Not reported	Not reported
2021 Terpos et al.	BNT162b2 1 dose	$N = 48$	MM Healthy controls ($N = 104$)	Median years MM: 83 Controls: 83	GenScript Neutralizing Ab kit	MM: 12/48 (25%) Controls: 57/104 (55%) 21 days	Median inhibition titer (%) MM: 20.6% Controls: 32.5%	Not reported
2021 Avivi et al.	BNT162b2 2 doses 3 weeks apart	$N = 171$	MM Healthy controls ($N = 64$)	Median years: MM: 70 Controls: 67	Roche Elecsys SARS-CoV-2 anti-S RBD IgG	MM: 133/171 (78%) Controls: 63/64 (98%) 14–21 days	Median (U/mL) Active MM: 91 Smouldering MM: 822 Controls: 992	≥1 vaccine related adverse event: MM: 53% Controls: 55% All grade 1–2
2021 Pimpinelli et al.	BNT162b2 2 doses 3 weeks apart	$N = 92$ (MM = 42 MPM = 50)	MM MPM Elderly controls ($N = 36$)	Median years: MM: 73 MPM: 70 Controls: 81	Diasorin Liaison SARS-CoV-2 S1/S2 IgG	21 days after dose 1: MM: 9/42 (21%) MPM: 26/50 (52%) Controls: 19/36 (53%) 14 days after dose 2: MM: 33/42 (79%) MPM: 44/50 (88%) Controls: 36/36 (100%)	Mean (AU/mL) After dose 1: MM: 7.5 MPM: 16.2 Controls: 17.1 After dose 2: MM: 106.7 MPM: 172.9 Controls: 353.3	After 1st dose there were mild local side effects and mild to moderate systemic effects Increased % mild to moderate local and systemic effects after 2nd dose than after 1st dose
2021 Van Oekelen et al.	BNT162b2 or mRNA-1273 2 doses (3.8% unknown type mRNA vaccine)	$N = 320$	MM	Median years: 68	Kantaro COVID-SeroKlir	219/260 (84%) >10 days (median 51 days)	Median (AU/mL) SARS-CoV-2-naïve: 149 Prior SARS-CoV-2: 801	Not reported
2021 Gavriatopoulou et al.	BNT162b2 or ChAdOx1 1 dose	$N = 58$	WM/CLL/NHL Healthy controls ($N = 213$)	Median years: HM: 75 Controls: 75	GenScript Neutralizing Ab kit	≥50% inhibition titer WM/CLL/NHL: 3/58 (5%) Controls: 50/213 (23%) 21 days	Median inhibition titer (%) WM/CLL/NHL: 17% Controls: 32%	Not reported
2021 Herishanu et al.	BNT162b2 2 doses 3 weeks apart	$N = 167$	CLL Healthy	Median years:	Roche Elecsys SARS-CoV-2 anti-S RBD IgG	CLL: 66/167 (40%) Controls: 100%	Median (AU/mL)	After 1st dose: Local: 31% Systemic: 13%

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Table 1 (*continued*)

Year, citation	Vaccination type, # of doses	# of subjects (# and type of Heme malignancy)	Test groups	Age at immunization	Spike IgG or NAb test	Seropositivity, days after completion of vaccine	SARS-CoV-2 IgG antibody titer or NAb inhibition titer	Safety & Reactogenicity
			controls (N = 52)	CLL: 71 Controls: 68		14–21 days	CLL: 0.824 Controls: 1084	After 2nd dose: Local: 34% Systemic: 23% All were mild reactions
2021 Roeker et al.	BNT162b2 or mRNA-1273 2 doses	N = 44	CLL	Median years: 71	Diasorin Liaison SARS-CoV-2 S1/S2 IgG	23/44 (52%) 14–28 days	Not reported	Not reported
2021 Ghione et al.	BNT162b2 or mRNA-1273 2 doses or Ad26.COV2.S 1 dose	N = 86	Lymphoma Nursing home residents >65y (N = 47) Health care workers <65y (N = 154)	Median years: Lymphoma: 70 Not reported for controls	Anti-spike RBD chemiluminescence immunoassay from KSL diagnostics	Lymphoma:36/86 (42%) Control >65y: 43/47 (91%) Control <65y: 154/154 (100%) 14–56 days	Numerical value not reported	Not reported
2021 Lim et al.	ChAdOx1 or BNT162b2 2 doses 10–12 weeks apart	N = 129	Lymphoma Healthy controls (N = 150)	Median years: Lymphoma: 69 Controls: 45	Meso Scale Discovery electro-chemiluminescent assay	Lymphoma on treatment: 9/31 (29%) after 1 dose 13/33 (39%) after 2 doses Lymphoma without treatment numbers not reported Controls: 150/150 (100%) after 1 or 2 doses 14 days after 1 dose 14–28 days after 2 doses	GMT (BAU/mL) after 2 doses Lymphoma on treatment: 2.5 Lymphoma without treatment: 141.8 Controls: not reported	Not reported
2021 Harrington et al.	BNT162b2 1 dose	N = 16	CML	Median years: 45	ELISA for SARS-CoV-2 anti-spike IgG	14/16 (88%) 21 days	Median (EC_{50}) 100.5	Local: 56% Systemic: 24%
2021 Kozak et al.	BNT162b2 or mRNA-1273 2 doses 3–4 weeks apart	N = 74	MPM	Median years: 68	Abbott IgG II Quant Assay	71/74 (96%) Median 100 days	Reported only for certain subgroups	Not reported
2021 Greenberger et al. October 2021	Homologous (33%) or heterologous (67%) booster after full mRNA-1273, BNT162b2, or AD26.COV2.S	N = 49	B-cell malignancies	Average years: 66	Roche Elecsys SARS-CoV-2 anti-S RBD IgG	Pre-booster baseline (median 27 days before booster): 11/49 (22%) Post-booster (median 28 days): 32/49 (65%)	Median (AU/mL) after booster Seronegative: <0.4 Sero-conversion: 23.1 Sero-elevation: 2500	Not reported

Abbreviations
CLL = chronic lymphocytic leukemia.
HM = Hematological malignancy.
MM = multiple myeloma.
MPM = myeloproliferative malignancy.
NHL = non-Hodgkin's lymphoma.
RBD = receptor binding domain.
WM = Waldenstrom macroglobulinemia.

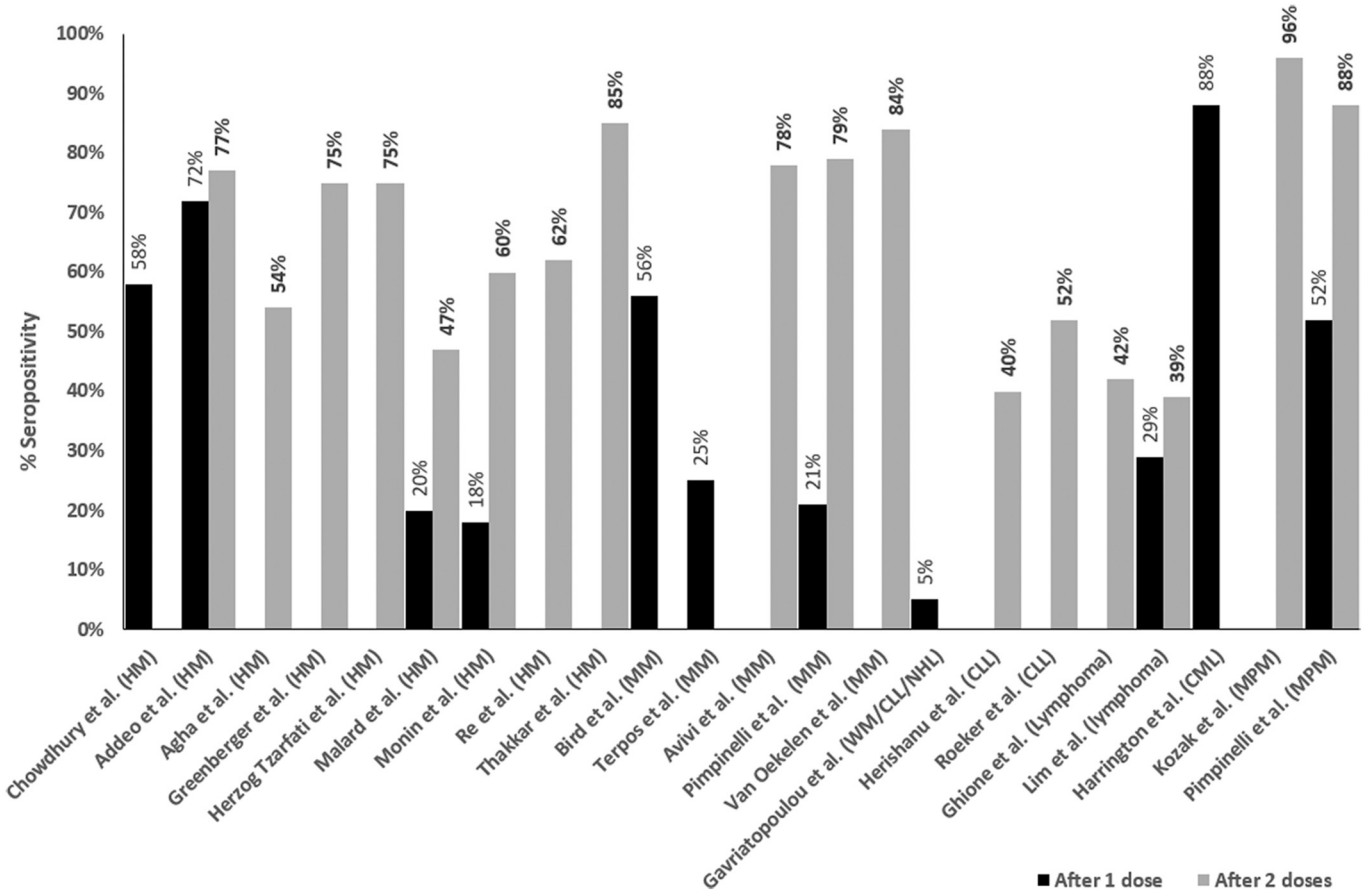

Fig. 1. Seropositivity frequency following SARS-CoV-2 vaccination in individuals with hematologic malignancy.
Seropositivity frequencies in individuals with hematologic malignancy following one dose of ChAdOx1 or an mRNA-based SARS-CoV-2 vaccine (black bars) and after two doses of an mRNA-based or a single dose of Ad26.COV2.S vaccine (gray bars). Abbreviations: MM-multiple myeloma; HM-hematologic malignancy; CML-chronic myeloid leukemia; CLL-chronic lymphoid leukemia; MPM-myeloproliferative malignancy.

Notably, Kozak et al. observed 96% seropositivity in patients with myeloid neoplasms following two doses of mRNA vaccine, which may be in part attributable to increased time to antibody measurement following vaccine series completion (median 100 days) [32]. In another study, the myeloid neoplasm group had similar seropositivity as the non-malignancy elderly controls (52% vs 53%) after a single dose of BNT162b2, which was significantly higher than those with multiple myeloma (21%) after a single vaccine dose. However, following the second vaccine dose, seropositivity frequencies between individuals with myeloid neoplasms and myeloma were more similar (79% vs 88%) while the proportional response in both groups was lower than in elderly controls (100%). Mean antibody level after two vaccine doses remained lowest in the myeloma group (106.7 AU/mL) in comparison to those with myeloid neoplasms (172.9 AU/mL) and elderly controls (353.3 AU/mL) [24].

With the exception of multiple myeloma patients, who demonstrated more robust serological responses following two doses of mRNA vaccines [23,24,38], individuals with lymphoid malignancies generally had lower rates of seropositivity than the overall hematologic malignancy group even after two doses of vaccines. Most notably, patients with CLL and lymphoma demonstrated poorer responses to SARS-CoV2 vaccines. Only 42% of lymphoma patients achieved seroconversion after two doses of mRNA vaccine or one dose of Ad26.COV2.S, which was significantly lower than the seropositivity frequency of controls both <65 years old (100%) and > 65 years old (91%) [39]. Lim et al. also saw a low seropositivity frequency among lymphoma patients receiving treatment (39%), although antibody levels for lymphoma patients not on treatment were higher, seropositivity frequency for this group was not reported [40]. Among all groups of hematologic malignancies included in a study, CLL patients had the lowest seropositivity frequency with only 47% achieving seroconversion after two doses of mRNA-based vaccine series [34]. Similarly low frequency of seropositivity among CLL patients were also observed by Roeker et al. (52%) and Herishanu et al. (40%) following two doses of mRNA vaccines [25,41]. Furthermore, CLL was frequently identified as a factor associated with decreased seroresponsiveness along with increased age and B-cell targeting therapies such as rituximab or BTK inhibitors [19,20,22,23,25,33–37,41]; however, these sub-analyses are generally limited by small numbers. Increased age is associated with decreased vaccine serologic responses [42,43]; however, lymphoid malignancies appear to foster deficient vaccine responses beyond age alone [39].

While seropositivity is the most easily assessed and utilized measure of vaccine response, it has multiple limitations. A plethora of antibody testing platforms have been used, ranging from commercial to research, with non-standardized performance characteristics, including antibody detection thresholds. Very limited cross-platform comparative data are available, which complicates synthesis of qualitative results from different test methods and hinders comparisons of quantitative or semi-quantitative measurements of specific antibody levels obtained using unique assays. Immunogenicity comparisons are further complicated by variable antibody assessment intervals after vaccination. Most importantly, there remain a lack of established antibody thresholds to correlate with level of protection against infection in immunocompromised hosts, and progress in this area continues for immunocompetent populations [44–46]. Ongoing SARS-CoV-2 evolution and emergence of novel antigenic variants will present persistent challenges to

standardized evaluation of humoral vaccine responses and immunity in immunocompromised as well as healthy individuals.

While detection of SARS-CoV-2-specific antibodies in binding assays confirms seropositivity or seroconversion, demonstration of viral neutralizing activity by antibodies may serve as a more rigorous assessment of the functional humoral response to vaccination. Levels of neutralizing antibodies have generally correlated with total anti-spike antibody levels in both healthy controls [47] and individuals with hematologic malignancy [22]. In a limited number of studies with small patient populations, lower titers of binding antibodies in hematologic malignancy patients generally predict lower levels of neutralizing antibodies [21,22,26,48]. However, some solid tumor and hematologic malignancy patients exhibited seropositivity but no demonstrable viral neutralization capacity following two doses of mRNA-based vaccine [21]. Although data are limited, patients with myeloid neoplasms may develop stronger neutralizing antibody responses than individuals with lymphoid malignancies. After a single dose of BNT162b2, 100% of patients with CML produced neutralizing antibodies [26] compared to only 25% of individuals with multiple myeloma [48], and after one dose of BNT162b2 or ChAdOx1 neutralizing antibodies were detected in only 5% of individuals with lymphoid malignancy [49]. As a group, hematologic malignancy patients had low neutralizing antibody titers, and those receiving rituximab were noted to have very low neutralizing antibody levels [22].

Cellular immune responses are another evaluable and functionally informative facet of the host response to vaccination. However, assessment of cellular responses is both technically intensive and challenging to interpret, as correlations between measured cellular responses and level of disease protection are yet to be determined for either immunocompetent or immunosuppressed hosts. In patients with hematologic malignancies, particularly those with B-cell dysfunction, cellular responses may play a larger role in mediating vaccine protection (Fig. 3). Monin et al. assessed T-cell responses to SARS-CoV-2 spike protein peptides in healthy controls and patients with malignancies and found that cellular responses generally correlate with serological responses in healthy populations, yet a few individuals with serological responses did not mount detectable cellular responses and vice versa [21]. Among patients with hematologic malignancies, 9 of 18 (50%) patients assessed after one dose of BNT162b2 exhibited T-cell responses to vaccine antigen, which exceeded the percentage with serological responses (18%). In comparison, 14 of 17 (82%) healthy control subjects and 22 of 31 (71%) solid malignancy patients generated T-cell responses following one dose of BNT162b2; overall, the range of T-cell responses was lower for hematologic malignancy patients than for either solid malignancy patients or healthy controls [21]. Generalizability of findings by Monin et al. is limited by small numbers of study subjects, and their results might possibly be explained by stimulation of memory T cells specific for endemic coronaviruses. In a report by Harrington et al., robust SARS-CoV-2-specific CD4 (12/15 patients) and CD8 (9/15 patients) T-cell responses were observed among a group of 15 patients with CML after a single dose of BNT162b2 vaccine (overall 14/15 patients had some form of memory T-cell response) [26]. Malard et al. observed that 53% (36/68) of hematologic malignancy patients developed a SARS-CoV-2 antigen-specific T-cell response following two doses of BNT162b2. Among those with positive T-cell responses were 17 individuals who did not achieve protective antibody levels, including 15 individuals with impaired B cell function [20]. Thus, potential exists for vaccine-induced T-cell mediated protection from COVID-19 in those patients with impaired or inadequate humoral vaccine immunogenicity, and new SARS-CoV-2 vaccine candidates aimed at inducing T-cell immune responses are currently under development [50]. However, much more data is needed to determine a protective threshold for T cell immunity and to determine the clinical impact of vaccine-imparted T cell immunity in hematologic malignancy and HCT patients.

2.3. Vaccine strategies

Much of the available SARS-CoV-2 vaccine data in patients with hematologic malignancies comes from studies using novel mRNA vaccines. Only six published studies captured in our literature search have included vector-based vaccines [19,29,30,39,40,49] and none as the exclusive vaccine strategy. Because some studies combined vaccine types (e.g. mRNA-based vs adenovirus vector-based) in the analysis and did not report individual immunogenicity data for product included, it is difficult to determine whether there are differences in immunogenicity due to vaccine type. Although Bird et al. noted no differences in antibody responses between types of vaccines, Thakkar et al. saw higher anti-spike antibody titers following mRNA-based vaccine compared to adenovirus vector vaccine, but did not find a difference between two approved mRNA vaccines [19,30]. However, other studies have noted greater likelihood of an antibody response following receipt of mRNA-1273 versus BNT162b2 in individuals with hematologic malignancies, possibly owing to the higher RNA content of mRNA-1273 [33].

Several studies documented an association between decreased SARS-CoV-2 vaccine responses with active treatment for malignancy [20,25,34,37,41]. Among a cohort of 315 hematologic malignancy patients, 95% of those who had never received treatment were seropositive following two doses of BNT162b2, compared to 73% of those receiving one line of therapy, and 63% of those receiving two or more lines of therapy [34]. Similarly, Roeker et al. detected vaccine-elicited antibodies in 17 of 18 (94%) never-treated CLL patients compared to 6 of 26 (23%) treated CLL patients after two doses of mRNA vaccine [41]. Having received B-cell depleting therapies within the past 12 months was significantly associated with decreased vaccine-induced antibody response [20], especially treatment with anti-CD20 monoclonal antibody [25,34,37,41]. None of the 22 CLL patients who received treatment with anti-CD20 monoclonal antibody in the previous 12 months were seropositive after two doses of BNT162b2, and only 25 of 55 (45.5%) CLL patients who received anti-CD20 therapy >12 months prior to vaccination developed serologic responses [25]. Furthermore, treatment with Bruton tyrosine kinase inhibitors (BTKi) was also associated with poor serologic responses to SARS-CoV-2 vaccine in several studies [25,34,37,41]. Notably, 8 of 50 (16%) CLL patients treated with BTKi [25] and 40% of hematologic malignancy patients who received BTKi therapy [34] were seropositive after two doses of mRNA vaccine. Currently, the CDC offers no recommendations on timing of vaccination with regard to cancer therapy. The American Society of Hematology (ASH) recommends completing at least two SARS-CoV-2 vaccine doses prior to initiation of cytotoxic or B-cell depleting therapies, whereas the National Comprehensive Cancer Network (NCCN) recommends delaying vaccination until neutrophil recovery, if possible, for those receiving intensive chemotherapy (Table 3). However, those who are undergoing or recently received cancer treatment prior to SARS-CoV-2 vaccination, especially with anti-CD20 or BTKi therapies, are likely to experience decreased serological responses.

Prior to BNT162b2 and mRNA-1273 EUA expansion to include a third vaccine dose in immunosuppressed patient populations as part of vaccine primary series, vaccine boosters were advocated for use in individuals with malignancies based on prior vaccine booster studies [51]. In a small study of homologous and heterologous SARS-CoV-2 vaccine boosting, the seropositivity frequency increased in boosted individuals with B-cell malignancies following a third dose [52]. Immunogenicity and reactogenicity of third dose primary series and vaccine boosters in this patient population are research priorities.

3. SARS-CoV-2 vaccines in patients with allogeneic stem cell transplants

Like individuals with hematologic malignancies, recipients of alloHCT have historically had decreased responses to vaccines, especially when compared to healthy controls [53–55] and also suffer from

high COVID-19 morbidity and mortality [9]. Variable vaccine responses may be due to heterogeneity in underlying disease and immune defects, B- and T-cell depleting therapies, and immunosuppression for GVHD. Furthermore, there is concern that immune stimulation by vaccination may lead to immunologic alterations that could elicit or worsen GVHD.

3.1. Safety and reactogenicity

Overall, SARS-CoV-2 vaccines appear to be well tolerated among alloHCT recipients. Only grade 1 or 2 adverse events were observed following a single dose of BNT162b2; while not statistically significant, a slightly lower adverse reaction rate was seen in alloHCT patients versus healthy controls (47.8% vs 66.6%) [56]. In a follow-up report, only grade 1 or 2 adverse events were observed following a second dose of BNT162b2, occurring in 39% (34/87) of patients [57]. Pinana et al. also observed mild and fewer adverse events after the second dose of an mRNA vaccine or ChAdOx1 in a mixed cohort of alloHCT and autoHCT recipients [58]. Other reports found more local and systemic reactions after the second dose of a two-dose mRNA vaccine series [37,59,60]; these included injection site pain (55.6%), headache (16.7–22.2%), fatigue (27.8–44.4%), gastrointestinal symptoms (11.1–16.7%), and fever/chills (5.6%–11.1%) [59], but rates remained lower than those for healthy controls [59,60]. While reactions were mild (grade 1–2), Matkowska-Kocjan et al. observed an adverse event rate of as high as 60% after one or two doses of BNT162b2; however, this was a unique cohort consisting of young adult patients who underwent alloHCT as children and therefore this cohort may be more similar to healthy controls than recently transplanted patients [61].

SARS-CoV-2 vaccination has been temporally linked to onset or exacerbation of GVHD in HCT recipients in a subset of retrospective cohorts. Ali et al. observed in a retrospective study new or worsening GVHD in 12% of participants, a cohort that also exhibited low antibody response rates [62]. Chiarucci et al. described mild GVHD in 42% of 12 patients after 2 doses of BNT162b2 [63]. In another report, an 8% GVHD exacerbation rate along with mild cytopenias in up to 12% of participants was noted following two doses of BNT162b2, and a case of impending graft rejection was felt to be vaccine-related [64]. Other studies that examined SARS-CoV-2 vaccine safety and reactogenicity in alloHCT recipients revealed no cases of new or exacerbated GVHD after vaccination [60,65,66]. Frequency and risk factors for vaccine-triggered GVHD are priority research questions in the design of safe, effective vaccines and vaccination strategies to prevent COVID-19 in HCT recipients.

3.2. Immunogenicity

Although SARS-CoV-2 vaccine-induced seropositivity rates and antibody titers remain lower than those of healthy controls, antibody response rates are overall high among alloHCT recipients (Table 2), especially when compared to the reported seropositivity rates in patients with solid organ transplant [67] or some subsets of patients with hematologic malignancy. After a single dose of mRNA or vector-based vaccine, 38–68% of alloHCT recipients seroconverted [56,68,69]. In other studies, following two doses of mRNA-based or one dose of adenovirus-based SARS-CoV-2 vaccine, seropositivity frequencies ranging from 50% to 97% (typically 70% to 80%) were observed in alloHCT recipients (Fig. 2) [26,37,57,59–61,63–66,69–73], in comparison to nearly 100% of healthy controls. Although a 97% seroconversion rate was induced in a cohort of young adult patients who had undergone HCT as children (median 10.5 years post-transplant at time of vaccination), this may not be reflective of the majority of alloHCT patients [61]. Among studies that included recipients of both autoHCT and alloHCT, some showed lower rates of seropositivity among alloHCT recipients than autoHCT recipients [19,58,63,71], while others reported the reverse [69,72], although both groups achieved lower rates of seropositivity and antibody titers when compared with healthy controls [69,71]. Despite detectable antibodies in many patients with alloHCT, threshold levels of protective antibody have not been established in this group.

Data are sparse regarding neutralizing antibody levels in alloHCT recipients following SARS-CoV-2 vaccination. After one dose of BNT162b2 or mRNA-1273 vaccine, 11 of 21 (52%) alloHCT recipients had neutralizing Ab above the positive threshold, which increased to 95 of 122 (78%) patients after two doses of mRNA vaccine, yet still significantly lower than neutralizing antibody rates in healthy controls following vaccination (93.2% after one dose and 100% after two doses) [69]. Canti et al. and Shem-Tov et al. found neutralizing antibody titers to correlate with binding antibody titers, but some patients positive for binding antibodies had undetectable neutralizing antibody levels [60,66]. In a multivariate analysis, increasing age, moderate or severe GVHD, and rituximab therapy within a year of vaccination were associated with lower neutralizing antibody titers [66]. Harrington et al. evaluated neutralizing antibody titers after BNT162b2 or ChAdOx1 vaccination in alloHCT recipients positive for binding antibodies and found that those receiving extracorporeal photopheresis for GVHD had lower levels of neutralizing and binding antibodies [74].

Harrington et al. found high rates of T-cell responses to spike protein peptides after two doses of BNT162b2 or ChAdOx1 vaccine in alloHCT recipients [74]. Interferon-γ or TNF-α production by SARS-CoV-2 antigen-specific CD4 or CD8 T cells after one dose of BNT162b2 or ChAdOx1 was detected in 35.3% (6/17) of patients while that number increased to 82.3% (14/17) after two doses. Polyfunctional T-cell responses (T-cells producing more than one pro-inflammatory cytokine) were detected in 70.6% (12/17) of two-dose recipients compared to only 29.4% (5/17) after one vaccine dose. In contrast, other investigators have observed low rates of SARS-CoV-2 antigen-specific T-cell responses, assessed by interferon-γ, IL-2, or IL-17 production, in alloHCT recipients, as well as lower magnitude cellular responses [64,70]. Lindemann et al. found that T-cell interferon-γ production in response to SARS-CoV-2 spike protein peptide stimulation ranged from 12 to 29% among alloHCT recipients compared to 54–80% for healthy controls following two doses of mRNA vaccine or one dose of ChAdOx1 followed by another dose of ChAdOx1 or BNT162b2, depending on the antigen [70]. Ram et al. detected T-cell responses in only 19% (7/37) of alloHCT recipients evaluated after two doses of BNT162b2 [64].

3.3. Vaccine strategies

Due to early vaccine availability and global vaccine shortages, much of the available data on SARS-CoV-2 vaccine responses in alloHCT recipients comes from patients who have received novel mRNA vaccines, with a minority having received at least one dose of an adenovirus-based vector vaccine. Most published studies do not differentiate between vaccine type in analyses of responses, but Easdale et al. did note a higher rate of seroconversion following one dose of ChAdOx1 (50%) compared to BNT162b2 (19%) [68]. However, no follow-up data are available following two or three vaccine doses in this cohort [68].

Several studies noted that vaccination closer to time of transplant [37,56,58,60,63–65,70], moderate to severe GVHD [58,60,66], and treatment with immunosuppressive therapy [56,60,63,65,68] are associated with decreased vaccine immune responses. In particular, vaccination within one year from time of HCT was associated with lower probability of seropositivity [57,58], whereas time interval >12 months between HCT and vaccination, as well as peripheral blood absolute lymphocyte count (ALC) $>1 \times 10^9$/l at time of vaccination was correlated with protective antibody titers [65]. Maillard et al. found 32% of alloHCT recipients vaccinated within six months of HCT to be seropositive, while that frequency increased to 50% for those vaccinated between 6 and 12 months and to 87% for those vaccinated more than one year following transplant [73]. Other studies identified a similar trend, demonstrating increased seropositivity rates associated with greater time from alloHCT to vaccination: 20–67% for those vaccinated within

Table 2
Summary of studies evaluating SARS-CoV-2 vaccine responses in allogeneic stem cell transplant, autologous stem cell transplant, and CAR-T cell therapy recipients.

Year, citation	Vaccination type, # of doses	# of subjects (# of transplant recipients)	Test groups	Age at immunization	Timing of vaccine administration post-transplant	Spike IgG test	Seropositivity, days after completion of vaccine	SARS-CoV-2 IgG antibody titer	Safety & Reactogenicity
2021 Bird et al.	BNT162b2 or ChAdOx1 1 dose	*N* = 93 (AutoHC*T* = 77)	MM (Subgroup with AutoHCT)	Median years (overall cohort): 67	10% ≤12 months 90% >12 months	Ortho Clinical Diagnostic	HCT: 43/77 (56%) MM: 52/93 (56%) >21 days	Not reported	Not reported
2021 Herzog Tzarfati et al.	BNT162b2 2 doses 3 weeks apart	*N* = 315 (AutoHCT = 21)	HM (subgroup with AutoHCT) Non-malignancy controls (*N* = 108)	Median years: HM: 71 Controls: 69	Not reported	Diasorin LIAISON	HCT: 17/21 (81%) HM: 211/286 (74%) Controls: 107/108 (99%) 30–60 days	Median (AU/mL) HCT: 95.4 HM: 85 Controls: 157	Not reported
2021 Rimar et al.	BNT162b2 2 doses 3 weeks apart	*N* = 7	AutoHCT (for scleroderma) Healthy controls (*N* = 7)	Median years: 60	Median (range) 24 (3–60) months	Abbott IgG II Quant Assay	HCT: 6/7 (86%) Controls: 7/7 (100%) 14 days	Mean (AU/mL) HCT: 9258 Controls: 17340	1 in HCT group reported fatigue None reported in controls
2021 Salvini et al.	BNT162b2 2 doses 3 weeks apart	*N* = 64	AutoHCT	Not reported	Median (range) 25.6 (1.2–58.1) months	Diasorin LIAISON	56/64 (87%) Median 28 days	Median (AU/mL): 747	Not reported
2021 Attolico et al.	BNT162b2 2 doses 3 weeks apart	*N* = 114 (AutoHCT = 52 AlloHCT = 62)	AutoHCT AlloHCT Healthy controls (*N* = 107)	Median years: AutoHCT: 57 AlloHCT: 56 Controls: 53	17% ≤1 year 45% 1–5 years 38% >5 years	Abbott immunoassay	AutoHCT: 49/52 (94%) AlloHCT: 47/62 (76%) Controls: 107/107 (100%) 28 days	Median (AU/mL): AutoHCT: 4023 AlloHCT: 6576 Controls: 7132	Not reported
2021 Chiarucci et al.	BNT162b2 2 doses 3 weeks apart	*N* = 50 (AutoHC*T* = 38 AlloHC*T* = 12)	AutoHCT AlloHCT	54% ≤60 years 46% >60 years	Median (range) 369 (5–736) days	Diasorin LIAISON	AutoHCT: 32/38 (84%) AlloHCT: 6/12 (50%) 30 days	Median (AU/mL): 282	Mild local reactions seen after injection, 2 cases of systemic reactions. 42% AlloHCT had mild GVHD
2021 Maneikis et al.	BNT162b2 2 doses 3 weeks apart	*N* = 857 (AutoHCT = 192 AlloHCT = 122)	AutoHCT AlloHCT HM Healthy controls (*N* = 68)	Median years: AutoHCT: 63 AlloHCT: 55 HM: 65 Controls: 40	Auto: 4% <6 months 10% 6–12 months 86% >12 months Allo: 4% <6 months 11% 6–12 months 85% >12 months	Abbott IgG II Quant Assay	Number seropositive not reported 7–21 days	Median (AU/mL) AutoHCT: 6203 AlloHCT: 6304 Controls: 21395	Up to 13% of heme malignancy cohort reported systemic adverse events (all grade 1–3), which was more common after second dose
2021 Pinana et al.	"Full vaccination" with BNT162b2 or mRNA-1273 or ChAdOx1 or Ad26.COV2.S	*N* = 397 (AutoHCT = 86 AlloHCT = 311)	AutoHCT AlloHCT	Median years: AutoHCT: 64.6 AlloHCT: 56.7	Median (range) AutoHCT: 88 (3–763) months AlloHCT: 98 (4–646) months	Various	AutoHCT: 73/86 (86%) AlloHCT: 242/311 (78%) 3–6 weeks	Not reported	Mild AE were reported by 9% and were more common after the first vaccine dose
2021 Dhakal et al.	BNT162b2 or mRNA-1273 2 doses 3–4 weeks apart or Ad26.COV2·S 1 dose	*N* = 130 (AutoHCT = 45 AlloHCT = 71 CAR-*T* = 14)	AutoHCT AlloHCT CAR-T	Median years: +response vs -response) AutoHCT: 65 vs 65 AlloHCT: 64	15% <6 months 85% ≥6 months	Euroimmun ELISA IgG	Total: 79/130 (60%) AutoHCT: 60% AlloHCT: 69% CAR-T: 11%	Not reported	Not reported

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Table 2 (*continued*)

Year, citation	Vaccination type, # of doses	# of subjects (# of transplant recipients)	Test groups	Age at immunization	Timing of vaccine administration post-transplant	Spike IgG test	Seropositivity, days after completion of vaccine	SARS-CoV-2 IgG antibody titer	Safety & Reactogenicity
				vs 68.5 CAR-T: not reported			≥14 days		
2021 Tamari et al.	BNT162b2 or mRNA-1273 2 doses 3–4 weeks apart	*N* = 217 (AutoHCT = 61 AlloHCT = 149 CAR-T = 7)	AutoHCT AlloHCT CAR-T Healthy controls (*N* = 54)	Median years: Cellular therapy: 66.4 Controls: 31	Median (IQR) 1007 (488, 1761) days	AdviseDx IgG II (Abbott)	After 1 dose: 24/39 (62%) AlloHCT: 17/25 (68%) AutoHCT: 7/13 (54%) CAR-T: 0/1 (0%) After 2 doses: 188/217 (87%) AlloHCT: 133/19 (89%) AutoHCT: 53/61 (87%) CAR-T: 2/7 (29%)	Median (AU/mL) After 1 dose: Cellular therapy: 479.75 Controls: 886.2 After 2 doses: Cellular therapy: 5379 Controls: 7720	Not reported
2021 Thakkar et al.	BNT162b2 or mRNA-1273 2 doses 3–4 weeks apart or Ad26.COV2.S 1 dose	*N* = 226 (AutoHCT = 23 AlloHCT = 3 CAR-T = 3)	HM (subgroups with HCT and CAR-T) Solid tumor Non-malignancy controls (*N* = 26)	Median years: Malignancy: 67 Controls: 64	12% ≤12 months 88% >12 months	Abbott IgG II Quant Assay	3 months HCT: 19/26 (73%) AutoHCT: 17/23 (74%) AlloHCT: 2/3 (67%) CAR-T: 0/3 (0%) HM: 56/66 (85%) Solid: 131/134 (98%) Controls: not reported	Median (AU/mL) HCT and CAR-T: values not reported HM: 2528 Solid: 7858 Controls: value not reported	26–37% with mild to moderate adverse effects after 1 or 2 doses of vaccine 1–3% with severe adverse effects after 1 or 2 doses of vaccine
2021 Chevallier et al.	BNT162b2 1 dose	*N* = 112	AlloHCT Healthy controls (*N* = 26)	Median years: AlloHCT: 57 Controls: 52	Median (range) 22.1 (3–206) months	Roche Elecsys	>7 days HCT: 62/112 (55%) Controls: 26/26 (100%) ~21 days	Mean (AU/mL) HCT: 14.2 Controls: 35.1	Adverse event rate: 48% for HCT, 67% for controls Only grade 1 or 2 adverse events observed
2021 Easdale et al.	BNT162b2 or ChAdOx1 1 dose	*N* = 55	AlloHCT	Median years: 50	Median (range) 460 (108–4533) days	Ortho Clinical Diagnostic	21/55 (38%) >14 days	Not reported	No significant events reported
2021 Ali et al.	BNT162b2 or mRNA-1273 1–2 doses 3–4 weeks apart	*N* = 113	AlloHCT	Median years: 66.5	Median (range) 588 (100–11,004) days	Not reported	Not reported	Not reported	Local 44% Systemic 4–29% 9.7% had new cGVHD 3.5% with GVHD exacerbation
2021 Canti et al.	BNT162b2 2 doses 3 weeks apart	*N* = 40	AlloHCT Healthy controls (*N* = 40)	Median years: AlloHCT: 60 Controls: 48	Median (range) 31 (5–51) months	WANTAI ELISA	AlloHCT: 32/37 (86%) Controls: 40/40 (100%) 21 days	Not reported	Pain (86%), fatigue (41%), headache (30%), myalgia (28%), chills (15%). No GVHD exacerbations reported. No vaccine related SAEs reported.
2021 Harrington et al.	BNT162b2 or ChAdOx1 2 doses	*N* = 23	AlloHCT	Median years: 55	Median (range) 55 (19–172) months	ELISA for SARS-CoV-2 anti-spike IgG	13/16 (81%) Median 12 weeks	Mean EC_{50}: 1043	Not reported

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Table 2 (*continued*)

Year, citation	Vaccination type, # of doses	# of subjects (# of transplant recipients)	Test groups	Age at immunization	Timing of vaccine administration post-transplant	Spike IgG test	Seropositivity, days after completion of vaccine	SARS-CoV-2 IgG antibody titer	Safety & Reactogenicity
	(interval not reported)								
2021 Le Bourgeois et al.	BNT162b2 2 doses 3 weeks apart	$N = 117$	AlloHCT	Median years: 57	Median (range) 654 (91–6168) days	Roche Elecsys	97/117 (83%) Median 35 days	72/117 (62%) achieved >250 AU/mL	Grade 1 or 2 adverse reactions occurred in 34/87 (39%) after dose 2
2021 Lindemann et al.	BNT162b2 or mRNA-1273 2 doses or ChAdOx1 followed by ChAdOx1 or BNT162b2 (interval not reported)	$N = 153$	AlloHCT Healthy controls ($N = 35$)	Median years: AlloHCT: 59 Controls: 53	Median (range) 30 (5–391) months	Euroimmun ELISA IgG	AlloHCT: 80/117 (68%) Controls: 35/35 (99%) Median 31 days for AlloHCT Median 30 days for controls	Median antibody ratio: AlloHCT: 4.7 Controls: 9	Not reported
2021 Matkowska-Kocjan et al.	BNT162b2 2 doses 5 weeks apart	$N = 65$	AlloHCT	Median years: 21	Median (range) 10.5 (3–27) years	Euroimmun ELISA IgG	55/57 (97%) 14–21 days	GMC: 3290.94	60% experienced at least one local or systemic AE after one or both doses of vaccine. All were grade 1–2.
2021 Ram et al.	BNT162b2 2 doses 3 weeks apart	$N = 80$ (AlloHCT = 66 CAR-T = 14)	AlloHCT CAR-T	Median years: 65	Median (range) HCT: 32 (3–263) months CAR-T: 9 (3–17) months	Roche Elecsys	HCT: 47/57 (82%) CAR-T: 5/14 (36%) 7–14 days	Median (AU/mL) HCT: 178 CAR-T: 0.4	14–24% with adverse effects (all grade 1 or 2) ~5% with transient grade 3 or 4 cytopenia ~8% with GVHD exacerbation 1 case impending late graft rejection
2021 Redjoul et al.	BNT162b2 2 doses 4 weeks apart	$N = 88$	AlloHCT	Not reported	Median (range) 23 (3−213) months	Abbott IgG II Quant Assay	69/88 (78%) Median 28 days	Not reported	Not reported
2021 Shem-Tov et al.	BNT162b2 2 doses 3 weeks apart	$N = 152$	AlloHCT Healthy controls ($N = 272$)	Median years: AlloHCT: 58.4 Controls: 55.6	Median (IQR) 3.4 (2, 6.3) years	ELISA for SARS-CoV-2 anti-RBD IgG	AlloHCT: 118/152 (78%) Controls: 269/272 (99%) Median 28 days for AlloHCT Median 26 days for controls	GMT: AlloHCT: 2.61 Controls: 5.98	Local 9.9–11.8% Systemic 5.3–13.2% No vaccine related SAE, no GVHD exacerbation. Healthy controls were more likely to have local and systemic AE than AlloHCT
2021 Sherman et al.	BNT162b2 or mRNA-1273 2 doses 3–4 weeks apart	$N = 20$	AlloHCT Healthy controls ($N = 24$)	Median years: AlloHCT: 66 Controls: 24	Median (IQR) 173 (111, 334) days	Quanterix Simoa or Roche Elecsys	AlloHCT: Simoa 15/20 (75%) Roche 16/20 (80%) Controls: Simoa 100% Roche 100% 28 days	Median (AU/mL): AlloHCT: Simoa anti-S 20.27 Simoa anti-RBD 17.63 Simoa anti-S1 30.04 Roche anti-S 205.05 Controls: Simoa anti-S 65.7	More local and systemic symptoms after dose 2: injection site pain 56%, fever 11%, headache 17–22%, chills 6–17%, fatigue 28–44%, GI symptoms 11–17%, myalgias 28%

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Table 2 (*continued*)

Year, citation	Vaccination type, # of doses	# of subjects (# of transplant recipients)	Test groups	Age at immunization	Timing of vaccine administration post-transplant	Spike IgG test	Seropositivity, days after completion of vaccine	SARS-CoV-2 IgG antibody titer	Safety & Reactogenicity
								Simoa anti-RBD 90.04 Simoa anti-S1 136.39 Roche anti-S 4435	
2021 Greenberger et al.	BNT162b2 or mRNA-1273 2 doses 3–4 weeks apart	$N = 1445$ (CAR-T = 12)	HM (subgroup with CAR-T)	Median years: 68	Not reported	Roche Elecsys	CD19 CAR-T: 1/7 (14%) BCMA or CD138 CAR-T: 4/5 (80%) >14 days (median 41–42)	Not reported	Not reported
2021 Maillard, et al.	BNT162b2 or mRNA-1273 2 doses 4 weeks apart, third dose median 54 days after 2nd dose	$N = 687$	AlloHCT	Median years: 2 doses: 59 3rd dose: 60.5	Median (IQR) 2 doses: 27 (14, 56) months 3rd dose: 15.8 (10.1, 42.6) months	Abbott IgG II or Roche Elecsys or Diarsorin Liaison or Siemens ECLIA or Wantai ELISA	538/687 (78%) after 2 doses Median 33 days after 2nd dose 140/181 (77%) after 3 doses Median 30 days after 3rd dose	Median (BAU/mL) After 2 doses: 749	Not reported
2021 Redjoul et al.	BNT162b2 First 2 doses 4 weeks apart, third dose ~51 (SD 22) days after second dose	$N = 42$	AlloHCT	Median years: 59	52% ≤12 months 48% >12 months	Abbott IgG II Quant Assay	20/42 (48%) reached "protective" Ab threshold ≥4160 Mean 26 (SD 6) days	Mean (AU/mL) Before 3rd dose: 737 After 3rd dose: 11099	No serious adverse events. No new or exacerbations of GVHD.

Abbreviations
AlloHCT = allogeneic stem cell transplant.
AutoHCT = autologous stem cell transplant.
CAR-T = chimeric antigen receptor T-cell therapy.
HM = hematologic malignancy.
MM = multiple myeloma.

12 months of alloHCT, 82–89% for those vaccinated between 12 and 24 months from alloHCT, and 79–91% for those who were >24 months post-transplant [60,69]. *Re*-vaccination following HCT is routinely recommended as antibodies to vaccine-preventable infections wane in the years following HCT [75,76]. While there is no efficacy data on SARS-CoV-2 re-vaccination after HCT, the recommendation for re-vaccination has been made by both ASH and NCCN for recipients of HCT, CAR-T cell therapy, and other cellular therapies [77–79].

Due to the variable and overall decreased level of vaccine responses in alloHCT recipients, booster or additional vaccine doses have been considered, although data are lacking on effectiveness of this strategy to improve responses. Redjoul et al. evaluated antibody responses following a third dose of BNT162b2 in alloHCT recipients who were previously seronegative or had low antibody titers after two doses of BNT162b2 and found that only 48% (20/42) subsequently developed an antibody titer reaching a "protective threshold" defined by the manufacturer as greater than or equal to 4160 AU/mL, which was previously demonstrated to correlate with 0.95 probability of virus neutralization in in-vitro neutralization tests. However, 52% (22/42) of those who were previously seronegative remained seronegative after a third vaccine dose [80].

4. SARS-CoV-2 vaccines in patients with autologous stem cell transplants

Although patients undergoing autoHCT are not subject to some of the risks associated with alloHCT such as GVHD, they have equally poor prognosis following COVID-19 diagnosis. Overall survival at 30 days following COVID-19 diagnosis was only 68% for alloHCT recipients and 67% for autoHCT recipients [9]. Furthermore, patients with lymphoma, compared with plasma cell disorder or multiple myeloma undergoing autoHCT, have worse outcomes, which may be additionally associated with poor SARS-CoV-2 vaccine responses. Therefore, assessing and optimizing vaccine-mediated protection of autoHCT recipients is of vital importance.

4.1. Safety and reactogenicity

Few studies have assessed safety of SARS-CoV-2 vaccines specifically in autoHCT recipients. Rimar et al. found that 1 of 7 (14%) autoHCT recipients reported any adverse response ("tiredness") following two doses of BNT162b2, compared to 0 of 7 healthy controls [81]. In mixed populations of vaccinated autoHCT and alloHCT recipients, reported

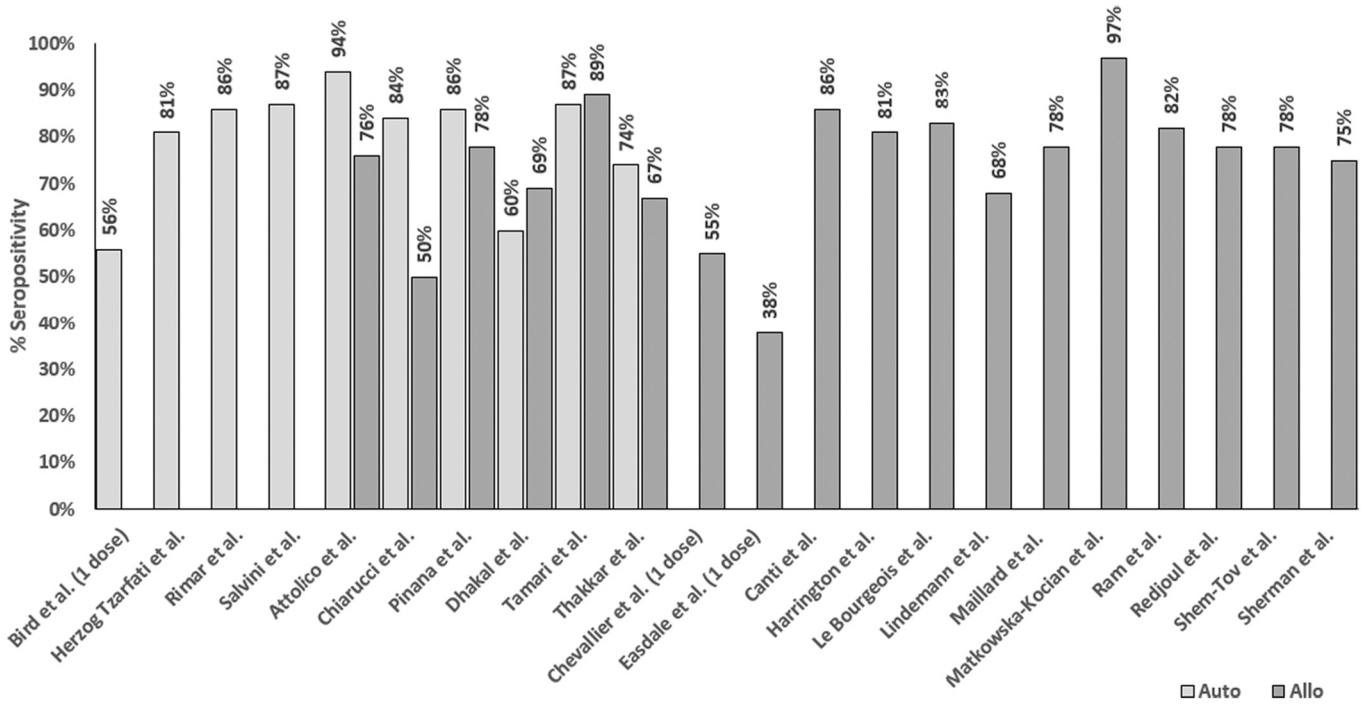

Fig. 2. Seropositivity frequency following SARS-CoV-2 vaccination in individuals with autologous or allogeneic stem cell transplant.
Seropositivity frequencies in autologous stem cell (light gray) and allogeneic stem cell transplant (dark gray) recipients after SARS-CoV-2 vaccination. "1 dose" indicates seropositivity after a single dose of an mRNA-based vaccine or ChAdOx1 and "booster" indicates an mRNA-based vaccine following two doses of mRNA-based vaccine or two doses of ChAdOx1. All others are seropositivity following two doses of ChAdOx1 or mRNA-based vaccine, or single dose AD26COV2.S. Sherman et al. saw seropositivity as high as 80% depending on testing platform.

adverse events were generally mild and consisted of both local and systemic reactions such as muscle aches, sore arm, fever, and fatigue [19,58,63]; Studies that included both vector-based and mRNA vaccines documented an overall adverse event rate of 9–37%, with similar rates of adverse reactions between mRNA and adenovirus-vector vaccines [19]; however, study populations were mixed, and autoHCT recipients were in the minority [19,58].

4.2. Immunogenicity

After a single dose of BNT162b2 or ChAdOx1 vaccine, 56% of multiple myeloma patients who underwent autoHCT seroconverted, the same seropositivity frequency as multiple myeloma patients who did not undergo autoHCT [30]. Overall, autoHCT recipients demonstrated high rates of seropositivity following SARS-CoV-2 vaccination (primarily studied following two doses of BNT162b2) with seropositivity frequencies ranging from 60 to 94% (Table 2 and Fig. 2) [19,58,63,69,71,72,81,82], similar to rates among vaccinees with myeloid compared to lymphoid neoplasms. However, antibody titers among autoHCT recipients were lower than those in healthy controls [69,71] and approximated titers in individuals with hematologic malignancies [19,34]. Tamari et al. evaluated neutralizing antibody levels in autoHCT recipients following one or two doses of BNT162b2 or mRNA-1273 and found that 4 of 11 (36%) had >30% neutralizing antibody titer after one vaccine dose, which increased to 49 of 61 (80%) of patients at approximately two months after a second dose. However, these frequencies were significantly lower than response rates in healthy controls (93.2% after one vaccine dose and 100% after two vaccine doses) [69].

Salvini et al. evaluated SARS-CoV-2 antigen-specific T-cell responses in autoHCT recipients following two doses of BNT162b2 and found an overall cellular response rate of 66% (10/16 patients tested). Notably, detectable T-cell responses were identified in both the seropositive (6/8 patients tested) and seronegative patients (4/8 patients tested), although T-cell responses were higher in the seropositive subset (75% for seropositive vs. 50% for seronegative) [82].

4.3. Vaccine strategies

Due to the widespread and early availability of mRNA vaccines, most studies have been comprised of individuals who received mRNA vaccines, especially BNT162b2, although individuals receiving vector-based vaccines are represented in low numbers. Bird et al. did not identify a difference in seropositivity rates in multiple myeloma patients, including those who received autoHCT, following a single dose of BNT162b2 or ChAdOx1 [30]. No direct comparisons between vaccine types in autoHCT recipients were made. Majority of available evidence indicates that poorly controlled or active malignant disease as well as active therapy, especially recent immunotherapy, is associated with worse vaccine responses [30,58,63,71,82] whereas greater time since HCT (6–12 months) associates with higher likelihood of an antibody response [30,37], though Dhakal et al. did not find an association between seropositivity rate and interval between HCT and vaccination in subgroup analysis for autoHCT recipients [72]. Salvini et al. assessed absolute lymphocyte count (ALC) as a predictor for vaccine-induced antibody responses and did not identify an association between ALC and seroconversion, but ALC was positively correlated with antibody titer [82]. Published data are lacking regarding third dose or additional booster vaccine immunogenicity in autoHCT recipients.

5. SARS-CoV-2 vaccines in patients undergoing CAR-T cell therapy

While CAR-T cell therapy recipients have very poor outcomes following SARS-CoV-2 infection (having a COVID-19 attributable mortality rate of 41%) [83], little published data are available regarding safety and immunogenicity of SARS-CoV-2 vaccines in CAR-T cell therapy recipients. A few studies included small subsets of patients

Table 3
Summary of SARS-CoV-2 vaccination recommendations for individuals with immunocompromise and malignancy.

	Primary series	Booster	Timing	*Re*-vaccination
CDC	5–17 years old: 3 doses BNT162b2 (21 days between doses 1 and 2; 28 days between doses 2 and 3) ≥18 years old: 3 doses BNT162b2 (21 days between doses 1 and 2; 28 days between doses 2 and 3) OR 3 doses mRNA-1273 (28 days between doses) OR Ad26.COV2.S followed by BNT162b2 or mRNA-1273 (28 days between doses)	5–11 years old: BNT162b2 booster ≥3 months after 3rd dose 12–17 years old: BNT162b2 booster ≥3 months after 3rd dose and 2nd booster dose ≥4 months after 1st booster ≥18 years old: ≥3 months* after 3rd dose and 2nd booster dose ≥4 months after 1st booster if primary series was mRNA vaccine OR ≥2 months* after 3rd dose and 2nd booster dose ≥4 months after 1st booster if primary series contained Ad26.COV2.S *mRNA vaccine is preferred for booster, but Ad26.COV2.S may be considered in some cases		
ASH-ASTCT	3 doses BNT162b2** (3 weeks between doses 1 and 2; ≥4 weeks between doses 2 and 3) OR 3 doses mRNA-1273 (4 weeks between doses 1 and 2; ≥4 weeks between doses 2 and 3) OR Ad26.COV2.S followed by BNT162b2 or mRNA-1273 (4 weeks between doses) **BNT162b2 only if age 5–17	Booster dose ≥3 months after mRNA primary series completion*** Booster dose ≥2 months after Ad26.COV2.S primary series completion ***BNT162b2 booster only if age 5–17; mRNA vaccine preferred in most cases	≥3 months post-HCT or CAR-T cell therapy, though efficacy may not be optimal Complete at least 2 vaccine doses ≥2 weeks prior to cytotoxic or B-cell-depleting therapies No delay in vaccination with IVIg therapy	≥3 months after HCT or CAR-T cell therapy regardless of vaccination status prior to transplantation or cellular therapy
NCCN	3 doses of mRNA vaccine per CDC recommendations is preferred	2 booster doses (mRNA vaccine preferred) per CDC guidelines recommended for: - Patients with hematologic malignancy regardless of active therapy - Patients who received HCT or engineer cellular therapy within past 2 years or are receiving immunosuppressive agents - Solid tumor patients who received cancer therapy within 1y of initial vaccine administration - Patients receiving immune checkpoint inhibitors	≥3 months post-HCT or cellular therapy For those receiving intensive cytotoxic chemotherapy, delay vaccination until ANC recovery, but for those not expected to recover start vaccination as soon as possible Separate date of surgery from vaccination by at least a few days for solid tumor malignancy patients undergoing major surgery	Repeat primary series and booster starting at 3 months post-treatment for HCT, CAR-T cell therapy, and other cellular therapy regimen recipients

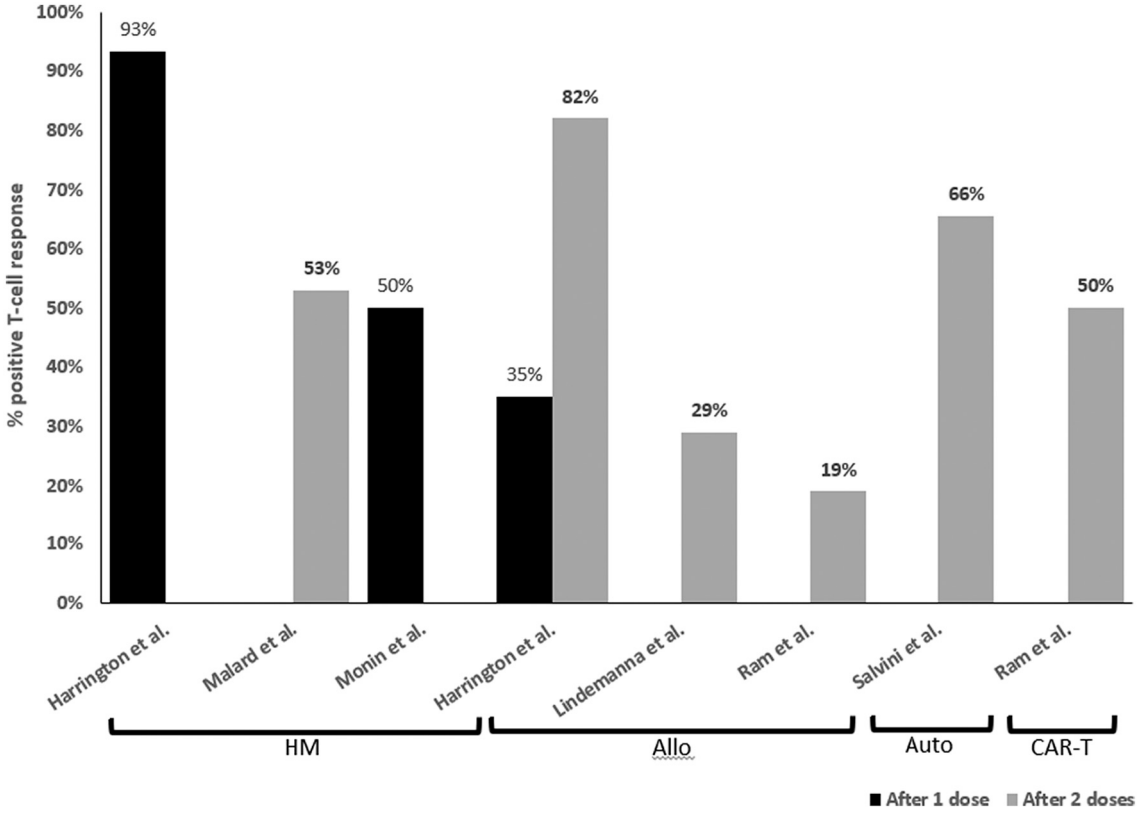

Fig. 3. Frequency of T-cell responses following SARS-CoV-2 vaccination in individuals with hematologic malignancy and cellular therapies.
Frequencies of T-cell responses in individuals with hematologic malignancy (HM), allogeneic stem cell transplant (Allo), autologous stem cell transplant (Auto), or CAR-T cell therapy following SARS-CoV-2 vaccination. "After 1 dose" indicates T-cell response frequency after a single dose of BNT162b2 or ChAdOx1 and "after 2 doses" indicates T-cell response frequency after two doses of mRNA-based vaccine, ChAdOx1, or ChAdOx1 followed by BNT162b2. Lindemann et al. observed T-cell responses ranging from 12 to 29% depending on the spike protein peptide used in the assay.

(3–14 individuals) who received CAR-T cell therapy, and generally low rates of seropositivity ranging from 0 to 36% and low binding antibody titers in those with positive serology were observed (Fig. 4 and Table 2) [19,33,64,69,72]. However, SARS-CoV-2 vaccine responses in CAR-T cell recipients may vary depending on type of CAR-T cell therapy; Greenberger et al. observed that recipients of B-cell maturation antigen (BCMA)- or CD138-targeted CAR-T therapy for multiple myeloma had better antibody responses (80% seropositivity) after two doses of mRNA-based vaccine than those receiving CD19-directed therapy (14% seropositivity) [33]. Moreover, poor antibody responses to SARS-CoV-2

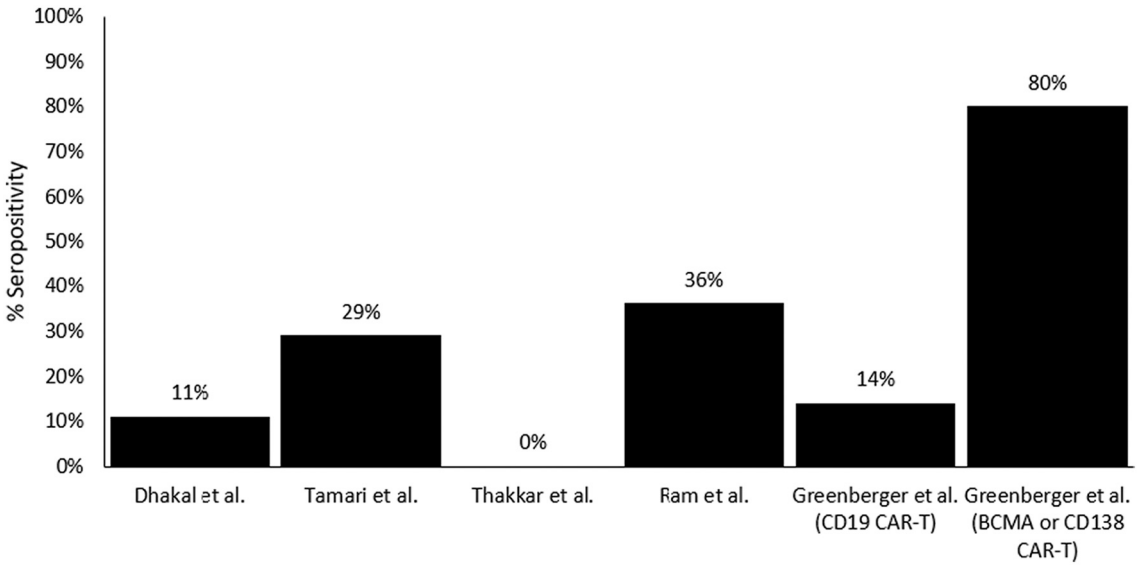

Fig. 4. Seropositivity frequency following SARS-CoV-2 vaccination in individuals with CAR-T cell therapy.
Seropositivity frequencies in individuals undergoing CAR-T cell therapy following vaccination with two doses of an mRNA-based vaccine (BNT162b2 or mRNA-1273) or one dose of Ad26.COV2.S.

vaccines may persist following CAR-T cell therapy. Lim et al. noted that their cohort included three patients who had completed CAR-T cell therapy 11–23 months prior to vaccination for non-Hodgkin lymphoma, and all three had no detectable antibodies after one dose of BNT162b2 or ChAdOx1 vaccine. Only one of these patients was tested following two doses of vaccine and had detectable antibodies, but a fourth patient who was tested only after two doses of vaccine did not [40]. T-cell responses among this population may be more similar to patients with hematologic malignancy or HCT. Ram et al. observed that 6 of 12 (50%) of CAR-T cell recipients generated detectable T-cell responses to a pool of SARS-CoV-2 spike and intracellular peptides as judged by interferon-γ, IL-2, or IL-17 production. Three of these patients had complete B cell aplasia and negative serology [64].

6. Summary and future directions

While the rapid development and deployment of SARS-CoV-2 vaccines have saved millions of lives globally, vaccine efficacy and safety in at-risk groups, particularly patients with hematologic malignancies and HCT recipients, are poorly defined due to the exclusion of these individuals from initial SARS-CoV-2 vaccine trials. Furthermore, the post-licensure vaccine effectiveness studies have lumped all immunocompromised individuals together. Safety and immunogenicity data on these special oncological and transplant populations are becoming incrementally available; however, studies are small and follow-up periods are short, which hampers identification of serious rare events, determination of vaccine-response durability, and assessment of protection from SARS-CoV-2 infection and disease.

Many of these studies include at least one mRNA vaccine (with the majority being BNT162b2), while a minority also include adenoviral vector vaccines ChAdOx1 and Ad26.COV2.S. In the US, BNT162b2 and mRNA-1273 are FDA approved, and Ad26.COV2.S carries FDA EUA. ChAdOx1 is not approved or authorized by the FDA in the US. SARS-CoV-2 vaccines appear to be generally well tolerated in these populations, with mild or moderate reactogenicity similar to that in healthy persons. Immune responses to vaccination are highly variable and may depend on the patient's underlying disease and therapy. Heterogeneous timing and methods of response measurement may also contribute to this variation. Therefore, large prospective studies powered to resolve differences in vaccine responses according to types of malignancy, transplant, and other therapy, as well as to determine optimal timing of vaccination in relation to HCT—accompanied by long-term follow-up for safety and durability—are required.

Furthermore, correlates of protection in these special populations may need to be separately defined since existing parameters are based on controlled clinical studies in immunocompetent individuals meeting stringent eligibility criteria [45,46] and may not accurately reflect predictors of vaccine protection in immunocompromised populations. At this time, the CDC recommendations for SARS-CoV-2 vaccination in immunocompromised individuals are 1) three doses of an mRNA vaccine (BNT162b2 or mRNA-1273) as primary series followed by two booster vaccines starting three months later or 2) single dose of Ad26.COV2.S followed by BNT162b2 or mRNA-1273 as primary series with two booster vaccine doses (mRNA vaccine or Ad26.COV2.S, although mRNA booster is preferred) beginning two months after primary series. Additional research on optimal timing of vaccination in relation to transplant and other therapies, as well as benefits of booster vaccines, is needed to define best practices for prevention of COVID-19 in the setting of hematologic malignancy and HCT.

6.1. Practice points

- Patients with hematologic malignancy and HCT recipients should be encouraged to receive SARS-CoV-2 vaccines. These vaccines are safe and likely provide some level of protection over no vaccination for many.
- Hematologic malignancy patients and HCT recipients who have received SARS-CoV-2 vaccines should continue to practice non-pharmacological infection mitigation strategies especially if they have active disease and/or are receiving immunosuppressive therapies.
- If time allows, vaccination should be offered to patients prior to chemotherapy or immunotherapy. However, vaccination during and shortly after chemotherapy, immunotherapy, or cellular therapy appears to be safe and should be considered especially if immunosuppression is likely to be prolonged, such as following anti-CD20 monoclonal therapy, despite possibly suboptimal serological response.
- Patients should be re-vaccinated following cellular therapies such as HCT and CAR-T cell therapy.
- Due to often suboptimal vaccine responses, healthcare workers and household and other close contacts of immunocompromised patients should be encouraged to receive SARS-CoV-2 vaccination and continue to practice non-pharmacological infection mitigation strategies such as masking, hand hygiene, and social distancing, especially when community rates of infection are high.
- Routine measurement of anti-spike antibody levels to determine vaccine responses is not recommended due to variability in test platforms and lack of data on interpretability of results in immunocompromised populations.

6.2. Research agenda

- Large scale studies powered to identify rare serious events and resolve differences in SARS-CoV-2 vaccine responses between vaccine types, malignancy, and HCT, as well as define optimal timing of vaccination in relation to time post-HCT, other cellular and immunosuppressive therapies, and chemotherapy cycles.
- Longer follow-up periods to assess vaccine-response durability and vaccine effectiveness in individuals with hematologic malignancies and HCT recipients.
- Immunogenicity, reactogenicity, and timing intervals of vaccine boosters in individuals with hematologic malignancies and HCT recipients.
- Large scale studies to characterize cellular immune responses following SARS-CoV-2 vaccination and vaccine effectiveness in individuals who do not mount a robust serological vaccine-induced immune response.
- Immune correlates of protection in individuals with hematologic malignancies and HCT recipients who may have altered serological responses due to disease or disease therapies.
- Vaccine effectiveness studies in this population are needed.

Authors' contributions

BN, NH, and AY conceptualized the idea for this review. BN performed literature review. BN and AY prepared the original draft. NH, LT, JC, DD, KD, AK, and CLK provided critical review, commentary, and revision of the draft. All authors reviewed the results and approved the final version of the manuscript.

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Declaration of Competing Interest

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