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COVID-19 vaccination in patients with multiple myeloma: a consensus of the European Myeloma Network

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Patients with multiple myeloma frequently present with substantial immune impairment and an increased risk for infections and infection-related mortality. The risk for infection with SARS-CoV-2 virus and resulting mortality is also increased, emphasising the importance of protecting patients by vaccination. Available data in patients with multiple myeloma suggest a suboptimal anti-SARS-CoV-2 immune response, meaning a proportion of patients are unprotected. Factors associated with poor response are uncontrolled disease, immunosuppression, concomitant therapy, more lines of therapy, and CD38 antibody-directed and B-cell maturation antigen-directed therapy. These facts suggest that monitoring the immune response to vaccination in patients with multiple myeloma might provide guidance for clinical management, such as administration of additional doses of the same or another vaccine, or even temporary treatment discontinuation, if possible. In those who do not exhibit a good response, prophylactic treatment with neutralising monoclonal antibody cocktails might be considered. In patients deficient of a SARS-CoV-2 immune response, adherence to measures for infection risk reduction is particularly recommended. This consensus was generated by members of the European Multiple Myeloma Network and some external experts. The panel members convened in virtual meetings and conducted an extensive literature research and evaluated recently published data and work presented at meetings, as well as findings from their own studies. The outcome of the discussions on establishing consensus recommendations for COVID-19 vaccination in patients with multiple myeloma was condensed into this Review.

Introduction

Patients with multiple myeloma have a substantially increased risk for bacterial and viral infection, and a two-fold increased risk for infection has been reported in patients with monoclonal gammopathy of unknown significance.[1,2] In a survey, 167 (52%) of 322 patients with multiple myeloma reported at least one infectious period in the year before starting anti-myeloma therapy and 133 (43%) of 314 patients reported at least one infectious period in the first 6 months after the start of anti-myeloma therapy.[3]

Multiple myeloma itself can lead to severe immunosuppression by impairing practically all immune effector mechanisms, including B cells, T cells, natural killer cells, dendritic cells, and the complement system, thereby increasing the risk for infections even before the start of multiple myeloma therapy. Most multiple myeloma drugs, including proteasome inhibitors, dexamethasone, high-dose melphalan, monoclonal anti-CD38 antibodies, bi-specific T-cell engagers, and cellular therapies (eg, chimeric antigen receptor T-cell therapy) result in specific and cumulative immune suppression. Immune impairment might be further aggravated by myeloma-related or treatment-associated organ dysfunction, comorbidities, and, frequently, by the immune senescence associated with older age,[4] as well as by T-cell exhaustion after long-standing therapy.[5]

Risk of SARS-CoV-2 infection and mortality in multiple myeloma

The first cluster of people with pneumonia with a novel coronavirus as suspected pathogen was reported in December, 2019.[6] Since this period, patients with multiple myeloma and other monoclonal gammopathies are at greater risk for SARS-CoV-2 infection, but precise data of the increase are not available as yet and depend on patient and treatment related factors as well as on the situation of the disease. Patients infected with SARS-CoV-2 more often have a prolonged course of infections and are at an increased risk of mortality.[7] The largest series reported by the International Myeloma Society included 650 hospitalised patients with plasma cell disorders (table 1). Their median age was 69 years and 617 (95%) of the 650 patients presented with multiple myeloma, with 331 (54%) of these 617 patients receiving first-line therapy.[7] Of those patients, 203 (33%) died, with substantial variability of mortality reported for individual countries, ranging from 27% to 57%. Risk factors for mortality were age, International Staging System stage 3 disease, high-risk cytogenetics, renal impairment, active or progressive disease, and one or more comorbidities. Importantly, specific therapies, such as autologous haematopoietic stem-cell transplantation (HSCT), or other treatments were not associated with adverse outcome. The Spanish Multiple Myeloma Cooperative group reported the outcome of 167 patients with multiple myeloma and COVID-19 disease (table 1).[8] In-hospital mortality of patients with multiple myeloma was higher (56 patients; 34%) compared with age-matched and sex-matched patients without cancer (38 patients; 23%). Independent risk factors for mortality were age, male sex, active or progressive disease, and renal impairment. A 2020 meta-analysis on outcome of patients with SARS-CoV-2

	Number of patients	Age median (range or IQR)	Median time from diagnosis	Mortality rate	Risk factors for mortality [OR (95% CI); p value]				
					Age	High-risk cytogenetics	Renal disease	Active disease or progressive disease	Comorbidities
Chari and colleagues[7]	617	69 years (34–92 years)	..	31·9%	1·04 (1·01–1·08; p=0·006)	2·35 (1·20–4·66; p=0·013)	2·71 (1·23–6·08; p=0·014)	1·91 (0·96–3·81; p=0·063)	0·88 (0·44–1·75; p=0·711)
Martinez-Lopez and colleagues[8]	167	71 years (62–78 years)	..	33·5%	3·0 (1·4–8·4; p=0·006)	4·6 (1·9–11·3; p<0·001)	4·6 (1·9–11·3; p<0·001)	2·7 (1·2–6·0; p=0·017)	1·7 (0·8–3·5; p=0·18)*
Wang and colleagues[9]	58	67 years (IQR 12·5 years)	30 months	24%	1·32 (0·29–5·47; p=0·744)	1·44 (0·33–6·03; p=0·747)	0·82 (0·12–3·97; p=1·000)	..	2·5 (0·55–15·93; p=0·220)*
Hultcrantz and colleagues[10]	100	68 years (41–91 years)	..	22%	1·8 (0·7–4·7; p=0·26)	..	..	..	2·2 (0·9–5·4; p=0·12)*
Cook and colleagues[11]	75	73 years (47–88 years)	28 months	Newly diagnosed multiple myeloma: 54·8%; relapsed or refractory multiple myeloma: 50%	..	..	..	..	..
Engelhardt and colleagues[12]	21	59 years (46–83 years)	20 months	0%	..	..	..	..	..

OR=odds ratio. *Hypertension.

Table 1: **Studies on outcome of mainly hospitalised patients with COVID-19 and multiple myeloma**

infection and haematological malignancies revealed a mortality rate of 33% (95% CI 25–41) in the subgroup of 412 patients with plasma cell disorders.[13] This study included mainly hospitalised patients reported by individual groups (table 1).[7,8,9–12] Generally, a higher risk of mortality was noted in the non-White patient population and in those aged 60 years or older.

SARS-CoV-2 vaccines

Presently, several vaccines are available in high-income countries and other vaccines are approved in other regions of the word; several additional vaccines will probably be approved soon (table 2). The vaccines aim for inducing immunity against the receptor-binding domain of the spike protein, or the full-length spike protein, nucleocapsid protein, or other viral epitopes. The vaccines using mRNA or DNA technology provide the genetic code for the respective peptide antigens and pack the genetic information either in lipid nanoparticles or liposomes (tozinameran [BNT162b2], elasomeran [mRNA-1273], and others), or use adenoviruses as vectors (ChAdOx1 nCoV-19, or Ad26.COV2-S, and others). Other vaccines use attenuated or inactivated SARS-CoV-2 virus (CoronaVac and BBIBP-CorV), or recombinant subunit protein (NVX-CoV2373 and ZF2001), or vesicular stomatitis virus (IIBR-100 and V590) or lentivirus (Covid-19/aAPC) as vector, or modified dendritic cells with lentivirus vectors (LV-SMENP-DC). The efficacy of the vaccines presently available in the high-income countries has been evaluated in randomised trials including 23 848–43 448 individuals. All the vaccines protect the majority of vaccinated people (72–95%) against mild-to-moderate COVID-19 disease, and even more (86–100%) are protected against severe COVID-19 disease and mortality. For almost all vaccines, two doses administered 3–12 weeks apart are recommended, although for the Ad26.COV2.S vaccine only one dose is required. Recently, a third dose (a second one for Ad26.COV2.S vaccine) has been recommended for patients with immunossupression by the Centers for Disease Control and Prevention.[22] WHO maintains a working document that provides updated information and includes most vaccines in development, which is available at the WHO website.

Immune response to vaccination against COVID-19 in the general population

Current information on the magnitude and type of the immune response required to protect against infection or severe disease is insufficient. Studies in rhesus macaques show that neutralising antibodies—and not $CD4^+$ and $CD8^+$ T-cell responses—correlate with median viral loads in bronchoalveolar lavage and nasal mucosa[23] and, in patients infected with COVID-19, receptor-binding domain antibodies were shown to correlate with neutralising antibodies as well as disease severity and predicted survival.[24] Studies in healthy controls showed substantial antibody responses to mRNA-1273[25] and ChAdOx1 nCoV-19,[26] and antibody and cellular immunity against BNT162b2.[27] IgG antibody responses occurred as early as 9–12 days after the first dose and peaked after the second dose in individuals who were COVID-19-naive, but antibody concentrations were significantly higher at all assessed time points in a sub-cohort of individuals with pre-existing immunity against SARS-CoV-2.[28] A recent study showed high antibody activity in healthy people against the spike protein receptor-binding domain, with nearly all enrolled individuals showing activity in the virus

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	Manufacturer	Vaccine type	Dosage	Overall efficacy	Current approvals*
mRNA-1273	Moderna (USA)	mRNA	Two doses 28 days apart	94·1% 14 days after second dose[14]	The USA, Europe, and the UK
BNT162b2	Pfizer–BioNTech (USA)	mRNA	Two doses 21 days apart	52% after one dose; 94·6% 7 days after the second dose[15]	The USA, Europe, and the UK
Ad26.COV2.S	Johnson & Johnson (USA)	Viral vector	One dose	Vaccine efficacy against COVID-19 is 66·1%; vaccine efficacy against severe COVID-19 is 85·4% (at 28 days)[16]	The USA and Europe
ChAdOx1 nCoV-19 (AZD1222)	Oxford–AstraZeneca (UK)	Viral vector	Two doses 28 days apart (intervals of >12 weeks studied)	Overall vaccine efficacy is 70·4% at 14 days or more after second dose[17]	WHO and COVAX, the UK, Europe, the USA, India, and Mexico
NVX-CoV2373	Novavax (USA)	Protein subunit	Two doses	89·7% in the UK after two doses[18]	Emergency use authorisation* application planned
Gam-COVID-Vac (Sputnik V)	Gamaleya National Research Center for Epidemiology and Microbiology (Russia)	Viral vector	Two doses (first, rAd26; second, rAd5) 21 days apart	91·6% at 21 days after first dose (day of dose two)[19]	Russia, Belarus, Argentina, Serbia, UAE, Algeria, Palestine, and Egypt
CoronaVac	Sinovac Biontech (China)	Inactivated virus	Two doses 14 days apart	83·5% at 14 days or more after dose two[20]	China, Brazil, Columbia, Bolivia, Chile, Uruguay, Turkey, Indonesia, and Azerbaijan
BBIBP-CorV	Sinopharm 1/2 (China)	Inactivated virus	Two doses 21 days apart	78·1% or more after dose two[21]	China, UAE, Bahrain, Serbia, Peru, and Zimbabwe

UAE=United Arab Emirates. *As of May 31, 2021.

Table 2: **Vaccines approved in the high-income countries and selected vaccines of global relevance**

neutralisation assay and in the more sensitive live-virus focus reduction neutralisation mNEeonGreen test.[29] Antibody concentrations were age dependent (with the highest concentrations reported in the cohort aged 18–55 years and the lowest concentrations reported in those aged 71 years or older) and persisted with a notable decline over 6 months after the second dose of the mRNA-1237 vaccine. Antibodies induced by BNT126b2 in healthy individuals protect against variants with the D614G substitution and the alpha (B.1.1.7) variant, whereas the neutralisation of the beta (B.1.351) variant is five-fold reduced.[30] Individuals vaccinated with either BNT126b2 or ChAdOx1 nCoV-19 showed three-fold to five-fold lower neutralisation titres against the delta variant (B.1.617.2) compared with the alpha variant.[31] A study showed vaccine effectiveness was 93·7% and 88·0% for the alpha and delta variant with the BNT126b2 vaccine and 74·5% and 67·0% with ChAdOx1 nCoV-19.[32] Despite this reduction in effectiveness, vaccinated individuals seemed to be largely protected against severe disease and hospitalisation.

Interesting data have also been reported on the cellular immune response. The BTN161b2 vaccine has been shown to induce a de novo S1-specific and S2-specific response in $CD4^+$ cells and $CD8^+$ T cells with reactivity against eight spike epitopes, with most of them being conserved on the mutant strains.[27] A preprint[33] has reported robust T-cell responses to the wild-type spike and nucleocapsid proteins in healthy individuals vaccinated with either BNT162b2 or mRNA-1273. This study also reported detectable, but diminished, T-cell responses to spike variants (alpha, beta, and B.1.1.248).

Immune response to non-SARS-CoV-2 vaccines in patients with multiple myeloma

Previous studies showed reduced antibody responses against several vaccines (eg, pneumococci, staphylococcal alpha toxin, tetanus, diphtheria toxoids, influenza, and other vaccines) in patients with multiple myeloma and significantly lower antibody concentrations were also observed in patients with monoclonal gammopathy of unknown significance.[34] The reduced vaccination response is a consequence of the myeloma-induced and treatment-induced immune suppression, but is also affected by comorbidities and older age. Older age has been shown to be associated with impaired ability to mount a strong vaccine response because of reduced $CD8^+$ T-cell effector responses, reduced $CD4^+$ T-cell functionally, and poor memory cell maintenance.[35]

Immune response to SARS-CoV-2 infection and to vaccines in patients with multiple myeloma

Terpos and colleagues[36] studied the neutralising antibody response 22 days after the first dose of the BNT162b2 vaccine in 48 older (median age 83 years) patients with multiple myeloma versus a control group of similar age. Of the 48 patients, 35 (73%) were receiving anti-multiple myeloma therapy, four (8·3%) were in remission without any therapy, and nine (18·8%) had smouldering multiple myeloma. Patients had significantly lower neutralising antibody titres compared with the control group (20·6% *vs* 32·5%; p<0·01) and neutralising antibody titres above 30% (positivity cutoff) were noted in only 12 (25%) of 48 patients with multiple myeloma compared with 57 (55%) of 104 controls. A clinically relevant virus

inhibition was observed in 4 (8%) of the 48 patients with multiple myeloma and 21 (20%) of the 104 individuals in the control group. All four patients with clinically relevant neutralising antibodies were in remission (three with a very good partial response, and one with a partial response) without any anti-multiple myeloma therapy and all of them had normal concentrations of uninvolved immunoglobulins. Similarly, only one of the nine patients with smouldering multiple myeloma had neutralising antibody titres above 30%. The patient with a positive response had normal concentrations of uninvolved immunoglobulins, whereas all eight non-responders had immunoparesis. In a follow-up study,[37] the authors noted neutralising antibody titres of 50% or more only in 158 (57%) of the 276 patients with plasma cell neoplasms (213 with symptomatic multiple myeloma, 38 with smouldering multiple myeloma, and 25 with monoclonal gammopathy of unknown significance) with a median age of 74 years versus 183 (81%) of 226 controls matched for age and sex (p<0·001) on day 50 after vaccination with BNT162b2 or 7 weeks after the first dose of ChAdOx1 nCoV-19. Only 114 (54%) of 213 patients with multiple myeloma and 23 (61%) of 38 patients with smouldering multiple myeloma had clinically relevant antibody concentrations (p=0·013). Patients with monoclonal gammopathy of unknown significance had a similar frequency of high antibody concentrations (84%) to individuals in the control group. When antibody concentrations were already assessed on day 20 after the first vaccination, a lower positivity rate was noted but with a similar ratio of response rates between patients with multiple myeloma, smouldering multiple myeloma, and monoclonal gammopathy of unknown significance. Antibody responses did not differ on day 22 between patients immunised with either one of the vaccines. Univariate analysis showed a higher risk for inadequate antibody response in patients with multiple myeloma, smouldering multiple myeloma, lymphopenia, low non-clonal IgA concentrations, and therapy with belantamab mafodotin and with anti-CD38-based therapies, whereas in female individuals, a lower risk was noted.

A UK group studied IgG anti-spike protein antibodies in 93 patients with multiple myeloma (median age 65 years [range 47–87 years] in antibody-positive group and median age 70 years [47–87 years] in antibody-negative group) after one dose of either BNT162b2 or ChAdOx1 nCoV-19.[38] After a median follow up of 33 days (range 21–61 days), antibodies were reported in 52 (56% [95% CI 46–66]) of the 93 patients, with no significant difference between both vaccines. Seven (8%) of the 93 patients already had pre-existing antibodies before vaccination due to previous PCR-proven or highly suspected clinical COVID-19 infection. Excluding these patients would still amount to a positive result in 45 (52%) of 86 patients. Factors associated with an antibody response were depth of response to multiple myeloma therapy (complete response or very good partial response), no immunoparesis at the time of vaccination, and fewer previous lines of therapy. Having treatment was associated with a lower response, but no specific therapy was associated with low response rates compared with other treatments. Nine (82%) of the 11 patients vaccinated within 12 months of autologous HSCT had tested positive for SARS-CoV-2 IgG antibodies. The authors then did a total antibody assay (which also measures IgM and IgA antibody response) in 40 IgG non-responders and observed a positive result in 13 (33%) of the 40 patients without detectable IgG antibodies. The authors also put their findings into perspective by comparing them with results of their hospital staff, which revealed a positive response in 175 (99%) of 177 tested individuals. A study from Italy reported a significantly reduced IgG response to spike protein subunits S1 and S2 in 42 patients with multiple myeloma (median age 73 years; range 47–78 years) receiving concomitant multiple myeloma therapy after the first and second dose of the BNT162b2 vaccine versus controls.[39] The geometric mean concentration of antibodies in patients with multiple myeloma was 7·5 AU/mL 3 weeks after the first dose and 106·7 AU/mL 2 weeks after the second dose, compared with 17·1 AU/mL (p<0·001) and 353·3 AU/mL (p=0·003), respectively, in an older control population (median age 81 years; range 79–87 years).[39] The authors defined a cutoff of 15 AU/mL as a positive response. According to this definition, the proportion of responders increased from 9 (21%) of the 42 individuals from week 3 after the first dose to 33 (79%) of the 42 individuals 2 weeks after the second dose in the multiple myeloma cohort, compared with 19 (53%) of the 36 individuals and all 36 (100%) of the individuals, respectively, in the control population (p<0·001). A univariate analysis of factors associated with response showed poor antibody response in patients receiving single-agent daratumumab or combination therapy which was not noted patients with proteasome inhibitor or immunomodulatory drug-based treatment, or with combinations thereof.

Researchers from New York, USA, reported highly variable SARS-CoV-2 IgG antibody concentrations in 320 patients with multiple myeloma vaccinated with either BNT162b2 or mRNA-1273, with antibody concentrations varying between 5 AU/mL and 7882 AU/mL, but their median concentration (149 AU/mL) was significantly lower compared with the value obtained in a small control cohort of 67 health-care workers (median 300 AU/mL, range 21–3335 AU/mL; p<0·0001, Mann-Whitney U test).[40] Patients with previous COVID-19 infection before full vaccination had ten times higher antibody concentrations compared with patients who were COVID-19-naive. Repeated antibody measurements from baseline to 60 days after full vaccination showed delayed suboptimal responses, and 41 (15·8%) of 260 patients with multiple myeloma did

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For more on **updates and vaccine development** see https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines

not mount detectable IgG anti-SARS-CoV-2 antibodies. Patients receiving active multiple myeloma treatment had significantly lower antibody concentrations, as well as those with more than three previous lines of therapy, grade 3 lymphopenia, and those receiving anti-CD38 therapy or B-cell maturation antigen-targeted therapy (70 AU/mL on active therapy *vs* 183 AU/mL without active therapy; p=0.004, Mann-Whitney U test). Another study from Italy assessed the IgG anti-SARS-CoV-2 response in patients with haematological malignancies, including 44 patients with multiple myeloma. Of these, 33 (75%) mounted an antibody response.[41] On the basis of the findings of the two studies,[40,41] the authors underscored the need for routine serological screening to assess responses to vaccination in patients with haematological malignancies, including multiple myeloma.

Clearance of SARS-CoV-2 virus and risk of reinfections

Prolonged COVID-19 disease and SARS-CoV-2 virus shedding has also been observed in patients with multiple myeloma (Terpos E, unpublished), which provides an optimal milieu for the evolution of virus mutations in an immunosuppressed host. Even in otherwise healthy people, SARS-CoV-2 virus can persist for some time, as has been shown in a recent study, which reported persistence of viral RNA 3 months after resolution of symptoms in five (5%) of 93 study participants.[42] All five individuals had similar antibody concentrations to the PCR-negative group, but had increased $CD8^+$ T-cell responses. Patients with multiple myeloma and vaccine-induced or previous SARS-CoV-2 infection-induced immunity might lose immune protection due to progression or reoccurrence of active disease or specific anti-multiple myeloma therapies, and might again become particularly vulnerable to SARS-CoV-2 reinfection.

Current effectiveness of vaccines against the different SARS-CoV-2 variants

All presently available mRNA, vector-based, or protein subunit vaccines show high activity against severe symptomatic infection by the original viral strain and reduce mortality by more than 95%. Mutations of the 30 000-base RNA genome of the SARS-CoV-2 virus occur at a rate of around two single letter mutations per month, which is roughly half as fast the rate of influenza, and a quarter of the rate of HIV.[43] Most of the SARS-CoV-2 mutations are harmless, and might even weaken the virus, but some of them give the virus an advantage over the other versions. Several variants of concern or of interest have been identified (table 3). All of these variants carry mutations in the receptor-binding domain that enhance their receptor binding affinity, leading to higher transmissibility. The delta variant has rapidly become the most dominant out of all of the existing variants, including the alpha variant, which was predominant before. The delta variant harbours mutations within the N-terminal domain of the receptor-binding domain of the spike protein,[31] which renders the variant 60% more transmissible than the original virus, and triggers surges in cases and deaths around the world. In-vitro studies showed that, compared with the alpha variant, a three-fold reduction of the neutralising activity against the delta variant and a 16-fold reduction against the beta variant occurred after two doses of the BNT126b2 vaccine.[31] Similarly, after two doses of ChAdOx1 nCoV-19, a six-fold reduction in neutralising activity against the delta variant and a nine-fold reduction in neutralising activity against the beta variant was noted compared with the alpha variant;[31] findings, which accord with another study showing lower neutralisation activity against the delta variant after vaccination with mRNA-1237 or with BNT126b2,[46] and a recent study in the UK showed slightly reduced effectiveness of the BNT126b2 and ChAdOx1 nCoV-19 vaccine against the delta variant.[32] Vaccination-induced and convalescent sera exert only minimally lower neutralisation activity against the alpha variant compared with the original variant, but alpha variants that acquire an E484K mutation showed a six-fold decreased sensitivity to immune sera from individuals vaccinated with BNT126b2.[47] Reports associate the delta variant with higher transmissibility, virulence, and greater disease severity and case fatality rates.[48] Substantially increased transmissibility, a three-fold reduction in binding, and a 3·5-fold reduction in neutralising antibodies has also been reported for the beta variant in individuals vaccinated with the mRNA-1273 vaccine.[49] The vaccine still provided protection against any documented infection, with an effectiveness of 75·0% and of 97·4% against severe disease.[50] Low concentrations of neutralising antibodies (against live virus and pseudovirus; for example, a chimeric vesicular stomatitis virus that expresses the SARS-CoV-2 spike protein) of the beta variant have been reported in young (aged 30 years; range 24–40 years) South African participants who were HIV-negative and vaccinated with the ChAdOx1 nCoV-19 vaccine. Notably, vaccine efficacy regarding mild-to-moderate disease against this variant was only 10·8%. Severe cases were not observed in the placebo or in the vaccinated group.[51] Recent results with the Ad26.COV2.S vaccine showed five-fold and 3·3-fold reduced neutralising antibody titres against the alpha variant and gamma variant, respectively, but functional non-neutralising antibodies and T-cell responses were largely preserved.[52] The protein-based NVX-CoV2373 vaccine showed 86% efficacy against the alpha variant, but only 60% against the beta variant.[53,54] For the gamma variant, a 4·8-fold reduction in neutralisation activity for people vaccinated with the mRNA-1273 vaccine, and 3·8-fold reduction for the BNT126b2 vaccine were shown.[55] Despite the reduction

	First detection, Country	Notable mutations	Evidence of clinical changes			Protected by
			Transmissibility	Virulence	Antigenicity	
Alpha (B.1.1.7*)	September, 2020, UK	N501Y, 69–70del, P681H, and some also acquire E484K	Increased by approximately 74% (NERVTAG)	61% (42–82%) more lethal[44]	Reduced antigenic activity (ECDC); in the 484K variants: six-fold decrease of immune sera (mRNA vaccines) and 11-fold decrease in sensitivity to convalescent sera	BNT162b2 (Pfizer–BioNTech), mRNA-1273 (Moderna), ChAdOx1 nCoV-19 (Oxford–AstraZeneca), and NVX-CoV2373 (Novavax)
Beta (B.1.351†)	December, 2020, South Africa	N501Y, K417N, and E484K	Increased 50% (ECDC)	No evidence of increased virulence	Reduced neutralisation by antibodies (ECDC)	BNT162b2 (Pfizer–BioNTech) and mRNA-1273 (Moderna) might be two-thirds less effective (serum neutralising antibodies); ChAdOx1 nCoV-19 (Oxford–AstraZeneca) is effective only in 10% of cases; Ad26COV2.S (Janssen) has 89% efficacy; and NVX-CoV2373 (Novavax) has 60% efficacy
Gamma (P.1†)	January, 2021, Brazil and Japan	N501Y, E484K, and K417T	Likely increased (CDC)	10–80% (approximately 45%) more lethal (CADDE)	Overall reduction in effective neutralisation (ECDC)	Possible reduction of vaccine efficacy (ECDC)
Eta (B.1.525*)	December, 2020, Nigeria and the UK	E484K and F888L	Likely increased (CDC)	Likely increased (CDC)	Modestly reduced neutralisation (COG-UK)	No data available yet
Epsilon (B.1.427*; B.1.429*)	May, 2020, USA; July, 2020, USA	L452R, D614G* plus S131, W152C	Around 20% increased (CDC)	Increased (CDC)	4·0–6·7-fold and two-fold decrease in neutralisation titres from convalescent patients and vaccine recipients (CDC); CoronaVac equally effective[45]	No data available yet
Iota (B.1.526*; B.1.526.1*)	November, 2020, USA	E484K,[‡] D614G, A701, L5F,[‡] T95I, D253, S477N,[‡] D80G, Δ144, F157S, L452R, D614G, and D950H	Likely increased (CDC)	Increased (CDC)	Reduced neutralisation by convalescent and post-vaccination sera, reduced susceptibility to monoclonal antibody cocktail of bamlanivimab and etesevimab	No data available yet
Kappa B.1.617.1*	October, 2020, India	E484Q, L452R, and P681R	Higher transmissibility	Under investigation	Reduction in effective neutralisation	No major impairment of efficacy of vaccines used in India reported
Delta B.1.617.2†	October, 2020, India	T478K, L452R, and P681R	Under investigation	Under investigation	Reduction in effective neutralisation	No major impairment of efficacy of vaccines used in India reported

CADDE=Centre for adenovirus, discovery, detection, genomics & epidemiology. CDC=Center for Disease Control and Prevention. COG-UK=COVID-19 Genomics UK Consortium. ECDC=European Center for Disease Prevention and Control. NERVTAG=New and Emerging Respiratory Virus Threats Advisory Group. *Variants of interest. †Variants of concern.

Table 3: **Virus mutations of concern and of recent interest**

in neutralising activity of vaccine-induced antibodies, the sera were still able to neutralise the kappa (B.1.617.1) variant, suggesting that those vaccines provide sufficient protective immunity. Additionally, all SARS-CoV-2 vaccines tested so far also induce non-neutralising antibody-dependent cytotoxicity and spike-specific $CD4^+$ and $CD8^+$ T cells, which also serve as immune effectors,[56] supporting their clinical effectiveness even against the newer, more transmissible variants.

Options for patients with poor antibody response

Patients with no or suboptimal immune responses might require additional doses of the same vaccine or a different vaccine, a strategy supported by the UK Joint Committee On Vaccination.[57] Preliminary data suggest high immunogenicity of an a priori heterologous prime-boost vaccination.[58] Whether other approaches, such as the use of other vaccines (eg, adjuvanted[59] or self-replicating RNA vaccines[60]), will lead to the desired increase in SARS-CoV-2 specific humoral and cellular immunity remains unclear. Some manufacturers are adapting their mRNA vaccines to better match the variants of concern, particularly the delta variant. Other vaccines of interest include those which use specific virus proteins, inactivated whole virus, adjuvanted vaccines, or self-amplifying mRNA vaccines that enable the production of more antigen. Different modes of vaccine administration (eg, oral or intranasal) should facilitate more frequent dosing and induce secretory IgA antibody responses. However, it remains unclear whether these options will elicit the desired protection in patients with a poor response due to disease-inherent immune deficiency or immune suppressive therapy. Immunsuppression induced by myeloma can only be improved by effective anti-myeloma therapy inducing a deep response. Immunsuppression due to anti-myeloma therapy can only be overcome by discontinuation of this therapy and, in particular, discontinuation of prolonged anti-CD38 therapy. Daratumumab therapy reduces polyclonal plasma cells and concentrations of polyclonal immunoglobulins of almost all isotypes,[61] and

daratumumab maintenance therapy has been associated with an increased risk of COVID-19 infection.[62] Hence, discontinuing anti-CD38 antibody therapy might increase the chance of a vaccine-induced anti-SARS-CoV-2 response. However, this consideration probably applies to similar immunosuppressive treatments, such as bi-specific T-cell engagers, antibody–drug conjugates, chimeric antigen receptor T-cell therapy, aggressive combination therapies, and others. By contrast, lenalidomide maintenance therapy, should not decrease the response to SARS-CoV-2 vaccination because it has been shown to enhance T-cell immunity and the response to a pneumococcal seven-valent conjugate vaccine[63] and to a hepatitis C DNA vaccine.[64] Nevertheless, the most promising approach is probably the vaccination of patients after a deep sustained response to multiple myeloma therapy during a treatment-free period.

For more on the **trials** see https://clinicaltrials.gov/ct2/results?cond=Covid19&\term=antivirals&cntry=&state=&city=&dist=

For patients not vaccinated and for those with no or insufficient response to vaccination against COVID-19, long-term prophylaxis with monoclonal antibodies with specificity against spike proteins might be a valuable option, particularly after exposure to an infected individual and during phases of uncontrolled disease and need for aggressive therapy.[65] One infusion of the neutralising monoclonal anti-SARS-CoV-2 antibody bamlanivimab reduced the incidence of COVID-19 infection by 57%, from 15·2% to 8·5%, and completely prevented mortality in 483 residents and staff in skilled nursing and assisted-living facilities compared with 482 individuals receiving placebo only.[66] A recent trial aiming to prevent COVID-19 disease after exposure to a person with SARS-CoV-2 infection with subcutaneous administration of 1200 mg of REGEN-COV, a cockatil consisting of two monoclonal antibodies against the spike protein (casirivimab and imdevimab) revealed significant efficacy.[67] Symptomatic infection developed in only 11 (2%) of 753 participants of the active treatment, but in 59 (8%) of the 752 participants of the placebo group. This treatment has already received emergence use authorisation by the US Food and Drug Administration (FDA) and European Medicines Agency (EMA). This antibody cocktail also significantly reduced hospitalisation or death in 2696 COVID-19-infected outpatients by 71·3% ($p<0·001$).[68] Only eight (1·3%) of 1355 of the study participants receiving the experimental therapy were admitted as inpatients or died, compared with 62 (4·6%) of 1341 of those randomly assigned to the placebo group. Furthermore, this monoclonal antibody cocktail resolved symptoms and reduced SARS-CoV-2 viral load more rapidly than placebo. Another monoclonal antibody cocktail consisting of bamlanivimab plus etesevimab has received emergency use authorisation by the US FDA for post-exposure prophylaxis for individuals who are at high risk of acquiring SARS-CoV-2 infection and for treatment of patients with mild-to-moderate COVID-19 infection and at high risk of progressing to severe disease.[69]

Convalescent plasma or plasma products could be another option for post-exposure or general prophylaxis. This treatment prevented severe COVID-19 disease in older adults (median age 76·4±8·7 years) with mild COVID-19 symptoms[70] and led to rapid SARS-CoV-2 clearance in SARS-CoV-2-infected patients who were immunocompromised and receiving anti-CD20 therapy.[71] However, in patients with severe COVID-19 disease, no benefit could be shown.[72] Apart from these options, the search for active treatments against COVID-19 infections has gained substantial momentum; more than 560 trials with investigational anti-COVID-19 drugs are currently listed on Clinical Trials.gov.

Vaccine hesitancy

The poor compliance with recommendations for vaccination with COVID-19 vaccines is a major challenge for society given that a vaccination acceptance of greater than 80% seems to be required for herd immunity. A large survey identified low knowledge, low income, and negative attitudes of social contacts, safety concerns, and religious beliefs, as hurdles for their willingness to get vaccinated.[73] By contrast, confidence in the importance of vaccines rather than in their safety or effectiveness was shown to be the strongest determinant for vaccine uptake in a large retrospective analysis.[74] A survey in Canadian school teachers showed that those with an educational background in science or engineering, a higher general knowledge of vaccines, and belief that COVID-19 was a serious illness, were more likely to intend to receive a COVID-19 vaccine.[75] We noted a high willingness of patients with multiple myeloma (279 [83%] of 335 patients) to receive COVID-19 vaccines, which is higher compared with the general population, possibly due to greater awareness that these patients probably have about the risks of SARS-CoV-2 infection,[3] more frequent contact with health-care personnel, and greater interest in medical developments.

Safety

Table 4 shows the side-effects listed in the Summary of Product Characteristics of the vaccines approved by the EMA and US FDA for emergency use; with the exception of the BINT162b2 vaccine (Comirnaty, Pfizer-BioNTech), which is fully approved by the US FDA. Side-effects after vaccination are reported by approximately two-thirds of vaccinated individuals. Most of the side-effects are observed with all common vaccines. Localised injection-site symptoms, such as pain, swelling, and erythema, occur within 24–48 h after vaccination and resolve spontaneously within days after vaccination.[28,76] Other common side-effects are muscle pain, fever, and joint pain. Vaccine recipients with pre-existing immunity have a higher frequency of common side-effects than those without pre-existing immunity—an observation that also applies to individuals who receive their second vaccine dose,[77] with the exception of ChAdOx1 nCoV-19 vaccine,

	BNT162b2 (Pfizer-BioNTech)	mRNA-1273 (Moderna)	ChAdOx1 nCoV-19 (Oxford–AstraZeneca)	Ad26COV2.S (Janssen)
Very common (more than 1 in 10)	Injection site pain and swelling, tiredness, headache, muscle pain, joint pain, chills, fever	Swelling in the underarm, headache, nausea vomiting, muscle ache, joint aches, and stiffness, injection site pain or swelling, feeling very tired, chills, fever	Injection site tenderness, pain, warmth, itching, or bruising, feeling tired (fatigue) or generally feeling unwell, chills or feeling feverish, headache, feeling sick (nausea), joint pain or muscle ache	Headache, nausea, muscle aches, injection site pain, feeling very tired
Common (up to 1 in 10)	Injection site redness, nausea	Rash, rash, redness, or hives at the injection site	Injection site swelling or redness, fever (>38°C), being sick (vomiting) or diarrhea	Injection site redness and swelling, chills, joint pain, cough, fever
Uncommon (up to 1 in 100)	Enlarged lymph nodes, feeling unwell, pain in limb, insomnia, injection site itching	Injection site itchiness	Sleepiness or feeling dizzy, decreased appetite, enlarged lymph nodes, excessive sweating, itchy skin, or rash	Rash, muscle weakness, arm or leg pain, feeling weak, feeling generally unwell, sneezing, sore throat, back pain, tremor, excessive sweating
Rare (up to 1 in 1000)	Temporary one-sided facial drooping (Bell's palsy)	Temporary one-sided facial drooping (Bell's palsy)	..	Allergic reaction, hives
Very rare (up to 1 in 10 000)	..	..	Blood clots often in unusual locations (eg, brain, liver, bowel, spleen) in combination with low concentrations of blood platelets	Blood clots often in unusual locations (eg, brain, liver, bowel, spleen) in combination with low concentrations of blood platelets
Not known	Severe allergic reaction	Severe allergic reactions (anaphylaxis), hypersensitivity	Severe allergic reactions (anaphylaxis), hypersensitivity	Severe allergic reaction

Table 4: **Adverse events and frequency thereof as listed in the Summary of Product Characteristics by the US Food and Drug Administration and the European Medicines Agency for the different COVID-19 vaccines**

which is typically better tolerated after the second administration.[78] Headaches and fatigue seem to be more common in women than in men, and more common in individuals younger than 55 years.[77] In a few patients, delayed localised cutaneous reactions have been reported 2–12 days after receiving the mRNA-1273 vaccine.[79] These reactions were described as pruritic, painful, and oedematous pink plaques. Skin biopsy showed a mild predominantly perivascular mixed infiltrate with lymphocytes and eosinophils, consistent with a dermal hypersensitivity reaction. After the second dose, a similar localised injection-site reaction developed, often sooner than with the first-dose reaction.

Severe allergic reactions have been reported with a frequency of 1:100 000 for the BNT162b2 vaccine, which is higher than the rate reported for non-COVID-19 vaccines (1:1 000 000).[76] The allergenic component is most likely the polyethylenglycol excipient, which is also used in the mRNA-1273 and the NVX-CoV2373 vaccines. In the ChAdOx1 nCoV-19 and Ad26.COV2.S vaccines, polysorbate 80 is used for embedding the viral vector, and could elicit allergic reactions in individuals sensitive to these compounds. Polysorbate 80 and polyethylenglycol are structurally related, and skin testing has shown cross-reactive hypersensitivity.[80] Anaphylactic reactions occur within a few minutes after injection and usually respond well to epinephrine injection. The US and European contraindications for BNT126b2 and mRNA-1273 vaccines differ in respect to the intensity of previous allergic episodes. In the USA, an anaphylactic reaction to a dose of one of the vaccines is considered as contraindication for a further dose; however, in Europe, a severe allergic reaction is considered as contraindication for a further dose. A similar discrepancy concerns the ChAdOx1 nCoV-19 vaccine. In the USA, patients with known hypersensitivity should not be re-exposed to this vaccine, whereas in Europe individuals allergic to the vaccine or any ingredient should not be re-exposed to the vaccine. Both adenovirus-vectored vaccines (ChAdOx1 nCoV-19 and Ad26.COV2.S) confer a potential risk of an unusual form of thrombotic complications manifesting predominantly as cerebral venous sinus thrombosis, but also in the form of splanchnic, portal vein, and hepatic vein thrombosis. High concentrations of D-dimers and low concentrations of fibrinogen are common, and suggest the activation of coagulation.[81] The occurrence of this vaccine-induced thrombotic thrombocytopenia (VITT) syndrome has initially been noted predominantly in women, but recent reports show no sex preponderance. Most affected people are younger than 60 years, but this syndrome has also been diagnosed in older patients. The underlying mechanisms have been delineated to the induction of autoantibodies against platelet factor 4 causing thrombotic thrombocythemia.[82] This syndrome has been termed vaccine-induced thrombotic thrombocytopenia, and its pathogenesis is not entirely clear. One theory includes the possibility that components of the vaccine bind to platelet factor 4 and generate a neoantigen, which induces an immune response. The antibody formation might be stimulated by inflammatory signals. A few days later, antibodies against platelet factor 4 arise, leading to activation of platelets and other cell types and, finally, to thrombosis often in atypical sites. In case this complication is suspected, testing for antibodies against platelet factor 4 should be ordered, and treatment with a non-heparin anticoagulant, high-dose glucocorticoids, and high-dose intravenous immunoglobulins should be initiated.[83] In June, 2021, new safety information was published by the EMA and by the Centers for Disease Control and Prevention: myocarditis and pericarditis has been observed after vaccination with BTN126b2 and also after administration of the mRNA-1273 vaccine. This side-effect

***Panel*: Summary of recommendations from the European Myeloma Network for vaccination against SARS-CoV-2**

The European Myeloma Network recommends that all patients with monoclonal gammopathy of unknown significance, smouldering multiple myeloma, multiple myeloma, and monoclonal gammopathies of clinical significance should be vaccinated with a COVID vaccine

Patients should be vaccinated preferably

- Before onset of active multiple myeloma
- During well controlled disease at times of minimal residual disease negativity, complete response, or very good partial response
- Before start of therapy, before stem-cell collection, and more than 3 months after autologous haematopoietic stem-cell transplantation
- During periods without therapy (exception: lenalidomide maintenance therapy)
- Vaccination might be considered on individual judgment in patients with poorly controlled disease or ongoing therapy, but induction of protective immune response is less likely
- Patients with previously confirmed COVID-19 infection should be vaccinated as well (one dose might be sufficient)

Consider risk factors for poor response

- Uncontrolled disease
- Immunoparesis
- Number of previous lines of therapy
- Age, certain treatments (eg, anti-CD38 antibodies and B cell maturation antigen-targeted therapy, including bi-specific T-cell engagers and chimeric antigen receptor T-cell therapy)

Routine evaluation of the immune response to vaccination is not supported by the Centers for Disease Control and Prevention and other organisations but allows identification of patients without any or with low anti-SARS-CoV-2 immune response

In case of immune impairment

- Administer a third vaccine dose
- Insufficiently protected patients should comply with principles for infection risk reduction
- Those patients will depend on herd immunity and will benefit from so-called ring vaccination of partners and close social contacts
- Administration of protective monoclonal antibodies might be considered in immunosuppressed patients who contract or have been exposed to COVID-19
- Health-care personnel caring for patients with multiple myeloma and household members should be vaccinated

For more on **pharmacovigilance** see https://bit.ly/30KmNJ7

For the **US Food and Drug Administration's Adverse Event Reporting System (FAERS) Public Dashboard** see https://open.fda.gov/data/faers/

is primarily observed in young male adults. Another recently reported adverse event is Guillain-Barre syndrome, which has been associated with the ChAdOx1 nCoV-19 and the BNT162b2 vaccine.[84,85] Furthermore, patients with previous capillary leak syndrome should not be vaccinated with Ad26.COV2.S.[86] An update of the incidence and possible management recommendations can be found on the pharmacovigilance pages of the EMA (EudraVigilance) website, and on the US FDA's Adverse Event Reporting System (FAERS) Public Dashboard.

Recommendations for clinical practice

All patients with monoclonal gammopathy of unknown significance, smouldering multiple myeloma, multiple myeloma, and monoclonal gammopathies of clinical significance should be vaccinated with a COVID-19 vaccine, and this recommendation applies to their family members as well. Whenever possible, patients should be vaccinated during phases of well controlled disease and without concomitant anti-myeloma therapy. The International Myeloma Society[87] recommends to vaccinate patients scheduled for stem-cell preparation shortly before the procedure and to vaccinate patients after autologous HSCT after a recovery period of 3 months or more (panel). Limited data show suboptimal or no response in patients with poorly controlled multiple myeloma with or without concomitant anti-myeloma therapy. Nevertheless, vaccination should be considered in those patients on the basis of individual judgement, but stimulation of a protective immune response is less likely. Protective antibody responses are less likely in older patients, in those with uncontrolled disease, lymphopenia, immunoparesis, and in those with more than one previous treatment line. Furthermore, specific multiple myeloma treatments, such as autologous HSCT, anti-CD-38 antibodies, anti-B cell maturation antigen therapies (including bi-specific T-cell engagers and chimeric antigen receptor T-cell therapy) impair immune reactivity, and often contribute to low vaccination response. Evaluation of the humoral and cellular immune response obtained after vaccination is presently not recommended by the Centers for Disease Control and Prevention[45] and several other organisations, but might be helpful for identifying patients with immunosuppression in order to recommend a third vaccine dose, as recently approved by the US FDA.[88] The main concern of these organisations is the absence of a generally accepted validated test system, and scarce data on the threshold of antibody titres that confer protection from infection or disease. Also, there is little information on the interplay between humoral and cellular immune responses and their role in protection. With the new approval of an additional (third) vaccine dose for patients who are immunosuppressed, the question arises how to define immunosuppression? Thus, clinicians are faced with a dilemma, which in clinical practice will cause them to assess the immune response to vaccination for patient selection for an additional dose, even in full knowledge that they are basing their decision on a still imperfect methodology. In patients who contract or have been exposed to COVID-19, administration of protective neutralising monoclonal antibodies might be considered, and one preparation consisting of casirivimab–imdevimab (REGEN-COV [Regeneron; Tarrytown, NY, USA] or Ronaprever [Roche; Basel, Switzerland]) has already been approved in many countries for exposure prophylaxis for patients with high risk for severe COVID-19, hospitalisation, and mortality.[89] Another monoclonal antibody cocktail consisting of bamlanivimab and etesevimab has received emergency authorisation in the USA for the same indication.[90] Convalescent plasma

Search strategy and selection criteria

A panel of 36 experts in multiple myeloma and malignant haematological diseases from 14 European countries was invited to participate to establish consensus recommendations for COVID-19 vaccination in patients with multiple myeloma. Some of the panel members are also experts in infection in patients with haematological diseases and almost all of them are members of the European Myeloma Network (EMN). The panel members convened three times during virtual meetings of the EMN between April and June, 2021, and evaluated and discussed the rapidly emerging data, which were obtained by a comprehensive literature research. We searched the electronic databases of PubMed, EMBASE, the Cochrane Library, and UpToDate. Searches were restricted to publications in English that were published from Dec 1, 2019, when the first cluster of people with pneumonia in Wuhan with a novel coronavirus as the suspected pathogen was reported,[6] until Aug 20, 2021. The following search terms were used: "vaccination", "COVID-19", "SARS-CoV-2", "BNT162b2", "mRNA-1273", "ChAdOx1", "Ad26.COV2.S", "NVX-CoV2373", and "variant", including old and novel virus nomenclature, and "COVID-variants". Furthermore, we searched data presented at recent meetings (Dec 7–10, 2019, and Dec 5–8, 2020) of the American Society of Hematology, the European Hematology Association (June 11 to Oct 15, 2020, and June 9–17, 2021), the American Society of Clinical Oncology (May 29–31, 2020, June 4–8, 2021), and the European Society for Medical Oncology (May 29–31, 2020). Additionally, we evaluated the recommendations on COVID vaccination of the International Myeloma Society, and the data generated by some of the panel members or through cooperation between them. Most vaccination studies on multiple myeloma are retrospective observational studies, with some designed as prospective investigations, and very few as systematic reviews. Most data qualify for level 2 evidence. This information was used as a basis for a first manuscript draft, which was circulated three times and commented on by all participants. The final manuscript was approved by all authors.

could also be considered for prophylaxis as it had been shown to reduce progression of mildly symptomatic COVID-19 disease in older patients,[70] but has as yet not been evaluated for post exposure or general prophylaxis. Active anti-SARS-CoV-2 antivirals are in development for prophylaxis or for after contact exposure. Notably, the first representative of an anti-SARS-CoV-2 drug is the nucleoside analogue molnupiravir, which has been submitted to the US FDA for emergency authorisation. Patients with immunosuppression need to be advised to adhere to recommendations for infection risk reduction issued by the Centers for Disease Control and Prevention—namely, social distancing, mask wearing, handwashing, cleaning and disinfecting surfaces which are frequently touched, and daily health monitoring. These patients might end up depending on the creation of herd immunity and on a strategy of so-called ring vaccination, including vaccinating all household members, close social contacts, and care givers.

Contributors

HL and ET developed the manuscript with the input from all authors. All authors have seen, commented on, and approved the final version of the manuscript.

Declaration of interests

HL declares research funding from Amgen and Takeda, and speaker's honoraria from and participation on advisory boards for Amgen, Takeda, Sanofi, Janssen, Celgene-Bristol Myers Squibb, and Seattle Genetics. PS declares research funding from Amgen, Celgene-Bristol Myers Squibb, Janssen, SkylineDx, and Takeda, and honoraria from and participation on advisory boards for Amgen, Celgene-Bristol Myers Squibb, Janssen, SkylineDx, and Takeda. TF declares participation on advisory boards for Janssen, Bristol Myers Squibb, Takeda, Amgen, Roche, Karyopharm, Oncopeptides, and Abbvie, and speaker's honoraria from Janssen and Bristol Myers Squibb. JS-M declares consulting fees from and participation on advisory boards for Amgen, Celgene-Bristol Myers Squibb, Janssen, MSD, Novartis, Takeda, Sanofi, Roche, Abbvie, GlaxoSmithKline, Regeneron, SecuraBio, and Karyopharm. M-VM declares honoraria from and participation on advisory boards for Janssen, Celgene-Bristol Myers Squibb, Takeda, Amgen, Sanofi, Oncopeptides, GlaxoSmithKline, Adaptive, Pfizer, Regeneron, Roche, Sea-Gen, and Blu Bird bio. PM declares honoraria from and participation on advisory boards for Janssen, Celgene-Bristol Myers Squibb, Amgen, Sanofi, and Abbvie. MC declares honoraria from Janssen, Celgene-Bristol Myers Squibb, GlaxoSmithKline, Amgen, Takeda, AbbVie, and Sanofi, and participation on advisory boards for Janssen, Celgene-Bristol Myers Squibb, GlaxoSmithKline, Amgen, Takeda, AbbVie, and Sanofi. CP declares consultancy fees from Amgen, Takeda, Celgene-Bristol Myers Squibb, and Sanofi; travel support from Amgen, Takeda, Janssen, and Celgene-Bristol Myers Squibb; and honoraria from Janssen, Celgene-Bristol Myers Squibb, and Sanofi. SZ declares research funding from Takeda and Janssen, and participation on advisory boards for Takeda, Janssen, Sanofi, Bristol Myers Squibb, and Oncopeptides. ME declares honoraria from and participation on advisory boards for Amgen, Celgene-Bristol Myers Squibb, GlaxoSmithKline, Janssen, Karyopharm, Sanofi, and Takeda, and research funding from Amgen, Celgene-Bristol Myers Squibb, Janssen, Karyopharm, and Takeda. GC declares honoraria from and participation on advisory boards for Celgene-Bristol Myers Squibb, Takeda, GlaxoSmithKline, Sanofi, Amgen, Janssen, and Oncopeptides, and research funding from GlaxoSmithKline and Takeda. MAD declares participation on advisory boards for Amgen, Takeda, Bristol Myers Squibb, Janssen, and Beigene. FG declares honoraria from Amgen, Janssen, Takeda, Celgene-Bristol Myers Squibb, AbbVie, and GlaxoSmithKline, and participation on advisory boards for Amgen, Celgene-Bristol Myers Squibb, Janssen, Takeda, AbbVie, GlaxoSmithKline, Roche, Adaptive Biotechnologies, Oncopeptides, and Bluebird Bio. HE declares honoraria from Amgen, Celgene-Bristol Myers Squibb, Janssen, Takeda, GlaxoSmithKline, Sanofi, Novartis; consultancy fees from and participation on advisory boards for Amgen, Celgene-Bristol Myers Squibb, Janssen, Takeda, GlaxoSmithKline, Sanofi, and Novartis; and research funding from Amgen, Celgene-Bristol Myers Squibb, Janssen, Sanofi, and GlaxoSmithKline. MD declares speaker's honoraria and research funding from Amgen, Celgene-Bristol Myers Squibb, Janssen, Sanofi, and Takeda. KW declares research funding from Amgen, Celgene-Bristol Myers Squibb, Janssen, and Sanofi, and honoraria from Amgen, Abbvie, Adaptive Biotech, Celgene-Bristol Myers Squibb, Janssen, Karyopharm, Novartis, Oncopeptides, Roche Pharma, Takeda, and Sanofi. GJ declares speaker's honoraria from and participation on advisory boards for Celgene-Bristol Myers Squibb, Takeda, GlaxoSmithKline, Sanofi, Amgen, Johnson & Johnson, and Oncopeptides, and research funding from Celgene-Bristol Myers Squibb and Takeda. LG declares participation on advisory boards for Amgen, Takeda, Celgene-Bristol Myers Squibb, and Janssen. NvdD declares research funding from Janssen Pharmaceuticals, Amgen, Celgene-Bristol Myers Squibb, Novartis, and Cellectis, and participation on advisory

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References

1 Kristinsson SY, Tang M, Pfeiffer RM, et al. Monoclonal gammopathy of undetermined significance and risk of infections: a population-based study. *Haematologica* 2012; **97:** 854–58.

2 Blimark C, Holmberg E, Mellqvist UH, et al. Multiple myeloma and infections: a population-based study on 9253 multiple myeloma patients. *Haematologica* 2015; **100:** 107–13.

3 Ludwig H, Meckl A, Engelhardt M. Compliance with recommendations of vaccination among myeloma patients: a real world experience. *HemaSphere* 2021; **5:** e597.

4 Suen H, Brown R, Yang S, et al. Multiple myeloma causes clonal T-cell immunosenescence: identification of potential novel targets for promoting tumour immunity and implications for checkpoint blockade. *Leukemia* 2016; **30:** 1716–24.

5 Zelle-Rieser C, Thangavadivel S, Biedermann R, et al. T cells in multiple myeloma display features of exhaustion and senescence at the tumor site. *J Hematol Oncol* 2016; **9:** 116.

6 Zhu N, Zhang D, Wang W, et al. A novel coronavirus from patients with pneumonia in China, 2019. *N Engl J Med* 2020; **382:** 727–33.

7 Chari A, Samur MK, Martinez-Lopez J, et al. Clinical features associated with COVID-19 outcome in multiple myeloma: first results from the International Myeloma Society data set. *Blood* 2020; **136:** 3033–40.

8 Martínez-López J, Mateos MV, Encinas C, et al. Multiple myeloma and SARS-CoV-2 infection: clinical characteristics and prognostic factors of inpatient mortality. *Blood Cancer J* 2020; **10:** 103.

9 Wang B, Van Oekelen O, Mouhieddine TH, et al. A tertiary center experience of multiple myeloma patients with COVID-19: lessons learned and the path forward. *J Hematol Oncol* 2020; **13:** 94.

10 Hultcrantz M, Richter J, Rosenbaum C, et al. COVID-19 infections and clinical outcomes in patients with multiple myeloma in New York City: a cohort study from five academic centers. *Blood Cancer Discov* 2020; **1:** 234–43.

11 Cook G, John Ashcroft A, Pratt G, et al. Real-world assessment of the clinical impact of symptomatic infection with severe acute respiratory syndrome coronavirus (COVID-19 disease) in patients with multiple myeloma receiving systemic anti-cancer therapy. *Br J Haematol* 2020; **190:** e83–86.

12 Engelhardt M, Shoumariyeh K, Rösner A, et al. Clinical characteristics and outcome of multiple myeloma patients with concomitant COVID-19 at Comprehensive Cancer Centers in Germany. *Haematologica* 2020; **105:** 2872–78.

13 Vijenthira A, Gong IY, Fox TA, et al. Outcomes of patients with hematologic malignancies and COVID-19: a systematic review and meta-analysis of 3377 patients. *Blood* 2020; **136:** 2881–92.

14 Baden LR, El Sahly HM, Essink B, et al. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. *N Engl J Med* 2021; **384:** 403–16.

15 Polack FP, Thomas SJ, Kitchin N, et al. Safety and efficacy of the BNT162b2 mRNA COVID-19 vaccine. *N Engl J Med* 2020; **383:** 2603–15.

16 European Medicines Agency. Summary of Product Characteristics. 2021. https://www.ema.europa.eu/en/ documents/product-information/covid-19-vaccine-janssen-eparproduct-information_en.pdf (accessed Aug 18, 2021).

17 Voysey M, Clemens SAC, Madhi SA, et al. Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK. *Lancet* 2021; **397:** 99–111.

18 Heath PT, Galiza EP, Baxter DN, et al. Safety and efficacy of NVX-CoV2373 COVID-19 vaccine. *N Engl J Med* 2021; **385:** 1172–83.

19 Logunov DY, Dolzhikova IV, Shcheblyakov DV, et al. Safety and efficacy of an rAd26 and rAd5 vector-based heterologous prime-boost COVID-19 vaccine: an interim analysis of a randomised controlled phase 3 trial in Russia. *Lancet* 2021; **397:** 671–81.

20 Tanriover MD, Doğanay HL, Akova M, et al. Efficacy and safety of an inactivated whole-virion SARS-CoV-2 vaccine (CoronaVac): interim results of a double-blind, randomised, placebo-controlled, phase 3 trial in Turkey. *Lancet* 2021; **398:** 213–22.

21 Al Kaabi N, Zhang Y, Xia S, et al. Effect of 2 inactivated SARS-CoV-2 vaccines on symptomatic COVID-19 infection in adults: a randomized clinical trial. *JAMA* 2021; **326:** 35–45.

22 Centers for Disease Control and Prevention. COVID-19 Vaccines for Moderately to Severely Immunocompromised People. 2021. https://www.cdc.gov/coronavirus/2019-ncov/vaccines/recommendations/immuno.html (accessed Oct 25, 2021).

23 Yu J, Tostanoski LH, Peter L, et al. DNA vaccine protection against SARS-CoV-2 in rhesus macaques. *Science* 2020; **369:** 806–11.

24 Garcia-Beltran WF, Lam EC, Astudillo MG, et al. COVID-19-neutralizing antibodies predict disease severity and survival. *Cell* 2021; **184:** 476–88.

25 Widge AT, Rouphael NG, Jackson LA, et al. Durability of responses after SARS-CoV-2 mRNA-1273 vaccination. *N Engl J Med* 2021; **384:** 80–82.

26 Folegatti PM, Ewer KJ, Aley PK, et al. Safety and immunogenicity of the ChAdOx1 nCoV-19 vaccine against SARS-CoV-2: a preliminary report of a phase 1/2, single-blind, randomised controlled trial. *Lancet* 2020; **396:** 467–78.

27 Sahin U, Muik A, Vogler I, et al. BNT162b2 vaccine induces neutralizing antibodies and poly-specific T cells in humans. *Nature* 2021; **595:** 572–77.

28 Krammer F, Srivastava K, Alshammary H, et al. Antibody responses in seropositive persons after a single dose of SARS-CoV-2 mRNA vaccine. *N Engl J Med* 2021; **384:** 1372–74.

29 Doria-Rose N, Suthar MS, Makowski M, et al. antibody persistence through 6 months after the second dose of mRNA-1273 vaccine for COVID-19. *N Engl J Med* 2021; **384:** 2259–61.

30 Jalkanen P, Kolehmainen P, Häkkinen HK, et al. COVID-19 mRNA vaccine induced antibody responses against three SARS-CoV-2 variants. *Nat Commun* 2021; **12:** 3991.

31 Planas D, Veyer D, Baidaliuk A, et al. Reduced sensitivity of SARS-CoV-2 variant Delta to antibody neutralization. *Nature* 2021; **596:** 276–80.

32 Bernal J, Andrews N, Gower C, et al. Effectiveness of COVID-19 vaccines against the B.1.617.2 (Delta) variant. *N Engl J Med* 2021; **385:** 585–94.

33 Gallagher KME, Leick MB, Larson RC, et al. SARS-CoV-2 T-cell immunity to variants of concern following vaccination. *bioRxiv* 2021; published online May 3: https://doi.org/10.1101/2021.05.03.442455 (preprint).

34 Karlsson J, Andréasson B, Kondori N, et al. Comparative study of immune status to infectious agents in elderly patients with multiple myeloma, Waldenstrom's macroglobulinemia, and monoclonal gammopathy of undetermined significance. *Clin Vaccine Immunol* 2011; **18:** 969–77.

35 Gustafson CE, Kim C, Weyand CM, Goronzy JJ. Influence of immune aging on vaccine responses. *J Allergy Clin Immunol* 2020; **145:** 1309–21.

36 Terpos E, Trougakos IP, Gavriatopoulou M, et al. Low neutralizing antibody responses against SARS-CoV-2 in older patients with myeloma after the first BNT162b2 vaccine dose. *Blood* 2021; **137:** 3674–76.

37 Terpos E, Gavriatopoulou M, Ntanasis-Stathopoulos I, et al. The neutralizing antibody response post COVID-19 vaccination in patients with myeloma is highly dependent on the type of anti-myeloma treatment. *Blood Cancer J* 2021; **11:** 138.

38 Bird S, Panopoulou A, Shea RL, et al. Response to first vaccination against SARS-CoV-2 in patients with multiple myeloma. *Lancet Haematol* 2021; **8:** e389–92.

39 Pimpinelli F, Marchesi F, Piaggio G, et al. Fifth-week immunogenicity and safety of anti-SARS-CoV-2 BNT162b2 vaccine in patients with multiple myeloma and myeloproliferative malignancies on active treatment: preliminary data from a single institution. *J Hematol Oncol* 2021; **14:** 81.

40 Van Oekelen O, Gleason CR, Agte S, et al. Highly variable SARS-CoV-2 spike antibody responses to two doses of COVID-19 RNA vaccination in patients with multiple myeloma. *Cancer Cell* 2021; **39:** 1028–30.

41 Passamonti F, Romano A, Salvini M, et al. COVID-19 elicits an impaired antibody response against SARS-CoV-2 in patients with haematological malignancies. *Br J Haematol* 2021; published online July 16. https://doi.org/10.1111/bjh.17704.

42 Vibholm LK, Nielsen SSF, Pahus MH, et al. SARS-CoV-2 persistence is associated with antigen-specific CD8 T-cell responses. *EBioMedicine* 2021; **64:** 103230.

43 Zimmer K. A Guide to Emerging SARS-CoV-2 variants. 2021. https://www.the-scientist.com/news-opinion/a-guide-to-emerging-sars-cov-2-variants-68387 (accessed Oct 18, 2021).

44 Davies NG, Jarvis CH, Edmunds WJ, et al. Increased mortality in community-tested cases of SARS-CoV-2 lineage B.1.1.72. *Nature* 2021; **593:** 270–74.

45 Centers for Disease Control and Prevention. Interim Guidelines for COVID-19 Antibody Testing. 2021. https://www.cdc.gov/coronavirus/2019-ncov/lab/resources/antibody-tests-guidelines.html (accessed Aug 17, 2021).

46 Edara VV, Pinsky BA, Suthar MS, et al. Infection and vaccine-induced neutralizing-antibody responses to the SARS-CoV-2 B.1.617 variants. *N Engl J Med* 2021; **385:** 664–66.

47 Collier DA, De Marco A, Ferreira I, et al. Sensitivity of SARS-CoV-2 B.1.1.7 to mRNA vaccine-elicited antibodies. *Nature* 2021; **593:** 136–41.

48 Ramanathan M, Ferguson ID, Miao W, Khavari PA. SARS-CoV-2 B.1.1.7 and B.1.351 Spike variants bind human ACE2 with increased affinity. *Lancet Infect Dis* 2021; **21:** 1070.

49 Edara VV, Norwood C, Floyd K, et al. Infection- and vaccine-induced antibody binding and neutralization of the B.1.351 SARS-CoV-2 variant. *Cell Host Microbe* 2021; **29:** 516–21.

50 Abu-Raddad LJ, Chemaitelly H, Butt AA. Effectiveness of the BNT162b2 Covid-19 Vaccine against the B.1.1.7 and B.1.351 variants. *N Engl J Med* 2021; **385:** 187–89.

51 Madhi SA, Baillie V, Cutland CL, et al. Efficacy of the ChAdOx1 nCoV-19 COVID-19 vaccine against the B.1.351 variant. *N Engl J Med* 2021; **384:** 1885–98.

52 Alter G, Yu J, Liu J, et al. Immunogenicity of Ad26.COV2.S vaccine against SARS-CoV-2 variants in humans. *Nature* 2021; **596:** 268–72.

53 Mahase E. COVID-19: Novavax vaccine efficacy is 86% against UK variant and 60% against South African variant. *BMJ* 2021; **372:** n296.

54 Shinde V, Bhikha S, Hoosain Z, et al. Efficacy of NVX-CoV2373 COVID-19 vaccine against the B.1.351 variant. *N Engl J Med* 2021; **384:** 1899–909.

55 Wang P, Casner RG, Nair MS, et al. Increased resistance of SARS-CoV-2 variant P.1 to antibody neutralization. *Cell Host Microbe* 2021; **29:** 747–51.

56 Liu Y, Liu J, Xia H, et al. Neutralizing activity of BNT162b2-elicited serum. *N Engl J Med* 2021; **384:** 1466–68.

57 Shrotri M, Krutikov M, Palmer T, et al. Vaccine effectiveness of the first dose of ChAdOx1 nCoV-19 and BNT162b2 against SARS-CoV-2 infection in residents of long-term care facilities in England (VIVALDI): a prospective cohort study. *Lancet Infect Dis* 2021; published online June 23. https://doi.org/10.1016/S1473-3099(21)00289-9.

58 Callaway E. Mix-and-match COVID vaccines trigger potent immune response. *Nature* 2021; **593:** 491.

59 Precision Vaccine. VLA2001 COVID-19 vaccine. 2021. https://www.precisionvaccinations.com/vaccines/vla2001-covid-19-vaccine (accessed June 4, 2021).

60 Démoulins T, Englezou PC, Milona P, et al. Self-replicating RNA vaccine delivery to dendritic cells. *Methods Mol Biol* 2017; **1499:** 37–75.

61 Frerichs KA, Bosman PWC, van Velzen JF, et al. Effect of daratumumab on normal plasma cells, polyclonal immunoglobulin levels, and vaccination responses in extensively pre-treated multiple myeloma patients. *Haematologica* 2020; **105:** e302–06.

62 Nahi H, Chrobok M, Gran C, et al. Infectious complications and NK cell depletion following daratumumab treatment of multiple myeloma. *PLoS One* 2019; **14:** e0211927.

63 Noonan K, Rudraraju L, Ferguson A, et al. Lenalidomide-induced immunomodulation in multiple myeloma: impact on vaccines and antitumor responses. *Clin Cancer Res* 2012; **18:** 1426–34.

64 Borhani K, Bamdad T, Hashempour T. Lenalidomide acts as an adjuvant for HCV DNA vaccine. *Int Immunopharmacol* 2017; **48:** 231–40.

65 Hurt AC, Wheatley AK. Neutralizing antibody therapeutics for COVID-19. *Viruses* 2021; **13:** 628.

66 Cohen MS, Nirula A, Mulligan MJ, et al. Effect of bamlanivimab *vs* placebo on incidence of COVID-19 among residents and staff of skilled nursing and assisted living facilities: a randomized clinical trial. *JAMA* 2021; **326:** 46–55.

67 O'Brien MP, Forleo-Neto E, Musser BJ, et al. Subcutaneous REGEN-COV Antibody Combination to Prevent Covid-19. *N Engl J Med* 2021; **385:** 1184-95.

68 Weinreich DM, Sivapalasingam S, Norton T, et al. REGEN-COV antibody combination and outcomes in outpatients with Covid-19. *N Engl J Med* 2021; published online September 29. https://doi.org/10.1056/NEJMoa2108163.

69 An EUA for bamlanivimab and etesevimab for COVID-19. *Med Lett Drugs Ther* 2021; **63:** 49–50.

70 Libster R, Pérez Marc G, Wappner D, et al. Early high-titer plasma therapy to prevent severe COVID-19 in older adults. *N Engl J Med* 2021; **384:** 610–18.

71 Kenig A, Ishay Y, Kharouf F, Rubin L. Treatment of B-cell depleted COVID-19 patients with convalescent plasma and plasma-based products. *Clin Immunol* 2021; **227:** 108723.

72 Abani O, Abbas A, Abbas F, et al. Convalescent plasma in patients admitted to hospital with COVID-19 (RECOVERY): a randomised controlled, open-label, platform trial. *Lancet* 2021; **397:** 2049–59.

73 Singh P, Dhalaria P, Ghosh S, et al. Strategies to overcome vaccine hesitancy. *Syst Rev* 2020; published online May 20. https://doi.org/10.21203/rs.3.rs-26923/v1 (preprint).

74 de Figueiredo A, Simas C, Karafillakis E, Paterson P, Larson HJ. Mapping global trends in vaccine confidence and investigating barriers to vaccine uptake: a large-scale retrospective temporal modelling study. *Lancet* 2020; **396:** 898–908.

75 Racey CS, Donken R, Porter I, et al. Intentions of public school teachers in British Columbia, Canada to receive a COVID-19 vaccine. *Vaccine X* 2021; **8:** 100106.

76 Castells MC, Phillips EJ. Maintaining safety with SARS-CoV-2 vaccines. *N Engl J Med* 2021; **384:** 643–49.

77 Menni C, Klaser K, May A, et al. Vaccine side-effects and SARS-CoV-2 infection after vaccination in users of the COVID Symptom Study app in the UK: a prospective observational study. *Lancet Infect Dis* 2021; **21:** 939–49.

78 European Medicines Agency. Vaxzevria (previously COVID-19 Vaccine AstraZeneca). 2021. https://www.ema.europa.eu/en/medicines/human/EPAR/vaxzevria-previously-covid-19-vaccine-astrazeneca (accessed Oct 18, 2021).

79 Johnston MS, Galan A, Watsky KL, Little AJ. Delayed localized hypersensitivity reactions to the moderna COVID-19 vaccine: a case series. *JAMA Dermatol* 2021; **157:** 716–20.

80 Banerji A, Wickner PG, Saff R, et al. mRNA vaccines to prevent COVID-19 disease and reported allergic reactions: current evidence and suggested approach. *J Allergy Clin Immunol Pract* 2021; **9:** 1423–37.

81 Cines DB, Bussel JB. SARS-CoV-2 Vaccine-induced immune thrombotic thrombocytopenia. *N Engl J Med* 2021; **384:** 2254–56.

82 Greinacher A, Thiele T, Warkentin TE, Weisser K, Kyrle PA, Eichinger S. Thrombotic thrombocytopenia after ChAdOx1 nCov-19 vaccination. *N Engl J Med* 2021; **384:** 2092–101.

83 Scully M, Singh D, Lown R, et al. Pathologic antibodies to platelet factor 4 after ChAdOx1 nCoV-19 vaccination. *N Engl J Med* 2021; **384:** 2202–11.

84 Sadoff J, Gray G, Vandebosch A, et al. Safety and efficacy of single-dose Ad26.COV2.S vaccine against COVID-19. *N Engl J Med* 2021; **384:** 2187–201.

85 Trimboli M, Zoleo P, Arabia G, Gambardella A. Guillain-Barré syndrome following BNT162b2 COVID-19 vaccine. *Neurol Sci* 2021; **42:** 4401–02.

86 Choi G-J, Baek SH, Kim J, et al. Fatal systemic capillary leak syndrome after SARS-CoV-2 vaccination in patient with multiple myeloma. *Emerg Infect Dis* 2021; **27:** 2973–75.

87 International Myeloma Society. Recommendations for anti-COVID-19 vaccination in patients with multiple myeloma (MM) and related conditions, AL amyloidosis and other monoclonal gammopathies of clinical significance. 2021. https://myeloma.wpengine.com/wp-content/uploads/2021/03/PM-COVID-vaccination-in-MM-guidelines-The-Final.pdf (accessed May 7, 2021).

88 US Food and Drug Administration. Coronavirus (COVID-19) update: FDA authorizes additional vaccine dose for certain immunocompromised individuals. 2021. https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-additional-vaccine-dose-certain-immunocompromised (accessed Aug 4, 2021).

89 Eurpoean Pharmaceutical Review. FDA approves emergency use of REGEN-COV™ for COVID-19 prevention. 2021. https://www.europeanpharmaceuticalreview.com/news/159504/fda-approve-emergency-use-of-regen-covtm-for-covid-19-prevention/ (accessed Aug 17, 2021).

90 US Food and Drug Administration. FDA authorizes bamlanivimab and etesevimab monoclonal antibody therapy for post-exposure prophylaxis (prevention) for COVID-19. 2021. https://www.fda.gov/drugs/drug-safety-and-availability/fda-authorizes-bamlanivimab-and-etesevimab-monoclonal-antibody-therapy-post-exposure-prophylaxis (accessed Oct 25, 2021).