COVID-19 vaccines in patients with cancer: immunogenicity, efficacy and safety

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Abstract | Patients with cancer have a higher risk of severe coronavirus disease (COVID-19) and associated mortality than the general population. Owing to this increased risk, patients with cancer have been prioritized for COVID-19 vaccination globally, for both primary and booster vaccinations. However, given that these patients were not included in the pivotal clinical trials, considerable uncertainty remains regarding vaccine efficacy, and the extent of humoral and cellular immune responses in these patients, as well as the risks of vaccine-related adverse events. In this Review, we summarize the current knowledge generated in studies conducted since COVID-19 vaccines first became available. We also highlight critical points that might affect vaccine efficacy in patients with cancer in the future.

Shortly after the emergence of a novel coronavirus towards the end of 2019, the virus was named SARS-CoV-2 by the WHO, and the corresponding disease was termed coronavirus disease (COVID-19)[1]. COVID-19 has a mild or moderate course in most people without comorbidities, whereas patients with cancer have a much higher risk of severe COVID-19 and associated mortality[2]. The presence of risk factors that are also relevant to the general population, such as advanced age and/or other comorbidities, can contribute to this increased risk, although active malignancy is an independent risk factor in almost all reports[3–5]. The adverse effects of the malignancy itself on the risk of severe COVID-19 are particularly visible in younger patients with cancer (<65 years of age)[3,5]. Mortality rates were exceptionally high among patients with active cancer and COVID-19 during the first wave, with mortality rates commonly reported to be around 40%, decreasing to approximately 25% in the following waves in European countries in 2021 (REFS[3–6]). However, mortality rates are usually reported from hospitalized cohorts; therefore, these rates might be an overestimate for patients with cancer. The incidence of long-term COVID-19 sequelae in patients with cancer is estimated to be 15–30%[7,8]. Besides the direct effects of the pandemic, cancer-specific mortality was also increased, for example, owing to the need for frequent treatment modifications and reduced screening[7].

Prevention of infection and subsequent severe COVID-19 is crucial for patients with cancer, with vaccination being the most effective method of achieving this goal. Fortunately, owing to a concerted global effort, several highly effective vaccines have been developed at an unprecedented speed. In large parts of the world, mass vaccination campaigns have considerably reduced the incidence of severe COVID-19 in the general population after at least two vaccine doses. Owing to the high risk of developing severe COVID-19, patients with cancer were prioritized for vaccination in most countries[9]. However, these patients were also excluded from the pivotal clinical trials; therefore, important questions concerning the efficacy and safety of currently available vaccines as well as the durability of vaccine responses remain for this population. Owing to disease-associated and therapy-induced impairment of the immune system, these patients are more likely to develop a less proficient immune response upon vaccination.

In this Review, we provide an overview of current knowledge of the effectiveness of COVID-19 vaccines in patients with cancer, the risk factors for a reduced vaccine response, safety and measures that might increase protection. Reflecting the available data, we focus primarily on mRNA vaccines and adenovirus-vectored vaccines, although we also discuss the available data on inactivated virus and protein subunit vaccines. Wherever possible, we attempt to address clinically relevant questions based on the available evidence. However, studies investigating clinical efficacy in patients with cancer are few and are often hampered by a retrospective design and limited granularity of the data. By contrast, studies investigating immune responses are numerous, often

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Key points

- Vaccination against COVID-19 administered according to current prime–boost concepts is both safe and clinically effective in patients with cancer.
- To date, no reliable correlate of protection that allows the definite deduction of clinical efficacy from immune responses has been established, either in patients with cancer or in the general population.
- Patient-associated factors such as advanced age, haematological malignancy and/or treatment-associated factors such as B cell depletion might all lead to less proficient immune responses following vaccination.
- Future research will determine the necessity of further booster regimens as well as therapeutic options for those who do not benefit from active COVID-19 vaccination.

prospective and provide high-quality data. From these data, conclusions can be drawn regarding the risks of reduced or absent responses to vaccination. However, how reliable and meaningful these laboratory values are in clinical terms is not entirely clear. This lack of clarity is particularly true for the expected changes in SARS-CoV-2 epidemiology owing to the emergence of novel variants of concern (VOCs).

COVID-19 vaccines

Effectiveness in the general population

The most widely used vaccines against COVID-19 in high-income countries are mRNA vaccines (BNT162b2 and mRNA-1273) and adenovirus-vectored vaccines (ChAdOx1 nCoV19, Ad26.COV2-S and Gam-COVID-Vac), both of which induce endogenous expression of modified versions of the viral spike protein to elicit immune responses[10–16]. More conventional vaccines use inactivated virus (CoronaVac and BBIBP-CorV)[17,18] or purified or recombinant viral proteins (NVX-CoV2373)[19] plus an adjuvant to promote an effective immune response (FIG. 1). The immune response elicited by vaccines relies strongly on the production of neutralizing antibodies by B cells and ideally also on the induction of memory cells for longer (potentially lifelong) durability[20,21]. Furthermore, specific T cells can be induced by the available vaccines to varying degrees[21]; these might persist for >6 months and seem to be less affected by antigenic drift[22–24]. Vaccine-induced immune responses occurred in most participants (>90%) in the trials testing all of the available vaccines[10,15,25,26]. However, these measures are surrogate end points and should not be viewed as reliable correlates of protection. Importantly, clinical vaccine efficacy (VE) in these trials was defined as self-reported symptomatic laboratory-confirmed COVID-19. This end point clearly underestimates the incidence of asymptomatic infections; therefore the primary end point of these studies is usually prevention of COVID-19 as opposed to prevention of SARS-CoV-2 infection. Usually, VE is quantified as the reduction of the risk ratio for an event, here symptomatic COVID-19, expressed as a percentage compared to the control group[11,12,15,18,27–30]. Secondary end points include the reduction in the incidence of severe COVID-19 or COVID-19-associated mortality (FIG. 2; Supplementary information).

Prime–boost concept

The VE of all COVID-19 vaccines appears to decrease within a few months after vaccination. In a large retrospective analysis of data from the UK, the initial VE for BNT162b2 of around 90% after the second dose dropped drastically to <60% after 25 weeks[31]. In the same study, the VE for ChAdOx1 nCoV19 dropped to around 40%[31], and in another study to 42–63% after 20 weeks[32]. There are two main reasons for these decreases. Firstly, immunity wanes over time, which is most prominent in older individuals[33]. This effect is typically quantified using the amount of virus-specific antibodies as a surrogate. Secondly, newly emergent VOCs capable of evading immunity to existing SARS-CoV-2 variants can drastically reduce VE[31,34]. To improve VE, an additional, so-called 'booster', dose is given around 6 months after the priming doses, which is an established practice in vaccination against various other infectious diseases. Importantly, the different types of vaccine can be safely combined, and all vaccines appear to increase immunogenicity when administered as boosters[35–40]. However, mRNA vaccines appear to result in higher antibody levels than adenovirus-vectored vaccines when administered as boosters (FIG. 2a). Retrospective data suggest that VE returned to >90% following administration of a booster dose of an mRNA vaccine after approximately 6 months during the predominance of the Delta VOC[31].

Variants of concern

Respiratory viruses are known to have high mutation rates, enabling their evolution to increase the extent of transmission between individuals. Adaptive immunity to viruses, induced by either vaccination or natural infection, can create selection pressures resulting in the selection of mutations that enable immune escape from antibodies and T cells. Despite the existence of proofreading mechanisms, SARS-CoV-2 is constantly acquiring mutations and can also diversify through recombination when an individual is simultaneously infected with more than one variant[41]. Depending on the location, most mutations in the viral genome will not, or will only minimally, affect the course of infection. Nonetheless, a minority of these alterations will provide the virus with a fitness advantage[42]. Most notably, mutations in the genome encoding the receptor-binding domain (RBD) or the amino terminal domain (NTD) of the spike protein (containing important antigen epitopes) can have implications for VE[43,44]. For example,

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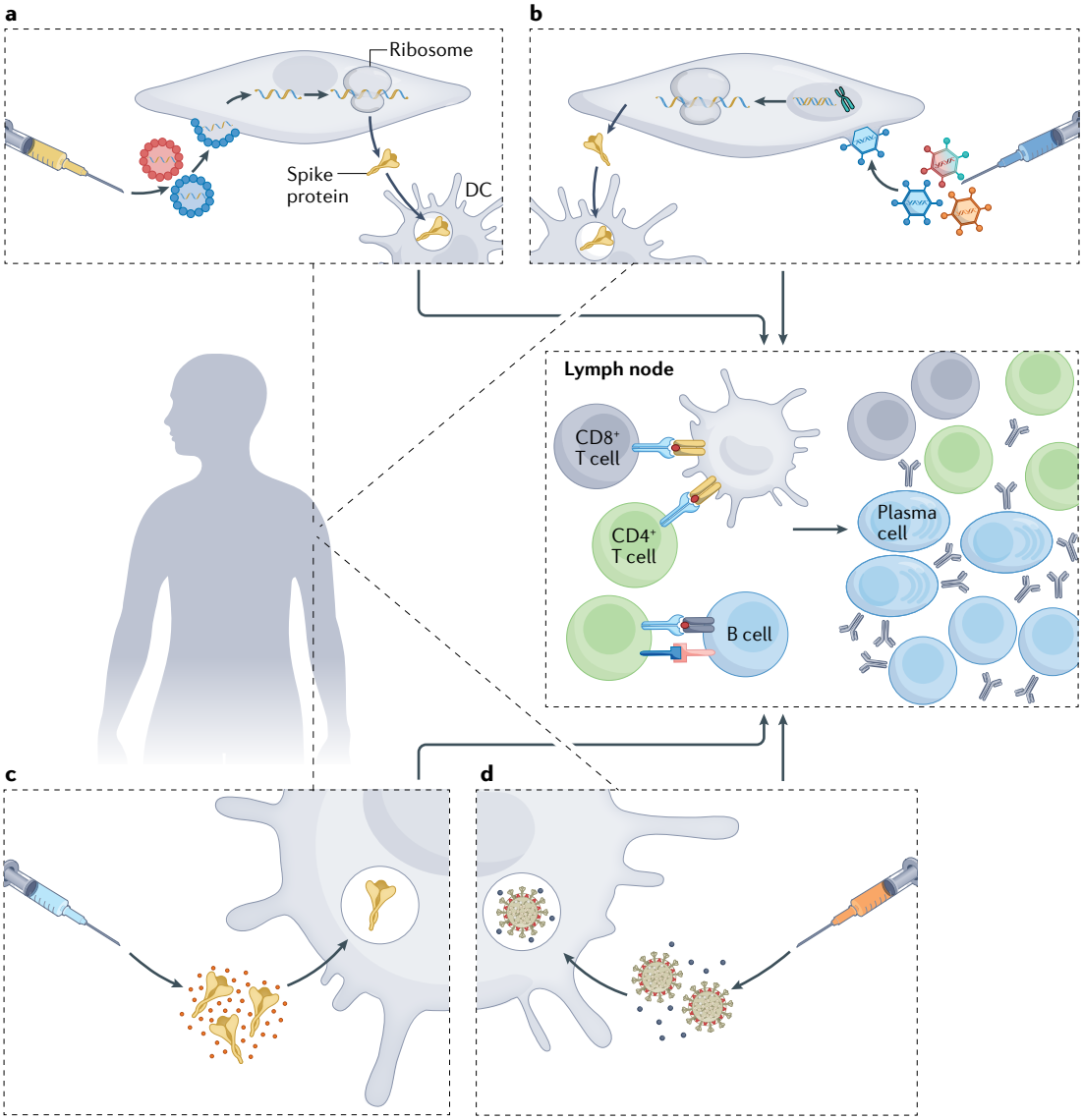
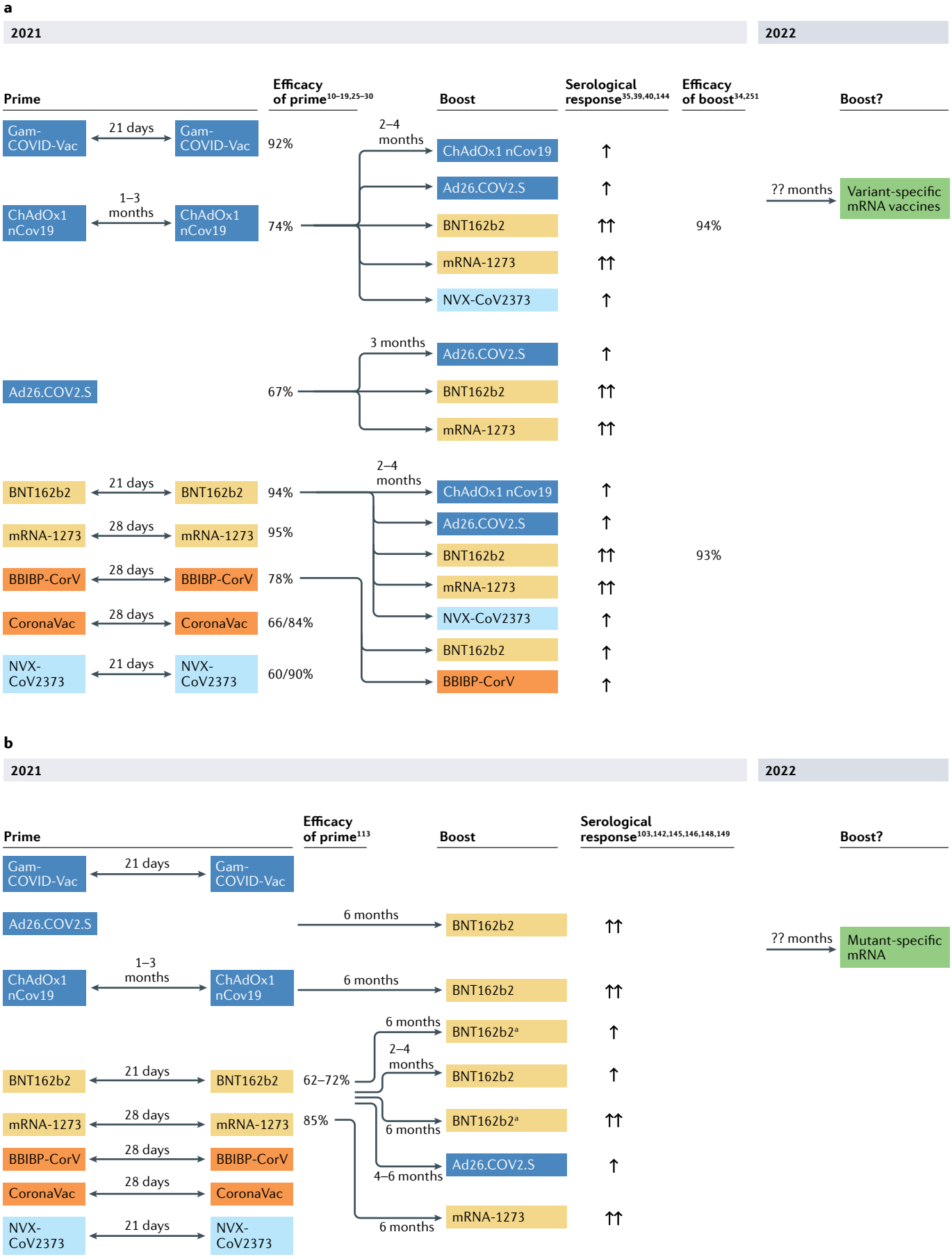


Fig. 1 | **Induction of immune responses by currently available COVID-19 vaccines. a** | mRNA vaccines (including BNT162b2 and mRNA-1273) are delivered to bystander cells inside lipid nanoparticles at the injection site. The mRNA encodes a modified version of the spike protein which is translated by ribosomes, secreted by the bystander cell and in turn taken up and processed by antigen-presenting cells (APCs; in this image dendritic cells (DCs)). **b** | Adenoviral vector vaccines (including ChAdOx1, Ad26.COV2.S and Sputnik V) contain cDNA encoding a full-length spike protein. While most vaccines use the same adenoviral vector for each vaccine dose, Sputnik V uses two different human adenoviral vectors to prevent immune reactions against the vector. cDNA is transported to the nucleus where it is transcribed to mRNA and subsequently translated into spike protein in the cytoplasm. This spike protein is then taken up and processed by APCs. **c** | Protein-based vaccines (including NVX-CoV2373) consist of the spike protein and an adjuvant which is directly processed by APCs. **d** | Attenuated virus vaccines (including CoronaVac and BBIBP-CorV) contain whole inactivated virus particles and adjuvants which are directly processed by APCs. In the lymph nodes, APCs will present processed peptides and thus activate T cell responses (including $CD4^+$ and $CD8^+$ responses) and B cell responses, and in turn antibody responses. The precise immune reaction and strength of activation depends on the vaccine type. Detailed information for each vaccine is summarized in Supplementary Table 1.

one of the earliest identified spike mutations, D614G, increases both the transmissibility and infectivity of SARS-CoV-2. This variant emerged independently in China and Europe, providing evidence of convergent evolution. According to the WHO, SARS-CoV-2 variants are regarded as VOCs if they meet one of the following criteria: (1) increase in transmissibility, (2) increase in virulence, and/or (3) decreased effectiveness of therapeutic and public health measures. To date, five major VOCs have been identified: Alpha, Beta, Gamma, Delta and Omicron. Alpha, Beta and Gamma share the N501Y mutation, which is associated with increased transmissibility[45]. By contrast, the E484K mutation, identified in Beta and Gamma, is associated with antibody escape[46]. A number of mutations in Delta also confer immune escape[47]. The latest VOC, Omicron,


a
2021
2022
Prime
Efficacy of prime[10–19,25–30]
Boost
Serological response[35,39,40,144]
Efficacy of boost[34,251]
Boost?
Gam-COVID-Vac
21 days
Gam-COVID-Vac
92%
2–4 months
ChAdOx1 nCov19
↑
Ad26.COV2.S
↑
?? months
Variant-specific mRNA vaccines
ChAdOx1 nCov19
1–3 months
ChAdOx1 nCov19
74%
BNT162b2
↑↑
94%
mRNA-1273
↑↑
NVX-CoV2373
↑
3 months
Ad26.COV2.S
↑
Ad26.COV2.S
67%
BNT162b2
↑↑
mRNA-1273
↑↑
BNT162b2
21 days
BNT162b2
94%
2–4 months
ChAdOx1 nCov19
↑
mRNA-1273
28 days
mRNA-1273
95%
Ad26.COV2.S
↑
BBIBP-CorV
28 days
BBIBP-CorV
78%
BNT162b2
↑↑
93%
mRNA-1273
↑↑
CoronaVac
28 days
CoronaVac
66/84%
NVX-CoV2373
↑
NVX-CoV2373
21 days
NVX-CoV2373
60/90%
BNT162b2
↑
BBIBP-CorV
↑
b
2021
2022
Prime
Efficacy of prime[113]
Boost
Serological response[103,142,145,146,148,149]
Boost?
Gam-COVID-Vac
21 days
Gam-COVID-Vac
Ad26.COV2.S
6 months
BNT162b2
↑↑
?? months
Mutant-specific mRNA
ChAdOx1 nCov19
1–3 months
ChAdOx1 nCov19
6 months
BNT162b2
↑↑
6 months
BNT162b2[a]
↑
BNT162b2
21 days
BNT162b2
62–72%
2–4 months
BNT162b2
↑
mRNA-1273
28 days
mRNA-1273
85%
6 months
BNT162b2[a]
↑↑
BBIBP-CorV
28 days
BBIBP-CorV
4–6 months
Ad26.COV2.S
↑
CoronaVac
28 days
CoronaVac
NVX-CoV2373
21 days
NVX-CoV2373
6 months
mRNA-1273
↑↑

◀ Fig. 2 | **Overview of reported COVID-19 vaccine prime-boost schemes and clinical efficacies. a** | Reported prime boost regimens and clinical efficacy in individuals without cancer. 'Efficacy of boost' data are from REFS[34,251]. **b** | Reported prime boost regimens and clinical efficacy in patients with cancer. Primary vaccination (prime) usually consists of two vaccine doses (except for Ad26.COV2.S) which are administered at intervals of variable length from 21 days to 3 months. Vaccine efficacy (VE) in these studies is defined as the prevention of symptomatic COVID-19. The strength of serological responses is summarized with arrows indicating a moderate (one arrow) or strong (two arrows) response. An additional booster dose is administered 2 to 6 months after completion of prime vaccination. Boosts can either be homologous (same vaccine type) or heterologous (different vaccine type) and consist of one dose. Additional booster doses either designed against wild-type or with variant-specific designs are expected to become available in the next months (and in some countries are already available for patients with a compromised immune system), although the clinical efficacy and the optimal regimens need to be determined. [a]Slightly varying responses reported from two different studies.

originally identified in November 2021, carries several mutations resulting in robust immune escape[48]. Specifically, this variant harbours 37 amino acid substitutions in the spike protein, of which 15 are in the RBD, thus impairing the effectiveness of available vaccines and monoclonal antibody therapeutic agents, which mostly target this domain[44,49–51]. Not surprisingly, reports on VE in the general population when the Omicron variant is highly prevalent suggest a dramatic reduction in VE after prime vaccination with mRNA vaccines or adenovirus-vectored vaccines[31,52].

In addition to immune escape, the mutations present in Omicron have also changed the infectivity of this variant. Omicron still binds ACE2 with similar (or even higher) affinity to other variants[53,54], although this variant can no longer facilitate cellular entry via cell fusion, which is dependent on TMPRSS2 (REF.[55]). These findings might be reflected by a propensity for infection of upper airway cells relative to other variants[56], as well as less severe lung pathology in animal models[57]. Importantly, retrospective clinical data as well as in vitro neutralization data uniformly support an increase in VE against the Omicron VOC following administration of an mRNA vaccine as a third vaccine dose[24,31,50,53,58,59].

Correlates of protection

Serology and neutralizing antibodies. In most individuals, neutralizing antibodies develop rapidly after infection with SARS-CoV-2 (REF.[60]), and high levels of neutralizing activity are associated with rapid clearance of the virus[61] and a lower risk of infection[62]. Most of the available COVID-19 vaccines are specifically directed against the spike protein, whereas infection is likely to induce a broad spectrum of functional and non-functional antibodies against other viral proteins (such as the nucleocapsid). Nonetheless, vaccine-induced antibodies against the spike RBD and NTD have potent SARS-CoV-2-neutralizing activity[63,64]. Thus far, the available vaccines were all developed to target the ancestral SARS-CoV-2 spike protein. Efficient cross-neutralization against VOCs has been described shortly after vaccination and after three vaccine doses, although a reduction in neutralizing activity specifically against the Beta, Delta and Omicron VOCs is generally observed[31,50,52,59,65,66]. Positive neutralization against VOCs is defined variably across studies with the lower limit of detection of the assay usually denoted, such measures are not a correlate of protection from either infection or severe COVID-19.

In clinical settings, the most common method of assessing an immune response after infection or vaccination is to measure the extent of antibody-mediated SARS-CoV-2 binding. To support the interpretation of results from different studies and enable international comparisons, binding antibody assays are often calibrated towards an international WHO serum standard, which recommends reporting the SARS-CoV-2 binding activity of antibody titres in SARS-CoV-2 binding-antibody units (BAU) per millilitre. Concentration in BAU per millilitre often serves as an end point in studies investigating vaccine immunogenicity. Up to now, BAU per millilitre against the wild-type spike antigen has correlated well with the extent of virus neutralization, even of VOCs. However, this correlation is less robust for the Omicron variant[24], and a higher cut-off of for positivity might be needed to accurately predict neutralizing antibody responses from BAUs[53]. Furthermore, the correlation between binding antibodies and virus neutralization will be affected by the time of sampling, the extent of maturation of the B cell response, type of vaccine and the inter-assay variability of virus neutralization assays[67].

In certain studies investigating breakthrough SARS-CoV-2 infections, including in patients with cancer, levels of virus-specific antibodies were either reduced or undetectable in those with infections[68,69], and correlated negatively with viral load[70]. Moreover, in patients with comorbidities, a trend towards a more severe breakthrough infection with lower antibody levels was observed[68]. Despite these observations, a specific antibody level defining the correlate of protection is currently unavailable. Reports confirm a high correlation of (neutralizing) antibodies with clinical VE against both the original Wuhan variant and several VOCs, including Beta, Delta and Gamma[71,72]. However, as described above, a dramatic reduction in neutralization of Omicron by vaccine-induced antibodies has been observed compared to the wild-type strain[24,50,53,58]. This observation further reduces the reliability of BAU per millilitre as a correlate of protection. Another piece of evidence against the value of antibody binding as a correlate of protection is the consistent finding that men have lower immune responses (BOX 1), despite data from a meta-analysis indicating that VE is higher in men than in women (OR 0.67, 95% CI 0.48–0.94)[73].

Cellular response. The use of serology as the sole measure of protection might lead to an underestimation of the proportion of protected individuals, specifically when looking into protection against severe disease. For example, studies in the context of influenza infection indicate the importance of T cell-mediated immunity as a correlate of protection in vulnerable populations, such as those >60 years of age[74]. In addition, T cells recognizing influenza or SARS-CoV-2 antigens are both cross-reactive and are thus less susceptible to waning immunity owing to emerging VOCs[43].

In a prospective study, seronegative individuals had a lower burden of H1N1 disease (following infection with the 2009 H1N1 or 'swine flu' strain of influenza) if they had pre-existing cross-reactive T cells[75]. Similarly in

Box 1 | **Patient-specific risk factors for reduced antibody response after vaccination**

Patients with solid tumours
- Metastatic disease[124]
- Advanced age[65,99,103,127,224]
- Male sex[99,103]

Patients with haematological malignancies
- Lymphoproliferative disorders (especially non-Hodgkin lymphoma) compared to myeloid malignancies[145]
- Active disease[119,122,125,225]
- Advanced age[122,131,226–228]
- Male sex[131,226,228]
- Immunoparesis (immunoglobulin deficiency or lymphopenia)[122,134,225,226,229–231]

Plasma cell disorders
- Higher number of prior lines of therapy (more than four)[122,225,228]

Allogeneic stem cell transplantation
- Advanced age[232,233]
- Active graft-versus-host disease[160,232,234,235]
- Lymphopenia[160,236–238]

experimental influenza, seronegative individuals showed a shorter duration of symptoms and lower disease severity if virus-specific T cells were pre-existing[76,77]. This observation remains true for T cells specific for another virus strain[76]. Initial observations regarding COVID-19 suggest a similar phenomenon: patients with X-linked agammaglobulinaemia (who are genetically incapable of producing B cells) can nonetheless clear SARS-CoV-2 infections[78]. Furthermore, a large retrospective UK cohort study analysing the likelihood of SARS-CoV-2 infection during the second wave showed that those with a prior SARS-CoV-2 infection had a probability of a second infection of 0.9%, while the probability was 4.3% in those without prior SARS-CoV-2 infection. This protective effect was independent of the presence of binding antibodies[79].

Currently approved COVID-19 vaccines elicit robust $CD4^+$ and $CD8^+$ T cell responses in trial participants[21–23]. This effect occurs to a similar extent in patients with cancer[65,66]. However, data correlating vaccine-induced specific T cells with clinical efficacy against COVID-19 remain limited. In one large UK keyworker cohort, T cell response was associated with protection from COVID-19 in participants with moderate serological responses[80], and cross-reactive T cells against the SARS-CoV-2 polymerase were protective against SARS-CoV-2 infection in a large cohort of health-care workers[81]. T cells can be induced by a broad range of epitopes, and are more likely to retain activity against VOCs compared with neutralizing antibody responses. In turn, vaccine-induced T cell responses against VOCs, including Omicron, are largely preserved[24,82–84].

Vaccination in patients with cancer

Previous clinical experience

Prior to the SARS-CoV-2 pandemic, most vaccination studies in patients with cancer involved vaccines against influenza, pneumococcal infection, hepatitis B or zoster reactivation. For most infections, the clinical benefit of the vaccination had already been established[85–88]. Of note, previous experience revealed that patients with cancer benefit from one or more additional vaccine doses. For example, in patients with cancer, two doses of vaccine against seasonal influenza leads to higher immunogenicity than a single dose[89,90]. Similarly, two doses of vaccine against hepatitis B or herpes zoster[91], three doses of vaccine against pneumococcal infection[92], three doses of a recombinant subunit zoster vaccine[93] and four doses of an inactivated herpes zoster vaccine[85,94,95] lead to high seropositivity rates and acceptable levels of protection. This experience supports the idea that patients who are either immunocompromised or immunosuppressed might require more vaccine doses than those who are immunocompetent. Vaccination strategies involving several doses have the additional advantage of being effective regardless of the timing of chemotherapy. Data from one study indicate a reduced response to single-dose influenza vaccination when administered close to chemotherapy, albeit with no reduction in immune response when two vaccine doses were administered[89]. Similarly, a study testing a recombinant zoster vaccine in patients with cancer demonstrated a better immune response after the first dose of the vaccine if it was administered 1 week prior to the start of the chemotherapy[96]. However, the overall immune responses after two doses of this vaccine were comparable in the group that received the first dose before chemotherapy and the group that received the first dose during chemotherapy[96]. In contrast to chemotherapy, most targeted cancer therapies do not seem to interfere with the immune response[89,97].

Of note, the above-mentioned studies focused on the antibody responses elicited by vaccines. Fewer studies have also investigated cellular responses to vaccination, but these have often found the cellular response to be more robust than the humoral response[93] even in patients who also received B cell-depleting agents[95]. In terms of clinical efficacy, the cellular response might also be more relevant. For example, one study investigating a recombinant subunit zoster vaccine in patients with haematological malignancies attributed the clinical efficacy of this vaccine (>60%) in patients with B cell non-Hodgkin lymphoma (B-NHL) to a robust T cell response that could be detected in all patients with B-NHL, whereas only 15% had a detectable serological response[88]. Not surprisingly, targeted therapies seem to have little effect on the cellular response to vaccination[97]. Regarding safety, no evidence exists that vaccines generally have a different toxicity profile in patients with cancer than in the general population, and even patients receiving immune checkpoint inhibitors at the time of influenza vaccination do not have an increased risk of immune-related adverse events (irAEs)[98].

Response to COVID-19 vaccination

Most studies investigating COVID-19 vaccination in patients with cancer only assessed the presence of spike-reactive or RBD-reactive antibodies, although some have additionally performed neutralizing assays, including against VOCs[65,66,99–102]. T cell responses have

been addressed in fewer studies and often in smaller subsets, and therefore additional research is needed to validate the observed effects. A summary of all studies investigating the immunogenicity of COVID-19 vaccines included in this Review, including end points analysed and number of participants is provided in the Supplementary information.

In general, patients with cancer seem more likely to develop a less proficient immune response following vaccination against COVID-19 than individuals without cancer[103–110] (FIG. 2b). The VE of mRNA vaccines against COVID-19 hospitalization in patients with cancer prior to the predominance of the Omicron variant was estimated to be ~75% and thus lower than the 90% in immunocompetent individuals, as described in a real-world study including >89,000 people, of whom >10,000 had cancer[111]. VE in this study was further reduced with advancing age. In a large US Veterans study including only patients with cancer who received mRNA vaccines, VE was about 60%[112]. Of note, no further reduction in VE was observed following a high prevalence of the Delta variant (VE pre-Delta 76%, during Delta 79%)[111]. VE was affected by the timing of cancer therapy and ranged from 54% in patients receiving any therapy (including endocrine therapies, targeted therapies and/or chemotherapy) to 85% in those not treated within the past 6 months. Unfortunately, separate estimates of these effects were not provided for solid and haematological malignancies. A prospective cohort study involving almost seven million vaccinated participants in the UK identified the following as risk factors for COVID-19-related death despite vaccination with two doses: receiving moderate-to-high intensity chemotherapy (HR 3.63–4.3), stem cell transplantation within the past 6 months (HR 2.5), haematological cancer (HR 1.86), and respiratory tract cancer (HR 1.35)[113]. Two of these studies[112,113] included data from patients up to late spring 2021. Therefore, these data include virtually no patients infected with the Delta VOC and are not well placed to consider the effects of waning immunity, both of which are important contributors to declining VE in the general population. Neutralizing responses to VOCs also decrease progressively in patients with cancer[65]. This observation is in line with reports from individuals without cancer[114], although the combined reductions in neutralizing responses owing to VOCs and malignancy can result in substantially reduced VE[72]. Patients with haematological malignancies are most likely to be affected by this effect. For example, 56% of these patients had detectable antibody titres with neutralizing activity against the ancestral Wuhan strain, whereas only 31% had detectable titres with activity against the Delta variant after two vaccine doses[65]. Importantly, the percentage of patients with detectable neutralizing responses to VOCs is broadened following booster vaccination[115]. Initial data on Omicron neutralization in patients with cancer confirm the expected findings deduced from the general population[116]: the percentage of patients with solid tumours with neutralizing responses against Omicron increased from 47.8% to 88.9% following a third vaccine dose[117]. In particular, patients with non-small-cell lung cancer have a 79-fold lower neutralizing response to Omicron compared with individuals without cancer after two doses of an mRNA vaccine[118]. In patients with haematological malignancies, neutralizing antibodies against Omicron are rarely detected after two vaccine doses, although approximately 50% have detectable neutralizing antibodies after a third dose[119].

Risk factors affecting vaccine responses in patients with solid tumours. A substantial majority (90–100%) of patients with solid tumours seroconvert after two vaccine doses, and data from several studies suggest that antibody titres are either comparable to those in individuals without cancer[65,66,120] or reduced[107,110,121]. A meta-analysis of data from four studies including fully vaccinated patients with solid tumours[108] found a reduced seroconversion rate relative to those without cancer (risk ratio 0.95, 95% CI 0.92–0.99). Differences in seroconversion between patients with solid tumours and those without cancer are probably moderate and/or restricted to specific subgroups. Therefore, such differences might not be detected in individual studies, highlighting the need for ongoing systematic meta-analyses to precisely define the at-risk groups among patients with solid tumours. Moreover, risk factors for reduced seroconversion in patients with solid tumours at least partially overlap with those of the general population, including older age[65], male sex[99] and vaccine type[65,120] (BOX 1). Differences in antibody response depending on the vaccine administered largely resemble the differences seen in the general population (that is, mRNA vaccines are more effective than adenovirus-vectored vaccines[65,120], and within the mRNA vaccines, mRNA-1273 is more effective than BNT162b2 (REFS[111,122])). No data are available on the performance of other types of vaccine compared with mRNA or adenovirus-vectored vaccines.

Several cancer therapies are known to impair vaccine-induced immune responses (BOX 2). Recent chemotherapy (defined variably as receiving chemotherapy from within 28 days to within 6 months of vaccination) has been repeatedly identified as a risk factor for lower seroconversion and neutralizing responses, although not in all studies[65], which is in line with the reported reduction in VE in this population[112]. Importantly, the timing of the vaccination with regard to the schedule of ongoing chemotherapy does not seem to affect seroconversion[100,120], which is consistent with prior experience with double-dose influenza vaccination[89]. Many centres therefore avoid administering vaccines and chemotherapy on the same day to minimize the risks of overlapping acute adverse effects, but do not reschedule cancer therapies. While the extent of seroconversion is generally high among patients receiving immune checkpoint inhibitors, 7% of these patients have a suboptimal response[66]. No indications exist that endocrine therapy or small molecules generally are associated with reduced seroconversion. Poly(ADP-ribose) polymerase inhibitors have been associated with reduced seroconversion in women with ovarian cancer[123], and CDK4/6 inhibitors with reduced but not absent antibody responses[120]. Besides cancer-specific therapies, chronic steroid use is also a risk factor for reduced seroconversion[124]. No specific solid tumour type has

Box 2 | **Risks of reduced antibody responses after COVID-19 vaccination associated with cancer treatments**

Relevant reduction in antibody response likely (>50% of patients, most prominent in patients currently undergoing therapy)

- B cell depletion with monoclonal antibodies[a], BTK inhibitors or BCL inhibitors[69,100,109,125,129,131,134,145,226,227,229,231,239–244]
- BCMA-targeted therapies[133,163,230,239]
- CD38-targeted therapies[133,163,230,239,244,245]
- JAK inhibitors[69,231]

Relevant reduction in antibody response possible (<50% of patients, probably dependent on dosing)

- Chemotherapy[b,99,100,105,106,121,154,224,231,246]
- Steroids[122,124,125,131,160,228]
- CDK4/6 inhibitors associated with lower binding antibody levels (not a risk factor in REF.[247], a risk factor in REF.[120])
- Poly(ADP-ribose) polymerase inhibition associated with lower binding antibody levels[123]

Relevant reduction in antibody response uncommon[c]

- Endocrine therapy[100,120,129,248]
- Tyrosine kinase inhibitors[69,106,231]
- Immune checkpoint inhibitors (reduced immune response may occur in approximately 10% of patients)[66,100,105,106,120,224,249]
- Immunomodulatory drugs[163,231,239]
- Proteasome inhibitors[163,231]

Cellular therapy

- Chimeric antigen receptor (CAR) T cell therapy is associated with a reduced immune response[120], although the duration of this effect is unknown.
- Uncomplicated stem cell transplantation (SCT) with stable engraftment is not associated with long-term impairment of the antibody response. The serological response is impaired shortly after SCT, although this response recovers to approaching that in age-matched individuals with no history of SCT after 6–12 months[69,100,125,130,160,232–234,236,237]

[a]Effects of anti-CD20 monoclonal antibodies last for at least 12 months after completion of therapy[131,134,226,240]. [b]Timing of chemotherapy may be irrelevant[100,120]. [c]No evidence of an adverse effect of intravenous immunoglobulins on vaccination in general[250,251].

been associated with a reduced antibody response. Neutralizing responses have mainly been evaluated for wild-type SARS-CoV-2 (the Wuhan or D614G variant)[100,102]. However, when considering neutralizing activities against VOCs, a progressive reduction in neutralizing titres is observed, especially against the Beta, Delta and Omicron VOCs[65,119].

T cell responses to vaccination against COVID-19, defined as IFNγ release[65,66,125], combined IFNγ and IL-2 release[102,110], or flow cytometric analysis of cellular activation-induced markers[126], are detectable in 46–79% of patients with solid tumours. In contrast to individuals without cancer, these patients often have discordant antibody and cellular responses[65,102,110,126]. Overall, establishing risk factors for poor T cell responses to vaccination is more challenging than for antibody responses. This observation can be attributed to several factors: firstly, differences between the assays can influence the observed responses, and no unified cut-off for T cell positivity exists. For example, some studies have measured T cell reactivity by broadly quantifying cellular cytokine secretion whereas others have used the presence of certain activation markers on virus-specific T cells for this purpose. Secondly, T cell responses have often been assessed in subsets of patients, such as those with no seroconversion, thereby limiting the ability to detect less overt risk factors. Nevertheless, receiving treatment for cancer[110,126], chemotherapy[102] or steroids within 15 days of vaccination[102] has been associated with reduced T cell responses to vaccination. Although reduced in patients receiving chemotherapy, T cells are detectable in the absence of antibody responses in patients receiving chemotherapy or immune checkpoint inhibitors[66]. T cell responses to spike peptide pools specific for VOCs have also been detected[65]. This observation confirms that T cell epitopes are more broadly conserved[82] and less overtly affected by mutations in viral peptides than antibody responses.

The data summarized above originate from studies investigating mRNA or adenovirus-vectored vaccines. Limited information exists on the performance of other COVID-19 vaccines in patients with cancer. In a study from Turkey, investigators analysed the immunogenicity of the inactivated virus vaccine CoronaVac in 47 patients with solid tumours who were mostly receiving chemotherapy. Here, 64% of patients had detectable seroconversion, including both patients receiving immune checkpoint inhibitors. Consistent with data from other studies, age was an independent risk factor for a reduced antibody response[127]. In another study, investigators in Iran assessed the effects of BBIBP-CorV. Serological responses after a full vaccination regimen comprising two doses of BBIBP-CorV were analysed in 364 patients with cancer. Most patients (87%) had a serological response, with older age and the presence of haematological malignancies emerging as the most important risk factors for a reduced response. The vaccine was overall well tolerated[128].

Risk factors affecting vaccine responses in patients with haematological malignancies. Patients with haematological malignancies have a higher risk of developing reduced immune responses to COVID-19 vaccination[65,100,109,110,120,125,129] and, as found in a large-cohort study in the USA, also show a lower VE (VE 74% versus 90% in non-immunocompromised individuals)[111]. Encouragingly, however, long-term survivors of haematological malignancies, including stem cell transplant recipients, have a response to vaccination similar to that in the general population, even if prior therapy was very immunosuppressive[112,130]. Regarding the type of vaccine, mRNA vaccines seem to elicit better immune responses in this population than adenovirus-vectored vaccines[65,120] and this seems to be particularly the case for mRNA-1273 (REFS[111,120,122]). Most studies to date have analysed the antibody-mediated immune response only. A number of individual risk factors have been associated with a reduced humoral immune response, including advanced age, active malignancy and/or lymphoproliferative disorders (BOX 1). Treatment with certain anticancer therapies has been consistently associated with a drastically reduced humoral immune response to vaccination (BOX 2). These suppressive effects are most evident for all B cell-depleting treatments (including CD20, BCMA and CD38 targeted therapies; BOX 2). The magnitude of a patient's spike protein-reactive IgG response correlates with the absolute number of B cells[131] and the suppressive effects of B cell-depleting therapies probably last

for ≥1 year after treatment cessation[120,132], putting these patients at an increased risk of breakthrough infections.

A few studies also investigated the cellular immune response, and perhaps unsurprisingly, T cell responses are consistently more robust, with 30–75% of seronegative patients having specific T cell responses to vaccination independent of disease subtype[65,125,133,134]. Patients with haematological malignancies often have discordant humoral and cellular responses to vaccination, a situation that is rarely observed in other populations[126]. T cell responses to vaccination appear to be less affected by ongoing treatment with B cell-depleting therapies[65,131], highlighting that the ability of these patients to develop adaptive immunity is not completely disrupted. Furthermore, T cell responses, most importantly $CD8^+$ responses, have been detected in patients with cancer receiving B cell-depleting therapies who subsequently developed COVID-19, even in the absence of humoral responses[135,136], indicating that T cell responses alone can provide protection from severe outcomes. Ongoing graft-versus-host disease prophylaxis after allogeneic stem cell transplantation is the only scenario that predisposes to a reduced T cell response despite adequate virus-specific antibody levels. In this setting the vast majority of patients have a detectable serological response, although T cell responses seem to occur in only 20–30% of patients[137,138].

Booster vaccination

Data from initial studies suggest that the waning of the immune response seen in the months following vaccination against COVID-19 is comparable among patients with cancer and in the general population[139], possibly with more pronounced waning in patients with cancer[140]. In the light of these waning antibody responses and a greater proportion of patients with cancer already being at risk of inferior immune responses to vaccination, these patients have been globally prioritized to receive booster vaccination. All studies to date confirm that booster vaccination in these patients is well tolerated[101]. The use of booster vaccines in patients with cancer is further supported by the observation that titres after vaccination are higher in those previously infected with SARS-CoV-2 than in infection-naive patients[65,141]. The available evidence suggests that heterologous vaccination is superior to homologous vaccination, at least in those originally vaccinated with adenovirus-vectored vaccines[142]. Interestingly, vaccination with an adenovirus-vectored vaccine followed by an mRNA vaccine seems to be more effective than a homologous adenovirus-vectored vaccination regimen, in contrast to the experience with mRNA vaccines followed by an adenovirus-vectored vaccine[37] (FIG. 2b). However, the heterogeneity of booster vaccination approaches used in patients with cancer presented thus far precludes any meaningful conclusions on the most effective vaccine combination. Data on immune responses after booster vaccination to date are mainly provided by small observational studies focused on measuring binding antibodies only.

Booster vaccination increases the antibody responses of patients with solid tumours[101,143] even in those vaccinated while also receiving treatment[140]. The level of benefit in these patients appears to be high even in those who were seronegative after the second vaccine dose[144].

Patients with haematological malignancies have a higher risk of not seroconverting following vaccination against COVID-19. This effect is most pronounced in patients with B cell malignancies receiving B cell-depleting therapies (CD20 targeted therapies or BTK inhibitors)[144–146]. Neutralizing antibody responses, which have been investigated only in limited numbers of patients with cancer, can also be boosted using the same vaccine that was initially administered, even in patients lacking a detectable response after the second dose[101,147]. Booster vaccination is also associated with an increased ability to neutralize VOCs[115]. T cell responses to booster vaccination have also only rarely been analysed, and the available data indicate no significant increase[101], a relevant increase only after booster vaccination with an mRNA vaccine[142] and discordant effects in patients who remain seronegative after booster vaccination[144].

In summary, many health-care systems have adopted the practice of routinely offering patients with cancer a total of three doses of a COVID-19 vaccine to provide a level of protection comparable to that in individuals without cancer. In the future, regular booster doses, possibly with novel vaccines, are likely to be required to maintain protection.

Toxicities

Data from prospective studies involving patients with cancer so far indicate that the rate of vaccine-induced adverse events is very similar to that demonstrated in the registration studies with the various vaccine platforms. As an example, the most common adverse events reported in an early study involving patients with cancer were soreness or pain at or around the injection site (63% of vaccinees), local swelling (9%) and systemic reactions including muscle pain (34%), fatigue (34%), headache (16%), fever (10%), chills (10%) and gastrointestinal events (10%)[148]. In the VOICE study, grade 3–4 local and/or systemic adverse events occurring in the first week following each vaccination were seen in 1–2% of patients, but only a quarter of these were deemed vaccine-related. By contrast, lower-grade events were more common following the second vaccination. For example, grade 1–2 fatigue, muscle ache, chills and/or joint ache occurred in up to 44% of patients whereas fever occurred in about 25%[66]. Another study involving both patients with solid tumours and patients with haematological malignancies also failed to reveal any new safety signals[110]. The incidences of both local and systemic vaccine-mediated reactions did not differ between the two patient populations included in this study. Very little knowledge of longer-term adverse effects of COVID-19 vaccines in individuals with and without cancer currently exists, owing to the short observation time.

Initially, receiving immune checkpoint inhibitors was considered a potential risk factor that might increase the risk of developing exacerbated irAEs after COVID-19 vaccination. However, in the VOICE trial, the incidence of grade ≥3 irAEs measured within 28 days of vaccination with mRNA-1273 was ~4% in the cohorts receiving immune checkpoint inhibitors either without or with

chemotherapy[66]. Similarly, data from two other studies reveal no significant increase in the incidence of irAEs in patients vaccinated with mRNA vaccines while also receiving immune checkpoint inhibitors[148,149]. Examples of possible vaccine-related irAEs include a case report describing grade 3–4 exacerbations of psoriasis shortly after COVID-19 vaccination. This patient had stopped receiving an anti-PD-1 antibody 3 months earlier[150]. In another case report, a patient developing multiple irAEs on nivolumab plus ipilimumab, developed a cotrimoxazole-attributed skin rash while receiving steroids and prophylactic cotrimoxazole. The rash disappeared after withdrawal of the systemic medication and topical steroids; however, a new flare occurred shortly after vaccination with a second dose of BNT162b2 (REF.[151]). Also, one patient with colorectal cancer receiving anti-PD-1 antibody monotherapy developed cytokine-release syndrome 5 days after vaccination with BNT162b2 (REF.[152]).

Local lymphadenopathy commonly occurs after COVID-19 vaccination. Vaccine-induced lymphadenopathy found on CT or PET could be mistaken for lymph node metastases in certain patients, such as those with breast cancer or melanoma[153–156], although unlike cancer, the lymph node enlargement usually completely resolves spontaneously[139]. A literature review of data from 15 studies involving >2,000 patients with breast cancer showed that the incidence of vaccine-induced lymphadenopathy ranges from 14.5% to 53%. This lymphadenopathy persisted for >6 weeks in 29% of patients[153]. Radiation recall phenomena, such as pneumonitis or dermatitis, have been described following COVID-19 vaccination[157–159]. These phenomena are rare, although an awareness of this complication is important in order to avoid accidental mis-attribution as an adverse effect of cancer therapy.

Patients who have undergone allogeneic peripheral stem cell transplantation are at risk of cytopenias and worsening of graft-versus-host disease following vaccination, even several years after transplantation. Furthermore, newly emergent graft-versus-host disease complications have been reported after vaccination with BNT162b2 or mRNA-1273 in up to 10% of patients[138,160,161].

In summary, the safety of COVID-19 vaccines in patients with cancer, including the incidence of severe adverse events such as vaccine-induced immune thrombotic thrombocytopenia, is comparable to that in the general population. Certain well-defined toxicity profiles have been reported in specific patient populations. Overall, similar to the general population, the benefits of vaccination against COVID-19 clearly outweigh the risks in all patients with cancer.

Breakthrough infections

Data from large prospective studies demonstrate that vaccination is highly effective at preventing COVID-19-related morbidity and mortality (FIG. 2), although sterilizing immunity will not be achieved and the probability of breakthrough infections increases over time owing to waning immunity[70,162]. Breakthrough infections have also been reported in several follow-up studies monitoring vaccinated patients with cancer[69,100,122,163–167]. Infection risk is clearly lower in patients with cancer after vaccination[168], although breakthrough infections can have a more severe course and a higher risk of mortality than in those without cancer[69,100,163,166].

Data from several studies indicate either reduced or absent antibody responses in those with breakthrough infections[69,100,122,163,165], while others suggest that antibody levels are comparable to those in patients without such infections[169]. Of note, these conclusions are based on limited numbers of patients with breakthrough infections (fewer than ten patients per study), highlighting an ongoing need to associate the immune responses seen in patients with cancer with patterns of infection in larger cohorts. Finally, all data on breakthrough infections were based on measurements of binding antibodies, although levels of neutralizing antibodies against VOCs might be reduced even in the presence of binding antibodies against the wild-type spike protein[65,69].

Increasing protection from COVID-19

Dietary supplementation

Cancer, and related symptoms such as treatment-associated immunodeficiencies, cannot be easily overcome. However, patients with cancer might be particularly prone to vitamin and nutrient deficiencies for several reasons and some of these, such as iron deficiency, have been associated with an impaired immune response to vaccination[170]. So far, no data are available on the benefits of interventional dietary supplementation around the time of vaccination despite increasing evidence that vitamin D or vitamin A might be protective against severe respiratory infections[171–174]. In conclusion, nutrient or vitamin deficiencies in patients with cancer deserve attention, although no evidence exists that dietary supplementation with additional nutrients or vitamins will improve vaccine response.

Role of antipyretic agents

To prevent COVID-19 vaccine-induced adverse effects, some doctors might be tempted to prescribe prophylactic antipyretic medications. However, prophylactic administration of antipyretics has been shown to suppress the immune response to several other vaccines administered during childhood[175–178]. By contrast, this effect is not evident when antipyretic agents are administered therapeutically upon the development of systemic adverse effects; therefore, this seems to be the favoured approach[175]. Despite this general recommendation, data from a subgroup of patients who received prophylactic paracetamol before vaccination with ChAdOx-1 in an early trial reveal no evidence of a reduced immune response[179].

Population immunity

Another way to protect patients with a deficient immune system and therefore an impaired response to COVID-19 vaccination is to adequately vaccinate all close contacts, such as family members, spouses and carers. Evidence supporting this strategy is provided by previous experience with respiratory virus infections such as influenza. Data from a cluster-randomized trial involving nursing home residents showed a 20% reduction in all-cause mortality when influenza vaccine

uptake among staff increased from 31.8% to 69.9%[180]. Similarly, a decrease in nosocomial influenza infections has been reported in an oncology department following the introduction of mandatory influenza vaccination for health-care workers[181]. A high level of population immunity to COVID-19 is expected to develop and this effect is likely to benefit patients with cancer during the later stages of the pandemic (if and when a high level of vaccination is achieved in both the general population and among health-care workers in particular). Initial data from Sweden demonstrate that COVID-19 vaccination of family members reduces the risk of COVID-19 by up to 97% in those who cannot be immunized[182].

Addressing vaccine hesitancy

Vaccine hesitancy is a global phenomenon that poses a major threat to the successful management of the pandemic. Attitudes to vaccination vary considerably across countries ranging from an acceptance rate of >90% to <50%[183,184]. Vaccine hesitancy is probably lower in patients with cancer, but still seems to occur in ~10% of patients[185–188]. High levels of vaccine hesitancy might also suppress population immunity, thus reducing the extent of protection for patients with cancer who cannot mount an adequate immune response themselves. Female and younger individuals, and those who do not believe that the disease itself poses a relevant risk to them, are more likely to have a critical attitude to vaccination. Common reasons for vaccine hesitancy include concerns regarding vaccine safety, misperception of the risks associated with the disease and/or persistent beliefs in misinformation. Importantly, certain examples of misinformation, such as the potential to increase the rate of miscarriage, regardless of a lack of any evidential basis when originally suggested, have been specifically disproven[189,190]. For patients with cancer, there is both no evidence and no rationale whatsoever supporting the suggestion that vaccination against COVID-19 leads to cancer recurrence.

A common method of addressing vaccine hesitancy uses the 5C model: build up confidence in the vaccine, tackle complacency regarding the risks of infection, increase convenience by providing easy access to vaccines, and promote accurate risk calculation and collective responsibility[191]. These 5Cs were derived from the populations of high-income countries. These measures might have to be adapted for lower-income countries, for example, by replacing the last two Cs with communication and context[192]. The last part might be particularly vital for a successful campaign and includes the prudent selection of the communication messenger by choosing individuals who are particularly respected within specific communities[192,193], which might well be the treating oncologist in certain scenarios. Providing valuable training regarding the content of the information[194] and in-depth knowledge on how to approach misinformation can support this[195]. Context-adapted 'nudging' approaches might be particularly helpful[193,196], especially if such measures are designed to counteract negative emotions[197]. Finally, allowing each individual to choose the type of vaccine they receive might increase acceptance[198]. In summary, vaccine hesitancy is largely underestimated and often addressed unprofessionally. A multidisciplinary, professional and context-specific approach is required to address vaccine hesitancy and thus increase vaccination coverage.

Alternatives to vaccination

Passive immunization

Monoclonal antibodies against SARS-CoV-2 would be the logical candidate for those who are unable to mount an immune response and thus require passive immunization. Such approaches are best studied early in the course of COVID-19 and are particularly effective in patients with multiple comorbidities. For example, in a retrospective study the number needed to treat (NNT) with the monoclonal antibodies bamlanivimab, bamlanivimab–etesevimab or casirivimab–imdevimab to prevent one COVID-19 hospitalization among the lowest risk group was 225, compared with an NNT of 4 among those deemed to have the highest risk, determined by number of medical comorbidities[199]. These monoclonal antibodies have shown promising activity in preventing COVID-19 in non-immunized patients. A randomized trial testing a post-exposure prophylaxis approach using casirivimab– imdevimab demonstrated a reduction in the incidence of symptomatic COVID-19 of 81% relative to placebo (in 1.5% versus 7.8% of patients; $P < 0.001$)[200] in people without comorbidities and at least one household contact with a detectable SARS-CoV-2 infection. Regarding pre-exposure prophylaxis, which would be the equivalent of passive immunization, a monthly dose of casirivimab–imdevimab for 6 months was >90% effective in preventing COVID-19 relative to placebo (clinically defined COVID-19 in 0.4% versus 5.4% of patients)[201]. Nonetheless, these studies were conducted prior to the emergence of the Omicron variant, against which there is a high probability that these agents will not be effective[202,203]. Another passive immunization approach involves a cocktail containing the two long-acting antibodies tixagevimab and cilgavimab, which has been tested as a single intramuscular 300 mg administration in >5,000 unvaccinated adults. According to media reports, the risk of developing symptomatic COVID-19 over 6 months was reduced by 83% in the group that received the antibody cocktail, despite >75% of study participants having comorbidities[204]. Given the long-lasting passive immunity and relative ease of administration, this alternative might be very attractive for those who cannot mount an adequate immune response to active vaccination. However, the same caveat regarding VOCs also applies here. The novel monoclonal antibody sotrovimab has been granted emergency use authorization in patients with laboratory-confirmed COVID-19 and at least one risk factor for severe disease[205]. This decision is based on data from a positive study in which 1% of outpatients with symptomatic COVID-19 in the sotrovimab group versus 7% in the placebo group required hospitalization (relative risk reduction 85%, 97.24% CI 44–96%; $P = 0.002$)[206] despite the fact that no significant improvement in clinical outcomes was observed among adults treated while hospitalized with COVID-19 (REF.[207]). Sotrovimab has in vitro activity against a broad range of VOCs including

Omicron; therefore, this agent might be of clinical value in prophylaxis (pre-exposure and post-exposure) and as an early intervention in patients with cancer[116,203,208,209]. In summary, passive immunization is feasible although many of the agents are hampered by a rapid loss of efficacy owing to mutations in VOCs that reduce the affinity of the antibodies. Furthermore, passive immunization strategies, unlike active vaccination, currently do not include a cellular immunity component.

Antiviral drugs

Antiviral prophylaxis, frequently used to prevent zoster reactivation in patients with cancer, provides another method of reducing the risk of severe COVID-19 (REFS[210,211]). The first trials aiming for COVID-19 prophylaxis clearly demonstrated that hydroxychloroquine is ineffective for this purpose[212]. More recently, molnupiravir, an oral prodrug form of a synthetic nucleoside analogue, which provides a 30% reduction in risk of hospitalization or death if taken within 5 days of COVID-19 symptom onset (COVID-19 hospitalization or mortality in 6.8% versus 9.7% of patients (difference 3%, 95% CI −5.9% to −0.1%)) received an FDA emergency use authorization in December 2021 (REF.[213]). Similarly, paxlovid, a combination of two protease inhibitors (PF-07321332 (REF.[214]) and ritonavir) administered orally within 3 days of COVID-19 infection reduces the incidence of hospitalization and death by 88.9% relative to placebo (COVID-19 hospitalization or mortality in 0.72% versus 6.53%, difference -5.81%, 95% CI, −7.78 to −3.84; $P < 0.001$ in the final analysis)[215,216]. Paxlovid has already received preliminary authorization for use from several regulatory authorities. However, interactions via CYP3A4 and p-glycoprotein have to be considered, especially in patients with cancer receiving ongoing therapy. Provided the safety profiles of these agents are deemed favourable and clinical activity against VOCs is retained, both drugs could provide effective pre-exposure or post-exposure prophylaxis for vulnerable patient populations.

Novel vaccines

Given the emergence of VOCs as well as the less-proficient immune responses of patients with cancer who receive vaccines against antigens derived from the spike protein, development of novel vaccination strategies is both necessary and ongoing. Various pharmaceutical companies, including BioNTech, Moderna and AstraZeneca, have initiated clinical trials assessing vaccines that have been modified for improved activity against specific VOCs. Booster vaccination with Beta-specific vaccines has already been shown to induce neutralizing responses against this VOC[217,218]. Studies on Omicron-specific vaccines are also currently ongoing.

Beyond variant-specific versions of current vaccines, other strategies might render vaccines more effective against VOCs. For example, a peptide vaccine composed of various SARS-CoV-2 derived epitopes combined with an adjuvant TLR agonist (CoVac-1) resulted in a very robust T cell immune response in addition to a mild antibody response, with only mild toxicities in a phase I/II trial[219]. Of note, the T cell response was largely unaffected by mutations in the VOC. With this mechanism of action and activity, the CoVac-1 vaccine could be ideal for patients who are likely to have an impaired serological response. Preclinical data indicate that vaccines targeting the highly conserved S2 subunit of the spike protein might induce broad responses against VOCs and, even against other coronaviruses[220].

Global vaccine disparities

Many aspects discussed in this Review are largely of relevance to residents of economically developed countries only. Everything said regarding differential responses to vaccines, toxicities and improvements in vaccine responses only applies if vaccines are available and accessible. Unfortunately, this is not the case for many countries that, owing to inequalities in vaccine distribution, can only achieve a 10% vaccine coverage of the population[221]. In addition to leaving patients in low-income countries potentially unprotected, this disparity contributes to the development of novel VOCs, thus prolonging the pandemic worldwide. Therefore, distributing the available vaccine doses fairly worldwide is of the utmost importance. In this context, from a global perspective in patients with cancer as much as in all other populations, providing primary vaccination is more effective than administering boosters to those who are already vaccinated[221,222].

Future directions

In response to the pandemic, an unprecedented number of studies have addressed the efficacy and immunogenicity of COVID-19 vaccines in patients with cancer. However, several open questions remain and will require additional research. Firstly, most studies have addressed immune responses, although granular data on VE are still needed for specific cancer subtypes and therapies. These data need to be defined for all available vaccines and are research end points that can only be completely addressed in large prospective trials. Secondly, the available data reported thus far mostly originated from heterogeneous patient cohorts, which makes drawing robust conclusions on the optimal approach to COVID-19 vaccination in patients with cancer challenging. Such conclusions include the number of vaccine doses needed, the optimal time between doses, the identification of at-risk patients after vaccination and strategies for additional protection of at-risk patients beyond vaccination — aspects that are especially relevant for patients with haematological malignancies. From these studies, recommendations regarding the management of vaccination in patients with cancer can be deduced[9,223] but many open questions remain. Vaccine responses in paediatric patients with cancer have not been investigated and should be the focus of future studies. Finally, the identification of a reliable correlate of protection is urgently needed for patients with cancer as well as for the general population.

Conclusions

The development of COVID-19 vaccines has been a massive global effort, leading to a marked reduction in the risk of severe COVID-19 and death. Encouragingly, the available vaccines are safe and effective in patients with

cancer, although lower VE has been observed than in those without cancer. A high proportion of patients with solid tumours will develop both humoral and T cell responses following vaccination, although cancer therapies such as chemotherapy can suppress these responses. Patients with haematological malignancies are more vulnerable to breakthrough infections given the reduced VE and often limited immune responses in many of these patients, especially those with B cell malignancies receiving B cell-depleting therapies. Booster vaccines can result in seroconversion in those who were previously seronegative following two vaccine doses. This observation indicates that regular booster vaccines might be effective for immunocompromised patients with cancer. Additionally, high vaccination rates in the community, especially among the families of vulnerable patients and in clinical care settings, will help protect those with impaired vaccine responses.

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Author contributions

A.F., E.G.E. de V., C.H.G., J.B.H., B.W., S.T. and M.v.L.T. researched data for this manuscript, A.F., E.G.E.de V. and M.v.L.T. wrote the manuscript and C.H.G., J.B.H. and B.W. made substantial contributions to discussions of content, and all authors reviewed and/or edited the manuscript prior to submission.

Competing interests

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