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SUMMARY

Vaccinations are fundamental tools in preventing infectious diseases, especially in immunocompromised patients like those affected by non-Hodgkin lymphomas (NHL). The COVID-19 pandemic made clinicians increasingly aware of the importance of vaccinations in preventing potential life-threatening SARS-CoV-2-related complications in NHL patients. However, several studies have confirmed a significant reduction of vaccine-induced immune responses after anti-CD20 monoclonal antibodies, thus underscoring the need for refined immunization strategies in NHL patients. In this review, we summarize existing data about COVID-19 and other vaccine's efficacy in patients with NHL and we propose multidisciplinary team-based recommendations for the management of vaccines in this specific group of patients.

INTRODUCTION

Vaccination is one of the most valuable tools in preventing infectious diseases in the general population. The immunocompromised host is at increased risk of developing complications from vaccine-preventable diseases[1], including SARS-CoV-2.[2,3] On the other hand, immune responses to vaccines may be impaired in people who are immunosuppressed due to chronic diseases or therapies that blunt the immune system (i.e. chemotherapy, immunotherapy, and targeted agents). Most of vaccine trials focused on healthy individuals, thus data on the effectiveness of vaccinations in patients affected by B-cell non-Hodgkin lymphomas (B-NHL), are limited and highly heterogeneous.

The extent of vaccine-induced immune response may vary under different immunosuppressive conditions. In general, moderate to strong reduction is observed in patients affected B-NHL.[4] Nevertheless, the latest Infectious Disease Society of America (IDSA) guidelines about vaccination of the immunocompromised host, published in 2014[5], as well as ECIL-7 guidelines for hematological malignancies (HM)[6], still recommended common vaccinations, with the exclusion of live-attenuated products, the latters excluded due to safety rather than efficacy concerns.

B-NHL patients may present functionally defective responses to antigenic stimuli, including vaccines. Moreover, further impairment in vaccine-induced immune response relates to antitumor therapy, especially when including anti-CD20 monoclonal antibodies (mAbs), such as rituximab. Sustained B-cell depletion occurs within 72 hours after rituximab administration, while recovery of B-cell counts usually starts only 6-9 months after the completion of therapy, with normal levels being reached only after 9-12 months.[7] In a seminal study, B-NHL patients who received rituximab displayed decreased humoral responses against tetanus and poliovirus vaccines.[8]

A systematic review and meta-analysis confirmed that patients on active anti-CD20 treatment develop very low humoral responses to different vaccines and evidenced that antibody levels, although incrementally improving over time, may not reach those of healthy controls even 12 months after therapy completion.[9]

The recent coronavirus disease 2019 (COVID-19) pandemic made clinicians increasingly aware of the importance of vaccinations in preventing potential life-threatening SARS-CoV-2-related complications in NHL patients. Moreover, the significant blunt of vaccine-induced immune responses after standard treatments like anti-CD20 mAbs underscored the need for better

effective immunization strategies in this specific setting of patients. A large body of studies showed limited seroconversion rates following mRNA SARS-CoV-2 vaccination in individuals affected by B-NHL and receiving B-cell depleting therapy,[10] with the time interval between anti-CD20 therapy and vaccination being critical on the probability of generating neutralizing anti-spike antibodies.[11,12] On the other hand, specific T-cell responses following COVID-19 vaccines have been detected in the majority of B-NHL patients treated with anti-CD20 mAbs independently from humoral responses.[13–16]

This review aims to summarize current evidence concerning the performance and safety of different vaccines in people affected by B-NHL, either treatment-naïve or treated with anti-CD20 mAbs and Bruton's tyrosin-kinase inhibitors (BTKi). Moreover, we try to suggest a comprehensive strategy of vaccine immunization for patients with B-NHL in the present early post-COVID-19 pandemic era, where modern novel vaccines have been developed.

METHODS

We identified the main vaccines that present a clinical relevance among adults diagnosed with lymphoma: i) COVID-19 ii) seasonal Influenza virus; iii) Varicella Zoster Virus (VZV); iv) encapsulated bacteria *(Streptococcus Pneumoniae, Neisseria Meningitidis, Haemophilus Influenzae);* and v) Diphtheria, Tetanus, Pertussis and Poliovirus; vi) hepatitis B virus (HBV) and hepatitis A virus (HAV); vii) respiratory syncytial virus (RSV). Both indolent and aggressive B-NHL were considered. The issues of vaccinations in NHL patients undergoing allogeneic stem-cell transplant or CAR T-cells[17] are beyond the scopes of the present review and are not discussed here. A qualitative literature review (using Mesh and free text terms) was conducted on PubMed up to September 2023, with no language restrictions.

COVID-19 VACCINATION

1) Introduction

Susceptibility to severe COVID-19 has been identified very early in patients with NHL, highlighting a mortality rate of up to 32%.[2] Similarly, the largest series in the pre-vaccine era pointed out a 100-day mortality of 21% in indolent and 30% in aggressive NHL. Independent risk factors for mortality were age >70 years, male gender, low platelets counts (<100 x 10^9/l), and low lymphocyte counts (<0.65 x 10^9/l).[18]

SARS-CoV-2 binds to angiotensin-converting enzyme 2 (ACE-2) receptors expressed on the epithelial cells of the oral mucosa and lung alveolar type II cells through the receptor-binding domain (RBD) of the spike protein.[19–21] The first vaccines against SARS-CoV-2 were approved between the end of 2020 and the beginning of 2021 based on diverse platforms, i.e. full-length spike messenger RNA (mRNA) (BNT162b2[22] and mRNA-1273[23]) and spike adenovirus-based DNA (ChAdOx1 and Ad26.COV2.S). The novel mRNA technology induced high titers of anti-RBD (or anti-spike) antibodies, which directly correlated with virus-neutralizing ability.[24] Both mRNA products consisted of two doses administered 21-28 days apart and were authorized based on >90% efficacy in the reduction of symptomatic COVID-19 disease in randomized clinical trials.[23,25] Although a variety of other vaccines based on adjuvanted recombinant spike protein immunization (i.e. NVX-CoV2373[26]) were developed later on, mRNA-based vaccines shortly became the standard at the global level. Booster doses of both mRNA products were approved in late 2021, as the effectiveness of primary vaccination declined over time, due to waning immunity[27] and to the emergence of variant of concerns (VOC), carrying neutralization escape mutations in RBD sequence (in particular omicron subtypes).[28] In the third quarter of 2022 two bivalent vaccines containing equal amounts of spike mRNA from the ancestral Wuhan strain and omicron BA.4–BA.5 sub-variants were approved as new boosters.[29] Finally, updated mRNA vaccines against currently dominant variants, such as XBB1.5, have been recently approved by the US Food and Drug Administration (FDA).

Notably, immunocompromised subjects were not included in registered clinical trials of SARS-CoV-2 vaccines. As lymphoproliferative diseases and B-cell depletion therapies attenuate immunologic responses to conventional vaccines,[9] many observational studies evaluating COVID-19 vaccine effectiveness in the setting of NHL patients have been carried out throughout the world. Overall, these studies are largely heterogeneous in terms of design, population, sample size, treatments, vaccine type and number of booster doses, endpoints, biologic assays for efficacy measures, and publication date (Tables 1-3).

2) Immune responses to SARS-CoV-2 vaccines in patients with non-Hodgkin lymphoma

Early studies evaluating immune responses after a primary full course of SARS-CoV-2 vaccines (2 doses) in patients with NHL were published in mid-2021 (Table 1).[30–34] A seminal Israeli study evaluating 149 patients with either aggressive or indolent NHL showed that overall serological responses to the BNT162b2 vaccine were nearly halved compared to healthy controls (49% vs 98.5%, p<0.001). Seroconversion was detected in 89% of treatment-naïve patients, in 66.7% of patients who received rituximab or obinutuzumab-based regimens earlier than 6 months, and only in 7.3% of those actively treated with anti-CD20-containing regimens, with longer interval since last anti-CD20 administration independently predicting positive serologic responses.[30] Another study from the United States (US) showed a similar pattern of antibody responses to mRNA vaccines after B-cell-directed treatments (11% <9 months vs 88% >9 months).[34]

The first meta-analysis was published in December 2021 by Gagelmann and colleagues who examined 49 studies including over 11.000 individuals with HM. Overall, primary vaccination with mRNA or vector-based anti-SARS-CoV-2 vaccines yielded a 58% seroconversion rate in patients with aggressive and 61% in those with indolent NHL (98% in healthy controls). Active treatment was associated with poor antibody response (35%). In particular, anti-CD20 within 1 year and BTK inhibitors treatment were associated with 15% and 23% response rates, respectively. In contrast, being in remission and prior COVID-19 were associated with high seroconversion rates (pooled responses 72% and 87%, respectively). Both mRNA vaccines yielded high response rates (>90%), without significant differences.[35] These key findings were substantially confirmed by subsequently published meta-analyses (Table 2).[36–38]

An important US study reported a reduced neutralizing capacity of vaccine-induced antibodies against novel SARS-CoV-2 VOC in patients with B-NHL: neutralizing titers against delta and omicron variants resulted in 6- and 42-fold lower than those against the ancestral Wuhan strain, respectively.[39]

The limited vaccine responses in patients with NHL led to a new strategy involving the increase of the number of doses (boosters). Among 584 patients with HM receiving a third mRNA-1273 vaccination, median anti-spike IgG levels were comparable to those observed in healthy individuals following primary vaccination. Of note, improvement in neutralizing ability was also observed. However, NHL patients with recent history (less than 12 months) or active anti-CD20

therapy were less responsive to the booster dose (seroconversion in 70.6% and 22.5%, respectively), as well as those treated with BTKi.[40] A similar pattern of seroconversion after a third booster dose was shown in other studies.[15,41,42] Interestingly, in a recent report a fourth dose increased seroconversion and neutralization titers against wild-type and omicron variants from about 50% to 90%, in patients with B-NHL.[43]

Generally, the incidence of breakthrough infections in NHL patients who received SARS-CoV-2 vaccines was low and largely dependent on the prevalent VOC. Notably, a prospective Italian study showed that in vaccinated HM patients the incidence of breakthrough infections increased from 1.17 to 9.82 per 10.000 person-days.[15] Nevertheless, COVID-19-related hospitalization and case fatality rates among patients with lymphoma during the omicron surge were lower (34% and 9%, respectively) compared to the early pandemic (60% and 34%, respectively),[44] possibly due to the progressive implementation of vaccination and treatments against SARS-CoV-2. In sequential EPICOVIDEHA reports, case fatality rates in vaccinated NHL patients decreased from 16% (1-2 vaccine doses, prevalence of alpha- and delta strain)[45] to 9% (2-4 vaccine doses, prevalence of omicron),[46] especially in the subgroup who received 4 doses.[47] However, NHL patients remained particularly susceptible to breakthrough infection and severe COVID-19, especially if recently treated with anti-CD20 mAbs.[48]

Interestingly, a recent multivariable analysis from the prospective UK PROSECO study on 592 lymphoma patients, who received one to four vaccine doses, recognized two threshold values for anti-spike IgG levels after three (820 BAU/ml) and four doses (41 BAU/ml), significantly associated with lower risk of breakthrough infections. The >20-fold lower threshold after four vaccinations implies that antibody affinity increases after multiple doses. Notably, lower anti-spike IgG levels were also associated with increased risk of hospital admission.[49] These data support a possible risk-stratification strategy for protecting lymphoma patients from COVID-19 disease based on anti-spike titers, advocating individualized booster uptake for the most vulnerable subjects.

Humoral and cellular responses work together against viral infections. SARS-CoV-2 specific cellular response has been recognized as essential for viral elimination and prevention of disease worsening.[50–52] Indeed, observational studies evidenced detectable SARS-CoV-2-specific T-cell responses in a substantial proportion of vaccinated B-NHL patients independently from humoral response status (Table 3).[15,16] In a study by Gressens et al., primary vaccination induced specific

CD4 and CD8 T cell responses in 14 lymphoma patients treated with anti-CD20 plus chemotherapy; of note, only one of them developed humoral response.[53]

The PROSECO study showed that 63% of patients displayed antigen-specific T-cell responses, which increased after a third dose irrespective of their treatment status.[54] Undetectable cellular response, as well as the absence of anti-spike antibodies, were associated with a higher proportion of hospitalization in case of breakthrough infection.[49] Similarly, an Italian study documented effective T-cell-mediated immune response in a high rate of NHL patients receiving anti-CD20 mAbs (74% of which were anti-spike seronegative).[16]In another small study T-cell response was conserved in patients undergoing rituximab or obinutuzumab maintenance, despite complete B-cell depletion.[55] Preliminary data suggest that cellular immunity is quite durable. A prospective Spanish observational study in 270 patients with mixed HM (85 with lymphoma, 49 treated with anti-CD20 mAbs) showed that 84.4% of patients maintained a detectable cellular response 6 months after the second mRNA-1273 dose. Notably, neither anti-CD20 or BTKi therapy did impact on cellular response persistence.[56]

Overall, mRNA vaccines may elicit SARS-CoV-2 specific T-cell response even in the absence of adequate B-cell function, suggesting a potential benefit for vaccination despite the lack of seroconversion, although it has to be acknowledged that all these studies about T-cell response were performed *in vitro*.[57–59]

All these findings substantially point out that patients with lymphomas treated with anti-CD20 antibodies should undergo vaccination. For newly diagnosed B-NHL patients who are candidates for anti-CD20-based therapy, current guidelines suggest completing the vaccination with a booster dose(s) before treatment initiation[60], as anti-CD20 mAbs seems to spare pre-established humoral immunity to COVID-19 vaccines. A seminal study showed that among 15 patients who initiated rituximab shortly after vaccination, 10 generated blocking antibody response, which persisted 4 months after lymphoma treatment initiation in 6 out of 10 cases. These data, although limited, suggest a policy of immunizing before treatment whenever possible.[12] Vaccinating against SARS-CoV-2 before starting treatment against lymphoma is also suggested by Passamonti et al. in a recently published review. However, the authors also underline that urgent treatment should not be delayed due to vaccination.[61]

Concerning BTKi treatment, a small proof-of-concept study in 17 patients with Waldenström Macroglobulinemia (WM) suggested that a closely monitored BTKi pause before (3 days) and after

(21 days) the third dose of vaccine might significantly improve antibody.[62] Based on these preliminary data, a consensus panel suggested considering this strategy in selected cases of WM patients under BTKi.[63]

Current US Centers for Disease Control and Prevention (CDC) guidelines recommend that HM patients should get vaccinated as soon as possible with 3 primary doses every 4 weeks, followed by a first booster dose after 3 months and a second booster after 4 months. Updated vaccines against the last omicron sub-variants (XBB1.5) are recommended. The timing of vaccination depends on individual therapy and may ideally occur before systemic therapy initiation. ESMO and ECIL-9 also suggest that relatives, family, and caregivers of patients should be vaccinated.[64,65]

Pre-exposure prophylaxis with the long-acting mAbs combination tixagevimab/cilgavimab, approved by FDA and EMA in December 2021 and March 2022, respectively, was employed with preliminary encouraging results in patients with B-NHL receiving B-cell depleting treatments.[66,67] However, the spreading of omicron sub-variants, such as BQ1.1 and XBB1.5, substantially insensitive to tixagevimab/cilgavimab[68], led FDA to retire its authorization on January 2023. Of note, new monoclonal antibodies potentially active against both historical and current SARS-CoV-2 variants, such as AZD3152, are currently being tested in clinical trials (NCT05648110). COVID-19 vaccination remains therefore the most effective approach to avert serious COVID-19 complications, including hospitalization and mortality. Additional booster doses (including yearly vaccination) with variants-specific vaccine products are among the possible tools. The trend of the pandemic and the emergence of novel viral variants will most likely impact future choices.

Seasonal influenza Virus

Seasonal influenza (flu) is one of the most common infectious diseases worldwide, impacting on all age groups and affecting morbidity and mortality. To date, the most effective method for preventing influenza is annual vaccination.

Patients with NHL are at particular risk of influenza virus infection and complications, because of constitutive immunodeficiency, immunosuppressive therapies, and frequent occurrence in people with advanced age. Indeed, the CDC as well as major clinical societies recommend seasonal influenza shots for cancer patients, including HM.

Data on the immunogenicity of influenza vaccination in patients with NHL are not homogeneous, possibly due to antigenic variability of seasonal influenza strains and heterogeneity of the studies

in terms of patients' characteristics, disease features, and treatment regimens (Table 4). Seminal studies in the pre-rituximab era yielded contrasting results. A study published in 2005 reported on the limited efficacy of influenza vaccination in 29 lymphoma patients during the 2003-2004 flu season[69]: only 10% of the patients were able to mount a significant response (defined as 4-fold antibody titer increase) to at least one influenza A or B antigen, compared to 45%-48% in the control group. Of note, most of the patients with lymphoma enrolled in this study were receiving (or had recently completed) chemotherapy at the time of vaccination. In contrast, in another study on 163 patients, influenza vaccination induced an adequate level of immune response in a substantial proportion of NHL patients.[70]

Increasing the number of doses (two versus one) does not seem to impact, as demonstrated by two randomized studies.[71,72] On the contrary, the amount of vaccine product administered may affect immunogenicity. In a double-blind controlled trial on 27 adult patients affected by B-NHL, 60% and 40% of patients receiving a recombinant vaccine containing respectively 135 μg and 45 μg of hemagglutinin A and B showed an increase in neutralizing antibody titers; in contrast, no significant response was observed in 4 patients vaccinated with a trivalent commercial vaccine containing 15 μg hemoagglutinin A and B.[73]

Published data generally indicate that rituximab-induced B-cell depletion may blunt response to influenza vaccination. A recent meta-analysis showed that seroconversion after seasonal flu vaccines seems to be abrogated for at least 6 months following anti-CD20 therapy, and may not reach the level of healthy controls even 12 months after treatment completion, with estimated seroconversion rates of 3-43%.[9] This finding seems to be related to persistent perturbation in B-cell subsets, as demonstrated in an early study on 31 NHL patients who were vaccinated against three influenza strains in the 2008-2009 season, at least 6 months after interruption of the rituximab-containing regimen. Compared to healthy controls, vaccine-induced increase of antibody titers was significantly lower among patients and was associated with limited seroconversion rates.[74]

Major international guidelines strongly recommend yearly vaccination against influenza in all immunocompromised individuals, including those affected by lymphoma,[75] except in patients receiving intensive chemotherapy or undergoing rituximab in the previous 6 months, where the response to the vaccine is unlikely.[6] Recombinant or inactivated (possibly quadrivalent) products should be used, whereas live, attenuated vaccines are generally contraindicated. For elderly

patients (≥65 years), an adjuvant or high-dose influenza vaccine is recommended.[6,75] Whenever possible, such as for patients with indolent lymphoma patients during the seasonal flu vaccine window, anti-CD20 therapy initiation should be delayed at least two weeks after vaccination.[8]

Varicella Zoster Virus vaccination

VZV, a DNA virus belonging to the *Herpesviridae* family, establishes latency in sensory neural ganglia after primary infection (varicella or chickenpox), in elderly or immunocompromised patients, due to waning of cellular immunity.[76] B-NHL patients are at high risk of VZV reactivation, due to disease- and treatment-related immunosuppression. It is known that VZV reactivations can occur up to 50 months after initial immuno-chemotherapy in B-NHL patients, especially if exposed to bendamustine plus rituximab.[77,78] Other risk factors for VZV reactivation in NHL patients are age >60 years, high cumulative dose of corticosteroids, and advanced lines of therapy.[77] Thus, antiviral prophylaxis with acyclovir or valacyclovir is recommended especially in B-NHL patients with these treatment-related risk factors for at least one year, although duration may be extended according to individual and treatment-related risk assessment.[79,80]

At present, two vaccines are available for the prevention of Herpes Zoster, i.e. the live attenuated VZV vaccine (*Zostavax*), which is contraindicated in immunosuppressed subjects due to risk of reactivation, and the adjuvanted recombinant (non-live) subunit zoster vaccine (*Shingrix*).

Shingrix was recently approved In Europe for the prevention of VZV and post-herpetic neuralgia in subjects aged more than 50 years and those aged ≥18 years who are at increased risk of reactivation. The ZOE-50 phase 3 randomized trial documented a clear reduction of the risk of VZV reactivation at 3 years (96-98% efficacy) in approximately 15,000 subjects aged >50 years.[80]

Dedicated studies specifically evaluated the safety, immunogenicity, and efficacy of *Shingrix* in patients with HM (Table 4). A large randomized study was conducted in approximately 600 patients with HM, including 41 NHL cases in the experimental arm and 39 in the placebo arm. The double dose of recombinant vaccine was given 1-2 months apart, either during chemotherapy or at the end of treatment. Seroconversion was defined as at least a fourfold increase from the cut-off in VZV anti-glycoprotein E IgG antibody for seronegative subjects or at least a fourfold increase from baseline for initially seropositive ones. A subset of patients underwent evaluation of cellular immunity (CD4+ T-cell frequencies using glycoprotein E peptides). Around 30% of patients received antiviral prophylaxis. Safety and mortality were comparable in the two arms. The risk

reduction in the incidence of VZV reactivation was 87.2%. Notably, the two patients who developed Herpes Zoster in the vaccine group received rituximab within 6 months.

A post-hoc analysis showed that *Shingrix* induced lower humoral immune response in patients with B-NHL with respect to patients with other HM at all time points (1, 2, and 13 months), likely due to anti-CD20 therapy. On the contrary, the percentage of NHL patients with cellular immunity responses was comparable and, glycoprotein E CD4+ T-cell responses remained above the pre-vaccine levels after 12 months from the second dose.[81]

The efficacy of *Shingrix* was also demonstrated in the autologous stem-cell transplant (ASCT) setting.[82] A recent pilot study confirmed the long-term efficacy of *Shingrix* in patients with chronic lymphocytic leukemia (CLL) or WM under active BTKi treatment, both in terms of humoral and cellular immunity (41.9% and 54.8% at 24 months, respectively).[83]

Overall, available data strongly argue in favor of vaccination with adjuvanted subunit VZV vaccine in patients with lymphoma. Notably, in patients who are candidates to receive anti-CD20 mAbs, it would be desirable to administer at least the first dose of *Shingrix* before the start of therapy. This strategy should be complemented by conventional prophylaxis with acyclovir or valacyclovir in patients undergoing treatments with high cellular immunity impairment potential (i.e. those receiving bendamustine).[79] Additional data are needed to clarify the long-term duration of vaccine-induced immunity and to address the possibility of safely omitting or discontinuing antiviral prophylaxis in patients who achieve seroconversion after *Shingrix,* as assessed one and 12 months after the second dose.

Encapsulated bacteria

Patients with B-NHL, especially when exposed to B-depleting cell therapies, exhibit a significantly lower immune response to encapsulated bacteria, increasing their risk of developing severe infections by these agents. Indeed, the main risk factors that predispose to severe or recurrent infection by these organisms reflect the importance of B-cell receptor in signaling and producing the complement-fixing and opsonizing IgG antibodies.[84]

Accordingly, vaccination against encapsulated bacteria, including *Streptococcus pneumoniae, Neisseria meningitidis* (also known as *Meningococcus*), and *Haemophilus influenzae B*, are recommended outside of the routine-age-based indications, as the risk for these vaccine-preventable diseases is particularly high in case of altered immunocompetence.[85] Since patients

receiving intensive chemotherapy or anti-CD20 mAbs are unlikely to respond, these vaccinations should be offered before treatment initiation, whenever possible, or delayed for at least 6 months after the last dose of anti-CD20 mAbs.[5,6]

Pneumococcal vaccination

Pneumococcal infections are a serious threat for subjects affected by B-NHL, as *S. pneumoniae* invasive diseases reach high incidences in this group of patients, along with a frequent severe clinical picture and high mortality.[86]

Currently, two types of vaccines against pneumococcus are available: the conjugate vaccines (PCV15 or PCV20) and the 23-valent polysaccharide vaccine (PPSV23).

PCV15/20 could produce a greater immune activation, immune response, and, in turn, long-lasting immune memory.[87] On the contrary, PPSV23 covers a greater number of pneumococcal serotypes but may not induce the same level of immune response, resulting in a less effective and lasting immunity, especially in older or immunocompromised patients.[88] In fact, PPSV23 contains capsular polysaccharide antigens, that elicit a T-cell independent antibody response, while conjugates vaccines, as a result of the addition of protein carrier combined with capsular polysaccharides, produce a T-cell dependent immune response with the development of immune memory.[89] Very few real-world data about pneumococcal vaccinations have been reported in patients with B-NHL (Table 4). A small pivotal study showed that only 1 out of 8 patients with indolent NHL who received the PPSV23 vaccine 6 or 12 months after rituximab therapy developed protective titers of pneumococcal antibodies (12.5%).[90]

According to ECIL-7 and US guidelines[6,91], adult patients with HM who have not previously received PCV should receive one dose of either PCV20 or PCV15. When PCV20 is used, no additional PPSV23 doses are recommended. When PCV15 is used, it should be followed by a dose of PPSV23 after a 2-month interval (sequential schedule), although definite evidence is lacking. At this purpose, compared to high serologic response rates observed in healthy population (82%)[92], a recent report pointed out a low serologic response to this strategy in patients with CLL (10.5%), especially if treated (3%).[93]

Overall, considering available data, pneumococcal vaccination may be recommended at the time of diagnosis, at least 14 days before starting B-cell depleting treatments, or after more than 6-12 months from the last administration of anti-CD20 mAbs.

Haemophilus influenzae B vaccine

Since the introduction of the *Haemophilus influenzae* type b (Hib) vaccine in the US and European countries, invasive infections by this bacterial agent have become uncommon. Nevertheless, life-threatening infections, including pneumonia, pleuritis, skin and soft tissue infections, septic arthritis, meningitis, and mediastinitis have been reported in immunocompromised and cancer patients.[94]

In general, the Hib conjugate vaccine is recommended for all children through age 59 months. As a result of universal vaccination started in the 1990s, a wide number of adults are currently immunized for Hib. Hib vaccination is mandatory for any unimmunized subject who is undergoing a splenectomy, such as in patients with splenic lymphomas.[95] Similarly, any other immunocompromising condition should be considered a reason to prioritize vaccination.

Hib conjugate vaccine was demonstrated to induce satisfactory rates of serologic responses (62.5%) even in lymphoma patients pre-treated with rituximab 6 to 12 months before (Table 4).[90] In unvaccinated adults, one single dose of conjugated Hib vaccine is advisable; no booster doses are recommended, even in patients undergoing immuno-chemotherapy.[5]

Meningococcal vaccination

Invasive meningococcal disease may occur as meningitis and/or bloodstream infection and represents an uncommon but life-threatening infection. Importantly, the principal risk factors for this infection are represented by congenital or acquired immunodeficiency, as well as hypo- or asplenia.[96]

Despite the availability of very effective and safe antimicrobial therapies for *Neisseria meningitidis*, the onset of invasive disease is burdened by high mortality and disabling sequelae, especially in immunocompromised hosts.[97] Hence, vaccination is recommended for subjects with anatomic or functional asplenia, including sickle cell disease, HIV infection, and persistent complement component deficiency, such as patients receiving eculizumab.[98] However, an increased mortality risk ranging from 2- to 40-fold was also noticed in subjects with other immune dysfunctions, including patients with lymphoma,[97] in which vaccination should be warranted.

To date, three types of meningococcal vaccines are available in the UK: meningococcal conjugate - either as tetravalent MenACWY (Nimenrix) and Hib-MenCY, a combination of *Haemophilus*

influenzae type B and *Neisseria meningitidis* serogroup C vaccine, serogroup B meningococcal quadricomponent vaccine, 4CMenB (Bexero) and FHBP-based B meningococcal vaccine (Trumenba). The schedule for adult immunocompromised patients should be composed of a MenACWY primary series followed by a booster dose after 5 years. In addition, the serogroup B meningococcal vaccine should be offered, followed by a booster dose after 1 year and then every 2-3 years in patients at prolonged increased risk for meningococcal disease.[99]

Dyphteria, Tetanus, Pertussis and Poliovirus

Very few data concerning the persistence of immunity to tetanus, pertussis, diphtheria, and polio vaccinations after anti-CD20-based therapy for lymphoma are available (Table 5).

In a single-center study, Einarsdottir et al[100] evaluated humoral immunity against tetanus, diphtheria, and polio in 104 adult patients with HM (80 with lymphoma) before and after treatment (rituximab-containing in 42). Both tetanus and diphtheria antibody levels were found significantly lower after chemotherapy, while the rates of patients who retained humoral immunity were 76% and 73% for tetanus and diphtheria, respectively. Notably, lower antibody levels were detected in older patients. Polio immunity seems to be better preserved, as, more than 90% of patients showed post-treatment protective antibody titers. Rituximab doesn't seem to significantly impair immunity to early childhood vaccination, although further data are warranted. However, approximately a quarter of patients undergoing rituximab-based treatment results unprotected against diphtheria and tetanus. It is well documented that immunity to tetanus and diphtheria declines over time[101] and it is speculated that the decrease could be accelerated by anti-CD20 therapy. As in the general population, booster doses are recommended every 10 years. In addition, serological testing and revaccination after six or more months from the last anti-CD20 administration should be considered in lymphoma patients.

Hepatitis B virus (HBV) and hepatitis A virus (HAV)

The universal vaccination of infants and adolescents with recombinant HBV vaccine (2-3 doses according to manufacturer) is now a common practice in many countries, yielding seroconversion in >95% of cases[102]. However, given the usually high median age of onset of lymphoma, the majority of patients are not vaccinated. HBV Screening (including HBsAg, anti-HBc antibodies, anti-HBs antibodies, and HBV-DNA if HBsAg negative/anti-HBc positive) is considered mandatory

for all lymphoma patients, especially if anti-CD20-containing treatment is planned. In this case, patients with evidence of HBsAg, anti-HBc antibodies and HBV-DNA positivity should receive antiviral prophylaxis concurrently with anti-CD20 treatment.[103] Whenever an immediate active treatment is not predicted, such as in indolent lymphoma patients undergoing a *"watch and wait"* strategy, unvaccinated subjects or those with undetectable protective anti-HBs antibodies may receive active immunization with a full course of HBV vaccination; HBV vaccine is indeed recommended if additional risk factors are present (e.g. sexual partner with chronic HBV infection, risk by percutaneous exposure, travelling in countries with high HBV infection prevalence).[102] Very few data about HBV vaccine efficacy in lymphoma patients are available. A recent study suggests a substantial rate of seroprotection (64%) in elderly B-NHL patients undergoing HBV vaccination after more than 12 months from rituximab completion (Table 5).[104]
HAV inactivated vaccine (two doses 6 months apart) is recommended in nonimmune subjects living or traveling to endemic areas. According to CDC, immunocompromised patients (including those undergoing transplantation or receiving immunosuppressive treatments) are at high risk of developing severe HAV disease.[105] Given the paucity of data about HAV vaccine efficacy in the specific setting of lymphoma patients (Table 5)[8], similar recommendations concerning the timing of vaccination after anti-CD20 administration (at least 6-12 months) can be inferred from other types of vaccines. Alternative immuno-prophylaxis with protective intravenous immunoglobulins may be adopted in case of short-term exposition in patients predicted not to develop protective immunity after anti-CD20 therapy.[106]

Respiratory syncytial virus

Respiratory syncytial virus (RSV) has been increasingly recognized as a relevant respiratory pathogen among older adults and people with pre-existing comorbid conditions[107], including immunocompromised hosts such as hematologic and transplanted patients.[108] In 2023, results from clinical trials were published concerning the effectiveness and safety of vaccination against RSV in pregnancy and adults aged 60 or older.[109] This led to the approval of the two vaccine products currently licensed in the US: RSVPreF3 (Arexvy) and RSVpreF (Abrysvo). CDC recommendations indicate that adults 60 years of age and older, including those immunocompromised or affected by hematologic diseases, should receive a single dose of RSV vaccine after discussion with their health care providers (shared clinical decision-making, SCDM)

to establish possible benefits at the single individual level.[110] Based on these data, we suggest to consider anti-RSV vaccination in elderly subjects affected by lymphoma, although further studies are needed to establish to what extent this and other groups such as adults aged 18-59 years bearing known risk factors may benefit from RSV vaccination.

DISCUSSION

The present review focuses on the available data concerning the effectiveness of vaccination in patients affected by lymphomas. Although vaccination is in general highly recommended in this cohort of at-risk patients, data are often limited and heterogeneous. Despite the frequent lack of comparison with healthy controls and the high variability in the design, type, and dimension of available studies, we believe that at least three general concepts can be extrapolated. First, the large majority of vaccines display reduced immunogenicity in patients with lymphoma. Second, patients undergoing anti-CD20 mAbs are at particular risk of limited or missed immune response to most vaccines. Third, the substantial biological heterogeneity across lymphoma subtypes could influence the ability of vaccines to mount an adequate immune response, making it difficult to apply the same conclusions to different lymphoma subtypes.

Nonetheless, vaccinations remain strongly recommended in patients with lymphoma, as they represent one of the most powerful tools to reduce the risk of life-threatening infections in this setting, without any substantial safety issues. Overall, response to vaccines among subjects undergoing B-cell depleting treatments such as anti-CD20 mAbs is considered “low” (<40% compared to healthy controls).[4] Programming vaccination in time intervals when patients are likely less immunosuppressed (i.e. before initiating immunosuppressive treatment or at least 6 months after therapy interruption) may improve vaccine protection.[111] As recently shown in the setting of SARS-CoV-2 prevention, an effective strategy was the increase the number of additional doses following primary vaccination[35,44,112]; however, this strategy may not be equally effective for other vaccines, such as seasonal influenza, for which the use of high-dose vaccines is preferred.[71] In addition, vaccines should be supported by non-vaccine strategies, such as shielding measures (e.g. face masks, hand hygiene, physical distancing) or passive immunization with long-acting mAbs, whose clinical effectiveness against SARS-CoV-2 infection has been documented, at least in periods when sensible variants were prevalent.[113]

Patients affected by lymphomas must be evaluated as soon as possible after diagnosis for the possible administration of vaccines, with special consideration given to the potential time available for effective immunization before treatment initiation, which could be very limited in the case of aggressive lymphomas. We believe that this comprehensive strategy represents ultimately a crucial step for the optimal management of patients and the success of lymphoma treatment, as it is convincingly demonstrated that a well-established vaccine-induced immunity is preserved during anti-CD20-containing therapies, whereas vaccinations after anti-CD20 therapy initiation are largely ineffective, at least at humoral immunity level.[12]

According to the available evidence, we summarized in Table 6 our recommendations about the management of different vaccines in patients affected by NHL.

In general, most countries around the world adopt similar vaccination programs; however, vaccination schedules may vary from country to country. For example, the US and Canada recommend influenza vaccine to everyone over 6 months of age, while the UK vaccination program targets children over the age of 2, adults over 65, pregnant women, and special groups such as those with serious medical conditions. Differences in COVID-19 vaccination policies worldwide and across European countries have been reported.[114,115] Possible reasons include epidemiological characteristics of a particular population, economic issues, health system organization, and policies. Thus, we recognize that making globally valid recommendations is complicated and that there is no single immunization schedule for worldwide use. It is therefore essential for physicians to know and follow vaccination schedules and indications in force in their country. Further information can be found at *https://vaccineknowledge.ox.ac.uk/* and *https://vaccine-schedule.ecdc.europa.eu/*. In addition, we acknowledge the rapid evolution and the consequent need for frequent updates in some fields (i.e. COVID-19 prevention and management), making it difficult to provide long-lasting recommendations.

In conclusion, although the response to vaccines in patients affected by lymphoma may be lower than in healthy people, vaccinations remain strongly recommended. Strategies to improve vaccine effectiveness should be pursued whenever possible, including additional doses, high-dose formulation, and repeated vaccination. Further studies addressing prospectively the efficacy and immune response duration of different types of vaccines in the setting of specific lymphoma subtypes, such as the ongoing Italian *FIL_FollVax22* and the British *STARVINSKY* study, are eagerly awaited.

AUTHOR CONTRIBUTION:

Michele Merli, Andrea Costantini, Silvio Tafuri, Davide Fiore Bavaro, Carla Minoia, Erika Meli, and Guido Gini reviewed the literature. Michele Merli, Andrea Costantini, Silvio Tafuri, Davide Fiore Bavaro, Carla Minoia, Erika Meli, Stefano Luminari, and Guido Gini wrote the final manuscript.

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BIBLIOGRAPHY

1. Eibl MM, Wolf HM. Vaccination in patients with primary immune deficiency, secondary immune deficiency and autoimmunity with immune regulatory abnormalities. *Immunotherapy*. 2015;7(12):1273–1292.
2. 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(25):2881–2892.
3. Passamonti F, Cattaneo C, Arcaini L, et al. Clinical characteristics and risk factors associated with COVID-19 severity in patients with haematological malignancies in Italy: a retrospective, multicentre, cohort study. *Lancet Haematol.* 2020;7(10):e737–e745.
4. See KC. Vaccination for the Prevention of Infection among Immunocompromised Patients: A Concise Review of Recent Systematic Reviews. *Vaccines*. 2022;10(5):800.
5. Rubin LG, Levin MJ, Ljungman P, et al. 2013 IDSA clinical practice guideline for vaccination of the immunocompromised host. *Clin. Infect. Dis. an Off. Publ. Infect. Dis. Soc. Am.* 2014;58(3):e44-100.
6. Mikulska M, Cesaro S, de Lavallade H, et al. Vaccination of patients with haematological malignancies who did not have transplantations: guidelines from the 2017 European Conference on Infections in Leukaemia (ECIL 7). *Lancet Infect. Dis.* 2019;19(6):e188–e199.
7. McLaughlin P, Grillo-López AJ, Link BK, et al. Rituximab chimeric anti-CD20 monoclonal antibody therapy for relapsed indolent lymphoma: half of patients respond to a four-dose treatment program. *J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol.* 1998;16(8):2825–2833.
8. van der Kolk LE, Baars JW, Prins MH, van Oers MHJ. Rituximab treatment results in impaired secondary humoral immune responsiveness. *Blood*. 2002;100(6):2257–9.
9. Vijenthira A, Gong I, Betschel SD, Cheung M, Hicks LK. Vaccine response following anti-CD20 therapy: a systematic review and meta-analysis of 905 patients. *Blood Adv.* 2021;5(12):2624–2643.
10. Fattizzo B, Bortolotti M, Rampi N, et al. Seroconversion to mRNA SARS-CoV-2 Vaccines in Hematologic Patients. *Front. Immunol.* 2022;13:852158.
11. Narita K, Nakaji S, Tabata R, et al. Antibody response to COVID-19 vaccination in patients with lymphoma. *Int. J. Hematol.* 2022;115(5):728–736.

12. Shree T, Shankar V, Lohmeyer JJK, et al. CD20-Targeted Therapy Ablates De Novo Antibody Response to Vaccination but Spares Preestablished Immunity. *Blood Cancer Discov.* 2022;3(2):95–102.
13. Liebers N, Speer C, Benning L, et al. Humoral and cellular responses after COVID-19 vaccination in anti-CD20-treated lymphoma patients. *Blood*. 2022;139(1):142–147.
14. Riise J, Meyer S, Blaas I, et al. Rituximab-treated patients with lymphoma develop strong <scp>CD8</scp> T-cell responses following <scp>COVID</scp> -19 vaccination. *Br. J. Haematol.* 2022;197(6):697–708.
15. Salvini M, Damonte C, Mortara L, et al. Immunogenicity and clinical efficacy of anti-SARS-CoV-2 vaccination in patients with hematological malignancies: Results of a prospective cohort study of 365 patients. *Am. J. Hematol.* 2022;97(8):E321–E324.
16. Marasco V, Carniti C, Guidetti A, et al. T-cell immune response after mRNA SARS-CoV-2 vaccines is frequently detected also in the absence of seroconversion in patients with lymphoid malignancies. *Br. J. Haematol.* 2022;196(3):548–558.
17. Hill JA, Seo SK. How I prevent infections in patients receiving CD19-targeted chimeric antigen receptor T cells for B-cell malignancies. *Blood*. 2020;136(8):925–935.
18. Visco C, Marcheselli L, Mina R, et al. A prognostic model for patients with lymphoma and COVID-19: a multicentre cohort study. *Blood Adv.* 2022;6(1):327–338.
19. Hoffmann M, Kleine-Weber H, Schroeder S, et al. SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. *Cell*. 2020;181(2):271-280.e8.
20. Walls AC, Park Y-J, Tortorici MA, et al. Structure, Function, and Antigenicity of the SARS-CoV-2 Spike Glycoprotein. *Cell*. 2020;181(2):281-292.e6.
21. Lan J, Ge J, Yu J, et al. Structure of the SARS-CoV-2 spike receptor-binding domain bound to the ACE2 receptor. *Nature*. 2020;581(7807):215–220.
22. Polack FP, Thomas SJ, Kitchin N, et al. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. *N. Engl. J. Med.* 2020;383(27):2603–2615.
23. 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(5):403–416.
24. 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(23):2259–

2261.
25. Walsh EE, Frenck RW, Falsey AR, et al. Safety and Immunogenicity of Two RNA-Based Covid-19 Vaccine Candidates. *N. Engl. J. Med.* 2020;383(25):2439–2450.
26. Dunkle LM, Kotloff KL, Gay CL, et al. Efficacy and Safety of NVX-CoV2373 in Adults in the United States and Mexico. *N. Engl. J. Med.* 2022;386(6):531–543.
27. Feikin DR, Higdon MM, Abu-Raddad LJ, et al. Duration of effectiveness of vaccines against SARS-CoV-2 infection and COVID-19 disease: results of a systematic review and meta-regression. *Lancet (London, England)*. 2022;399(10328):924–944.
28. Hachmann NP, Miller J, Collier AY, Barouch DH. Neutralization Escape by SARS-CoV-2 Omicron Subvariant BA.4.6. *N. Engl. J. Med.* 2022;387(20):1904–1906.
29. Lin D-Y, Xu Y, Gu Y, et al. Effectiveness of Bivalent Boosters against Severe Omicron Infection. *N. Engl. J. Med.* 2023;388(8):764–766.
30. Perry C, Luttwak E, Balaban R, et al. Efficacy of the BNT162b2 mRNA COVID-19 vaccine in patients with B-cell non-Hodgkin lymphoma. *Blood Adv.* 2021;5(16):3053–3061.
31. Gurion R, Rozovski U, Itchaki G, et al. Humoral serological response to the BNT162b2 vaccine is abrogated in lymphoma patients within the first 12 months following treatment with anti-CD2O antibodies. *Haematologica*. 2021;107(3):715–720.
32. Lim SH, Campbell N, Johnson M, et al. Antibody responses after SARS-CoV-2 vaccination in patients with lymphoma. *Lancet Haematol.* 2021;8(8):e542–e544.
33. Ollila TA, Lu S, Masel R, et al. Antibody Response to COVID-19 Vaccination in Adults With Hematologic Malignant Disease. *JAMA Oncol.* 2021;7(11):1714.
34. Ghione P, Gu JJ, Attwood K, et al. Impaired humoral responses to COVID-19 vaccination in patients with lymphoma receiving B-cell-directed therapies. *Blood*. 2021;138(9):811–814.
35. Gagelmann N, Passamonti F, Wolschke C, et al. Antibody response after vaccination against SARS-CoV-2 in adults with haematological malignancies: a systematic review and meta-analysis. *Haematologica*. 2021;107(8):1840–1849.
36. Piechotta V, Mellinghoff SC, Hirsch C, et al. Effectiveness, immunogenicity, and safety of COVID-19 vaccines for individuals with hematological malignancies: a systematic review. *Blood Cancer J.* 2022;12(5):86.
37. Rinaldi I, Pratama S, Wiyono L, et al. Efficacy and safety profile of COVID-19 mRNA vaccine in patients with hematological malignancies: Systematic review and meta-analysis. *Front.*

644 *Oncol.* 2022;12:951215.
645 38. Ito Y, Honda A, Kurokawa M. COVID-19 mRNA Vaccine in Patients With Lymphoid
646 Malignancy or Anti-CD20 Antibody Therapy: A Systematic Review and Meta-Analysis. *Clin.*
647 *Lymphoma. Myeloma Leuk.* 2022;22(8):e691–e707.
648 39. Chang A, Akhtar A, Linderman SL, et al. Humoral Responses Against SARS-CoV-2 and
649 Variants of Concern After mRNA Vaccines in Patients With Non-Hodgkin Lymphoma and
650 Chronic Lymphocytic Leukemia. *J. Clin. Oncol.* 2022;2:1–13.
651 40. Haggenburg S, Hofsink Q, Lissenberg-Witte BI, et al. Antibody Response in
652 Immunocompromised Patients With Hematologic Cancers Who Received a 3-Dose mRNA-
653 1273 Vaccination Schedule for COVID-19. *JAMA Oncol.* 2022;8(10):1477.
654 41. Della Pia A, Kim GYG, Ip A, et al. Anti-spike antibody response to the COVID vaccine in
655 lymphoma patients. *PLoS One*. 2022;17(12):e0266584.
656 42. Greenberger LM, Saltzman LA, Gruenbaum LM, et al. Anti-Spike T-cell and Antibody
657 Responses to SARS-CoV-2 mRNA Vaccines in Patients with Hematologic Malignancies.
658 2022;(November):481–489.
659 43. Pinder CL, Jankovic D, Fox TA, et al. Humoral and cellular responses to SARS-CoV-2 in
660 patients with B-cell haematological malignancies improve with successive vaccination. *Br. J.*
661 *Haematol.* 2023;
662 44. Della Pia A, Zhao C, Jandir P, et al. Improved Survival of Lymphoma Patients with COVID-19
663 in the Modern Treatment and Vaccination Era. *Cancers (Basel).* 2022;14(17):4252.
664 45. Pagano L, Salmanton-García J, Marchesi F, et al. COVID-19 in vaccinated adult patients with
665 hematological malignancies: preliminary results from EPICOVIDEHA. *Blood*.
666 2022;139(10):1588–1592.
667 46. Pagano L, Salmanton-García J, Marchesi F, et al. Breakthrough COVID-19 in vaccinated
668 patients with hematologic malignancies: results from the EPICOVIDEHA survey. *Blood*.
669 2022;140(26):2773–2787.
670 47. Salmanton-García J, Marchesi F, Glenthøj A, et al. Improved Clinical Outcome of COVID-19 in
671 Hematologic Malignancy Patients Receiving a Fourth Dose of Anti-SARS-CoV-2 Vaccine: An
672 EPICOVIDEHA Report. *HemaSphere*. 2022;6(11):e789.
673 48. Rubinstein SM, Bhutani D, Lynch RC, et al. Patients Recently Treated for B-lymphoid
674 Malignancies Show Increased Risk of Severe COVID-19. *Blood Cancer Discov.* 2022;3(3):181–

193.

49. Wijaya R, Johnson M, Campbell N, et al. Predicting COVID-19 infection risk in people who are immunocompromised by antibody testing. *Lancet*. 2023;402(10396):99–102.

50. Le Bert N, Tan AT, Kunasegaran K, et al. SARS-CoV-2-specific T cell immunity in cases of COVID-19 and SARS, and uninfected controls. *Nature*. 2020;584(7821):457–462.

51. Sette A, Crotty S. Adaptive immunity to SARS-CoV-2 and COVID-19. *Cell*. 2021;184(4):861–880.

52. Sekine T, Perez-Potti A, Rivera-Ballesteros O, et al. Robust T Cell Immunity in Convalescent Individuals with Asymptomatic or Mild COVID-19. *Cell*. 2020;183(1):158-168.e14.

53. Gressens SB, Wiedemann A, Déchenaud M, et al. Anti-SARS-CoV-2 cellular response after 2 and 3 doses of BNT162b2 mRNA vaccine in lymphoma patients receiving anti-CD20 antibodies. *Vaccine*. 2023;41(9):1550–1553.

54. Lim SH, Stuart B, Joseph-Pietras D, et al. Immune responses against SARS-CoV-2 variants after two and three doses of vaccine in B-cell malignancies: UK PROSECO study. *Nat. Cancer*. 2022;3(5):552–564.

55. Candon S, Lemee V, Leveque E, et al. Dissociated humoral and cellular immune responses after a three-dose schema of BNT162b2 vaccine in patients receiving anti-CD20 monoclonal antibody maintenance treatment for B-cell lymphomas. *Haematologica*. 2021;107(3):755–758.

56. Jiménez M, Fernández-Naval C, Navarro V, et al. Kinetics of cellular and humoral immunogenicity and effectiveness of <scp>SARS-CoV</scp> -2 booster vaccination in hematologic neoplasms. *Am. J. Hematol.* 2023;(February):1–10.

57. Rydyznski Moderbacher C, Ramirez SI, Dan JM, et al. Antigen-Specific Adaptive Immunity to SARS-CoV-2 in Acute COVID-19 and Associations with Age and Disease Severity. *Cell*. 2020;183(4):996-1012.e19.

58. Khoury DS, Cromer D, Reynaldi A, et al. Neutralizing antibody levels are highly predictive of immune protection from symptomatic SARS-CoV-2 infection. *Nat. Med.* 2021;27(7):1205–1211.

59. Bange EM, Han NA, Wileyto P, et al. CD8(+) T cells contribute to survival in patients with COVID-19 and hematologic cancer. *Nat. Med.* 2021;27(7):1280–1289.

60. El Chaer F, Auletta JJ, Chemaly RF. How I treat and prevent COVID-19 in patients with

hematologic malignancies and recipients of cellular therapies. *Blood*. 2022;140(7):673–684.
61. Passamonti F, Nicastri E, Di Rocco A, et al. Management of patients with lymphoma and COVID-19: Narrative review and evidence-based practical recommendations. *Hematol. Oncol.* 2023;41(1):3–15.
62. Rankin K, Hastak P, Wong A, et al. Immune response to COVID-19 vaccination in patients with Waldenström macroglobulinaemia who pause their BTKi therapy. 2023;(May):2–6.
63. Terpos E, Branagan AR, García-sanz R, et al. Seminars in Hematology Report of consensus panel 5 from the 11th international workshop on Waldenstrom ' s macroglobulinemia on COVID-19 prophylaxis and management. *Semin. Hematol.* 2023;60(2):107–112.
64. Buske C, Dreyling M, Alvarez-Larrán A, et al. Managing hematological cancer patients during the COVID-19 pandemic: an ESMO-EHA Interdisciplinary Expert Consensus. *ESMO open*. 2022;7(2):100403.
65. Cesaro S, Ljungman P, Mikulska M, et al. Recommendations for the management of COVID-19 in patients with haematological malignancies or haematopoietic cell transplantation, from the 2021 European Conference on Infections in Leukaemia (ECIL 9). *Leukemia*. 2022;36(6):1467–1480.
66. Suribhatla R, Starkey T, Ionescu MC, et al. Systematic review and meta-analysis of the clinical effectiveness of tixagevimab/cilgavimab for prophylaxis of COVID-19 in immunocompromised patients. *Br. J. Haematol.* n/a(n/a):
67. Davis JA, Granger K, Roubal K, et al. Letters to Blood Ef fi cacy of tixagevimab-cilgavimab in preventing SARS-CoV-2 for patients with B-cell malignancies. *Blood*. 2023;141(2):200–203.
68. Wang Q, Iketani S, Li Z, et al. Alarming antibody evasion properties of rising SARS-CoV-2 BQ and XBB subvariants. *Cell*. 2023;186(2):279-286.e8.
69. Mazza JJ, Yale SH, Arrowood JR, et al. Efficacy of the influenza vaccine in patients with malignant lymphoma. *Clin. Med. Res.* 2005;3(4):214–220.
70. Centkowski P, Brydak L, Machała M, et al. Immunogenicity of influenza vaccination in patients with non-Hodgkin lymphoma. *J. Clin. Immunol.* 2007;27(3):339–346.
71. Ljungman P, Nahi H, Linde A. Vaccination of patients with haematological malignancies with one or two doses of influenza vaccine: a randomised study. *Br. J. Haematol.* 2005;130(1):96–98.
72. Villa D, Gubbay J, Sutherland DR, et al. Evaluation of 2009 pandemic H1N1 influenza

vaccination in adults with lymphoid malignancies receiving chemotherapy or following autologous stem cell transplant. *Leuk. Lymphoma*. 2013;54(7):1387–1395.

73. Safdar A, Rodriguez MA, Fayad LE, et al. Dose-related safety and immunogenicity of baculovirus-expressed trivalent influenza vaccine: a double-blind, controlled trial in adult patients with non-Hodgkin B cell lymphoma. *J. Infect. Dis.* 2006;194(10):1394–1397.

74. Bedognetti D, Zoppoli G, Massucco C, et al. Impaired Response to Influenza Vaccine Associated with Persistent Memory B Cell Depletion in Non-Hodgkin's Lymphoma Patients Treated with Rituximab-Containing Regimens. *J. Immunol.* 2011;186(10):6044–6055.

75. Murthy N, Wodi AP, Cineas S, Ault KA. Recommended Adult Immunization Schedule, United States, 2023*. *Ann. Intern. Med.* 2023;0(0):null.

76. Levin MJ, Weinberg A, Schmid DS. Herpes Simplex Virus and Varicella-Zoster Virus. *Microbiol. Spectr.* 2016;4(3):.

77. Lee HS, Park JY, Shin SH, et al. Herpesviridae Viral Infections After Chemotherapy Without Antiviral Prophylaxis in Patients With Malignant Lymphoma: Incidence and Risk Factors. *Am. J. Clin. Oncol.* 2012;35(2):.

78. Manos K, Lasica M, Grigg A, et al. Prolonged Lymphopenia and Infection Risk Is Mitigated By Antimicrobial Prophylaxis in Patients with Indolent Non-Hodgkin Lymphoma (iNHL) Treated with Bendamustine +/- Anti-CD20 Antibody: The Australasian Lymphoma Alliance Experience. *Blood*. 2020;136(Supplement 1):47–49.

79. Henze L, Buhl C, Sandherr M, et al. Management of herpesvirus reactivations in patients with solid tumours and hematologic malignancies: update of the Guidelines of the Infectious Diseases Working Party (AGIHO) of the German Society for Hematology and Medical Oncology (DGHO) on herpes simp. *Ann. Hematol.* 2022;101(3):491–511.

80. Lal H, Cunningham AL, Godeaux O, et al. Efficacy of an Adjuvanted Herpes Zoster Subunit Vaccine in Older Adults. *N. Engl. J. Med.* 2015;372(22):2087–2096.

81. Dagnew AF, Ilhan O, Lee W-S, et al. Immunogenicity and safety of the adjuvanted recombinant zoster vaccine in adults with haematological malignancies: a phase 3, randomised, clinical trial and post-hoc efficacy analysis. *Lancet Infect. Dis.* 2019;19(9):988–1000.

82. Bastidas A, de la Serna J, El Idrissi M, et al. Effect of Recombinant Zoster Vaccine on Incidence of Herpes Zoster After Autologous Stem Cell Transplantation: A Randomized

768 Clinical Trial. *JAMA*. 2019;322(2):123–133.
769 83. Brady MT, Laniewski N, Strawderman M, et al. Long-term results of vaccination with
770 adjuvanted recombinant varicella zoster glycoprotein E during initial Bruton tyrosine kinase
771 inhibitors therapy for chronic lymphocytic leukemia or lymphoplasmacytic lymphoma. *Am.*
772 *J. Hematol.* 2023;98(10):E288–E290.
773 84. Vinuesa CG, de Lucas C, Cook MC. Clinical implications of the specialised B cell response to
774 polysaccharide encapsulated pathogens. *Postgrad. Med. J.* 2001;77(911):562–569.
775 85. Freedman MS, Hunter P, Ault K, Kroger A. Advisory Committee on Immunization Practices
776 Recommended Immunization Schedule for Adults Aged 19 Years or Older - United States,
777 2020. *MMWR. Morb. Mortal. Wkly. Rep.* 2020;69(5):133–135.
778 86. Garcia Garrido HM, Knol MJ, Heijmans J, et al. Invasive pneumococcal disease among adults
779 with hematological and solid organ malignancies: A population-based cohort study. *Int. J.*
780 *Infect. Dis. IJID Off. Publ. Int. Soc. Infect. Dis.* 2021;106:237–245.
781 87. Jackson LA, Gurtman A, Rice K, et al. Immunogenicity and safety of a 13-valent
782 pneumococcal conjugate vaccine in adults 70 years of age and older previously vaccinated
783 with 23-valent pneumococcal polysaccharide vaccine. *Vaccine*. 2013;31(35):3585–3593.
784 88. Pitsiou GG, Kioumis IP. Pneumococcal vaccination in adults: does it really work? *Respir.*
785 *Med.* 2011;105(12):1776–1783.
786 89. Hayward S, Thompson LA, McEachern A. Is 13-Valent Pneumococcal Conjugate Vaccine
787 (PCV13) Combined With 23-Valent Pneumococcal Polysaccharide Vaccine (PPSV23)
788 Superior to PPSV23 Alone for Reducing Incidence or Severity of Pneumonia in Older Adults?
789 A Clin-IQ. *J. patient-centered Res. Rev.* 2016;3(2):111–115.
790 90. Svensson M, Dahlin U, Kimby E. Better response with conjugate vaccine than with
791 polysaccaride vaccine 12 months after rituximab treatment in lymphoma patients. *Br. J.*
792 *Haematol.* 2012;156(3):407–409.
793 91. Kobayashi M, Farrar JL, Gierke R, et al. Use of 15-Valent Pneumococcal Conjugate Vaccine
794 and 20-Valent Pneumococcal Conjugate Vaccine Among U.S. Adults: Updated
795 Recommendations of the Advisory Committee on Immunization Practices - United States,
796 2022. *MMWR. Morb. Mortal. Wkly. Rep.* 2022;71(4):109–117.
797 92. Garcia Garrido HM, Vollaard A, D'Haens GR, et al. Immunogenicity of the 13-Valent
798 Pneumococcal Conjugate Vaccine (PCV13) Followed by the 23-Valent Pneumococcal

Polysaccharide Vaccine (PPSV23) in Adults with and without Immunosuppressive Therapy. *Vaccines*. 2022;10(5):795.

93. Haggenburg S, Garcia Garrido HM, Kant IMJ, et al. Immunogenicity of the 13-Valent Pneumococcal Conjugated Vaccine Followed by the 23-Valent Polysaccharide Vaccine in Chronic Lymphocytic Leukemia. *Vaccines*. 2023;11(7):1201.

94. Singh V, Nanjappa S, Pabbathi S, Greene JN. Invasive Haemophilus influenzae Infection in Patients With Cancer. *Cancer Control*. 2017;24(1):66–71.

95. Briere EC, Rubin L, Moro PL, et al. Prevention and control of haemophilus influenzae type b disease: recommendations of the advisory committee on immunization practices (ACIP). *MMWR. Recomm. reports Morb. Mortal. Wkly. report. Recomm. reports*. 2014;63(RR-01):1–14.

96. Taha M-K, Weil-Olivier C, Bouée S, et al. Risk factors for invasive meningococcal disease: a retrospective analysis of the French national public health insurance database. *Hum. Vaccin. Immunother.* 2021;17(6):1858–1866.

97. Lundbo LF, Harboe ZB, Sandholdt H, et al. Comorbidity Increases the Risk of Invasive Meningococcal Disease in Adults. *Clin. Infect. Dis. an Off. Publ. Infect. Dis. Soc. Am.* 2022;75(1):125–130.

98. Bilukha OO, Rosenstein N. Prevention and control of meningococcal disease. Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR. Recomm. reports Morb. Mortal. Wkly. report. Recomm. reports*. 2005;54(RR-7):1–21.

99. CDC meningococcal vaccination recommendations, available at: https://www.cdc.gov/vaccines/vpd/mening/hcp/recommendations.html.

100. Einarsdottir S, Ljungman P, Kaijser B, et al. Humoral immunity to tetanus, diphtheria and polio in adults after treatment for hematological malignancies. *Vaccine*. 2020;38(5):1084–1088.

101. Böttiger M, Gustavsson O, Svensson A. Immunity to tetanus, diphtheria and poliomyelitis in the adult population of Sweden in 1991. *Int. J. Epidemiol.* 1998;27(5):916–925.

102. Schillie S, Vellozzi C, Reingold A, et al. Prevention of Hepatitis B Virus Infection in the United States: Recommendations of the Advisory Committee on Immunization Practices. *MMWR. Recomm. Reports*. 2018;67(1):1–31.

103. Merli M, Rattotti S, Gotti M, Arcaini L. Antiviral therapies for managing viral hepatitis in

lymphoma patients. *Expert Opin. Pharmacother.* 2017;18(4):363–376.

104. Avivi I, Zisman-Rozen S, Naor S, et al. Depletion of B cells rejuvenates the peripheral B-cell compartment but is insufficient to restore immune competence in aging. *Aging Cell*. 2019;18(4):e12959.

105. Nelson NP, Weng MK, Hofmeister MG, et al. Prevention of Hepatitis A Virus Infection in the United States: Recommendations of the Advisory Committee on Immunization Practices, 2020. *MMWR. Recomm. Reports*. 2020;69(5):1–38.

106. Lee S, Kim HW, Kim KH. Antibodies against Hepatitis A and Hepatitis B Virus in Intravenous Immunoglobulin Products. *J. Korean Med. Sci.* 2016;31(12):1937–1942.

107. Njue A, Nuabor W, Lyall M, et al. Systematic Literature Review of Risk Factors for Poor Outcomes Among Adults With Respiratory Syncytial Virus Infection in High-Income Countries. *Open Forum Infect. Dis.* 2023;10(11):ofad513.

108. Villanueva D-DH, Arcega V, Rao M. Review of respiratory syncytial virus infection among older adults and transplant recipients. *Ther. Adv. Infect. Dis.* 2022;9:204993612210914.

109. See KC. Vaccination for Respiratory Syncytial Virus: A Narrative Review and Primer for Clinicians. *Vaccines*. 2023;11(12):1809.

110. Melgar M, Britton A, Roper LE, et al. Use of Respiratory Syncytial Virus Vaccines in Older Adults: Recommendations of the Advisory Committee on Immunization Practices - United States, 2023. *MMWR. Morb. Mortal. Wkly. Rep.* 2023;72(29):793–801.

111. Soy M, Keser G, Atagunduz P, et al. A practical approach for vaccinations including COVID-19 in autoimmune/autoinflammatory rheumatic diseases: a non-systematic review. *Clin. Rheumatol.* 2021;40(9):3533–3545.

112. Ludwig H, Boccadoro M, Moreau P, et al. Recommendations for vaccination in multiple myeloma: a consensus of the European Myeloma Network. *Leukemia*. 2021;35(1):31–44.

113. Bruel T, Hadjadj J, Maes P, et al. Serum neutralization of SARS-CoV-2 Omicron sublineages BA.1 and BA.2 in patients receiving monoclonal antibodies. *Nat. Med.* 2022;28(6):1297–1302.

114. Cameron-Blake E, Tatlow H, Andretti B, et al. A panel dataset of COVID-19 vaccination policies in 185 countries. *Nat. Hum. Behav.* 2023;7(8):1402–1413.

115. van Kessel R, Forman R, Milstein R, et al. Divergent COVID-19 vaccine policies: Policy mapping of ten European countries. *Vaccine*. 2023;41(17):2804–2810.

116. Haggenburg S, Lissenberg-Witte BI, van Binnendijk RS, et al. Quantitative analysis of mRNA-1273 COVID-19 vaccination response in immunocompromised adult hematology patients. *Blood Adv.* 2022;6(5):1537–1546.
117. Ollila TA, Masel RH, Reagan JL, et al. Seroconversion and outcomes after initial and booster <scp>COVID</scp> -19 vaccination in adults with hematologic malignancies. *Cancer*. 2022;128(18):3319–3329.
118. Keppler-Hafkemeyer A, Greil C, Wratil PR, et al. Potent high-avidity neutralizing antibodies and T cell responses after COVID-19 vaccination in individuals with B cell lymphoma and multiple myeloma. *Nat. cancer*. 2023;4(1):81–95.
119. Bedognetti D, Ansaldi F, Zanardi E, et al. Seasonal and pandemic (A/H1N1 2009) MF-59-adjuvanted influenza vaccines in complete remission non-Hodgkin lymphoma patients previously treated with rituximab containing regimens. *Blood*. 2012;120(9):1954–1957.
120. Horwitz SM, Negrin RS, Blume KG, et al. Rituximab as adjuvant to high-dose therapy and autologous hematopoietic cell transplantation for aggressive non-Hodgkin lymphoma. *Blood*. 2004;103(3):777–783.
121. Mustafa SS, Jamshed S, Vadamalai K, Ramsey A. The Use of 20% Subcutaneous Immunoglobulin Replacement Therapy in Patients With B Cell Non-Hodgkin Lymphoma With Humoral Immune Dysfunction After Treatment With Rituximab. *Clin. Lymphoma Myeloma Leuk.* 2020;20(9):e590–e596.
122. Small TN, Zelenetz AD, Noy A, et al. Pertussis Immunity and Response to Tetanus-Reduced Diphtheria-Reduced Pertussis Vaccine (Tdap) after Autologous Peripheral Blood Stem Cell Transplantation. *Biol. Blood Marrow Transplant.* 2009;15(12):1538–1542.

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Table 1. Selected studies about humoral responses after COVID-19 vaccination in patients with non-Hodgkin lymphomas

Study, year	N	Population	m Age	Vaccine type	Dose	Tx, Anti-CD20 mAb	Interval between anti-CD20 and vax	Serocon-version	Assay	Factors predicting anti-SARS-CoV2 positive serology
Perry, 2021[30]	149	a-B-NHL, 69 i-B-NHL, 80	64	BNT162b2	2nd	Tx-naïve, 28 RTX/Obi ≤6 mo, 55 RTX/Obi >6 mo, 66	Median 7.3 mo (0-204)	89% 7.3% 66.7%	Elecsys	Longer interval from RTX/Obi ALC ≥0.9 x 10^3/µl
Gurion, 2021[31]	162	DLBCL, 32 i-B-NHL, 88 Others, 42	65	BNT162b2	2nd	Tx-naïve, 30 RTX, 68 Obi, 30 Chemo/others, 34	No anti-CD20, 56 0-45 days, 34 46-120 days, 21 121-180 days, 4 180-365 days, 7 ≥366 days, 21	80% 3% 24% 25% 14% 81%	AdviseDx Abbott	≥12 mo from anti-CD20 No active lymphoma
Lim, 2021[32]	129	a-B-NHL, 34 i-B-NHL, 79 Others, 13	69	BNT162b2, ChAdOx1	1st+2nd	On Tx or ≤6 mo , 52 None or ≥6 mo, 67	NA	28% (1st) 39% (2nd)	Meso Scale Discovery	a-B-NHL/HL *vs* i-B-NHL ≥6 mo from Tx
Ollila, 2021[33]	97	a-B-NHL, 58 i-B-NHL, 34 Others, 15	72	BNT162b2, mRNA-1273, Ad26.COV2.S	2nd	RTX, 85 Obi, 7 Bispecifics, 12	NA	29%	AdviseDx Abbott	Tx-naïve or no active lymphoma ≥12 mo from anti-CD20
Ghione, 2021[34]	86	a-B-NHL, 28 i-B-NHL, 49 Others, 9	70	BNT162b2, mRNA-1273	2nd	65 (76%)	<9 mo, 52 >9 mo, 13	11% 88%	Platelia	≥9 mo from anti-CD20
Shree, 2022[12]	126	a-B-NHL, 49 i-B-NHL, 75 Others, 2	68	BNT162b2, mRNA-1273, Ad26.COV2.S	2nd	Tx-naïve, 17 Treated ≥6 mo, 65 BTKi, 11 Anti-CD20 ≤6 mo, 31	≤6 mo, 31	100% 82% 67% 16%	EuroImmun	No active lymphoma Time since last anti-CD20
Narita, 2022[11]	500	a-B-NHL, 227 i-B-NHL, 217 Others, 56	73	BNT162b2, mRNA-1273	1st+2nd	Tx-naïve, 28 Anti-CD20±chemo, 327 BTKi, 14	Median 40 mo (0-271)	78.2% (all)	Elecsys	≥6 mo from anti-CD20

Study, year	N	Population	m Age	Vaccine type	Dose	Tx, Anti-CD20 mAb	Interval between anti-CD20 and vax	Serocon-version	Assay	Factors predicting anti-SARS-CoV2 positive serology
Haggenburg, 2022[116]	117	Lymphoma	59	mRNA-1273	1^{st}+2^{nd}	Anti-CD20±chemo, 86 ASCT, ≤12 mo, 31	On anti-CD20, 46 ≤12 mo anti-CD20, 40	0% 26%	bead-based multiplex	No use of RTX, venetoclax, CAR-T ≥8 mo from Tx
Chang, 2022[39]	121	a-B-NHL, 44 i-B-NHL, 27 CLL, 50	64	BNT162b2, mRNA-1273	2^{nd}	Anti-CD20, 92 BTKi, 15 BCL2i, 15 ASCT, 17	≤12 mo, 35 >12 mo, 57	67% (all)	Meso Scale Discovery	Age ≥12 mo from anti-CD20 B-cell count ≥ 4.31/μL
Ollila 2022,[117]	244	a-B-NHL, 105 i-B-NHL, 100 Others, 39	70	BNT162b2, mRNA-1273, Ad26.COV2.S	2^{nd} + 3^{rd}	Anti-CD20, 214 (RTX 171, Obi 14, bispecifics 20, polatuzumab 8) No anti-CD20, 30	NA	35% (2^{nd}) vs 65% (2^{nd}) 56% SN (3^{rd})	AdviseDx Abbott	Booster dose (3^{rd}): none
Haggenburg, 2022[40]	101	Lymphoma	60	mRNA-1273	3^{rd}	Anti-CD20±chemo, 76 ASCT, ≤12 mo, 25	On anti-CD20, 40 ≤12 mo anti-CD20, 36	15% (2^{nd}), 22.5% (3^{rd}) 40% (2^{nd}), 72.6% (3^{rd})	bead-based multiplex	Booster dose (3^{rd}): no ongoing anti-CD20 or BTKi
Salvini, 2022[15]	103	a-B-NHL, 29 i-B-NHL, 55 Others, 41	66	BNT162b2, mRNA-1273	2^{nd} + 3^{rd}	Anti-CD20, 40	NA	4% (Anti-CD20, 2^{nd}) 15% SN (3^{rd})	DiaSorin	No active lymphoma No anti-CD20
Della Pia, 2022[41]	243	a-B-NHL, 72 i-B-NHL, 68 Others, 103	67	BNT162b2, mRNA-1273, Ad26.COV2.S	2^{nd} + 3^{rd}	Anti-CD20, 101	≤12 mo, 45 >12 mo, 56	65% all (2^{nd}) 47% (Anti-CD20, 2^{nd}) 57% SN (3^{rd})	HMH–Quest Diagnostics	≥12 mo from anti-CD20
Greenberger, 2022[42]	407	a-B-NHL, 79 i-B-NHL, 225 (90 WM, 72 FL) Other, 103	68	BNT162b2, mRNA-1273	2^{nd} + 3^{rd}	WM: anti-CD20, 24 FL: anti-CD20, 39	NA	22% SN (3^{rd})	Elecsys	Anti-CD20 Tx (FL, WM)

Study, year	N	Population	m Age	Vaccine type	Dose	Tx, Anti-CD20 mAb	Interval between anti-CD20 and vax	Serocon-version	Assay	Factors predicting anti-SARS-CoV2 positive serology
Pinder, 2023[43]	69	a-B-NHL, 29 i-B-NHL, 31 Others, 9	60	BNT162b2, ChAdOx1	2^{nd} + 3^{rd} + 4^{th}	Anti-CD20, 58 BTKi, 16 CAR-T, 11	≤6 mo, 41 >6 mo, 28	46.8% (2^{nd}) 54.3% (3^{rd}) 87.9% (4^{th})	In house ELISA	Higher B-cell number

N: number; m: median; Tx: therapy; a-B-NHL: aggressive B-cell non-Hodgkin lymphomas; i-B-NHL: indolent B-cell non-Hodgkin lymphomas; DLBCL: diffuse large B-cell lymphoma; FL: follicular lymphoma; WM: Waldenström Macroglobulinemia; mAb: monoclonal antibody; vax: vaccination; RTX: rituximab; Obi: obiutuzumab; BTKi: Bruton's Tyrosine kinase inhibitors; BCL2i: BCL2 inhibitors; mo: months; ASCT: autologous stem-cell transplantation; NA: not available; SN: seronegative

Table 2. Published meta-analyses about humoral responses after COVID-19 vaccination in patients with non-Hodgkin lymphomas

Study, year	N studies	N pts	Doses	Pooled responses	I^2	Sub-group responses	Safety	Factors predicting anti-SARS-CoV2 positive serology
Gagelmann, 2022[35]	*All HM, 39* a-B-NHL, 7 i-B-NHL, 6	*6516* 386 494	2	*64% (95% CI 59-69)* 58% (95% CI 44-70) 62% (95% CI 48-72)	*93%* 84% 85%	Anti-CD20 ≤12 mo, 15% (95% CI 9-24) Anti-CD20 >12 mo, 59% (95% CI 46-72) BTKi, 23% (95% CI 14-35)	Local pain, 15-41% Fatigue, 6-30% Muscle pain, 4-30%	Being in remission Prior COVID-19 No active treatment
Piechotta, 2022[36]	*All HM, 57* a-B-NHL, 13 i-B-NHL, 14	*7393* 577 2033	2 3 (2 studies)	*38.1-99.1%* 41.9-100% 42.9-100%	91%	Anti-CD20 ≤12 mo, 0-22.2% Anti-CD20 >12 mo, 34.8-81.8% BTKi, 14.3-50%	Any AE, 0-50.9% SAE, 0-7.5% Anaphylaxis, 0-1.3%	3rd dose (31-65%) No or >12 mo anti-CD20 Tx
Rinaldi, 2022[37]	*All HM, 15* NHL, 5	*2055* 336	2	60% *(95% CI 59-69)* 50% (95% CI 35-71)	*96%* 85%	Active Tx, 54% No active Tx, 80% (RR 0.59, 95% CI 0.46-0.75)	Local pain, erythema, transient adenopathies (1-2.5%)	No active Tx
Ito, 2022[38]	*52, lymphoid* 8, NHL	*2203* 282	2	RR 0.60 (95% 0.53-0.69) *vs* HC	94%	NHL, RR 0.58 (95% 0.48-0.71) vs HC Anti-CD20, RR 0.37 (95% 0.24-0.57) ≤12 mo, RR 0.23 (95% 0.10-0.57) >12 mo, RR 0.61 (95% 0.41-0.73) BTKi, RR 0.49 (95% 0.37-0.64)	NA	Anti-CD20 >6 mo, >12 mo

N: number; I^2; heterogeneity; HM: haematological malignancies; Tx: therapy; a-B-NHL: aggressive B-cell non-Hodgkin lymphomas; i-B-NHL: indolent B-cell non-Hodgkin lymphomas; mo: months; BTKi: Bruton's Tyrosine kinase inhibitors; RR: relative risk; HC: healthy controls; NA: not available; pts: patients; AE: adverse events; SAE: serious adverse events

Table 3. Selected studies about cellular responses after COVID-19 vaccination in patients with non-Hodgkin lymphomas

Study, year	N	Population	m Age	Vaccine type	Dose	Assay	Positive cellular responses	Influence of anti-CD20 Tx	Correlation with antibody-response	Factors predicting anti-SARS-CoV2 positive cellular responses
Lim, 2022[54]	189	a-B-NHL, 57 i-B-NHL, 96 HL, 36	67 67 40	BNT162b2, ChAdOx1	2nd + 3rd	IFNγ-ELISpot	52% On Tx *vs* 76.5% No Tx 72.5% On Tx *vs* 44.6% No Tx 75% On Tx *vs* 73.9% No Tx	No ≤12 mo, 62.5% >12 mo, 71.4%	No	ChAdOx1 vaccine
Keppler-Hafkemeyer, 2023[118]	38	a-B-NHL, 7 i-B-NHL, 31	63.5	BNT162b2, mRNA-1273, ChAdOx1	2nd + 3rd	IFNγ-ELISpot	85%	No ≤12 mo, 100%	No	NA
Salvini, 2022[15]	50	a-B-NHL, 17 i-B-NHL, 26 Other, 7	68	BNT162b2, mRNA-1273,	2nd + 3rd	IFNγ-ELISpot	66%	No ≤12 mo, 66%	No	No active disease
Marasco, 2022[16]	99	a-B-NHL, i-B-NHL, HL	63	BNT162b2, mRNA-1273,	2nd	IFNγ-, TNFα, IL-2 ELISA	86%	No	No	Chemotherapy >2 mo
Candon, 2021[55]	20	FL, 16, MZL, 1 MCL, 3	65.5	BNT162b2	1st + 2nd + 3rd	IFNγ-ELISpot	89% (2nd and 3rd)	No (all on maintenance, 10 RTX, 10 Obi)	No	No difference between RTX and Obi
Riise, 2022[14]	29	a-B-NHL, 18 i-B-NHL, 11	71	BNT162b2, mRNA-1273, ChAdOx1	2nd	peptide-HLA multimer analysis (CD8+)	69% (vs 75% in HD)	No (all treated with Anti-CD20)	No	CD8+ responses similar between anti-CD20 and HD

Study, year	N	Population	m Age	Vaccine type	Dose	Assay	Positive cellular responses	Influence of anti-CD20 Tx	Correlation with antibody-response	Factors predicting anti-SARS-CoV2 positive cellular responses
Greenberger, 2022[42]	174	NHL, 154 HL, 20	68	BNT162b2, mRNA-1273	2^{nd} + 3^{rd}	NGS-based	49% 55%	No Anti-CD20, 45%	Yes, 58% in SP *vs* 45% in SN	mRNA-1273
Pinder, 2023[43]	69	a-B-NHL, 29 i-B-NHL, 31 Others, 9	60	BNT162b2, ChAdOx1	2^{nd} + 3^{rd} + 4^{th}	IFNγ-ELISpot	75.5% (2^{nd}) 83.3% (3^{rd}) 90.3% (4^{th})	No	No (similar in SN and SP after 3^{rd} - 4^{th} dose)	Higher number of booster doses, especially vs Omicron-mutated Spike regions
Jimenez, 2023[56]	85	Lymphoma	63	mRNA-1273	2^{nd} + 3^{rd}	IGRA	84.4% (2^{nd}) 84.2% (3^{rd})	No	No	No lymphopenia, to be in response

N: number; m: median; Tx: therapy; HM: haematological malignancies; a-B-NHL: aggressive B-cell non-Hodgkin lymphomas; i-B-NHL: indolent B-cell non-Hodgkin lymphomas; FL: follicular lymphoma, HL: Hodgkin lymphoma; MZL: marginal zone lymphoma; MCL: mantle cell lymphoma; HD: healthy donors; mAb: monoclonal antibody; RTX: rituximab; Obi: obiutuzumab; mo: months; NA: not available; SN: seronegative; SP: seropositive

Table 4. Published studies about vaccinations against seasonal influenza, varicella zoster virus and encapsulated bacteria in patients with non-Hodgkin lymphomas

Study, date	Design	Population	N	Vaccine type	Anti-CD20 mAb	m Age	Interval between anti-CD20 and vax	Seroconversion	Comments
Seasonal Influenza									
Mazza, 2005[69]	Cohort	NHL, 27 HL, 2	29	Trivalent	No, only chemo	62	NA, recent chemo	10% (A), 31% (B)	SC lower than HC (45% A, 48% B)
Centkowski, 2007[70]	Cohort	NHL (chemo 87, Tx naïve 76)	163	Trivalent	No, only chemo	60	NA, recent chemo	74.4-77.7%	SC similar to HC
Safdar, 2006[73]	Randomized	NHL	27	Trivalent	RTX, 11	55	NA	40% (45 μg) 60% (135 μg)	Highest response with highest doses
Bedognetti, 2011[74]	Cohort	a-B-NHL, 18 i-B-NHL, 13	31	Trivalent	RTX, 31 (100%)	66	≤12 mo, 6 >12 mo, 25	29% (A/H1N1), 3% (B)	SC lower than HC (41% A/H1N1, 29% B)
Bedognetti, 2012[119]	Cohort	NHL	14	H1N1 followed by trivalent	RTX, 14 (100%)	65	Median 33 mo (14-78)	29-64%	SC similar to HC, attenuated but not suppressed
Varicella Zoster Virus (VZV)									
Dagnew, 2019[81]	Randomized, placebo-controlled	*All HM* B-NHL	*562* 80	Adjuvanted recombinant zoster vaccine	Yes, N not specified	57	NA	*80.4% vs 0.8%* 45% vs 0%	100% cellular response in B-NHL
Bastidas, 2019[82]	Randomized, placebo-controlled	*All pts with ASCT* B-NHL with ASCT	*1846* 514	Adjuvanted recombinant zoster vaccine	No	55	NA	67% at 1 mo 45% at 24 mo	10% *vs* 20% zoster
Brady, 2023[83]	Cohort	*CLL* *LPL*	*23* *8*	Adjuvanted recombinant zoster vaccine	Yes in 12 CLL pts. All BTKi treated	58	Median 5.2 years	75% at 4 weeks 41.9% at 24 mo	Cellular response: 81.3% at 4 weeks 54.8% at 24 mo
Pneumococcus									

Study, date	Design	Population	N	Vaccine type	Anti-CD20 mAb	m Age	Interval between anti-CD20 and vax	Seroconversion	Comments
Horwitz, 2004[120]	Cohort	R/R Aggressive B-NHL, after ASCT and RTX	22	PCV-23 polysaccharide	RTX	51	6-9 mo	32% pre-vaccine vs 41% post-vaccine	Worst response than tetanus vaccine
Svensson, 2011[90]	Randomized, 6 vs 12 mo after RTX	i-B-NHL (FL, MZL) a-B-NHL (MCL)	8	PCV-23 polysaccharide	4, 6 mo 6, 12 mo	63	6 or 12 mo	1/8 (12.5%)	Low efficacy of polysaccharide vaccine
Haemophilus Influenzae B									
Svensson, 2011[90]	Randomized, 6 vs 12 mo after RTX	i-B-NHL (FL, MZL) a-B-NHL (MCL)	8	Hib	4, 6 mo 6, 12 mo	63	6 or 12 mo	5/8 (62.5%)	Better response than pneumococcal vaccine
Horwitz, 2004[120]	Cohort	R/R Aggressive B-NHL, after ASCT and RTX	22	Hib	RTX	51	6-9 mo	27% pre-vaccine vs 77% post-vaccine	Better response than pneumococcal vaccine

N: number; m: median; NHL: non-Hodgkin lymphomas; B-: B-cell; mAb: monoclonal antibody; vax: vaccination; RTX: rituximab; Tx: therapy; mo: months; R/R: relapsed or refractory; ASCT: autologous stem-cell transplantation; NA: not available; FL: follicular lymphoma; MZL: marginal zone lymphoma; MCL: mantle cell lymphoma; HL: Hodgkin lymphoma; SC: seroconversion; HC: healthy controls; CLL: chronic lymphocytic leukemia; LPL: lymphoplasmacytic lymphoma; BTKi: Bruton's Tyrosine kinase inhibitors

Table 5. Published studies about vaccinations with diphtheria, tetanus, pertussis, polio, hepatitis B virus and hepatitis A virus in patients with non-Hodgkin lymphomas

Study, date	Design	Population	N	Anti-CD20 mAb	m Age	Interval between anti-CD20 and vax	Seroconversion	Comments
Diphtheria								
Einarsdottir, 2020[100]	Cohort	NHL, frontline *Healthy controls*	53 *28*	RTX (N=44)	61	Vaccinated pre-Tx	81% pre-Tx vs 77% post-Tx (p=NS)	No difference in immunity and Ab levels with controls
Mustafa, 2020[121]	Cohort	B-NHL, frontline	15	RTX	71	9 mo (1-24)	20%	67% had IgG (seroprotection)
Tetanus								
Horwitz, 2004[120]	Cohort	R/R Aggressive B-NHL, after ASCT and RTX	22	RTX	51	6-9 mo	55% pre-vaccine vs 68% post-vaccine	Better response than pneumococcal vaccine
Einarsdottir, 2020[100]	Cohort	NHL, frontline *Healthy controls*	48 *28*	RTX (N=41)	61	Vaccinated pre-Tx	88% pre-Tx vs 75% post-Tx (p=0.06)	No difference in immunity and Ab levels with controls
Mustafal, 2020[121]	Cohort	B-NHL, frontline	15	RTX	71	9 mo (1-24)	7%	93% had IgG (seroprotection)
Pertussis								
Small, 2009[122]	Cohort	R/R NHL after ASCT	15	RTX	31	31 mo	7%	0% in pts who received RTX post-ASCT
Polio								
Einarsdottir, 2020[100]	Cohort	NHL, frontline *Healthy controls*	44 *28*	RTX (N=38)	61	Vaccinated pre-Tx	87% pre-Tx vs 89% post-Tx (p=NS)	No difference in immunity and Ab levels with controls
Hepatitis B virus								

Study, date	Design	Population	N	Anti-CD20 mAb	m Age	Interval between anti-CD20 and vax	Seroconversion	Comments
Avivi, 2018[104]	Cohort	B-NHL elderly, frontline *Healthy controls ≥55 yrs* *Healthy controls <35 yrs*	22 *17* 8	RTX	65	38 mo (14-56)	64% vs 59% (p=NS) vs 100% (p=0.03)	High antibody titers in responding elderly B-NHL pts
Hepatitis A virus								
Van Der Kolk, 2002[8]	Phase 1/2	Relapsed low-grade NHL	11	RTX	53	4 weeks	0%	

NHL: non-Hodgkin lymphomas; B-: B-cell; mAb: monoclonal antibody; vax: vaccination; RTX: rituximab; Tx: therapy; mo: months; R/R: relapsed or refractory; ASCT: autologous stem-cell transplantation

Table 6. Summary of key recommendations about management of vaccinations in patients with non-Hodgkin lymphomas

COVID-19
Vaccine product and schedule: people who received at least two doses of monovalent or bivalent mRNA vaccine should receive one additional dose of updated mRNA vaccine (e.g. against XBB subvariant), at least 4-8 weeks apart from the last dose (depending on vaccine product). People who previously received less than two doses of monovalent or bivalent mRNA vaccine should complete a three-dose cycle by updated mRNA formula. Patients must be checked for the number, type, and timing of prior vaccine doses and natural infection episodes. For all patients who received less than 5 total prior vaccine doses and are undergoing active treatment, especially if including B-cell depleting treatments, an additional dose of updated mRNA vaccine is recommended at least 2 weeks before the scheduled treatment initiation. Serological testing using the two recently validated threshold values for anti-spike IgG levels after 3 (820 BAU/ml) and 4 doses (41 BAU/ml) may be useful to guide for need of further doses.
VZV
Vaccine product and schedule: two doses of recombinant adjuvanted vaccine, 2-6 months apart. *Population*: all patients, with or without evidence of previous varicella natural infection. *Timing*: at diagnosis, or at least 14 days before starting of B-cell depleting treatments (at least first dose), or after ≥6-12 months from last administration of anti-CD20 mAbs.
Seasonal influenza
Vaccine product and schedule: recombinant or inactivated vaccines. Adjuvanted or high-dose vaccine is recommended for elderly patients and in those under active B-cell depleting treatments. *Timing:* every year during the autumn and before the circulation of influenza viruses. *Population*: all patients. Whenever possible, anti-CD20 therapy initiation should be delayed at least two weeks after vaccination. For patients on active anti-CD20 mAbs treatment (e.g. during maintenance) consider at least 4 weeks before the next scheduled therapy.
Pneumococcus
Vaccine product and schedule: sequential schedule with one dose of conjugated 15-valent vaccine and one dose of polysaccharide 23-valent vaccine (with an interval of 8 weeks) or one dose of conjugated 20-valent vaccine. *Timing*: at diagnosis, or at least 14 days before starting B-cell depleting treatments, or after ≥6-12 months from the last administration of anti-CD20 mAbs.
Meningococcus
Vaccine product: primary series including both tetravalent conjugated and monovalent B vaccines. Consider periodic booster doses in subjects who remain at high risk of meningococcal disease. *Timing*: at diagnosis, or at least 14 days before starting of B-cell depleting treatments, or after ≥6-12 months from the last administration of anti-CD20 mAbs.
Haemophilus influenzae B
Vaccine product and schedule: Hemophilus b conjugated vaccine, administered as a single dose (three doses 4 weeks apart after hematopoietic stem cell transplantation).

Diphtheria, tetanus, pertussis
Vaccine product: tetanus-diphtheria-acellular pertussis vaccine (Tdap) or tetanus-diphtheria (Td), inactivated. Patients must be checked regarding the last booster of Tdap or Td and those who did not receive a dose in the last 10 years must be immunized. *Special considerations*: serological testing and revaccination after at least 6 months from the last administration of anti-CD20 mAbs should be considered.
Hepatitis B
Vaccine product: two to three doses of recombinant HBV vaccine (depending on vaccine product). Some manufacturer recommend a four-dose vaccination schedule for adults undergoing hemodialysis or immunocompromised. *Special considerations*: for adults aged ≥60 years vaccination recommended in presence of risk factors for HBV, advisable in absence.
Hepatitis A
Vaccine product: two doses of inactivated HAV vaccine (some manufacturer recommend a three doses vaccination schedule). *Special considerations*: immunocompromised patients are at high risk for severe HAV disease course.
Respiratory syncytial virus
Vaccine product: a single dose of recombinant stabilized RSVPreF3 or RSVpreF *Special considerations*: recommended in adults aged 60 years or older, following a shared clinical decision-making process.