

## REVIEW

# Anti-infective vaccination strategies in patients with hematologic malignancies or solid tumors—Guideline of the Infectious Diseases Working Party (AGIHO) of the German Society for Hematology and Medical Oncology (DGHO)

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Infectious complications are a significant cause of morbidity and mortality in patients with malignancies specifically when receiving anticancer treatments. Prevention of infection through vaccines is an important aspect of clinical care of cancer patients. Immunocompromising effects of the underlying disease as well as of antineoplastic therapies need to be considered when devising vaccination strategies. This guideline provides clinical recommendations on vaccine use in cancer patients including autologous stem cell transplant recipients, while allogeneic stem cell transplantation is subject of a separate guideline. The document was prepared by the Infectious Diseases Working Party (AGIHO) of the German Society for Hematology and Medical Oncology (DGHO) by reviewing currently available data and applying evidence-based medicine criteria.

**Key words:** infection, anti-infective vaccination, cancer, immunosuppression, autologous stem cell transplantation

## Introduction

In patients with malignancies, infections significantly contribute to morbidity and mortality by delaying or impeding appropriate antineoplastic treatment. Besides prophylactic treatment, vaccination is effective in preventing infections. Patients receiving cancer treatments may experience potentially harmful long-term

immunocompromising side effects and loss of previous immunizations. Such cancer survivors deserve additional care to prevent infections, but uncertainties exist concerning optimal vaccination strategies, including the choice of vaccine (passive or active, dead or life-attenuated) and time-schedules of vaccination. Therefore, the Strength of Recommendation/Quality of Evidence

sometimes applies in general for the respective recommendations and not necessarily on specific settings (e.g. prime-boost-strategy for pneumococcal vaccine).

This guideline was developed to aid clinicians with decisions concerning vaccination strategies in cancer patients and recipients of autologous stem cell transplants (SCTs). These recommendations apply to the epidemiological situation in Germany, but are also applicable for regions with similar epidemiologic features.

## Methods

This guideline was developed by an expert panel designated by the Infectious Diseases Working Party (AGIHO) of the German Society for Hematology and Medical Oncology (DGHO). The panel consisted of 17 specialists of internal medicine, hematology, medical oncology and/or infectious diseases led by a guideline coordinator (CTR). After definition of topics regarding specific malignant conditions and therapeutic situations, a systematic search of MEDLINE and recent scientific meetings' databases was performed to identify relevant publications which were then thoroughly reviewed and rated. Following data extraction and assessment, preliminary recommendations were first discussed and revised by the specialist panel, then discussed and agreed upon by the AGIHO general assembly resulting in the final guideline presented here.

For grading of strength of recommendation and quality of evidence, the grading system proposed by the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) was applied (Table 1) [1].

A general limitation in vaccination studies is that success of vaccination is mostly measured by immune response to vaccination. While in some cases also the impact on incidence of infections is reported, usually no detailed information on the reduction of infection rates due to the specific sero-/genotypes against which patients had been immunized has been reported.

## General recommendations

The basis of decision-making should include the knowledge of preventable diseases for which vaccination is available and feasible in immunocompromised patients. The risk of severe infection is influenced by the underlying malignancy and by the cancer-specific therapies. Therefore, vaccination recommendations for cancer patients should be based on these two major aspects.

Moreover, close family members or contact persons should be evaluated for their current vaccination status and possibly be (re-)vaccinated. Special attention is required in patients with small children, as some live-attenuated childhood vaccines may bear risks for chemotherapy recipients. For instance, Rota-virus vaccination is strongly discouraged in family members of cancer patients (DIII).

An overview of all vaccinations discussed in this review in the context of underlying malignancies and specific therapies is given in the [supplementary Table S1](#), available at *Annals of Oncology* online.

## Disease entity-specific vaccination strategies

Here, disease entity-specific vaccination strategies are delineated. An overview of disease entity-specific vaccination strategies is given in Table 2.

### Acute leukemia

Immunosuppression due to acute leukemia (AL) is most relevant during induction and consolidation therapy. Response to immunization is affected and concerns primary immunization more than booster response. Live vaccines are contraindicated in the immunocompromised patient (DIIt); inactivated, non-conjugated vaccines may not induce sufficient antibody production.

**Inactivated vaccines.** Protection against diphtheria, tetanus and pertussis (DTP) is impaired in patients with AL [2]. Data on immune response and antibody production to DTP vaccination are only available in children on maintenance and after completion of therapy, showing an antibody response comparable to healthy children [3–5]. We therefore recommend a DTP booster immunization for these patients. They should be vaccinated before starting treatment and after end of therapy if the immune system is reconstituted (BIII).

Influenza increases morbidity and mortality in cancer patients [6–8]. Therefore, all patients >6 months with leukemia should be vaccinated annually against influenza (AIItu) [7, 9, 10]. Patients receiving rituximab should receive the vaccine ≥6 months after therapy because of poor immune response (BIIu) [11]. Data for children with AL show reduced immune response to influenza vaccination [12, 13]. Two doses of influenza vaccine may be more immunogenic than one and are well tolerated in children and young adults [14]. Live-attenuated influenza vaccine cannot be recommended (DIIt).

AL patients should receive antipneumococcal vaccination before treatment (AIIIt). The conjugated 13-valent vaccine PCV13 should be administered first; if a patient has not received prior antipneumococcal vaccination, he should be revaccinated with polysaccharide vaccine PPSV23 8–12 weeks later. Priming with a conjugated vaccine may be considered in AL patients as it improves the response to PPSV23 in patients with Hodgkin-lymphoma and patients after bone marrow transplants [15, 16]. If pretreatment vaccination is not feasible, we recommend vaccination after the first chemotherapy cycle and repetition 3 months after chemotherapy, although this strategy has not been specifically evaluated in studies (BIII).

If vaccination against human papilloma virus (HPV) is indicated, vaccination should be performed regardless of immunosuppression; however, immune-response might be reduced [17].

While children with leukemia are at increased risk for *Haemophilus influenzae* type B (HiB) infections [18], this was not shown for adults except in the context of SCT. Thus, immunization against HiB is only recommended for adults after SCT (CIII) [19].

Patients at risk for hepatitis A virus (HAV) infection, e.g. often receiving blood products, should be vaccinated [20], but immune-response may be impaired [21]. Patients at high risk of

**Table 1. ESCMID grading system of strength of recommendation and quality of evidence [1]**

Strength of recommendation	
A	Strongly support a recommendation for use
B	Moderately support a recommendation for use
C	Marginally support a recommendation for use
D	Support a recommendation against use
Quality of evidence	
I	Evidence from at least one properly designed randomized, controlled trial
II*	Evidence from at least one well-designed clinical trial, without randomization; from cohort- or case-control analytic studies (preferably from more than one center); from multiple time series; or from dramatic results from uncontrolled experiments
III	Evidence from opinion of respected authorities, based on clinical experience, descriptive case studies, or report of expert committees
*Added index	
r	Meta-analysis or systematic review of randomized controlled trials
t	Transferred evidence, i.e. results from different patients' cohorts or similar immune status situation
h	Comparator group is a historical control
u	Uncontrolled trial
a	Abstract published at an international meeting

imminent immunosuppression need protection against hepatitis B virus (HBV) [20] and sero-negative patients should be vaccinated [22]. As immune-response for HBV-vaccine was shown to be impaired in this population [23], patients with AL should receive several doses (**AIII**). Three HBV-vaccinations in AL-patients within 6–12 months after remission was effective in 93.3% of patients vaccinated after bone marrow recovery [24]. Another approach is to combine passive and active prophylaxis with both vaccine and hyperimmunoglobulin [23, 25]. Also, Hepatitis A&B co-immunization is feasible.

Treatment recommendation for rabies is postexposure vaccination [26] with a postexposure double dosage (**AIII**) due to low immune-response [27]. Pre-exposure vaccination may be indicated for patients with potential occupational exposure (**CIII**).

There is no general recommendation for vaccination against typhus in patients with AL for lack of data in adults.

Vaccination against tick-born encephalitis may be indicated for patients in endemic areas according to local policy (**CIII**).

**Live vaccines.** Vaccination against yellow fever is contra-indicated in AL patients (**DIIt**) as it may entail severe, life-threatening adverse events like encephalitis [28, 29]. Immunization should not be performed <24 months after immunosuppressive treatment [28].

Measles in immunocompromised patients cause high mortality [30] and, in analogy to children with AL, antibody titers likely decline after chemotherapy [31, 32]. A booster with combined immunization against measles, mumps and rubella (MMR) after completion of treatment is hence recommended for patients with AL (**BIIt**). This should be performed >24 months after completion of therapy and along serostatus [31].

Adult cancer patients seronegative for varicella zoster virus (VZV) show increased rates of complications (e.g. dissemination, mortality), if primarily infected. Only one study investigated immunity and safety of VZV vaccine in (pediatric) leukemia patients and showed benefits regarding immunity against chickenpox for at least 3 years [33]. Immunization against VZV >24 months after completion of therapy may thus be considered for patients with AL (**CIII**).

## Malignant lymphoma, multiple myeloma and myeloproliferative neoplasms

This section focuses on chemotherapy-treated patients. For vaccination recommendations regarding rituximab-treated patients, refer to 'Monoclonal antibodies, kinase inhibitors and checkpoint blockade' section.

**Inactivated vaccines.** There is solid evidence supporting yearly vaccination of patients with malignant lymphoma, multiple myeloma or myeloproliferative neoplasms with inactivated influenza vaccine to reduce lower respiratory tract infections and hospitalization rates (**AIIIt**) [34–41]. However, there is no conclusive evidence that vaccination also reduces influenza-related mortality [34]. Furthermore, immune-response to single shot vaccination in patients with hematologic malignancies is often impaired [38]. Improved rates of seroconversion were shown after a second shot [35, 37].

A second vaccination against influenza seems reasonable, but can only be recommended with weak evidence (**BIIt**) and the optimal timing remains unclear. Two small studies suggest improved effectiveness when administering the vaccination directly after a cycle of chemotherapy rather than shortly before the next cycle [42, 43].

Regarding antipneumococcal vaccination, all unvaccinated adult patients should first receive PCV13 followed by PPSV23 vaccine (**AIIIt**) [15, 44, 45]. Vaccination against HiB may be considered in unvaccinated patients (**CIIIt**) [41, 46]. While children are endangered by HiB-induced epiglottitis or meningitis, in adults vaccination aims at preventing HiB-induced lower respiratory tract infection. Vaccination early in the course of disease seems to be associated with superior immune responses [46]. There is little data on vaccination against meningococci apart from asplenia; however, it may be considered in lymphoma patients after chemotherapy (**CIII**).

Most data available for vaccination against DTP have been obtained from pediatric and allogeneic SCT patients. However, achieving seroprotection is also desirable in adult patients. Therefore vaccination is recommended in case of incomplete

Table 2. Disease entity-specific vaccination strategies

	Tetanus	Diphtheria	Pertussis	Pneumococci	HiB	Influenza	Meningococci	Hepatitis A	Hepatitis B	Measles <sup>a</sup>	Mumps <sup>a</sup>	Rubella <sup>a</sup>	Varicella <sup>a</sup>
Acute leukemias	BIIt	BIIt	BIIt	AIIt	CIII	Alltu	CIII	BIIt	AIII	BIIt	BIIt	BIIt	CIII
Lymphoma, myeloma, MPN	Allt	Allt	Allt	Allt	CIIt	Allt	CIII	BIIt	BIIt	BIIt	BIIt	BIIt	CIII
Solid tumors	Allt	Allt	Allt	Allt	CIII	Allu	CIII	BIIt	BIIt	BIIt	BIIt	BIIt	CIII

Strength of recommendation and quality of evidence according to the ESCMID/ECMM grading system is given for each disease—vaccination pair. Further details, especially regarding scheduling of vaccination and therapeutic interventions, are given in the text.

<sup>a</sup>Vaccination with live vaccines during immunocompromising therapy is strongly discouraged (**DIIt**).

HiB, *Haemophilus influenzae* type B; MPN, myeloproliferative neoplasms.

vaccination status or requirement of booster vaccination (**AIIt**) [3, 47, 48].

As insufficient reactivity to tetanus toxoid antigen was reported [48], assessment of antibody titers post vaccination might be considered. Vaccination against HBV is recommended in case of incomplete vaccination status or if a vaccination refreshing is required (**BIIt**) [23]. Inadequate immune-response should always be considered [23], and in individual patients, passive immunization against HBV could offer short-term protection [23].

**Live vaccines.** Live vaccines, e.g. against MMR, yellow fever and varicella, are generally contraindicated during chemotherapy (**DIIt**) [3, 49], including maintenance therapy with monoclonal antibodies or immunomodulatory agents, e.g. lenalidomide, as well as conditions with significant immunosuppression. After completion of immunosuppressive therapy, live vaccines against MMR (**BIIt**) and varicella (**CIII**) might be considered after assessment of antibody titers.

### Solid tumors

Chemotherapy can induce immune deficiency, including long-term impairment of humoral immunity. Administration of inactivated vaccines in patients with solid tumors is safe while the specific immune response varies and depends on tumor type and immunosuppression [50].

All adult solid tumor patients should receive yearly vaccination with inactivated influenza vaccine, regardless of age (**AIIt**). Influenza virus infection increases hospitalization and mortality rates in oncology patients across different tumor types [51]—a population at increased risk of serious influenza-related complications [36]. Additionally, many solid tumor patients are elderly and may benefit from vaccination regardless of cancer. Influenza vaccination has been shown to reduce infection rates and interruption of treatment, possibly contributing to better survival [51–53]. While some studies report a response rate similar to healthy subjects [43, 54–56], the authors of the VACANCE trial suggest a second administration of influenza vaccine in cancer patients as this increased seroconversion from 44% to 73% [57], but further investigations are needed. It was recently shown that

cancer patients can be vaccinated independent of chemotherapy and simultaneous administration vaccination and chemotherapy is possible [58].

All unvaccinated adult solid tumour patients should receive antipneumococcal vaccination with PCV-13, followed by PPSV-23 vaccine within 6–12 weeks (**AIIt**). Vaccinated patients have better survival and are less frequently hospitalized [59]. Response to the vaccine is lower compared with healthy persons [60]. Analogous to findings in Hodgkin's lymphoma [15], the approach of prime-boost vaccination by PCV13 may provide a better protection for this population, too.

Patients with incomplete vaccination status or indicated refresher vaccination should be vaccinated against DTP. Reportedly, chemotherapy lowers protective antibody titers of diphtheria and pertussis, but not tetanus, in children [47]. However, revaccination is promising: patients showed appropriate antibody response during maintenance treatment and upon completion [3].

Similar to vaccination against DTP, patients with incomplete vaccination status or indicated refresher vaccination should be vaccinated against HBV (**BIIt**). Older data show immunogenicity and safety of hepatitis B vaccination in patients younger than 60 years under chemotherapy [61]. Assessing titers of diphtheria, tetanus and HBV might be useful after chemotherapy [50].

Vaccination against HAV should be considered (**BIIt**) as it might prevent fulminant hepatitis or prolonged and relapsing course, potentially delaying therapy. Immunogenicity was demonstrated in children [62], adult HIV patients [63] and post-SCT patients [64]. In addition, STIKO recommends vaccination against HAV for patients receiving transfusions [20], including cancer patients.

Adult patients with malignancies are at increased risk for HiB infections, particularly HiB-induced pneumonia [65]. Immune response to the vaccine is reduced during chemotherapy [65, 66]; therefore, vaccination should be avoided during treatment. Patients vaccinated >14 days before antineoplastic treatment do not require revaccination, unless vaccination status is incomplete or refresher vaccination is indicated. Patients vaccinated during chemotherapy should be revaccinated ≥3 months after therapy. Infection rates have increased in the elderly since establishment

**Table 3. Vaccination strategies following autologous stem cell transplantation**

Vaccine	SoR/QoE	Time post-SCT (months)	Doses	Comment
Influenza	Allt	3–6	1–2	Improved seroprotection with two doses (BIIt)
Pneumococci	Allt	3–6	4	Three doses PCV13 followed by one dose PPSV23
Tetanus	BIlu	6–12	3	
Diphtheria	BIlu	6–12	3	Full dose (“D”) preferred (BIII)
Pertussis	CIII	6–12	3	Full dose acellular vaccine (aP) preferred
Poliomyelitis	BIIt	6–12	3	Inactivated vaccine only
HiB	BIIt	6–12	3–4	Conjugate vaccine preferred
Meningococci	BIIt	6–12	1–2	Conjugate vaccine preferred
Hepatitis B	BIIt	6–12	3	
Measles	BIIt	24	1–2	No live vaccine < 24 months post ASCT (DIIt)
Mumps	BIIt	24	1–2	No live vaccine < 24 months post ASCT (DIIt)
Rubella	BIIt	24	1–2	No live vaccine < 24 months post ASCT (DIIt)
Varicella	Allt	24	1–3	No live vaccine < 24 months post ASCT (DIIt)

Strength of recommendation (SoR) and quality of evidence (QoE) according to the ESCMID grading system is given for each vaccine preventable disease as well as the recommended time point and number of doses of vaccination. Further details are given in the text.

of childhood immunization, particularly in those with significant comorbidities with a high fatality rate of invasive infections [67]. Vaccination is recommended if vaccination status is incomplete or vaccination refresher is indicated (CIII).

Vaccination against *Meningococcus* is routinely recommended for patients with (functional) asplenia. Data for adult solid tumor patients do not exist. There is no rationale to assume increased risk for infections with *Meningococcus* except for patients with local risk factors such as intrathecal instillation of cytotoxic agents or irradiation of the cranium [68]. Vaccination is only recommended if vaccination status is incomplete or vaccination refresher is indicated (CIII).

In summary, vaccination positively influences hospitalization, morbidity and mortality, but the impact on different solid tumors requires further investigation. However, the aforementioned vaccines should be promoted by treating physicians and discussed with each patient. Further trials are needed to assess the benefit of vaccines in different tumor types taking into account effects of distinct treatments and immune status of patient subgroups.

### Intervention-specific vaccination strategies

Certain therapeutic interventions result in profound immunologic challenges and thus require specific vaccination strategies.

#### Asplenia

Asplenia, both functional and anatomic, is associated with an increased risk of infections by polysaccharide encapsulated bacteria [69]. The risk of severe or fatal infections is also substantially increased, e.g. for fulminant sepsis by pneumococci [70] or HiB [67].

If preoperative vaccination is not possible, vaccination should be performed 14 days after surgery (AI)—longer delay does not yield additional benefit [71], while a shorter wait induces

insufficient antibody response. No comparable data are available regarding preoperative vaccination. However, patients should be vaccinated 2 weeks before planned splenectomy at the latest as antibody formation generally takes 9 days [72] (AIII).

In addition to anatomic asplenia, many patients with hematologic diseases should be regarded as functionally asplenic (e.g. all sickle cell patients or patients with hemoglobinopathies) and should thus be vaccinated (AII) [73]. All vaccines recommended in this guideline can be given at once if administered at different injection sites [74].

Patients with anatomic or functional asplenia should first be vaccinated against *Streptococcus pneumoniae* with PCV13, 6–12 weeks later with PPSV23 [50]. Revaccination should be performed every 6 years (AIIu). While the prime-boost strategy is currently recommended [20], the results of available data vary: benefit was shown for healthy subjects [75] and HIV patients [76], but not for liver/renal transplant recipients [77, 78].

Asplenic patients should be vaccinated with conjugated HiB vaccine (AIIIt). A patient is regarded as immunized if he was sequentially vaccinated with the primary series of HiB (by the age of 6 months) and a booster (6–8 months later), or was vaccinated once with HiB vaccine after the age of 14 months. Revaccination is then not needed [79]. While good immunogenicity of conjugated HiB vaccine was repeatedly demonstrated [80–82], further studies showing decreased mortality are needed.

The risk of infections with *Neisseria meningitidis* is high in asplenic patients and mortality rates range from 40% to 70% [79]. Therefore, these patients should be vaccinated with the tetravalent conjugated meningococcal vaccine, including activity against serogroups A, C, W, Y (MenACWY) (AII), with revaccination every 5 years [83]. Vaccination against serogroup B meningococcus (MenB) is under consideration and currently recommended for use in risk groups (STIKO). MenB was added to the immunization schedule in the United States for those at highest risk—including persons with asplenia—as serogroup B now accounts for 40% of cases [84, 85]. Immunogenicity in

asplenic patients has not been shown yet. If the tetravalent conjugate vaccine is not available, a prime-boost strategy (monovalent serogroup C, followed by tetravalent polysaccharide vaccine) is recommended. Scheduled vaccination with MenB vaccine should be re-evaluated and is highly recommended (**BII**). Measuring of immune response to MenACWY 1 month after administration and—if necessary—a second dose of vaccine should be considered [83, 86].

Patients with asplenia do not have a higher risk of influenza virus infection compared with the general population, but influenza may increase the risk for secondary bacterial pneumonia and sepsis [74, 87]. Thus, the STIKO recommends annual vaccination for all patients with immunodeficiency with influenza vaccine, including asplenic patients [50]. Influenza vaccination was shown to be associated with a 54% reduced mortality compared with unvaccinated asplenic patients [87]. We recommend performing annual vaccination in these patients  $\geq 6$  months with inactivated influenza vaccine (**AIIIt**).

### Monoclonal antibodies, kinase inhibitors and immune checkpoint blockade

Recent advances in antitumor therapy have significantly improved prognosis of many cancer patients but may pose particular challenges in terms of vulnerability toward infectious agents and success of vaccination strategies. As the field of small-molecule inhibitors and immunotherapy is evolving rapidly, data from large controlled trials regarding safety and efficacy of vaccines in this context are extremely scarce.

Monoclonal antibodies against CD20 result in near complete B cell depletion for up to 6 months after therapy [88]. Although the majority of patients show complete recovery of B cells 1 year after therapy [88], prolonged B cell depletion and hypogammaglobulinemia may occur [89, 90], making vaccination strategies challenging. As a functioning B cell compartment is required for an adequate immuneresponse, vaccination within the first 6 months after anti-CD20 therapy is generally discouraged (**DIIt**) [56, 91]. Within the first year after anti-CD20 therapy, assessment of antibody titers and revaccination if indicated might be an effective strategy to achieve protective antibody levels despite a diminished immune response (**AIIIt**) [35]. Particularly in case of seasonal influenza vaccine after anti-CD20 therapy, administration of a second booster vaccine has been shown to significantly increase humoral immune response [35]. While most data on vaccination strategies have been obtained with the oldest anti-CD20 antibody rituximab, we believe these recommendations to be transferable to other anti-CD20 antibodies such as ofatumumab or obinutuzumab as well as to other temporarily B cell depleting therapies such as the anti-CD3 $\times$ CD19 bispecific T-cell engager blinatumomab. As to the vaccination of patients treated with potentially indefinitely B-cell depleting anti-CD19 chimeric antigen receptor T cells, there is virtually no reliable data up to now and decisions regarding vaccination in this setting should be made on an individual basis keeping the patient's current immune status in mind.

Kinase inhibitors have become standard cancer therapy. Due to the different pathways affected, the effect of kinase inhibitors on immune response to vaccination is entirely dependent on the drug in question. In a small study of patients with metastatic renal cell carcinoma treated with the tyrosine kinase inhibitors

sorafenib or sunitinib, no significant difference regarding protective antibody responses after influenza vaccination could be observed compared with healthy controls [92]. Another small study with chronic lymphocytic leukemia patients treated with ibrutinib showed seroprotective titers against common influenza virus strains after vaccination in up to 74% of patients [93]. Inhibitors of the mammalian target of rapamycin such as everolimus or temsirolimus even seem to enhance immune responses [94, 95]. Therefore, decisions on vaccination need to be made on a case-by-case basis. In patients receiving kinase inhibitors, assessment of antibody titers and revaccination (if necessary) is recommended for adequate seroprotection.

Due to their novelty, data on vaccination strategies in patients treated by immune checkpoint blockade, such as anti-PD1, anti-PD-L1 or anti-CTLA4 antibodies, are rare. However, considering their mechanism of action, immune checkpoint inhibitors are likely to enhance rather than diminish immune response and have even been safely explored as vaccine adjuvants [96]. As patients receiving immune checkpoint inhibitors are still at increased risk of infections due to their underlying malignancy, they should receive all appropriate vaccines at the earliest convenience to avoid infectious complications or delay in therapy (**BIII**).

### Autologous stem cell transplantation

Autologous stem cell transplantation (ASCT) following high-dose chemotherapy profoundly impacts the immune system with often persistent reduction of antibody titers to vaccine-preventable diseases requiring a full revaccination to re-establish seroprotection [97, 98]. An overview of recommended vaccines following ASCT is given in Table 3.

Data on the impact of maintenance therapy after ASCT (e.g. with lenalidomide) on vaccination are scarce. While live-attenuated vaccines must not be administered in this setting (**DIIt**), inactivated vaccines might be considered.

Starting 3–6 months after ASCT, seasonal vaccination against influenza is recommended (**AIIIt**) [97, 99–101]. ASCT patients are at increased risk of severe courses when developing influenza infection [102, 103]; hence, vaccination early after transplantation might be favored in certain epidemiologic situations. However, immune response to influenza vaccine seems to be significantly impaired within 6 months following ASCT [101], which has to be particularly kept in mind in the setting of prior anti-CD20 therapy [56, 104]. In several small patient series, administration of a second dose of influenza vaccine was shown to significantly increase antibody titers and might therefore be considered in patients following ASCT, especially in case of early vaccination [105, 106].

Despite the lack of a definite head-to-head comparison of the antipneumococcal vaccines PCV13 and PPSV23 in ASCT patients, available data suggest superior immune response to the conjugate vaccine in the setting of an impaired immune system [107]. We therefore recommend, starting 3–6 months after ASCT, administration of three doses of PCV13, each 4–6 weeks apart, followed by one dose of PPSV23 after at least another 8 weeks (**AIIIt**) [97, 108–110].

Vaccination against HiB is recommended 6–12 months after ASCT with administration of at least three doses of conjugated

vaccine in order to achieve adequate titers (**BIIt**) [109, 111–113]. Additionally, vaccination before stem cell harvest may be considered [113]. Against meningococci, the conjugate tetravalent vaccine is preferable and one to two doses are recommended 6–12 months after ASCT according to national endemics (**BIIt**) [97, 114].

Vaccination with tetanus and diphtheria toxoid is recommended starting 6–12 months after ASCT (**BIIt**) [97, 98, 109, 114–116]. Administration of three doses of tetanus toxoid usually leads to adequate protective titers [97, 98, 109, 114–116]. In case of diphtheria, vaccination with the full dose of toxoid (D) as licensed for children is preferable to achieve adequate seroprotection (**BIIt**) [97, 98]. Vaccination against poliomyelitis should be performed in three doses only with the inactivated vaccine 6–12 months after ASCT (**BIIt**) [97, 117, 118]. Regarding pertussis, single vaccination with the lower, adult licensed dosage of acellular pertussis vaccine (ap) seems to be insufficient in adult transplant recipients [119]. Therefore, administration of three full doses acellular pertussis vaccine (aP) are recommended 6–12 months after ASCT (**CIIt**) [97, 120, 121]. Similarly, 6–12 months after ASCT, vaccination with three doses recombinant HBV vaccine is recommended (**BIIt**) [97, 122]. Patients with a previous history of hepatitis B need to be revaccinated following ASCT (**AIIt**) [123]. After a full course of HBV vaccination, assessment of antibody titers is recommended to identify nonresponders (**CIIt**) [97].

Current vaccines against MMR, yellow fever and varicella are live-attenuated vaccines and should not be administered during the first 2 years following ASCT or while still undergoing maintenance therapy (**DIIt**) [3, 49, 97, 124]. After >24 months post-ASCT, administration of live-attenuated vaccines seems to be safe and efficacious, and vaccination against MMR with one to two doses is recommended (**BIIt**) [97, 114, 115, 125, 126]. In case of measles, assessment of antibody titers before vaccination and administration of vaccine only to seronegative adults might be considered (**CIIt**) [97, 115].

Herpes zoster resulting from reactivation of VZV poses a relevant threat with incidence rates as high as 30% within the first 12 months after ASCT [127]. For seronegative ASCT recipients, primary infection with VZV may pose a significant health hazard. While the risk of herpes zoster seems to be highest within the first year after ASCT [128], early vaccination using a live-attenuated vaccine against VZV has been associated with both low immune response and cases of vaccine virus-induced varicella-like rash [124] and is therefore not recommended, especially given the availability of acyclovir prophylaxis. However, at 2 years after ASCT, vaccination with live-attenuated varicella vaccine seems to be safe [129, 130] and efficient in reducing incidence and severity of herpes zoster in transplant recipients [127, 131]. We recommend vaccination against varicella at >24 months after ASCT using either one dose of Zostavax<sup>®</sup> [130], licensed for prevention of herpes zoster, or 2 doses of Varilrix<sup>®</sup> [124, 132], licensed for prevention of primary varicella infection, both containing the live-attenuated Oka strain (**BIIt**). In the future, earlier vaccination against varicella might be feasible, as two large phase III trials evaluating a herpes zoster subunit vaccine in older adults showed promising results [133, 134] and a further phase III trial utilizing inactivated varicella vaccine in SCT recipients has already

completed enrolment. Inactivated VZV vaccines could be available soon and would possibly change current recommendations.

Vaccinations against other vaccine-preventable diseases depend on local epidemiology and individual risk. Vaccination against HAV seems feasible in ASCT recipients (**CIIt**) and might be coadministered with HBV vaccine [97, 115, 135]. For post-exposure prophylaxis, passive immunization is reasonable [97]. In endemic areas, vaccination against tick-borne encephalitis might be recommended according to national policies despite limited data (**CIIt**) [97, 136]. No data on the immunogenicity of HPV in SCT recipients exists, but in adolescents and younger adults, HPV vaccination might be useful (**CIIt**) [97]. Vaccination against travel-associated infectious diseases, such as yellow fever, cholera, typhus, pre-exposure rabies, and Japanese B encephalitis, warrants caution for patients following ASCT, and data on safety and efficacy in these patients are very limited. Decisions regarding vaccination should therefore be only made after thorough risk evaluation for the individual patient. Live-attenuated vaccines (e.g. yellow fever) should not be administered within the first 2 years following ASCT or during maintenance therapy (**DIIt**) [3, 49, 97, 124].

Following a complete revaccination program, regular assessment of seroprotection against tetanus, diphtheria, poliomyelitis, measles and hepatitis B every 4–5 years is recommendable in patients after ASCT (**BIIt**) [97].

### Allogeneic stem cell transplantation

Patients following allogeneic SCT are particularly prone to severe infectious complications. Regarding vaccine-preventable diseases, studies show a decline in protective antibody titers in allogeneic SCT recipients [137]. For these patients, a separate AGIHO guideline exists [138].

### Conclusion and outlook

Prevention of infectious diseases by vaccination has proven to be highly effective in many patient populations. This guideline was written to give practical advice for clinicians in hematology and oncology.

As coverage of vaccination is currently suboptimal in the general population as well as in patients at risk, detailed information and clear recommendations by physicians can have a high impact on acceptance of vaccination, especially as the main reasons for denial of vaccination are concerns about interaction with the malignant disease and potential side-effects [139, 140]. Implementation of an institutional vaccination program might further aid in increasing vaccination rates. To eliminate misperception and improve vaccination coverage in the population of cancer patients, educational programs for patients and for physicians focusing on safety and efficacy of vaccines are warranted in the future.

### Acknowledgements

The authors would like to thank the “Deutsche Gesellschaft für Hämatologie und Medizinische Onkologie” and the

“Arbeitsgemeinschaft Infektionen in der Hämatologie und Onkologie” for their support in establishing this guideline.

### Funding

This guideline was in part sponsored by travel grants from the “Deutsche Gesellschaft für Hämatologie und Medizinische Onkologie” (no grant number applies).

### Disclosure

DB is consultant to Basilea, Gilead Sciences, Merck Sharp & Dohme/Merck, received research grants from Gilead Sciences and Pfizer, serves on the speakers’ bureau of Astellas, Basilea, Gilead Sciences, Merck Sharp & Dohme/Merck, Pfizer and TEVA, and received travel grants from Astellas, Gilead Sciences, Merck Sharp & Dohme/Merck and Pfizer.

OAC has received research grants from Actelion, Amplyx, Arsanis, Astellas, AstraZeneca, Basilea, Bayer, Cidara, Duke University (NIH UM1AI104681), F2G, Gilead, GSK, Leeds University, Matinas, Medicines Company, MedPace, Melinta, Merck/MSD, Miltenyi, Pfizer, Rempex, Roche, Sanofi Pasteur, Scynexis, Seres, is a consultant to Amplyx, Actelion, Astellas, Basilea, Cidara, Da Volterra, F2G, Gilead, Janssen, Matinas, Menarini, Merck/MSD, Paratek, PSI, Scynexis, Seres, Summit, Tetrphase, Vical, and received lecture honoraria from Astellas, Basilea, Gilead, Merck/MSD and Pfizer.

GE received research and travel grants from MSD Sharp and Dohme and Pharmamar; serves on the speakers bureaus of MSD Sharp and Dohme and Gilead Science and is participant of MSD-Advisory Board.

WJH received research grants from MSD Sharp & Dohme/Merck and Pfizer; serves on the speakers bureaus of Alexion, Astellas, Basilea, Bristol-Myers Squibb, Gilead Sciences, Janssen, MSD Sharp & Dohme and Pfizer; and received travel grants from Alexion, Astellas, Lilly, MSD Sharp & Dohme, Novartis and Pfizer.

MH served on the speakers’ bureaus for Amgen, Celgene, Janssen, MSD Sharp & Dohme, Novartis and Takeda, and served on advisory boards of Amgen, Celgene, Gilead, Janssen, Sanofi and Takeda.

MvL-T is supported by the German Federal Ministry of Research and Education (BMBF grants 01EO1002 and 13GW0096D); has received research grants from Pfizer, Novartis, Gilead, Celgene and MSD, is a consultant to Merck/MSD; and received honoraria or travel grants from Basilea, Gilead, Merck/MSD, Janssen/Cilag and Astellas.

NL has received speakers’ honoraria from Merck Sharp & Dohme and Roche.

GM has been a consultant to Gilead and F2G and received honoraria for lectures from Gilead, Pfizer, Basilea and Astellas. CTR has been a consultant to AbbVie, Astellas Pharma, BMS, Gilead Sciences, Merck Sharp & Dohme, Novartis and Pfizer and served at the speakers’ bureau of Astellas Pharma, Bayer, BMS, Gilead Sciences, Janssen, Merck Sharp & Dohme, Novartis, Pfizer and Roche.

GS has received honoraria from Astellas, Gilead Sciences, GSK, Pfizer, Merck Sharp & Dohme and Neovii.

MS has received honoraria and served at the speakers’ bureau of Roche.

MJGTV has served at the speakers’ bureau of Pfizer, Merck, Gilead Sciences and Astellas Pharma, received research funding from 3M, DaVolterra, Astellas Pharma, Gilead Sciences and Merck and is a consultant to Berlin Chemie, Astellas Pharma and Merck. All remaining authors have declared no conflicts of interest.

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