Recommendations for immunization of patients diagnosed and treated for malignant diseases and their household contacts

April 2022

Content

1. Introduction

Malignant diseases today represent the second major cause of death in Switzerland. The incidence rate of cancer diagnosis in the Swiss population is reported to be 544 and 421 per 100'000 inhabitants for males and females respectively in the years 2015-2017. Between 2006 and 2017 overall annual incidence rates became stable showing even a slight decrease in cases from 488 to 475 cases per 100'000 inhabitants. 10 years survival rates increased by 3% for men and women over the last years mostly because of early detection (1). Cancer diagnosis and subsequent cancer therapy is usually associated with relevant immunosuppression caused by the underlying disease and by the applied treatment (cytotoxic substances, cell depletion, additional radiotherapy, intensity etc.). As a consequence, adherence to regular immunization schedules - especially in pediatric patients – is interrupted resulting in insufficient protection rates against vaccine-preventable diseases. Additionally, chemotherapeutic regimens may lead to loss of protection against vaccine-preventable disease in previously immunized patients. This is a result from treatment-associated cytotoxic immunosuppressive effects such as reduced white blood cell counts, B and T lymphocyte counts and function, immunoglobulin levels and loss of specific vaccine-induced antibody titers (2-6). As a consequence, cancer patients are vulnerable to invasive infections in general, but show also higher susceptibility and complication rates for vaccine preventable diseases such as invasive pneumococcal disease, influenza, varicella zoster, measles and human papillomavirus associated malignancies (7-18). This particular situation of patients with malignant diseases emphasizes the need for a specific vaccination strategy to best care for this special population of patients.

Vaccination strategies to best protect cancer patients against vaccine preventable diseases can be divided in **five main strategies** with respect to relative risks:

- Immunization strategy at cancer diagnosis **(see chapter 2)**
- Immunization strategy during conventional cytotoxic chemotherapy/radiotherapy (and until 3 months after chemotherapy) (**see chapter 3)**
- Immunization strategy after completion of conventional cytotoxic chemotherapy/radiotherapy (i.e. > 3months) **(see chapter 4)**
- Immunization strategy in patients treated with targeted therapies with (potential) impact on immunization **(see chapter 5)**
- Management of cancer patients after measles, varicella virus or tetanus exposure **(see chapter 6)**

These recommendations provide information on assessment and indication of missing, regular and additional vaccinations of patients diagnosed, treated and followed after treatment for cancer and include recommendations concerning the vaccination of their household contacts. Specific recommendations are proposed for patients treated with targeted therapies with particular effects on the immune function and impact immunization response. These recommendations do not cover specific vaccination recommendations for SARS-CoV2 and for patients suffering from hematological malignancies treated with hematopoietic stem cell transplantation, as these have been issued

separately (see BAG Empfehlung zur Impfung von Empfängerinnen und Empfänger von Blut-Stammzellen, 19,Covid-19-Impfung).

Sources of information: These guidelines are based on recent literature and expert reviews and guidelines published in North America, Europe and Australia (20-27). Wherever relevant, original studies have also been cited. Overall there is only few data about vaccination needs and effectiveness in cancer patients under and after chemotherapy and data is mostly restricted to specific treatments protocols and cancer diagnoses.
Given that the general recommendations for immunization in cancer patients are based on routine schedules, this guideline draws on the Swiss immunization plan.

Off label use: Some of the recommendations for vaccinations provided here involve off label use of vaccines, as no files including these patients have been submitted to the regulatory authorities as they are currently not registered in Switzerland yet. As such, limitations for reimbursement may apply and would have to be discussed with the patient. In addition, patient information leaflets accompanying vaccine preparations may contain general or specific precautions for the use of vaccines in immunocompromised or cancer patients. It must be stressed that for inactivated vaccines the safety profile is excellent and there are no known concerns substantiated by evidence that would prohibit their use in cancer patients before, under or after chemotherapy.

2. Immunization strategy at cancer diagnosis

2.1. Background: Risk and burden of disease

A higher susceptibility and complication rate in cancer patients is reported for the following specific vaccine preventable diseases: Invasive pneumococcal disease (7-10), influenza (11-13), varicella zoster infection (14-15, 28-30) and measles (16).

2.1.1 Invasive pneumococcal disease

Not only the incidence of invasive pneumococcal disease (IPD) in adult cancer patients is 4 to 60 times higher compared to the adult population (7) but also fatality rate is reported to be five times higher comparing cancer patients to healthy controls (31). Especially patients under chemotherapy are at substantial risk for IPD. In children with cancer four out of five invasive pneumococcal infections occur on undergoing chemotherapy (32). Satisfactory vaccine response rates with protection rates between 70-100% to mostly conjugated pneumococcal vaccines (PCV) in selected adult and pediatric cancer patients under mild to moderate chemotherapy have been reported (33-36). Moreover and importantly, no difference in immunogenicity was detected if gastric and colorectal cancer patients were vaccinated with PCV two weeks before or at the day of initiation of chemotherapy (37). Furthermore, a decline in incidence of IPD in cancer patients has been observed after the implementation and high coverage of the routine childhood immunization with the 7-valent conjugate vaccine (38). Overall, pneumococcal vaccination of lung cancer patients under chemotherapy resulted in a lower cumulative hospitalization rate for community-acquired pneumonia and a higher overall survival rate (39). Based on these findings we recommend:

Recommendation: A single dose of PCV should be applied to all newly diagnosed cancer patients who were not immunized in the past 5 years.
Timing: Ideally 2 weeks before the chemotherapy start. If not feasible or done, PCV is to be caught up until start of chemotherapy or at the latest during maintenance chemotherapy ***(see Table 1).***

2.1.2 Influenza infection

Influenza-related complications and mortality are increased in cancer patients and illness due to influenza infection in children with hematological malignancies causes significant delay in chemotherapy (11, 13, 40). Despite the decreased immunogenicity of the influenza vaccine in cancer patients (41-42) clinical benefits i.e. a decrease in mortality, lower odds for influenza-like-Illness and confirmed influenza infection have been demonstrated in influenza-vaccinated adult cancer patients (43-46). Influenza vaccination in colorectal adult cancer patients moreover reduced the occurrence of pneumonia and resulted in less delays of chemotherapy courses due to infection-related illness (45). Influenza vaccination remains effective in preventing influenza infection and its complications in children treated for cancer. An adjusted estimated vaccine effectiveness of 72% was identified in preventing laboratory-proven influenza infection in children undergoing treatment for cancer (47).

Furthermore, a lower rate of hospitalizations in influenza-vaccinated children with hematologic malignancies has been demonstrated (48). Based on these findings we recommend:

Recommendation 1: Annual administration of one dose of inactivated quadrivalent influenza vaccine is recommended for all diagnosed and treated cancer patients and their household contacts until 6 months after completion of therapy. In addition to the conventional inactivated flu vaccines, a flu vaccine with a four times higher antigen dosage is also licensed for people ≥ 65 years.
Timing: Annually before and during influenza season ***(see Table 1).***

2.1.3. Varicella zoster virus (VZV)

2.1.3.1. Varicella zoster virus infection (chickenpox)

VZV infection causes significant excess morbidity and mortality in immune-compromised patients. In immunosuppressed children, including those undergoing treatments for cancer mortality rates of 7% have been reported (28-29). Additionally, exposure to and infection with VZV in children under maintenance therapy for acute lymphoblastic leukemia resulted in significant interruption or delay in chemotherapy (30). Administration of passive immune prophylaxis with VZV immune globulin (VZIG) has reduced attack rates after varicella exposure and modulated the expression of disease in healthy individuals as well as in pediatric cancer patients (51-53). Use of oral acyclovir (7-9 days after exposure for a duration of 7 days) for prevention of varicella was only investigated in healthy children so far and showed significant decrease of development of chickenpox after household exposure if treated with acyclovir vs. placebo (16% vs. 100%) (54). Antiviral therapy with intravenous acyclovir in children with malignancies presenting with VZV infection leads to a reduction of visceral dissemination and severe complications (55-56).

Recommendation 1:
VZV serum antibodies (IgG) must be determined at cancer diagnosis in all cancer patients without two documented varicella vaccine doses (see Table 2).
Recommendation 2: Household contacts of cancer patients must be immune against VZV and vaccinated with the life-attenuated varicella vaccine (twice with an interval of one month) as soon as possible if not ***(see Table 3).***
Recommendation 3: In case of exposure to varicella, VZIG should be administered within 4 days to patients with malignancies without two documented varicella vaccine doses or without protective serum VZV IgG levels at cancer diagnosis. Prophylactic antiviral therapy is to be considered if VZIG was not administered in these patients.
Recommendation 4: VZIG or prophylactic antiviral therapy is not recommended in patients with protective serum VZV IgG levels at cancer diagnosis or in cancer patients with two documented varicella vaccine doses before diagnosis. Close monitoring for varicella infection during 28 days after exposure is needed and antiviral treatment must be initiated if signs and symptoms of varicella infection occur ***(see Table 2 and 7***).

2.1.3.2. Herpes Zoster (HZ)

Adult and pediatric cancer patients are at substantially increased risk for herpes zoster (14-15, 18). Compared with incidence rates reported in a general population, rates of HZ were 4.8 and 1.9 times higher respectively in adult patients with hematologic malignancies and solid tumors (14). Incidence rate of HZ in children diagnosed with cancer was about 10 times higher compared to a non-cancer children cohort (15). The live attenuated zoster vaccine (ZVL, Zostavax®) can reduce HZ episodes, but is contraindicated during immunosuppression. Patients older than 70 years who were previously vaccinated with Zostavax® and underwent cancer chemotherapy later in life showed significantly reduced incidence of HZ compared to patients not previously vaccinated (57). As the initiation of chemotherapy after cancer diagnosis is mostly urgent and a minimal time interval of 4 weeks between ZVL and initiation of chemotherapy must be guaranteed to apply the immunization, alternative vaccination strategies are desirable.

The new recombinant subunit herpes zoster vaccine (RZV, Shingrix®) has been recently approved by Swissmedic for healthy adults > 50 years of age and immunosuppressed patients > 18 years of age. RZV showed 90.2% efficacy in reducing HZ in patients older than 70 years and 97.2% in adults 50 years of age or older (58). ZVL accounted for 63% efficacy in 60-69-year-old patients and 37.6% in patients older than 70 years respectively (59). Good immunogenicity and safety of RZV has been demonstrated for cancer patients > 18 years of age with solid tumors when two doses of RZV were administered before or during chemotherapy (60). Similar effects of RZV were found in adults with hematological malignancies when administered under or up to 6 months after immunosuppressive cancer treatment (61). Additionally, a vaccine efficacy of 87.2% at preventing herpes zoster (follow up period of 11 months) was demonstrated in these patients (61). Similarly, another study among adult autologous stem cell transplant recipients aged > 18 years of age who received 4 doses of RZV (first dose 5-60 days before, second, third and fourth doses at about 30, 60 and 90 days after transplantation) showed significant efficacy at preventing 68% of HZ episodes and 89% of episodes with post herpetic neuralgia (62).

Recommendation: Due to high burden of herpes zoster in cancer patients and in particular in those with hematological malignancies the administration of 2 doses of RZV in patients > 18 years of age is recommended.
Timing: First dose ideally 2 weeks before the initiation of chemotherapy, if not feasible or done to be caught up until start of chemotherapy or at the latest during maintenance chemotherapy.
Second dose with an interval of 2 months after the first dose (in case of time constraint a minimal interval of 1 month can be chosen), or as soon as possible at a later time point during or after chemotherapy ***(see Table 1).***

2.1.4 Measles

Measles is a severe illness, especially in immunocompromised patients with case fatality rates of 70% for oncology patients (16). The live-attenuated vaccine (MMR) is contraindicated under cancer chemotherapy. Administration of intravenous immunoglobulins within 6 days after measles exposure

leads to significant reduction of attack rates in healthy individuals (63-64). There are no studies available investigating need and efficacy of IVIG in preventing measles infection in cancer patients.

Recommendation 1: Measles serum antibodies (IgG) must be determined at cancer diagnosis in all cancer patients without two documented MMR vaccine doses ***(see Table 2).***
Recommendation 2: Household contacts of cancer patients must be immune against measles and vaccinated with the life-attenuated MMR vaccine (twice with an interval of one month) as soon as possible if not ***(see Table 3)****.*
Recommendation 3: In case of exposure to measles, IVIG should be administered within 6 days to patients with malignancies without protective serum IgG levels at cancer diagnosis or without two documented MMR doses before diagnosis. The same approach is to be considered in severely immunocompromised cancer patients (definition see Table 7) independent of measles serum antibody level or documentation of 2 MMR doses before diagnosis ***(see Table 2 and 7).***
Recommendation 4: IVIG is not indicated in mildly immunocompromised patients with protective serum IgG levels at cancer diagnosis two documented MMR doses before diagnosis ***(see Table 2 and 7).***

2.1.5 Meningococci (Asplenia)

Cancer therapy can lead to anatomical or functional asplenia either following surgical splenectomy or splenic irradiation or by cancer therapy. In addition to immunization against **invasive pneumococcal disease** that is recommended to all patients at cancer diagnosis, immunization against **meningococcal disease** must be added in patients suffering from asplenia (see BAG document "Prävention schwerer Infektionen bei anatomischer oder funktioneller Asplenie" Stand 2015, (65)) and have to be taken in account in these cancer patients.

Recommendation: In patients with present or future asplenia (by cancer therapy) 2 doses of quadrivalent conjugated meningococcal vaccine, 2 doses of recombinant meningococcal B vaccine and 1 dose of conjugated pneumococcal vaccine (MCV-ACWY, 4CMenB and PCV) should be administered at cancer diagnosis.
Timing: First dose ideally two weeks before or until initiation of cancer treatment, if missed to be caught up until start or during maintenance chemotherapy. Second dose of MCV-ACWY and 4CMenB *with a minimal interval of 1 month after the first dose and 2 months after the first dose respectively, if not feasible, as soon as possible at any later time point* ***(see Table 1).***

2.2. Practical immunization strategy at cancer diagnosis

- Assess and document immunity against measles (defined as: 1. two documented vaccine doses or 2. serum IgG antibody level above threshold with correlation to protection **(see Table 2)**) and varicella (defined as: 1. two documented vaccine doses or 2. serum IgG antibody level above threshold with correlation to protection **(see Table 2)**) before initiation of cancer therapy of:

    - all newly diagnosed cancer patients
    - household contacts
- Administer immunizations according to **Table 1** to all newly diagnosed cancer patients
    - **Comment**: Low platelet count, coagulopathy/anticoagulation as well as recent administration of intravenous immunoglobulins and blood products are no contraindication to the administration of intramuscular immunizations with all vaccines listed in Table 1 (see BAG Schweizerischer Impfplan 2019, 5e page 30, (66)).
- Patients planned to undergo splenectomy or receive splenic irradiation as part of the cancer therapy should additionally be immunized against meningococcal disease at cancer diagnosis (see also BAG document "Prävention schwerer Infektionen bei anatomischer oder funktioneller Asplenie", (65))
- Administer immunizations to all household contacts of newly diagnosed cancer patients according to **Table 3**.

Table 1. Recommended immunizations in newly diagnosed cancer patients.
Highlighted in blue are immunizations that are only relevant for children and adults with known future asplenia.

Vaccine (age restriction)	**Number of doses**	**Time to therapy initiation**
PCV [1) 2)] (≥5 years of age) [3)]	1 **off label ≥ 5 years of age**	At diagnosis, ideally >2 weeks before or to be caught up until start of chemotherapy or at latest under maintenance therapy
Quadrivalent inactivated influenza vaccine (≥ 6 months)	1 [4)]	Annually before or during influenza season
RZV (Shingrix ®) (≥18 years) [5)]	2 [6)]	At diagnosis, ideally >2 weeks before or to be caught up until start of chemotherapy or at latest under maintenance therapy
MCV-ACWY [7)] - (2-6 months) - (≥7 months) **4CMenB (Bexsero®)**[7)] - (2-11 Monate) - (12-23 Monate) - (≥ 24 Monate)	 4 [8)] 2 [9)] 3 [10)13)] 3 [11)13)] 2 [12)13)]	At diagnosis, ideally >2 weeks before or to be caught up until start of chemotherapy or at latest under maintenance therapy

	off label beyond the age between 11-24 years	

Abbreviations: pneumococcal conjugated vaccine (PCV), recombinant zoster vaccine (RZV), conjugated meningococcal vaccine (MCV-ACWY), recombinant vaccine against invasive meningococcal disease serogroup B (4CMenB)

1) Only if patient was not immunized in the past 5 years

2) Only available PCV at the moment (=PCV13), off label in persons ≥ 5 years of age

3) Administration of 1 dose PCV in patients ≤5 years if not up to date with regular schedule, see Table 9

4) In children not vaccinated previously and age between 6 months and 8 years administration of 2 doses with a minimal interval of 1 month

5) In particular for patients with hemato-oncological diseases

6) Second dose to be administered with an interval of 2 months (minimal interval 1 month) or if not feasible as soon as possible at a later time point

7) If (future) functional or anatomic asplenia

8) Second dose to be administered with an interval of 2 month, third dose with an interval of 4 months and fourth with a minimal interval of 12 months after the first dose

9) Second dose to be administered with a minimal interval of 1 month or if not feasible as soon as possible at later time point. Second dose to be given in the second year of life.

10) Second dose with a minimal interval of 2 months, third dose during the second year of life (minimal 6 months after second dose) or if not feasible as soon as possible at a later time point

11) Second dose with a minimal interval of 2 months, third dose 12 months after the second dose or if not feasible as soon as possible at a later time point

12) Second dose with a minimal interval of 2 months or if not feasible as soon as possible at a later time point

13) Booster dose every 5 years if ongoing risk

Note: If patient is not up to date with regular Swiss immunization plan (see Table 9 Appendix) consider accelerated administration of missing booster doses (other than mentioned in Table 1) before chemotherapy start. This is only possible if patient is not severely immunocompromised by the disease (no acute hemato-oncological disease, chronic lymphatic leukemia, and metastatic cancer disease (67)) and a minimal time interval of 2 weeks for inactivated vaccines and 4 weeks (exception: 6 weeks if planned treatment with alemtuzumab, see chapter 5) for live attenuated immunizations before initiation of therapy can be guaranteed.

Table 2. Recommended analysis of serum antibody levels in newly diagnosed cancer patients

Antibody	**Indication for serum antibody analysis at diagnosis**	**Serum antibody level with correlation to protection**
Measles IgG	< 2 MMR vaccine doses	> 150 IU/l [1)]
Varicella (ELISA VZV gp)	< 2 varicella vaccine doses	> 150 IU/l [1) 2) 3)]

1) If result beyond level of protection, time span of 4 weeks before initiation of chemotherapy can be withheld and patient is not severely immunocompromised by disease itself (no acute hemato-oncological disease, chronic lymphatic leukemia, and metastatic cancer disease) evaluate application of one dose of MMR (> 6 months of age) or varicella vaccine (> 9 months of age) before initiation of chemotherapy

2) Test available at “Laboratoire de vaccinologie des Hôpitaux Universitaires de Genève

3) Any other laboratory is valid but if antibody level is low consider to repeat test at 2) due to insufficient sensitivity

Table 3. Recommended immunizations for household contacts of newly diagnosed cancer patient (additionally to immunizations recommended by Swiss immunization plan (66))

Vaccine	**Minimal age and number of doses**	**Schedule (interval in months)**
Quadrivalent inactivated influenza vaccine	6 months - 8 years: 2 doses [1)] ≥ 9 years: 1 dose	0, 1
Varicella zoster [2)] - **VZV-live-attenuated vaccine®**	≥ 9 months: 2 doses [3)]	0,1
Measles	≥ 6 months: 2 doses [4) 5)]	0,1

Abbreviations: recombinant zoster vaccine (RZV)

1) If not previously vaccinated with influenza vaccine, otherwise 1 dose

2) If negative personal medical history for chickenpox

3) If first dose < 12 months of age, give 2nd dose after 12 months of age. If two doses have been administered before 12 months, add a 3rd dose after 12 months of age

4) Administer one dose at age 9 and at 12 months. If first dose is administered between 6 to 8 months of age, a total of three doses is needed with 2nd dose at 9 and 3rd dose at 12 months of age

5) Combination-vaccine MMR-V possible if both, MMR and VZV vaccination, are indicated (not on list of specialties = not necessarily reimbursed)

3. Immunization strategy during conventional cytotoxic chemotherapy/radiotherapy (and until 3 months after chemotherapy)

3.1. Background

Conventional cytotoxic chemotherapy is defined as chemotherapy with unselective cytotoxic effect and does not include therapies like monoclonal antibodies, tyrosine kinase inhibitors or hormonal therapy (68).

Data about safe administration of live-attenuated exists only for varicella vaccine in pediatric patients suffering from acute lymphoblastic leukemia with lymphocyte counts above 700/µl under paused maintenance therapy (49-50). Still given the lack of data, generally the application of live attenuated vaccines in immunosuppressed patients under conventional cytotoxic chemotherapy is contraindicated as vaccine-induced disease can occur (69). Immunization with inactivated vaccines in highly immunocompromised patients under intense conventional cytotoxic chemotherapy is known to be associated with either missing, or more frequently, insufficient vaccine response as shown for inactivated influenza vaccines (42, 70). Booster doses of inactivated vaccines administered under maintenance chemotherapy or shortly after completion of chemotherapy (<3 months) against diphtheria, tetanus and *Haemophilus influenza* type b (Hib) showed satisfactory serum antibody protection rates without occurrence of adverse reactions (71-73). Patients suffering from breast or colorectal cancer showed best immune response to inactivated vaccines under chemotherapy if administered at the beginning of a chemotherapy cycle (111-113), when therapy was least intense or if lymphocyte count was (>1000/µl) (111,114).

The data on the effects of radiotherapy on immune function are sparse and the effects are likely less significant than those of conventional cytotoxic chemotherapy (25). International guidelines do not recommend particular or different immunization strategies or intervals for those cancer patients undergoing additional radiotherapy (21, 23-25).

3.2. Practical immunization strategy during conventional cytotoxic chemotherapy/radiotherapy (and until 3 months after chemotherapy)

- The administration of live attenuated vaccines is contraindicated
- If missing, inactivated vaccines according Table 1 including PCV, inactivated influenza, RZV, MCV-ACWY and 4CMenB should be completed
    - If possible administer at beginning of chemotherapy cycle, when therapy is least intense or when lymphocyte count is >1000/µl
- The administration of other inactivated vaccines can be considered if a high epidemiological or individual risk is present. Still, whether vaccines first administered during chemotherapy induce long-term protection is unclear. Thus, specific antibody levels (where available) can be checked (4 weeks after last dose of primary vaccination) and vaccine booster doses be considered after completion of cancer therapy
- If a cancer patient under treatment is exposed to measles, varicella, hepatitis B or tetanus follow the recommendations according to **Table 7** (74-79)

4. Immunization strategy after completion of conventional cytotoxic chemotherapy / radiotherapy (i.e. > 3months)

4.1. Background: Risk and burden of disease

Conventional cytotoxic chemotherapy results in waning immunity as indicated by loss of protective serum antibody titers (80-81). Rates of protective serum antibody titers of vaccine preventable diseases after chemotherapy vary widely in different studies and are mostly studied in children with acute lymphoblastic leukemia (5, 71-72, 80, 82-85). Risks associated with loss of antibodies are difficult to evaluate because studies mostly focus on patients with particular malignancies and results cannot be generalized. Some studies found an association between loss of protective antibody titers against measles, rubella and tetanus with younger aged children and higher aged adults following chemotherapy (80-81,86-87), while other studies found no association between patient's age, type of cancer, chemotherapy intensity and loss of protecting serum antibody titers (71, 82, 88). Because of lack of data and contradictory results specific vaccination policies for chosen risk groups (excluding patients treated with targeted therapies, see chapter 5) cannot be recommended.

Booster doses of inactivated vaccines (tetanus, polio, diphtheria, Hib as well as meningococcal serogroup ACWY) three to six months after completion of chemotherapy induce good immune responses (71-72, 82, 88-89). Booster dose of live attenuated measles, mumps and rubella vaccine three months after the end of therapy were associated with lower seroconversion rates (71-72) compared to booster doses after at least 6 months after the end of chemotherapy (80, 82, 88). Based on these findings we recommend:

Recommendation 1: Indication for booster doses depend on the age and immunization status before initiation of cancer chemotherapy/radiotherapy ***(see Table 4a and 4b)***

Recommendation 2: Administration of ***inactivated vaccines*** *is recommended 3 months after completion of conventional cytotoxic chemotherapy/radiotherapy independently of the type of malignancy.*

Recommendation 3: Administration of ***live attenuated vaccines*** *is recommended 6 months after completion of conventional cytotoxic chemotherapy/radiotherapy independently of the type of malignancy.*

*Recommendation 4: The evaluation of serum antibody titers to elaborate individual vaccine strategies is not recommended but an alternative favored by some patients. However, depending on the age of the patient, if booster doses have to be given according to the regular vaccination plan, they should be administered without first performing serology. The administration of supplementary doses can be dictated by the result of the serology where available (****see Appendix Table 9 and 10****)*

4.2. Practical immunization strategy 3 to 6 months after conventional cytotoxic chemotherapy/radiotherapy

- Administration of **inactivated vaccines** is recommended **3 months** after completion of conventional cytotoxic chemotherapy/radiotherapy

- Administration of **live attenuated vaccines** can be administered **6 months** after completion of conventional cytotoxic chemotherapy/radiotherapy
- Indication for a vaccine and number of needed doses are dependent on previously applied number of vaccine doses and age of patient but independent of underlying malignancy **(see Table 4a and 4b)**

Table 4a. Recommended immunizations 3 to 6 months after completion of conventional cytotoxic chemotherapy/radiotherapy in **adult** cancer patients.

Vaccine (age restriction)	**Number of doses received before CCT**	**Needed number of doses after CCT**	**Schedule (months)**	**Interval after completion of CCT (months)**
dTpa-IPV, HBV	0-1	3 [1)]	0, 2, 8	3
	≥2	1		3
RZV (Shingrix®) (≥18 years)	0 1 2	2 1 0	0, 2 (1)	3
MMR, Varicella vaccine [3)]	0	2	0, 1	6 [4)]
	≥1	1		6 [4)]

Abbreviations: conventional cytotoxic chemotherapy/radiotherapy (CCT), Recombinant zoster vaccine (RZV)

1) Total 3 doses, with one pertussis-containing dose: 1xdTpa plus 2x dT-IPV

2) The timing of the 2nd RZV dose may be brought forward - or delayed - if indicated by the individual immune status. A minimum interval of 1 month and a maximum interval of 6 months between the 2 doses were considered in the registration studies.

3) Only if VZV IgG ≤ 150 IE/l at diagnosis and negative personal history of chickenpox

4) If wished to be administered from 3 to 6 months after CCT measure CD4 count. If CD4 count >200/µl (0.2 g/l) vaccine can be administered in this time period.

Table 4b. Recommended immunizations 3 to 6 months after completion of conventional cytotoxic chemotherapy/radiotherapy in **child/adolescent** cancer patients

Vaccine	Age	Number of doses received before CCT	Needed number of doses after CCT	Schedule (months)	Interval after completion of CCT (months)
DTPa-IPV	<1yr.	0-1	3	0,1, 8	3
		2	1		3
	≥1yr. [1)]	0-1	3	0, 2, 8	3
		≥ 2	1		3
HBV [2)]		0-1	3	0, 1, 6	3
		≥ 2	1		3
Hib	<1yr.	0-1	3	0, 1, 8	3
		2	1		3
	12-14 months	0-1	2	0,2	3
		≥ 2	1		3
	15-59 months	0-3	1		3
PCV	<1yr.	0-1	3	0, 1, 8	3
		2	1		3
	12-23 months	0-1	2	0, 2	3
		2-3	1		3
	24-59 months	0-3	1		3
MCV-ACWY	2-5 years and 11-19 years	0-2	1		3
HPV	11-14 years	0-1	2	0, 6	3
		2	1		3
	15-26 years	0-1	3	0, 2, 6	3
		2-3	1		3
MMR[5)]	≥ 6 months	0	2	0, 1	6, [3)]
		≥ 1	1		6, [3)]
Varicella vaccine	≥9 months [4)]	0	2	0, 1	6, [3)]
		≥ 1	1		6, [3)]

Abbreviations: conventional cytotoxic chemotherapy/radiotherapy (CCT)

1) >7 years use dTpa-IPV

2) If no HBV vaccination so far and patient < 15 years of age complete now or at latest at age 11-15

3) If wished to be administered from 3 to 6 months after CTT measure CD4 count. If patient > 5 years and CD4 count > 200/µl (0.2 g/l), <1 year and CD4 >750/µl (0.75 g/l) or 1-5 years and CD4 > 500/µl (0.5 g/l) vaccine can be administered in this time period.

4) Only if VZV IgG between 0-150 IE/l at diagnosis and negative personal history of chickenpox
5) If 1st dose is given between 6 and 8 months, give 3 doses, the 2nd at 9 months and the 3rd at 1 year.

Catch-up courses of immunizations according to Table 4a and 4b are recommended. Alternatively, in previously incompletely immunized patients an immunization schedule guided by serum antibody levels determined 4-8 weeks after applying a booster dose can be considered. Serum antibody (IgG) levels as surrogate markers are available and have been defined only for the following immunizations.

- Tetanus
- Hepatitis B
- *Haemophilus influenzae* type b
- Measles
- Varicella

The tests and threshold values for serum antibody titers correlating with protection are described in the regular Swiss immunization plan and added in appendix of this manuscript **(see Table 10*)***

5. Immunization strategy in patients treated with targeted therapies with (potential) impact on immunization

5.1. Background

In hemato-oncology and oncology the use of targeted therapies like several monoclonal antibodies has substantially evolved over the last years. Data on immunization of patients treated with these agents is still sparse. The most extensive experience comes from treatments with rituximab (anti-CD-20).

5.1.1. B-Cell depletion

Administration of **rituximab** (anti-CD20) results in a B-cell depletion and therefore an absent response to vaccination (67, 70). Berglund et al. confirmed the lack of induction of an immune response to influenza and pneumococcal immunization in oncological patients treated with rituximab (70). Data from patients treated with rituximab for autoimmune diseases showed insufficient immune responses following an immunization for at least 6 months after the last dose of rituximab (91-94). Satisfactory immune response following tetanus immunization was demonstrated when the vaccine was administered 6 months after completion of rituximab therapy (93).

*Recommendation 1: In subjects that will receive B cell depleting therapies the administration of immunizations according to **Table 1** is recommended if applied before initiation of therapy, ideally > 2 weeks.*
*Recommendation 2: During and until 6 months after completion of B cell depleting therapies administration of any **inactivated vaccine** is not recommended.*
*Recommendation 3: **During and until 12 months after completion of B cell depleting therapies the administration of live-attenuated vaccines is contraindicated.***

*Recommendation 4: Administration of inactivated vaccines after B cell depleting therapies is recommended as described in **Table 4a and 4b** but only after a minimal time interval of*

- *6 months, if booster dose (20, 27)*
- *12 months, if primary vaccination (26)*

*Recommendation 5: Administration of live attenuated vaccines after B cell depleting therapies is recommended as described in **Table 4a and 4b** but only after a minimal time interval of 12 months. Immune recovery must be documented after therapy with CAR-T cells and alemtuzumab before administration of live attenuated vaccines **(see Table 5)** (67, 94-95).*

*Recommendation 5: Recommendation 1-4 is true for all patients treated with B cell depleting agents listed in **Table 5**.*

5.1.2. Tyrosine kinase inhibitors (TKI)

Immune modulating **tyrosine kinase inhibitors (TKI)** comprises another class of similarly acting targeted therapies (Table 6) used in oncology. TKI have various effects on the immune system i.e. the inhibition of T cell proliferation and activation and inhibition of expansion of cytotoxic memory T cells (67, 96-97). Small molecule inhibitors like ibrutinib and idealisib inhibit signal translation via B-cell receptors thereby possibly preventing an immune response under therapy (97). Immune responses to influenza vaccination (H1N1) in patients with chronic myeloid leukemia (CML) under TKI therapy with imatinib, dasatinib or nilotinib are impaired (98-99). Still, conclusive studies concerning immunization of patients under such therapies are sparse which makes recommendations difficult. So far, the interpretation of the mechanisms and of the available data may lead to different conclusions, when balancing benefits and risks. Wiedermann et al. (67) in a review advise against any immunization under therapy with TKI whereas European Conference on Infections in Leukaemia (ECIL 7) recommendations support the administration of PCV and inactivated influenza vaccine at cancer diagnosis even if already under therapy with TKIs like imatinib, dasatinib, nilotibib, bosutinib and ponatinib (26).

*Recommendation 1: The administration of immunizations according to **Table 1** is recommended if applied before initiation of a TKI therapy, ideally > 2 weeks. If lifelong therapy: administration of PCV, annual influenza and RZV can be considered under treatment.*

*Recommendation 2: During and up to 3 months after completion of TKI therapy administration of any **inactivated and live-attenuated vaccine** is not recommended.*

*Recommendation 3: Immunizations can be administered according **Table 4a and 4b** 3 to 6 months after end of TKI therapy.*

*Recommendation 4: Recommendation 1-3 is true for all patients treated with agents listed in **Table 6**.*

5.1.3. Checkpoint inhibitors

Therapy **with immune checkpoint inhibitors** has remarkably improved cancer therapy of patients with advanced disease by acting on proteins that block the inhibition of T-cell activation so that cancer cells cannot escape the antitumor effect of the immune system (100-102). The enhanced T-cell activation is associated with immune-mediated events targeting host tissues (103). From their mode of action, checkpoint inhibitors are generally not considered as being immunosuppressive. Läubli et al (104) described good humoral immune response among patients treated with immune checkpoint inhibiting antibodies (Nivolumab, Pembrolizumab) when immunized against influenza but an unexpected high incidence of immune-related adverse events. These findings were not confirmed in a larger retrospective review by Chong et al. (105) where no increase in incidence or severity of immune-related adverse events was detected (27). Overall routine seasonal influenza vaccination today is encouraged in patients treated with immune checkpoint inhibitors (115).

Recommendation: The immunization strategy does not differ from that recommended for patients with conventional cytotoxic chemotherapy ***(Table 1, 4a and 4b)***

5.1.4. Targeted therapies with unknown impact on immunization

New oncological therapies that may influence the immune response to vaccination are emerging and applied in oncology very rapidly. Their impact on immunization responses is mostly unknown. In such situations to best protect these vulnerable patients we recommend to consult with a vaccine expert. Section 5.5. **(see Figure 1)** provides a possible practical approach how to vaccinate these patients (94).

Recommendation 1: A vaccine expert should be involved in vaccine recommendations for patients under targeted therapies with unknown impact on immunization
Recommendation 2: A possible approach to evaluate the individual potential of vaccine immune response is to administer of one dose of tetanus vaccine 3 months after therapy with consecutive serum antibody analysis ***(see Figure 1)***
Recommendation 3: To evaluate safety of administration of live attenuated vaccines analysis of CD4+ cell count is recommended ***(see Figure 1)***

5.2. Practical immunization strategy in patients treated with B cell depleting therapies

- Immunization strategy at cancer diagnosis:
    - The administration of immunizations according to **Table 1** is only recommended if applied before initiation of B cell depleting therapy, ideally > 2 weeks **(see Table 5)**
        - Exception: If treated with **Alemtuzumab (Lemtrada)** ideally > 6 weeks before initiation of therapy (95) **(see Table 5)**
- Immunization strategy during and until 6 months after completion of B cell depleting therapies:
    - Administration of any inactivated vaccine is not recommended
    - The administration of live-attenuated vaccines is contraindicated

- Immunization strategy 6 months after completion of B cell depleting therapies:
    - Administration of inactivated vaccines after B cell depleting therapies is recommended as described in Table 4a and 4b but only after a minimal time interval of
        - 6 months, if booster dose (20, 27)
        - 12 months, if primary vaccination (26) **(see Table 5)**
    - Administration of live attenuated vaccines after B cell depleting therapies is recommended as described in Table 4a and 4b but only after a minimal time interval of 12 months (67, 95) **(see Table 5) (expert opinion)**
        - Exception 1: CD4+ count must be >200/µl before administration of live attenuated vaccine
            - If treated with alemtuzumab **(expert opinion)**
        - Exception 2: B cell count recovery must be documented before administration of live attenuated vaccine
            - if vaccine is wished to be administered between 6 and 12 months after B cell depleting therapy (115)
            - if treated with CAR-T cells (Kymriah®, Yescarta®) **(expert opinion)**

Table 5: Minimal time interval before and after B cell and plasma cell-targeted therapies to immunize with inactivated and live attenuated vaccines.

Drug	**Target receptor**	**Effect on B cells**	**Minimal interval before initiation of therapy**		**Minimal interval after completion of therapy**	
			IV	**LAV**	**IV**	**LAV (expert opinion)**
Rituximab (Mabthera®, Rixathon®)	Anti-CD-20	B cell depletion	2 weeks [1)]	4 weeks	6 months [2)]	12 months [3)]
Obinutuzumab (Gazyvaro®)	Anti-CD-20	B cell depletion				
Brentuximab-Vedotin (Adcetris®)	Anti-CD-30	B cell depletion				
Alemtuzumab (Lemtrada®)	Anti-CD-52	B and T cell depletion	6 weeks [1)]	6 weeks		12 months [4)]
Daratumumab (Darzalex®)	Anti-CD-38	Plasma cell and plasmablast depletion	2 weeks [1)]	4 weeks		12 months [3)]

Elotuzumab (Empliciti®)	Anti-SLAMF7	Plasma cell depletion				
Blinatumomab (Blincyto®)	Anti-CD3xCD19	B cell depletion				
CAR-T Cells (Kymriah®, Yescarta®)	CD19	B cell depletion				12 months 5)
Venetoclax (Venclyxto®)	BCL2 inhibitor	B cell apoptosis				12 months 3)
Ibrutinib (Imbruvica®)	Bruton-tyrosine-kinase-inhibitor (Small molecule inhibitor)	Reduced B cell maturation, proliferation and function				
Idealisib (Zydelig®)	PI3Kdelta-kinase-inhibitor (Small molecule inhibitor)	Enhancement B cell depletion				

Abbreviations: inactivated vaccine (IV), live-attenuated vaccine (LAV)

1) If not feasible or done to be caught up until start of chemotherapy

2) 12 months if primary vaccination

3) Normal CD 19+ B cell count must be documented if LAV is wished to be administered between 6 and 12 months after B cell depleting therapy

4) Administer LAV only if CD4+ count > 200/µl (0.2 g/l)

5) Normal CD19+ B cell count must be documented before administration of LAV

5.3. Practical immunization strategy in patients treated with tyrosine kinase inhibitors (TKI)

- Immunization strategy at cancer diagnosis:
  - The administration of immunizations according to **Table 1** is only recommended if applied before initiation of TKI therapy, ideally > 2 weeks **(see Table 6)**
- Immunization strategy during and until 3 months after completion of TKI therapy:
  - Administration of inactivated vaccines is not recommended
    - If lifelong therapy administration of PCV, annual influenza and RZV under treatment can be considered
  - Administration of live attenuated vaccines is contraindicated
- Immunization strategy 3 to 6 months after TKI therapy
  - According **Table 4a and 4b**
- These recommendations are true for all TKI and similar drugs listed in Table 6.

Table 6. Minimal time interval before and after TKI therapy to immunize with inactivated and live attenuated vaccines.

Drug	**Mode of action**	**Minimal time interval before initiation of therapy**		**Minimal time interval after completion of therapy**	
		IV	**LAV**	**IV**	**LAV**
Imatinib (Glivic®)	Tyrosine kinase inhibitor	2 weeks [1)]	4 weeks	3 months	6 months
Dasatinib (Sprycel®)	Tyrosine kinase inhibitor				
Nilotinib (Tasigna®)	Tyrosine kinase inhibitor				
Bosutinib (Bosulif®)	Tyrosine kinase inhibitor				
Ponatinib (Iglusic®)	Tyrosine kinase inhibitor				
Ruxolitinib (Jakavi®)	Januskinase-Inhibitor				

Abbreviations: inactivated vaccine (IV), live-attenuated vaccine (LAV)

1) If not feasible or done to be caught up until start of chemotherapy

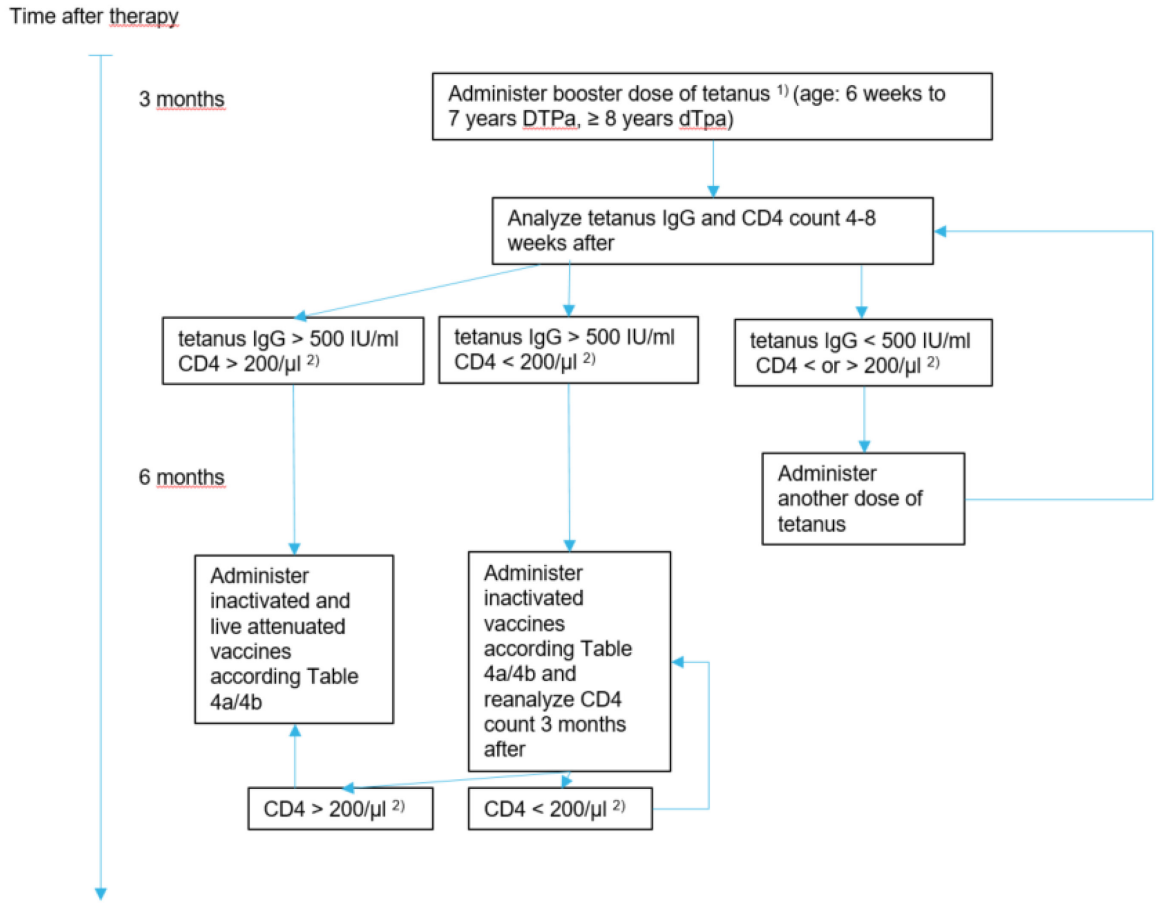
5.4. Practical immunization strategy in patients treated with immune checkpoint inhibitors

Immunization strategy according to **Table 1, 4a and 4b**.

5.5. Practical immunization strategy in patients treated with other targeted therapies and unknown impact on immunization

- A vaccine expert should be involved in vaccine recommendations for patients under targeted therapies with unknown impact on immunization
- Figure 1 shows a possible practical approach to evaluate the individual potential of vaccine immune response and the safety of administration of live attenuated vaccines in patients treated with targeted therapies with unknown impact on immunization

Figure 1. Recommended vaccination strategy for persons after specific oncological treatment with unknown impact on immunization



1) If known to have high tetanus IgG (> 1000 IU/ml) before cancer treatment an inactivated vaccine containing a neoantigen (e.g. hepatitis A vaccine) can be used to evaluate the individual potential of vaccine immune response instead of tetanus.

2) Age depended thresholds: <1 year >750/µl (0.75 g/l), 1-5 years > 500/µl (0.5 g/l)

6. Management of cancer patients after measles, varicella zoster virus or tetanus exposure

Table 7. Recommended postexposure prophylaxis for cancer patients under therapy **after exposure to varicella zoster or measles** (74-79)

Exposure to	**Serum antibody level at diagnosis**	**Measure of antibody level after exposure**	**Passive immunization**	**Antiviral treatment**
Measles	< 150 IU/l	No	IVIG 0.4g/kg iv. [1] as soon as possible, maximal within 6 days after exposure	No
	≥150 IU/l or [2]	No, except [3]	refer [3]	No
Varicella	≥ 150 IU/l	No	Varitect® 12.5 IE/kg iv. (maximal dose 625 IE) as soon as possible, maximal within 4 days [4] [5]	- Consider prophylactic therapy if too late for passive immunization (within 10 days after exposure) [6] - Therapeutic antiviral treatment if varicella infection despite passive immunization or prophylactic antiviral [7]
	> 150 IU/l or [2]	No	No	- Antiviral treatment if present varicella infection [7]

1) Consider to calculate dose with ideal body weight if obese patient

2) Two documented vaccine doses of measles or varicella zoster virus respectively

3) Analyze in highly immunocompromised patients defined as:

- Patients under high intense conventional cytotoxic chemotherapy
- ALL patients within and until at least 6 months after completion of immunosuppressive chemotherapy
- patients with lymphoproliferative disorders
- patients receiving or within 6 months of completing biological therapies as listed in Table 5 (76)

and administer IVIG 0.4 g/kg if current level <150 IU/l or test result not available within 72 hours

4) If Varitect® not available administer IVIG 0.4 g/kg alternatively under same conditions

5) Monitor for varicella infection for 28 days after exposure since passive immunization may prolong incubation period

6) Valaciclovir orally, 20 mg/kg/dose, 3 times daily (max. daily dose 3000 mg) for 7 days or Aciclovir orally, 20 mg/kg/dose, 4 times daily (max. daily dose 3200 mg) (see swisspeddose for pediatric dosage)

7) Aciclovir iv., 10 mg/kg/dose, 3 times daily (see swisspeddose for pediatric dosage)

Table 8a. Recommended tetanus postexposure prophylaxis (PEP) in case of injury for cancer patients **with severe immunosuppression (expert opinion)**

Cancer patients with severe immunosuppression are defined as 1. Patients under high intense conventional cytotoxic chemotherapy, 2. ALL patients within and until at least 6 months after completion of immunosuppressive chemotherapy, 3. Patients with lymphoproliferative disorders and 4. Patients under and up to 6 months after B cell depleting therapies (see Table 5) (67, 116)

Clean, superficial wounds		**All other wounds** [1)]	
dT/dTpa/dT-IPV, DTPa-IPV [2)]	**Anti-T-IgG** [3)]	**dT/dTpa/dT-IPV, DTPa-IPV** [2)]	**Anti-T-IgG** [3)]
No	No, except [4)]	No	Yes

1) see also Swiss immunization plan (66): Deep or dirty wounds, injuries with tissue damage and reduced oxygen supply, severe burns or frostbite, tissue necrosis, septic abortion or skin penetration with foreign bodies (bite wound, contused wound, lacerated wound, stab, bullet wound)

2) < 8 years of age administer DTPa-IPV

3) Anti-T-IgG: Tetanus immunoglobulin (250 IE im., if high risk 500 IE im.) (118)

4) Number of tetanus vaccine doses before initiation of therapy <3 or ≥3 but last vaccine dose ≥ 5 years. In infants aged 5-11 months who have received 2 doses of vaccine, the administration of tetanus immunoglobulins is generally not recommended. It may be considered in individual cases with a very high risk of tetanus.

Table 8b. Recommended tetanus postexposure prophylaxis in case of injury for cancer patients **without severe immunosuppression**

Definition severe immunosuppression see Table 8a. Patients under maintenance therapy or patients <3 months after completion of conventional cytotoxic chemotherapy are no longer severely immunosuppressed.

Clean, superficial wounds		**All other wounds** [1)]	
dT/dTpa/dT-IPV, DTPa-IPV [2)]	**Anti-T-IgG** [3)]	**dT/dTpa/dT-IPV, DTPa-IPV** [2)]	**Anti-T-IgG** [3)]
Yes	No	Yes	Yes, except [4)]

1) Deep or dirty wounds, injuries with tissue damage and reduced oxygen supply, severe burns or frostbite, tissue necrosis, septic abortion or skin penetration with foreign bodies (bite wound, contused wound, lacerated wound, stab, bullet wound)

2) < 8 years of age administer DTPa-IPV

3) Anti-T-IgG: Tetanus immunoglobulin (250 IE im., if high risk 500 IE im.) (118)

4) Number of vaccine doses before therapy ≥3 and last vaccine dose < 5 years. In infants aged 5-11 months who have received 2 doses of vaccine, the administration of tetanus immunoglobulins is generally not recommended. It may be considered in individual cases with a very high risk of tetanus.

For post exposure prophylaxis after Hepatitis B exposure see BAG document „Empfehlungen zur Prävention von Hepatitis B“(117).

6. References

1. Schweizerischer Krebsbericht 2021. Stand und Entwicklungen. Neuchâtel 2021.
2. Alanko S, Pelliniemi TT, Salmi TT. Recovery of blood B-Lymphocytes and serum immunoglobulins after chemotherapy for childhood acute lymphoblastic leukaemia. Cancer. Mar 15 1992; 69(6):1481-6
3. Alanko S, Samli TT, Pelliniemi TT. Recovery of blood T-cell subsets after chemotherapy for childhood acute lymphoblastic leukemia. Pediatr Hematol Oncol. 1994 May-Jun;11(3):281-92
4. Abrahsamsson J, Marky I, Mellander L. Immunoglobulin levels and lymphocyte response to mitogenic stimulation in children with malignant disease during treatment and follow-up. Acta Paediatr. 1995 Feb;84(2):177-82
5. Mustafa MM, Buchanan GR, Winick NJ et al. Immune recovery in children with malignancy after cessation of chemotherapy. J Pediatr Hematol Oncol. 1998 Sep-Oct;20(5):451-7
6. Mackall CL, Fleisher TA, Brown MR et al. Lymphocyte depletion during treatment with intensive chemotherapy for cancer. Blood. 1994 Oct 1; 84(7): 2221-8
7. Wong A, Marrie TJ, Garg S et al. Increased risk of invasive pneumococcal disease in haematological and solid-organ malignancies. Epidemiol Infect. 2010 Dec; 138(12) :1804-10.
8. Hjuler T, Wohlfahrt J, Staum Kaltoft M et al. Risks of invasive pneumococcal disease in children with underlying chronic disease. Pediatrics. 2008 Jul; 122(1):e26-32
9. Kyaw MH, Rose CE Jr, Fry AM et al. The influence of chronic illnesses on the incidence of invasive pneumococcal disease in adults. J Infect Dis. 2005 Aug 1; 192(3): 377-86
10. Meisel R, Toschke AM, Heiligensetzer C et al. Increased risk for invasive pneumococcal diseases in children with acute lymphoblastic leukemia. Br J Haematol. 2007 Jun; 137(5):457-60
11. Cooksely CD, Avritscher EB, Bekele BN et al. Epidemiology and outcomes of serious influenza-related infections in the cancer population. Cancer. 2005 Aug 1; 104(3):618-28
12. Kunisaki KM, Janoff EN. Influenza in immunosuppressed populations: a review of infection frequency, morbidity, mortality and vaccine responses. Lancet Infect Dis. 2009 Aug;9(8):493-504
13. Chemaly RF, Vigil KJ, Saad M et al. A multicenter study of pandemic influenza A (H1N1) infection in patients with solid tumors in 3 countries: early therapy improves outcomes. Cancer. 2012 Sept 15;118(18):4627-33
14. Habel LA, Ray GT, Silverberg MJ et al. The epidemiology of herpes zoster in patients with newly diagnosed cancer. Cancer Epidemiol Biomarkers Prev. 2013 Jan;22(1):82-90
15. Lin HC, Chao YH, Wu KH et al. Increased risk of herpes zoster in children with cancer: A nationwide population-based cohort study. Medicine (Baltimore). 2016 Jul;95(30):e4037
16. Kaplan LJ, Daum RS, Smaron M et al. Severe measles in immunocompromised patients. JAMA. 1992 Mar 4;267(9):1237-41
17. Ojha RP, Tota JE, Offutt-Powell TN, et al. Human papillomavirus-associated subsequent malignancies among long-term survivors of pediatric and young adult cancers. PLoS One. 2013 Aug 5;8(8):e70349

18. Hansson E, Forbes HJ, Langan SM et al. Herpes zoster risk after 21 specific cancers: population-based case-control study. Br J Cancer. 2017 Jun 6;116(12):1643-51
19. Bundesamt für Gesundheit (BAG) und Eidgenössische Kommission für Impffragen (EKIF) Stand April 2012, (angepasst Januar 2014). Empfehlung zur Impfung von Empfängerinnen und Empfängern von Blut-Stammzellen.
20. Rubin LG, Levin MJ, Ljungman P et al. 2013 IDSA clinical practice guideline for vaccination of the immunocompromised host. Clin Infect Dis. 2014;58(3):309-18
21. Canadian Immunization Guide: Part 3 - Vaccination of Specific Populations. https://www.canada.ca/en/public-health/services/publications/healthy-living/canadian-immunization-guide-part-3-vaccination-specific-populations/page-8-immunization-immunocompromised-persons.html#a15. Downloaded 13.08.2019
22. Royal College of Paediatrics and Child Health www.rcpch.ac.uk. Immunisation of the immunocompromised child. Best Practice Statement. February 2002. http://rcpch.adlibhosting.com/files/Immunisation%20of%20the%20Immunocompromised%20CChil%C2%A02002-02.pdf. Downloaded 13.08.2019
23. Red Book (2018). Report of the Committee on Infectious Diseases, 31st Edition. By American Academy of Pediatrics, Committee on Infectious Diseases. Edited by David W. Kimberlin, MD, FAAP, Michael T. Brady, MD, FAAP and Mary Ann Jackson, MD, FAAP. Immunization and other considerations in immunocompromised children.
24. Australian Immunization Handbook. Vaccination for people who are immunocompromised. 2018. https://immunisationhandbook.health.gov.au/vaccination-for-special-risk-groups/vaccination-for-people-who-are-immunocompromised. Downloaded 13.08.2019
25. Vaccinations for Paediatric Patients Treated With Standard-Dose Chemotherapy and Haematopoietic Stem Cell Transplantation (HSCT) Recipients. Authors: Dr. Soonie R. Patel, Professor Rod Skinner and Professor Paul T. Heath. 2016. Children's Cancer and Leukaemia Group. https://www.cclg.org.uk/write/MediaUploads/Member%20area/Treatment%20guidelines/Vaccinations_for_Children_treated_with_Standarddose_Chemotherapy_and_HSCT_Recipients-Sept_2014-FINAL_CCLG.pdf. Downloaded 13.08.2019
26. 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 Jun;19(6):e188-199
27. Riger CT, Liss B, Mellinghoff S et al. 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). Annal Oncol. 20189 Jun 1;29(6):1354-1365
28. Feldman S, Lott L. Varicella in children with cancer: Impact of antiviral therapy and prophylaxis. Pediatrics. 1987 Oct; 80(4):465-72
29. Morgan E, Smalley L. Varicella in immunocompromised children. Am J Dis Child 1983;137:883-5

30. Bud K, Tubergen D, Levin MJ. The Frequency and consequences of varicella exposure and varicella infection in children receiving maintenance therapy for acute lymphoblastic leukemia. J Pediatr Hematol Oncol. 1996 May;18(2): 106-12
31. Robinson KA, Baughman W, Rothrock G et al. Epidemiology of invasive Streptococcus pneumoniae infections in the United States, 1995-1998: Opportunities for prevention in the conjugate vaccine era. JAMA. 2001 Apr 4;285(13):1729-35
32. Siber GR. Bacteremias due to Haemophilus influenzae and Streptococcus pneumoniae: their occurrence and course in children with cancer. Am J Dis Child. 1980 Jul; 134(7):668-72
33. Nordoy T, Aaberge IS, Husebekk A et al. Cancer patients undergoing chemotherapy show adequate serological response to vaccinations against influenza virus and Streptococcus pneumoniae. Med Oncol. 2002;19(2):71-8
34. Cheng FW, Ip M, Chu YY et al. Humoral response to conjugate pneumococcal vaccine in paediatric oncology patients. Arch Dis Child. 2012 Apr;97(4):358-60
35. Crawford NW, Balloch A, Tikkanen L et al. Pneumococcal conjugate vaccine administration during therapy for pediatric leukemia. Pediatr Infect Dis J. 2015 Jan;34:e9-e15
36. Hung TY, Kotecha RS, Blyth CC et al. Immunogenicity and safety of single-dose, 13-valent pneumococcal conjugate vaccine in pediatric and adolescent oncology patients. Cancer. 2017 Nov 1;123(21):4215-4223
37. Choi W, Kim JG, Beom SH et al. Immunogenicity and optimal timing of 13-valent pneumococcal conjugate vaccination during adjuvant chemotherapy in gastric and colorectal cancer: A randomized controlled trial. Cancer Res Treat 2019 Jul 9. Doi: 10.4143/crt.2019.189
38. Lee YJ, Huang YT, Kim SJ et al. Trends in Invasive Pneumococcal Disease in Cancer Patients After the Introduction of 7-valent Pneumococcal Conjugate Vaccine: A 20-year Longitudinal Study at a Major Urban Cancer Center. Clin Infect Dis. 2018; 66(2):244-253
39. Chiou WY, Hung SK, Lai CL et al. Effect of 23-Valent Pneumococcal Polysaccharide Vaccine Inoculated During Anti-Cancer Treatment Period in Elderly Lung Cancer Patients on Community-Acquired Pneumonia Hospitalization: A Nationwide Population-Based Cohort Study. Medicine (Baltimore). 2015 Jul; 94(26):e1022
40. Kersun LS, Reilly AF, Coffin SE et al. Protecting pediatric oncology patients from influenza. Oncologist 2013; 18(2):204-11
41. Pollyea DA, Brown JM, Horning SJ. Utility of influenza vaccination for oncology patients. J Clin Oncol. 2010 May 10;28(14):2481-90
42. Goossen GM, Kremer LC, van de Wetering MD. Influenza vaccination in children being treated with chemotherapy for cancer. Cochrane Database Syst Rev. 2013 Aug 1;(8) CD006484
43. Vinograd I, Eliakim-Raz N, Farbman L et al. Clinical effectiveness of seasonal influenza vaccine among adult cancer patients. Cancer. 2013 Nov 15; 119(22):4028-35
44. Beck CR, McKenzie BC, Hashim AB, et al. Influenza vaccination for immunocompromised patients: systematic review and meta-analysis by etiology. J Infect Dis. 2012 Oct;206 (8):1250-9

45. Earle CC. Influenza vaccination in elderly patients with advanced colorectal cancer. J Clin Oncol. 2003 Mar 15;21(6):1161-6
46. Bitterman R, Eliakim-Raz N, Vinograd I. Cochrane Database Sys Rev. 2018 Feb 1;2:CD008983
47. Kotecha RS, Wadia UD, Jacoby P et al. Immunogenicity and clinical effectiveness of the trivalent inactivated influenza vaccine in immunocompromised children undergoing treatment for cancer. Cancer Med 2016 Feb;5(2):285-93
48. Esposito S, Cecinati V, Scicchitano B et al. Impact of influenza-like illness and effectiveness of influenza vaccination in oncohematological children who have completed cancer therapy. Vaccine. 2010 Feb 10;28(6):1558-65
49. Levin MJ. Varicella vaccination of immunocompromised children. J Infect Dis 2008;197:S200-6
50. Gershon AA, Steinberg SP, Gelb L. Live attenuated varicella vaccine use in immunocompromised children and adults. Pediatrics 1986;78:757-62
51. Brunell PA, Ross A, Miller LH, Kueo B. Prevention of varicella by zoster immune globulin. N Engl J Med 1969; 280:1191
52. Zaia JA, Levin MJ, Preblud SR et al. evaluation of varicella-zoster immune globulin: protection of immunosuppressed children after household exposure to varicella. J Infect Dis 1983; 147:737
53. Orenstein WA, Heymann DL, Ellis RJ et al. Prophylaxis of varicella in high-risk children: dose-response effect of zoster immune globulin, J Pediatr 1981; 98:386
54. Asano Y, Yoshikawa T, Suga S et al. Postexposure prophylaxis of varicella in family contact by oral acyclovir. Pediatrics 1993; 92:219
55. Nyerges G, Meszner Z, Gyarmati E et al. Acyclovir prevents dissemination of varicella in immunocompromised children. J Infect Dis 1988; 157:309
56. Prober CG, Kirk LE, Keeney RE. Acyclovir therapy for chickenpox in immunosuppressed children – a collaborative study. J Pediatr 1982; 101:622
57. Tseng HF, Tartof S, Harpaz R et al. Vaccination against zoster remains effective in older adults who later undergo chemotherapy. Clin Infect Dis. 2014 Oct;59(7):913-9
58. Cunningham AL, Lal H, Kovac M et al. Efficacy of Herpes Zoster Subunit Vaccine in Adults 70 Years of Age or Older. N Engl J Med. 2016 Sep 15;375(11):1019-32
59. Lal H, Cunningham AL, Godeaux O et al. Efficacy of an adjuvanted herpes zoster subunit vaccine in older adults. N Engl J Med. 2015 May 28;372(22):2087-96
60. Vink P, Delgado Mingorance I, Maximiano Alonso C et al. Immunogenicity and safety of the adjuvanted recombinant zoster vaccine in patients with solid tumors, vaccinated before or during Chemotherapy: A randomized trial. Cancer. 2019 Apr 15;125(8):1301-1312
61. Dagnew AF, Ilhan O, Lee WS et al. Immunogenicity and safety of the adjuvanted recombinant zoster vaccine in adults with haematological malignancies: a phase 3, randomized, clinical trial and post-hoc efficacy analysis. Lancet Infect Dis. 2019 Sep; 19(9): 988-1000

62. Winston DJ, Mullane KM, Cornely OA et al. Inactivated varicella zoster vaccine in autologous haemopoietic stem-cell transplant recipients: an international, multicentre, randomized, double-blind, placebo-controlled trial. Lancet. 2018 May 26;391(10135):2116-2127
63. Janeway CA. Use of concentrated human serum γ-globulin in the prevention and attenuation of measles. Bull N Y Acad Med 1945;21:202–22
64. Ordman CW, Jennings CG, Janeway CA. Chemical, clinical, and immunological studies on the products of human plasma fractionation. XII. The use of concentrated normal human serum gamma globulin (human immune serum globulin) in the prevention and attenuation of measles. J Clin Invest 1944;23:541–9
65. Prävention schwerer Infektionen bei anatomischer oder funktioneller Asplenie. Empfehlungen der Schweizerischen Gesellschaft für Infektiologie (SGINF), der Eidgenössischen Kommission für Impffragen (EKIF) und des Bundesamtes für Gesundheit (BAG). Stand 2015
66. Bundesamt für Gesundheit (BAG) und Eidgenössische Kommission für Impffragen (EKIF), Schweizerischer Impfplan 2019.
67. Wiedermann U, Sitte HH, Burgmann H et al. Guidelines for vaccination of immunocompromised individuals. Wien Klin Wochenschr. 2016 Aug;128 Suppl 4:337-76
68. Duale Reihe, Pharmakologie und Toxikologie. Karl Heinz Graefe, Werner K. Lutz, Heinz Bönisch. 2016, 2. überarbeitete Auflage Thieme (Verlag).
69. Croce E, Hatz C, Jonker EF et al. Safety of live vaccinations on immunosuppressive therapy in patients with immune-mediated inflammatory diseases, solid organ transplantation or after bone-marrow transplantation – a systematic review of randomized trials, observational studies and case reports. Vaccine 2017; 35:1216-26
70. Berglund A, Willen L, Grödeberg L et al. The response to vaccination against influenza A (H1N1) 2009, seasonal influenza and Streptococcus pneumoniae in adult outpatients with ongoing treatment for cancer with and without rituximab. Acta Oncol. 2014 Sep;53(9):1212-20
71. Ercan TE, Soycan LY, Apak H et al. Antibody titers and immune response to diphtheria-tetanus-pertussis and measles-mumps-rubella vaccination in children treated for acute lymphoblastic leukemia. J Pediatr Hematol Oncol. 2005 May;27(5):273–7
72. Zengin E, Sarper N. Humoral immunity to diphtheria, tetanus, measles, and haemophilus influenzae type b in children with acute lymphoblastic leukemia and response to re-vaccination. Pediatr Blood Cancer. 2009 Dec;53(6):967-72
73. Ridgway D, Wolff LJ, Deforest A et al. Immunization response varies with intensity of acute lymphoblastic leukemia therapy. Am J Dis Child. 1991 Aug;145(8):887-91
74. American Academy of Pediatrics. Varicella-Zoster Virus Infections. In: Kimberlin DW, Brady MT, Jackson MA, Long SS, eds. Red Book: 2018 Report of the Committee on Infectious Diseases. American Academy of Pediatrics; 2018; 869-883
75. Measles. Red Book 2018. Committee on Infectious Diseases; American Academy of Pediatrics; David W. Kimberlin, MD, FAAP; Michael T. Brady, MD, FAAP; Mary Anne Jackson, MD, FAAP; Sarah S. Long, MD, FAAP

76. Guidelines for Post-Exposure prophylaxis for measles June 2019. Public Health England. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/814203/Guidance_for_measles_post-exposure_prophylaxsis.pdf. Downloaded 27.04.2020
77. Prevention of varicella: recommendations of the Advisory Committee on Immunization Practices (ACIP). Güris D, Chaves SS, Schmid S, Seward JF; Advisory Committee on Immunization Practices, Centers for Disease Control and Prevention (CDC). MMWR Recomm Rep. 2007 Jun 22;56(RR-4):1-40.
78. Marin M, Guris D, Chaves SS et al. Prevention of varicella: recommendations of the Advisory Committee on Immunizations Practices (ACIP). MMWR Recomm Rep. 2007:56(RR-4):1-40.
79. Centers for Disease Control and Prevention. Prevention of measles, rubella, congenital rubella syndrome, and mumps, 2013 summary: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep. 2013;62(RR-4):1–34
80. Zignol M, Peracchi M, Tridello G et al. Assessment of humoral immunity to poliomyelitis, tetanus, hepatitis B, measles, rubella, and mumps in children after chemotherapy. Cancer. 2004 Aug 1;101(3):635-41
81. Bochennek K, Allwinn R, Langer R et al. Differential loss of humoral immunity against measles, mumps, rubella and varicella-zoster virus in children treated for cancer. Vaccine. 2014 Jun 5;32(27):3357-61
82. Patel SR, Ortin M, Cohen BJ et al. Revaccination of children after completion of standard chemotherapy for acute leukemia. Clin Infect Dis. 2007 Mar 1;44(5):635–42
83. Feldman S, Andrew M, Norris M et al. Decline in rates of seropositivity for measles, mumps and rubella antibodies among previously immunized children treated for acute leukemia. Clin Infect Dis. 1998 Aug;27(2):388-90
84. Kantar M, Cetingül N, Kansoy S et al. Immune deficiencies following cancer treatment in children. J Trop Pediatr. 2003 Oct;49(5):286-90
85. Ek T, Mellander L, Hahn-Zoric M et al. Intensive Treatment for Childhood acute lymphoblastic leukemia reduces immune responses to Diphtheria, Tetanus and Haemophilus influenza type b. J Pediatr Hematol Oncol. 2004 Nov;26(11):727-34
86. Nilsson A, De Milito A, Engström P et al. Current chemotherapy protocols for childhood acute lymphoblastic leukemia induce loss of humoral immunity to viral vaccination antigens. Pediatrics. 2002 Jun;109(6):e91
87. Hamarström V, Pauksen K, Svensson H et al. Tetanus immunity in patients with hematological malignancies. Support Care Cancer. 1998 Sep;6(5):469-72
88. De la Fuente Garcia I, Coic L, Leclerc JM et al. Protection against vaccine preventable diseases in children treated for acute lymphoblastic leukemia. Pediatr Blood Cancer. 2017 Feb;64(2):315-320
89. Lehrnbecher T, Schubert R, Allwinn R et al. Revaccination of children after completion of standard chemotherapy for acute lymphoblastic leukemia: a pilot study comparing different schedules. Br J Heaematol. 2011 Mar;152(6), 754-7

90. Impfempfehlungen für Personen vor und nach Transplantation eines soliden Organs. Bundesamt für Gesundheit (BAG) und Eidgenössische Kommission für Impffragen (EKIF). Stand Februar 2014.
91. Pescovitz MD, Torgerson TR, Ochs HD et al. Effect of rituximab on human in vivo antibody immune responses. J Allergy Clin Immunol. 2011 Dec;128(6):1295-1302.e5
92. Nazi I, Kelton JG, Larché M et al. The effect of Rituximab on vaccine responses in patients with immune thrombocytopenia. Blood. 2013; 122(11): 1946-53.
93. Bingham CO, Looney RJ, Deodhar A et al. Immunization responses in rheumatoid arthritis patients treated with rituximab: results from a controlled clinical trial. Arthritis and Rheum. 2010 Jan;62(1):64-74
94. Bühler S, Eperon G, Ribi C et al. Vaccination recommendations for adult patients with autoimmune inflammatory rheumatic diseases. Swiss Med Wkly, 2015 Jul 28;145:w14159
95. Wagner N, Assmus F, Arendt G et al. Impfen bei Immundefizienz: Anwendungshinweise zu den von der Ständigen Impfkommission empfohlenen Impfungen. (IV) Impfen bei Autoimmunkrankheiten, bei anderen chronisch-entzündlichen Erkrankungen und unter immunmodulatorischer Therapie. Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz. 2019 Apr;62(4):494-515.
96. Seggewiss R, Loré K, Greiner E, et al. Imantinib inhibits T-cell receptor mediated T-cell proliferation and activation in a dose dependent manner. Blood. 2005 Mar 15;105(6):2473-9
97. Mumprecht S, Matter M, Pavelic V et al. Imantinib mesylate selectively impairs expansion of memory cytotoxic T cells without affecting the control of primary viral infections. Blood. 2006 Nov 15;108(10):3406-13
98. De Lavallade H, Garland P, Sekine T et al. Repeated vaccination is required to optimize seroprotection against H1N1 in immunocompromised host. Haematologica 2011; 96:307-14
99. De Lavallade H, Khoder A, Hart M et al. Tyrosine kinase inhibitors impair B-cell immune responses in CML through off-target inhibition of kinases important for cell signaling. Blood 2013; 122:227-38
100. Shama P, Allison JP. Immune checkpoint targeting in cancer therapy toward combination strategies with curative potential. Cell. 2015;161(2):205-14
101. Topalian SL, Drake CG, Pardoll DM. Immune checkpoint blockade: a common denominator approach to cancer therapy. Cancer Cell. 2015;27(4):450-61
102. Chen DS, Mellman I. Elements of cancer immunity and the cancer-immune set point. Nature.2017;541(7637):321-30
103. Postow MA, Hellmann MD. Adverse events associated with immune checkpoint blockade. N Engl J Med 2018;378:1165
104. Läubli H, Balmelli C, Kaufmann L et al. Influenza vaccination of cancer patients during PD-1 blockade induces serological protection but may rise the risk for immune-related adverse events. J Immunother Cancer 2018;6:40

105. Chong CR, Park VJ, Cohen B et al. Safety of inactivated influenza vaccine in cancer patients receiving immune checkpoint inhibitors. Clin Infect Dis. 2019 Mar 15. Pii:ciz202
106. Levin MJ, Gershon AA, Weinberg A et al. Administration of live varicella vaccine to HIV-infected children with current or past significant depression of CD4(+) T cells. J Infect Dis. 2006; 194(2):247-255.
107. Sprauer MA, Markowitz LE, Nicholson JK, et al. Response of human immunodeficiency virus-infected adults to measles-rubella vaccination. J Acquir Immun Defic Syndr. 1993;6(9):1013-1016
108. McLaughlin M, Thomas P, Onorato I, et al. Live virus vaccines in human immunodeficiency virus-infected children: a retrospective survey. Pediatrics. 1988:82(2):229-233
109. Onorato IM, Markowitz LE, Oxtoby MJ. Childhood immunization, vaccine-preventable diseases and infection with human immunodeficiency virus. Pediatr. Infect Dis J. 1988;7(8):588-595
110. Palumbo P, Hyt L, Demasio K et al. Population-based study of measles and measles immunization in human immunodeficiency virus-infected children. Pediatr Infect Dis J. 1992;11(12):1008-1014
111. Mackay HJ, Mcgee J, Villa D et al (2011) Evaluati- on of pandemic H1N1 (2009) influenza vaccine in adults with solid tumor and hematological malignancies on active systemic treatment. J Clin Virol 50:212–216
112. Meerveld-Eggink A, De Weerdt O, Van Der Vel- den AM et al (2011) Response to influenza viru vaccination during chemotherapy in patients with breast cancer. Ann Oncol : Off J Eur Soc Med Oncol 22:2031–2035
113. WumkesML,VanDerVeldenAM,LosMetal (2013) Serum antibody response to influenza vi- rus vaccination during chemotherapy treatment in adult patients with solid tumours. Vaccine 31:6177–6184
114. Martire B, Azzari C, Badolato R et al (2018) Vaccination in immunocompromised host: Recommendations of Italian Primary Immuno- deficiency Network Centers (IPINET). Vaccine 36:3541–3554
115. Laws HJ, Baumann U, Bogdan C et al. Impfen bei Immundefizienz. Anwendungshinweise zu den von der Ständigen Impfkommission empfohlenen Impfungen. (III) Impfen bei hämatologischen und onkologischen Erkrankungen (antineoplas- tische Therapie, Stammzelltransplantation), Organtransplantation und Asplenie. Bundesgesundheitsbl 2020. 63:588-644
116. Assen S van, et al. EULAR recommendations for vaccination in adult patients with autoimmune inflammatory rheumatic diseases. Ann Rheum Dis. 2011;70(3):414–22.
117. Empfehlungen zur Prävention von Hepatitis B Bundesamt für Gesundheit (BAG), Eidgenössische Kommission für Impffragen (EKIF). März 2019
118. Postexpositionelle passive Immunisierung. Oktober 2004 Bundesamt für Gesundheit (BAG), Schweizerische Kommission für Impffragen (SKIF)

7. Appendix

Table 9. Definition of complete immunizations status in relation to age and recommended accelerated catch-up schedule before initiation of cancer therapy for patients with incomplete immunization status.

Vaccine	**Age restriction**	**Number of doses**	**Accelerated schedule (minimal interval in months)**
DTPa, IPV	> 6 weeks (> 8 years dTpa)	3 doses	<1 year: 0,1 + 1x ≥12 months 1) > 1 year: 0,1,6
dT(pa) booster	> 8 years	1 dose every 10 years	
Hib	6 weeks - 59 months	First dose < 1 year: 3 doses 12-59 months: 2 doses	0, 1 +1x ≥12 0,2
HBV	at any age	3 11-15 years: 2 adult doses	0,1,4 0, 4
PCV	6 weeks - 59 months (off label >5 years)	First dose <1 year: 3 doses < 2 years: 2 doses 24-59 months: 1 dose	0,1,8 0,2
MCV-ACWY	2 - 5 years (off label > 1 year) and 11-19 years	2 doses: first dose 2-5 years, second dose 11-19 years	
FSME	> 6 years	3 doses	day 1, 7, 21
HPV	9-25 years	2 doses if first dose <15 years 3 doses if first dose ≥15	0, (1), 4
MMR	> 6 months	2 doses	0,1 2)
Varicella - **RZV (Shingrix®)**	≥ 18 years	2 doses	0, 2

Table 10. Serum antibody levels with correlation to protection. (66)

Vaccine	**Specific antibody-test (Unit)**	**Threshold of protection**	
		Short term protection	**Long term protection**
Tetanus	Anti-tetanus-toxoid (IU/l)	100-999	≥1000
Haemophilus influenza Typ b	Anti-PRP-IgG (mg/l)	0.15-0.99	≥1
Hepatitis B	Anti-HBs-IgG (IU/l)	10-99	≥100
Measles	Measles-IgG in EIA (IU/l)	50-150	≥150
Varicella	VZV-IgG or VZV gp (IU/l)	50-150	≥150