Vaccinations

29

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29.1 General Concepts

Vaccination should be considered a *routine practice for all HSCT receptors*, either autologous or allogeneic, adults or children. It should be implemented in all HSCT programs. Adult cover is particularly important as they represent 90% of HSCTs. To obtain this objective, the following are necessary:

- To have in place a standardized program specific for HSCT patients.
- The collaboration of the Preventive Department of the hospital and primary care physicians.
- The program must be simple, with a clear chronology, and convenient for the patient and physician (no increase in the number of visits).
- FACT-JACIE Standards (version 7.0, March 2018) require that policies/SOP are in place for post transplant vaccination schedules and indications.

The vaccination program should include not only the patient but also those who live with the patient and the healthcare workers (HCWs).

There is no a unique vaccine schedule for all HSCT patients. Each center should discuss and adapt a specific vaccine program.

- The practical application of the immunization programs shows important variations across centers (Miller et al. 2017).
- Auto-HSCT is generally vaccinated with the schedule used for allogeneic patients with small differences (see Tables 29.1 and 29.2).

Reasons for universal vaccination of HSCT patients:

- *General interest*: as a general healthcare principle, all the population should be correctly vaccinated, including adults and of course HSCT patients. If an increasing collective of patients, like HSCT, is not well vaccinated, that can generate holes of immunity that can be a risk for the health of the general population.
- *Individual interest for each HSCT patient*: vaccination protects the patient against infections that can cause important morbi-mortality. There are frequent infections in HSCT that have safe vaccines (pneumococcus, influenza, HBV) and other rare infections associated with high mortality that have an unsatisfactory prevention/treatment but can be prevented by immunization (tetanus, diphtheria, measles, polio).

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Table 29.1 International consensus recommendations (Ljungman et al. 2009)

Vaccine	No. of doses	Time post-HSCT to initiate vaccine	Grading
Influenza (inactivated)	1 2 for children <9 years, or if <6 m from HSCT (C III)	4–6 months, yearly, lifelong seasonal vaccination	AII
Measles[a] Mumps[a] Rubella[a] (in adults for sero(-) females with pregnancy potential)	1 (2 in children)	24 months	AII children BII seronegative adults CIII BIII
Hepatitis B virus (HBV) (follow country recommendations for general population)[b]	3	6–12 months	BII
Human papillomavirus	Follow recommendations for general population in each country		CIII
Inactivated polio	3	6–12 months	BII
Pneumococcal conjugate (PCV) – polysaccharide pneumococcal vaccine (PPS) – in case of GVHD, use PCV instead of PPS for this 4th dose	3 1 1	3–6 months 6 months after last PCV	BI BII CIII
Meningococcal conjugate (follow country recommend for general population)	1	6–12 months	BII
Haemophilus influenzae conjugate	3	6–12 months	BII
Diphtheria-tetanus (DT preferred over Td)	3	6–12 months	BII
Pertussis (acellular) (DTaP preferred over Tdap)	3	6–12 months	CIII

[a]MMR. These vaccines are contraindicated (EIII) before 24 months post-HSCT or in case of active GVHD or IS. These vaccines are usually given together as a combination vaccine

[b]VHB. Vaccination is recommended for HBV surface Ag-negative or HBV core Ab-positive patients, as vaccination can reduce the risk of reverse seroconversion (BII). For HBV surface Ag-negative or HBV core Ab-negative HSCT patients, recommendations for the general population in their country of residence should be followed

29.2 General Principles of Vaccination in HSCT Patients

29.2.1 The Pretransplant Vaccination

The pretransplant vaccination is not effective to maintain a prolonged post transplant immunity. In other to protect the HSCT patient, a complete series of post transplant vaccinations is required. This is different from what is recommended for solid organ transplant (SOT) recipients for whom pretransplant vaccination is an essential part of the vaccination program. Post-HSCT patients should be viewed as "never vaccinated" regardless of the pre-HSCT vaccination history of the patient or the donor (Rubin et al. 2014).

29.2.2 The Pre-HSCT Immunity

The pre-HSCT immunity for a specific pathogen is not a reason to withhold vaccination after transplant. The majority of patients will lose their immunity after HSCT.

As general rule, *live vaccines should be considered contraindicated* (there are exceptions, see later). The inactivated, subunit, or protein/polysaccharide vaccines can be safely administered.

There are few randomized trials in HSCT patients, and many of the studies have been done in patients transplanted with BM/PB, using

Table 29.2 ECIL recommendations for allo-HSCT recipients (Cordonnier et al. 2017)

Vaccine	No. of doses[a]	Time post-HSCT to initiate vaccine	Grading
Influenza (inactivated)	1 (or 2, special cases)[b]	>6 months As long as patient is judged to be IS Yearly, lifelong from 3 months in case of a community outbreak	AIIr BIIr BIIr
Measles–mumps–rubella • Measles In sero(-) patients, with no GVHD, no IS, no REL of underlying disease, and no IGIV at least 8 months • Rubella In sero(-) women and of childbearing potential, with same precautions as for measles vaccine	 1 (2 in children) MMR 1 MMR	 ≥24 months ≥12 months in case of measles outbreak in patients with low grade IS ≥24 months	 BIIu CIII CIIu
Virus hepatitis B[c] • Sero(-) patients before HSCT and patients vaccinated pre-HSCT but lost their immunity at 6 months) • Previously infected and anti-HBs <10 IU/L • Sero(-) patients with a donor with positive anti-HBc	 3[d]	 6–12 months 6–12 months Vaccine before transplant	 BIIt BIII BIII
Human papilloma virus (HPV) Follow recommendations for general population in each country	According to official label	From 6–12 months	BIIu
Inactivated polio	3[e]	6–12 months	BIIu
Live-attenuated varicella vaccine	1	Can be considered in sero(-) patients, with ALL the following: >24 m from HSCT, no GVHD, no IS, no REL of the underlying disease, and no IGIV in the last 8 months	BIIr
	2	The addition of a second dose in adults may be considered in patients who were sero(-) before HSCT or had no history of VZ infect	
Live-attenuated zoster vaccine	Not recommended		DIII
Pneumococcal conjugate (PCV) Polysaccharidic vaccine In case of GVHD, use PCV instead of PPS for this 4th dose (BIIr)	3 1	3 months 12 months (no earlier than 8 weeks after last PCV)	AI BI
Meningococcal conjugate (in accordance with country recommendations and local prevalence)	2	From 6 months For men-C or tetravalent vaccine For men-B vaccine	 BIIu BIII
Haemophilus influenzae conjugate	3	3 months or 6 months	BIIr
Diphtheria-tetanus (DT is preferred to Td)	3[e]	From 6 months	BIu
Pertussis (acellular) (DTaP is preferred over Tdap)	3	From 6–12 months	CIII

[a]If not specified otherwise, the interval between dose is 1 month

[b]Influenza: A second dose of influenza vaccine, after 3–4 weeks from the first, may have a marginal benefit and should preferably be considered in patients with severe GVHD or low lymphocyte count (B II r) and also for the patients vaccinated early (from 3 months after transplant) (B II r). Children ≥6 months through 8 years, receiving influenza for the first time after transplant, should receive a second dose at least 4 weeks after the first dose

[c]HBV. After post transplant vaccination, if anti-HBs is <10 mIU/ml, an additional three doses should be considered, but the benefit of this second series of vaccination is uncertain. IDSA guidelines (Rubin et al. 2014) give the same recommendations (strong, low). For adolescents and adults, a high dose of vaccine (40 μg) is recommended for these booster doses (strong, low)

[d]Three doses: interval 0, 1, and 6 months

[e]At 1–2 months interval

Note for auto-HSCT: same recommendations but grading changes for some vaccines: influenza BIIr (instead AII); PCV BIII (instead AI)

MAC. The experience with other sources (CBU), conditioning regimens (RIC), and donors (haplo) is scarce.

Many vaccines are administered by *intramuscular route*, which can be a problem for severe thrombocytopenic patients (less than 50×10^9 platelets/L). For severe thrombocytopenic patients, some vaccines can be safely administered SC (inactivated poliomyelitis, conjugate pneumococcal vaccine) or even intradermic route (for influenza vaccine). Clinical experience suggests that intramuscular injections are safe if the platelet count is ≥30 to 50×10^9/L, a ≤23-gauge needle is used, and constant pressure is maintained at the injection site for 2 min (Rubin et al. 2014).

29.2.3 The Dose of Vaccine

The dose of vaccine used is the same for general population, with some exceptions (see Table 29.2). A uniform specific interval between doses cannot be recommended, as various intervals have been used in studies. As a general guideline, a minimum of 1 month between doses may be reasonable.

29.2.4 Several Patient and Vaccine Characteristics Impact on the Vaccine Response

Time from Transplantation As a general rule, the later time a vaccine is administered, the better response is obtained (there are exceptions; see pneumococcal vaccine section). Usually >12 months from transplant is associated with better responses.

Type of Vaccine T-cell-dependent vaccine obtains better response than T-cell-independent vaccines, because it triggers memory response that leads to a longer protection compared with T-cell-independent vaccine.

The presence of GVHD or ongoing IS treatment has been associated with a decrease in vaccine response, particularly for polysaccharide-based vaccines.

- Some vaccine responses seem to be not impaired by the presence of GVHD/IS treatment. This is the case of conjugated *Haemophilus* vaccine, conjugated pneumococcal vaccine, conjugated meningococcal vaccine, inactivated polio vaccine, and diphtheria-tetanus vaccine.
- International guidelines recommend different attitudes in patients with GVHD for the moment of vaccine administration.
- The international consensus guidelines (Ljungman et al. 2009) recommend to not postpone vaccinations with non-live vaccines in patients with ongoing active or resolved cGVHD of any severity grade.
- However, the International Consensus Conference on Clinical Practice in chronic GVHD (Hilgendorf et al. 2011) recommends postponing vaccination in patients with GVHD: if patients receive prednisone >0.5 mg/kg bodyweight as part of a combination therapy or a three-agent IS treatment is given, vaccination may be postponed until IS is reduced to a double combination or prednisone <0.5 mg/kg bodyweight in order to achieve better vaccine response. In any case, IS therapy should not lead to postponing vaccination for more than 3 months, and this applies for patients with ongoing active or resolved cGVHD of any severity grade.
- In practices, the majority of centers seems to delay vaccinations if GVHD is present (Miller et al. 2017).

The use of rituximab decreases serological vaccine response at least to tetanus and influenza.

- ECIL 2017 guidelines (Cordonnier et al. 2017): patients who have received rituximab from transplant should have their vaccine

program delayed at least more than 6 months after the last dose.
- As the antibody response is uncertain, specific antibody assessment after vaccination can be helpful.

29.2.5 Types of Vaccines in HSCT Patients

Generally recommended for all HSCT (auto and allogeneic)

- Influenza (inactivated/subunit), poliomyelitis (inactivated), human papillomavirus, pneumococcus, *Haemophilus influenzae*, hepatitis B, meningococcus, tetanus, diphtheria, pertussis, and measles–mumps–rubella (special conditions, see Sects. 29.4 and 29.5).

Optional/special situations, to cover situations such as after disease exposure or before travel to areas endemic for infections:

- Hepatitis A, tick-borne encephalitis, Japanese B encephalitis, rabies, yellow fever (live), varicella (Varivax®, live).

Contraindicated: As general rule, *all live vaccines*:

- Oral polio vaccine, bacillus Calmette-Guérin, oral typhoid, zoster vaccine (Zostavax®), intranasal influenza vaccine, oral rotavirus vaccine.
- The exceptions for this rule are live vaccines for measles–mumps–rubella that are recommended following strict safety rules (see Sect. 29.4), yellow fever (live) (see specific section), and varicella (Varivax®, live); all these vaccines are contraindicated (EIII) before 24 m post-HSCT or in case of active GVHD or IS.

Use of IVIG and Vaccines For inactivated vaccines, Ig do not inhibit immune responses. For live virus vaccines, vaccination should be delayed 8 months after the last dose of Ig administration.

29.3 Benefits and Risks of Vaccination in HSCT Patients

29.3.1 Benefits

Direct Benefits The prevention of the specific infectious disease, as shown by influenza and varicella vaccination. Nonetheless, the majority of the efficacy studies in HSCT patients are based on surrogate markers (serology response) and not on the demonstration of a reduced risk of the infectious disease.

Indirect Benefits The benefits of vaccination can go beyond the prevention of a particular infection, as shown by influenza vaccine. Influenza immunization with inactivated vaccine is recommended by cardiologists as part of comprehensive secondary prevention with the same enthusiasm as the control of cholesterol, blood pressure, and other modifiable risk factors (Davis et al. 2006). It reduces cardiovascular mortality (risk ratio (RR) 0.45) (Clar et al. 2015), all-cause mortality (odds ratio (OR) 0.61), myocardial infarction (OR 0.73), and major adverse cardiovascular events (OR 0.47) (Loomba et al. 2012). Although all these studies were performed in general population, it is logical to assume a similar trend in HSCT patients.

29.3.2 Risks

Limited evidence indicates that *inactivated vaccines* have the same safety profile in immunocompromised patients as in immunocompetent individuals (Beck et al. 2012; Rubin et al. 2014; Cordonnier et al. 2017), and there is no evidence that they induce or aggravate GVHD (Cordonnier et al. 2017).

Live vaccines represent a real risk for HSCT and should not be used except in special situations with strict requirements (see section of varicella vaccine and ECIL vaccination guidelines table). Fatal disseminated VZV infections due to vaccine strain have been reported in HSCT patients after varicella vaccine and zoster vaccine, even when vaccine was administered several years after transplant (Cordonnier et al. 2017).

29.4 Vaccination Recommendations

There are several international recommendations focused on HSCT patients. The best known are those by the Infectious Disease Working Party (IDWP) of the EBMT, ECIL, CDC, and Infectious Diseases Society of America (IDSA).

The IDWP of the EBMT was one of the first cooperative groups that published recommendations specific for HSCT patients. The first ones were published in 1995, with updates in 1999 and 2005. In 2017 guidelines were reviewed and updated under the umbrella of the ECIL group, available online (Cordonnier et al. 2017) (Table 29.2).

In 2009 an international consensus guideline was published cosponsored by the main groups involved in HSCT and immunocompromised hosts (Ljungman et al. 2009) and probably is the most widely used in practice (Table 29.1).

The IDSA published their last recommendations in 2014 (Rubin et al. 2014).

There are other more specific guidelines focused on one pathogen (Engelhard et al. 2013) or on patients with GVHD (Hilgendorf et al. 2011).

29.5 Specific Vaccines

29.5.1 Influenza

29.5.1.1 Clinical Manifestations (Ljungman et al. 2011; Engelhard et al. 2013)

Twenty percent of HSCT with confirmed influenza are afebrile.

It is a serious disease in HSCT: One third develop pneumonia, 10% require mechanical ventilation, and 6% died (Ljungman et al. 2011) (i.e., 100–300 times higher the mortality of influenza in general population). Other complications include encephalitis that can be lethal and myocarditis.

29.5.1.2 Influenza and Cardiovascular Disease (CVD)

The majority of influenza deaths are related to lung complications. Nonetheless, in general population up to a third of deaths related to influenza are CV deaths (Loomba et al. 2012).

The risk of acute myocardial infarction is significantly increased after laboratory-confirmed influenza infection (Kwong et al. 2018).

HSCT patients are at high risk of developing CVD. At 10 years, 8% will develop CVD (Armenian et al. 2012).

29.5.1.3 Vaccine

Evidence of Vaccine Efficacy

- A retrospective study showed a protection rate of 80% in the rates of virologically confirmed influenza (Machado et al. 2005).
- A systematic review and meta-analysis showed significantly lower odds of influenza-like illness after vaccination in transplant recipients (HSCT and SOT) compared with patients receiving placebo or no vaccination (Beck et al. 2012). Seroconversion and seroprotection were lower in transplant recipients compared with immunocompetent controls.
- Given the suboptimal immunogenicity in HSCT patients, family members and healthcare professionals involved in the care of these populations should be vaccinated.

Vaccine Response (Engelhard et al. 2013; Cordonnier et al. 2017)

- Longer interval from transplant is associated with better serology response. Vaccination within the first 6 months after transplant produces poor serology responses. Nonetheless, seasonal vaccination against

influenza can boost the cellular immune response in HSCT patients as early as 3 months after HSCT, but the protective effect is lower compared with healthy controls (Engelhard et al. 2013).
- Conflicting data exist on the benefit of a second dose of vaccine, and marginal benefit was seen with the use of GM-CSF.
- In HSCT the superiority of high-dose influenza vaccine has not been demonstrated (Halasa et al. 2016).
- Rituximab administration during the year before vaccination was associated with a lack of seroprotective titer.
- Active GVHD and low lymphocyte counts at vaccination are associated with poor immune response.

Live, attenuated influenza vaccine is contraindicated in HSCT patients (Rubin et al. 2014).

There is a difference in *the duration of influenza vaccine recommendation* in the European (Cordonnier et al. 2017) and US guidelines (Rubin et al. 2014):

- ECIL recommends vaccination as long as patient is judged to be immunosuppressed (A II r) although considered, with a lower strength, the use of yearly, lifelong (B II r) (Cordonnier et al. 2017).
- IDSA recommends lifelong immunization (Rubin et al. 2014).
- There are no trials to support one or other recommendations, but a lifelong immunization seems logical as fatal influenza illness can occur several years after HSCT, without clear risk factors in some patients, particularly in auto-HSCT (Ljungman et al. 2011), and the proved safety of influenza vaccine in this population. Moreover, for general population, the CDC recommends routine annual influenza vaccination for all persons aged ≥6 months (Grohskopf et al. 2017).

For severe thrombocytopenic patients, the intradermic influenza vaccine can be safely administered although it has not yet been evaluated in transplant recipients.

29.5.2 Measles, Mumps, and Rubella

The clinical impact and the reasons for immunization in HSCT patients differ among these viruses:

- *Measles*: Severe and also fatal measles infections (pneumonia, encephalitis) have been reported in SCT recipients. The aim of vaccination is to protect the patient of severe consequences of infection.
- *Rubella*: There are no reports of severe rubella disease occurring in HSCT recipients. The main indication for rubella vaccination is prevention of congenital rubella in fertile women.
- *Mumps*: There are no reports of severe mumps occurring in HSCT recipients. The indication for mumps vaccination is therefore weak. There is no indication for routine mumps vaccination after HSCT. However, mumps is included in combination vaccines with measles and rubella.

Vaccines Only live-attenuated vaccines are available. Presentations: measles alone, combined measles–mumps–rubella, combined measles–mumps–rubella–varicella (live).

29.5.3 Hepatitis B Virus (HBV)

Prevention of infection and reverse seroconversion:

- Approximately 40–70% of HSCT patients obtain a titer of anti-HBs of >10 mIU/mL after post-HSCT vaccination, a rather low response compared with healthy controls. Even those who fail to obtain a response may benefit from vaccination as it can prevent reverse seroconversion.
- Patients that have evidence of a previously resolved hepatitis B infection prior to the transplant (i.e., HBsAg negative but anti-HBs and/or anti-HBc) are at risk or reverse seroconversion.

- Immunization for HBV can prevent HBV reverse seroconversion even in non-responders to hepatitis B vaccine after allo-HSCT (Takahata et al. 2014). Probably, antigen-specific memory T cells and cytotoxic T cells induced by hepatitis B vaccine are largely responsible for prevention of reverse seroconversion in non-responders to the vaccine. This reinforces the need of HBV vaccination.

29.5.4 Human Papilloma Virus (HPV)

In HSCT women nearly 40% will have genital HPV infection in long-term follow-up (Shanis et al. 2018). HPV is associated with cervical, vulvar, and vaginal cancer in females, penile cancer in males, and anal cancer and oropharyngeal cancer in both females and males.

In long-term survivors, second neoplasias are a significant complication after allo-HSCT. Cervix cancer is one of the most frequent. Squamous cell cancers, the commonest post transplant solid tumors, are associated with HPV infection. Genital HPV disease is a significant late complication of allo-HSCT, occurring in one third of women. Prolonged systemic IS treatment for cGVHD is associated with a higher risk of developing HPV-related squamous intraepithelial lesions.

Regular gynecologic examination, cervical cytology, and HPV testing after HSCT is recommended for all women (Majhail et al. 2012) as preventing measure for HPV-related cancer and as a tool for early diagnose and treatment of genital GVHD.

29.5.4.1 Vaccine

- HPV vaccine is a noninfectious, virus-like particle (VLP) vaccine. There are three formulations of HPV vaccines that differ in the number of HPV covered: a 9-valent HPV vaccine (6, 11, 16, 18, 31, 33, 45, 52, and 58 VLPs) (Gardasil 9®), quadrivalent HPV vaccine (6, 11, 16, and 18 VLPs) (Gardasil®), and bivalent vaccine (16, 18 VLPs) (Cervarix®).
- The experience with HPV vaccine in HSCT is limited, 20 children (MacIntyre et al. 2016) and 64 adults (Stratton et al. 2018), but shows a good immune response, similar to health women, with no specific safety issue.
- HPV vaccine is recommended in all guidelines (Ljungman et al. 2009; Hilgendorf et al. 2011; Rubin et al. 2014; Cordonnier et al. 2017) but with a low grade of recommendation (B II u to C III) due to the limited experience in HSCT patients. The recommended number of doses is three (Hilgendorf et al. 2011; Rubin et al. 2014).

29.5.5 Poliovirus

The WHO European Region was declared polio-free in 2002. Imported wild-type and vaccine-type polioviruses still remain a threat to unvaccinated people in the EU/EEA. Maintaining high vaccination coverage in all population groups remain an essential tool for keeping Europe polio-free.

Only inactivated poliovirus vaccines are used in all EU/EEA countries.

Oral polio vaccine (OPV) is contraindicated for HSCT patients due to the risk of paralytic poliomyelitis. This complication has occurred after vaccination of patients with severe combined immune deficiency but has not been described in HSCT patients.

29.5.6 Varicella Zoster Virus (VZV)

Prevention of VZV After HSCT Antiviral prophylaxis (acyclovir/valacyclovir) is the primary mode of prevention. It should be given for at least 1 year after allo-HSCT and for 3–6 months after auto-HSCT (Cordonnier et al. 2017).

Types of Vaccines There are three types of available vaccines and one not commercially available. None is licensed for use in IS patients.

- Live-attenuated varicella vaccine, a low-titer VZV vaccine (Varivax®, Varilix®). It is also available in combination in the same vaccine with measles, mumps, and rubella.

  - Varicella vaccine can be used in HSCT following strict requirements (see ECIL and IDSA vaccination guidelines) (Cordonnier et al. 2017; Rubin et al. 2014). Although vaccination with varicella-attenuated vaccine is indicated/considered in guidelines, in practice it is rarely used due to concerns of safety, particularly in adults (Miller et al. 2017). The commercial availability of the VZ subunit vaccine and maybe in the future the inactivated vaccine will make the use of the attenuated vaccines even lower.
- Live-attenuated zoster vaccine, a high-titer vaccine (Zostavax®). It contains more than 14 times more virus than varicella vaccine. In all guidelines, this vaccine is contraindicated in HSCT patients.
- New phase III studies with new VZL vaccines in auto-HSCT.
  - *Adjuvanted VZV subunit vaccine* (Shingrix®) (de la Serna et al. 2018; Sullivan et al. 2018) consists of recombinant VZV gE antigen mixed with AS01B adjuvant. It was recently approved by the FDA (October 2017) and EMA (March 2018) for prevention of herpes zoster (HZ) and post-herpetic neuralgia, in adults 50 years of age or older. It is administered IM in two doses separated by 60 days.
  - *Inactivated VZV-vaccine (V212), in auto-HSCT* (Winston et al. 2018), is not yet commercially available. It is administered in four doses by SC injection, beginning ~5 days prior to chemotherapy or ~30 days prior to auto-HSCT and the remaining doses being administered at 30, 60, and 90 days later.
  - Both vaccines showed a high vaccine efficacy for preventing zoster which was 68–64%, post-herpetic neuralgia 89–84%, VZV-related hospitalizations 85%, and for other VZV complications 78–75%. The positive results of these studies probably are going to change the prevention of VZV complications after auto-HSCT.

29.5.7 Pneumococcus

Pneumococcus is a frequent and *serious complication in HSCT*. The incidence of invasive pneumococcal disease (IPD) in HSCT is 50 times higher compared to the general population (Shigayeva et al. 2016). In spite of this high incidence of IPD, less than one in five HSCT patients with IPD had received pneumococcal vaccine.

29.5.7.1 Types of Vaccine

- Polysaccharidic (PS) vaccine
  - 23-valent polysaccharidic (PS) vaccine (Pneumo 23®, Pneumovax23®): poor immunogenic, T-cell-independent response, no boost benefit
  - Poor responses, particularly in patients with GVHD
  - PS after PCV vaccine increases and expands the response obtained with PCV. Some non-responders to PCV will achieve a response with PS vaccine.
- Conjugate vaccine (PCV): highly immunogenic, T-cell-dependent response, with boost benefit
  - 13-valent in the majority of countries (Prevenar 13r®) (that replace the previous 7-valent vaccine) or 10-valent available in some countries (Synflorix®).
  - Five trials have shown a good response to PCV after three doses (range 54–98%). Four trials used 7-valent conjugated vaccine and one the 13-valent vaccine (Cordonnier et al. 2017). These responses are much better compared with what is obtained with PS vaccine.
  - Early vaccination at 3 months is not inferior to late vaccination (9 months) after allo-HSCT.
  - PCV should always be administered before PS vaccine.

29.5.8 Diphtheria-Tetanus-Pertussis

The exposure to *tetanus* in the environment is a real risk for HSCT patients, so the aim of vaccination after transplant is to protect the patient.

Diphtheria has essentially been eradicated but ongoing vaccination is critical for immunity. Diphtheria cases are still happening in Europe with an increase of 280% from 2009 to 2014. The reappearance of diphtheria cases in countries like Spain diphtheria-free for more than 30 years (Jane et al. 2018) is alarming and another reason to vaccine all our HSCT patients.

There are very limited published data of *pertussis* in HSCT and no reported case of severe or fatal pertussis infection after SCT in adults. Therefore, the objective of vaccination in these patients is avoiding pertussis transmission by HSCT patients.

29.6 Vaccinations Before Travel to Areas Endemic for Infections (See Table 29.3) (Ljungman et al. 2009)

29.7 Serological Testing

For the majority of vaccines, no pre- or postvaccination serology is recommended. Nonetheless, there are exceptions for this rule (Ljungman et al. 2009).

29.7.1 Pre-Vaccination

Testing for Abs to measles is recommended in adults, with vaccination performed only if the patient is seronegative (CIII).

If vaccination against varicella is contemplated, testing of immunity should be carried out and vaccination should be administered to seronegative patients only (CIII).

29.7.2 Postvaccination

Pneumococcal vaccine: Testing to assess the response to vaccination is recommended at

Table 29.3 Vaccinations before travel to areas endemic for infections (Ljungman et al. 2009)

If contraindications for the vaccine exist, the patient should be advised not to travel to endemic areas (CIII) Vaccination is one of the precautions that the HSCT patients should observe. There are other equal important measures that should be followed: chemoprophylaxis against malaria; mosquito-oriented precautions; food safety to prevent traveler's diarrhea; avoiding sun exposure, particularly for those under treatments associated with photosensitivity (like voriconazole)	
Tick-borne and Japanese B encephalitis	• According to local policy in endemic areas (CIII)No data exist regarding the time after HCT when vaccination can be expected to induce an immune response
Rabies	• Rabies vaccine is made from killed virus and cannot cause rabies. Nonetheless, there are no data regarding safety, immunogenicity, or efficacy among HCT recipients • Preexposure rabies vaccination should probably be delayed until 12–24 months after HCT • Postexposure administration of rabies vaccine with human rabies Ig can be administered any time after HCT, as indicated
Yellow fever (live)	• Limited data regarding safety and efficacy (C III). Yellow fever vaccine has been safely administered to a limited number of post-HSCT patients (Rubin et al. 2014) • The risk–benefit balance may favor the use of the vaccine in patients residing in or traveling to endemic areas
Hepatitis A	• Follow recommendations for general population in each country (CIII) • Ig should be administered to hepatitis A-susceptible HCT recipients who anticipate hepatitis A exposure (for example, during travel to endemic areas) and for postexposure prophylaxis
Typhoid (IM), inactivated vaccine	• No data were found regarding safety, immunogenicity, or efficacy among HCT recipients. DIII. Remember that typhoid oral vaccine is live attenuated and is contraindicated in HSCT patients (EIII)
Cholera	• No data were found regarding safety and immunogenicity among HCT recipients. Vaccine is not recommended (DIII)

1 month or later after the third or fourth dose of pneumococcal vaccine (BIII). As a widely accepted definition of adequate response to pneumococcal vaccine is lacking, guidelines for revaccination of non-responders are not given. Testing for immunity to pneumococcus might reasonably be repeated every 2 years for the first 4 years (BIII).

Hepatitis B: Testing should be carried out 1 month or later after the third vaccine dose (BIII). A second three-dose vaccination schedule is recommended in non-responders (CIII)

Testing should be conducted approximately every 4–5 years to assess for immunity to HBV, measles, tetanus, diphtheria, and polio (BIII).

29.8 Vaccinations for Donors, Close Contacts/Family, and HCWs of HSCT Recipients (See Table 29.4) (Ljungman et al. 2009; Cordonnier et al. 2017; Rubin et al. 2014)

Table 29.4 Vaccinations for donors, close contacts/family, and HCWs of HCT recipients

General comments		
Inactivated vaccines can be safely given for donors, close contacts, and HCWs of HSCT patients For live vaccines a careful evaluation should be done (see below). Some have no safety issues for HSCT recipients but other can cause severe damage		
Donors		
Guidelines do not recommend donor vaccination for the benefit of the recipient[a,b] • Only vaccines that are indicated and recommended based on the donor's age, vaccination history, and exposure history should be administered • Nonetheless, vaccination of the donor has been shown to improve the post transplant immunity of the patient in the case of tetanus, diphtheria, 7-valent pneumococcal conjugate vaccine (PCV), and *Haemophilus influenzae* type b-conjugate vaccines. Donation is an opportunity to update the donor vaccination calendar. If the donor has to receive any of these vaccines in his/her own interest, the administration of at least one dose pre-collection of stem cells could benefit also the receptor Administration of MMR, MMRV, varicella, and zoster vaccines should be avoided within 4 weeks of stem cell harvest[b]. By extension, all live vaccines should be avoided before stem cell collection due to the risk of transmission of the pathogen with the graft[c]		
Vaccines recommended for close contacts and HCWs of HSCT recipients		
Who?	*Vaccine*	*Dose/notes*
All	Influenza, inactivated	•Annually, as long as there is contact with an IS recipient[a]: Close contacts: AII[a]-AIII[c]; HCWs: AI[a]-AIIt[c]
All sero(-) VZ	Varicella: AIII[a]	• 2 doses, separated by at least 28 days
HCWs Sero(-)	Measles	• AIII[a]; recommended, not graded[b,c]
Live vaccines given for *close contacts or HCWs* of HCST patients: precautions		
Intranasal influenza vaccine		• If live influenza vaccine is administered to a close contact/HCWs, contact between the IS patient and household member should be avoided for 7 days (weak, very low)[b]
Measles-mumps-rubella		• No risk for the HSCT patient
Varicella		• The vaccination dose or doses should be completed >4 weeks before the conditioning regimen begins or >6 weeks (42 days) before contact with the HCT recipient is planned (BIII)[a] • If a varicella vaccinee develops a postvaccination rash within 42 days of vaccination, the vaccinee should avoid contact with HCT recipients until all rash lesions are crusted or the rash has resolved[a]

(continued)

Table 29.4 (continued)

Oral polio vaccine (OPV)	• Oral polio vaccine (OPV) should not be administered to individuals who live in a household with IS patients (strong, moderate)[b]. These vaccinated contacts shed the live-attenuated poliovirus strains of the vaccine in the stools that can induce paralytic poliomyelitis in immunocompromised patients like HSCT • If live-attenuated oral polio vaccine, that is still available in some non-US/non-European countries, is given to a household contact, a 4- to 6-week furlough is advised
Rotavirus	• Rotavirus vaccine is included in the children vaccine calendar of many countries, so it will be frequent that a HSCT patient has a child candidate for the vaccine • Virus is shed in stools for 2–4 weeks after vaccination. Transmission from vaccinated to IS person has been confirmed, but there are no reported cases of symptomatic infection in contacts • Highly IS patients should avoid handling diapers of infants who have been vaccinated with rotavirus vaccine for 4 weeks after vaccination (strong, very low) • HSCT recipients should have no contact with the stools or diapers of vaccinated children for 4 weeks following vaccination[c]
Vaccines for travel: yellow fever vaccine; oral typhoid vaccine	• Can safely be administered[b]

HCWs healthcare workers
[a]Ljungman et al. (2009)
[b]Rubin et al. (2014)
[c]Cordonnier et al. (2017)

Key Points

- Vaccination should be considered a routine practice for all HSCT receptors, either autologous or allogeneic, adults or children. It should be implemented in all HSCT programs.
- There is no a unique vaccine schedule for all HSCT patients. Each center should discuss and adapt a specific vaccine program.
- To obtain this objective, it is necessary to have in place a standardized program specific for HSCT patients with a simple and clear chronology and the collaboration of the Preventive Department of the hospital and primary care physicians.
- The vaccination program should include not only the patient but also those who live with the patient and the healthcare workers (HCWs).
- There are two main reasons for universal vaccination of HSCT patients: (a) the general interest as all the population should be correctly vaccinated to avoid holes of immunity that can be a risk for the health of the general population and (b) individual interest for each HSCT patient.

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