Vaccination guidelines in haematopoietic transplant patients: recommendations from the BHS Transplant Committee

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Haematopoietic stem cell transplantation is increasingly used as consolidation therapy in severe haematological diseases. In the post-transplantation period, the immunity of haematopoietic stem cell transplantation recipients is impaired due to toxicity of the pre-haematopoietic stem cell transplantation treatment (chemo- and/or radiotherapy), the conditioning regimen with a reset of the immune system, and – in case of allogeneic haematopoietic stem cell transplantation – the use of immunosuppressive drugs and potentially graft-versus-host-disease. This leads to a considerably increased risk of infections, with high morbidity and mortality. Therefore, prevention of infections, i.a. by revaccination, is of major importance to improve outcomes. We present the Belgian guidelines for vaccination after haematopoietic stem cell transplantation, based on available data in the literature and international guidelines, taking into account the availability of vaccines and - if applicable - their reimbursement in Belgium. We describe a general vaccination schedule for post-haematopoietic stem cell transplantation patients, indications for pre-transplant vaccination and donor vaccination and an overview of special indications, such as travel vaccinations, vaccinations of close contacts and health care workers, with recommendations for titer follow-up.
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Introduction

Advances in the field of haematopoietic stem cell transplantation (HSCT) have led to improved survival and reduced morbidity, resulting in its increased use as a consolidation therapy in several haematological and some oncological diseases.

The immunity of HSCT patients is impaired due to toxicity of the pre-HSCT treatment (chemo- and/or radiotherapy) and of the conditioning regimen, with a reset of the immune system, further aggravated by the use of immunosuppressive drugs and graft-versus-host-disease (GVHD) in the context of allogeneic HSCT. After transplantation, there is a marked decrease in the antibody titer to vaccine-preventable diseases, which will fail to recover unless revaccination is performed.[1-3] HSCT patients have a significantly higher risk of infections in comparison with the general population.[4] Kumar et al. for instance report a 30.2-fold risk of pneumococcal

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Table 1. General conditions to start vaccination in patients after haematopoietic stem cell transplantation.

BOX 1 - General conditions for all vaccinations	BOX 2 - Additional conditions for all live vaccines
Complete remission confirmed, (unless indolent disease does not require further treatment) B-cells ≥ 1/µL ≥ 2 weeks after or before IVIG administration	≥ 24 months after HSCT ≥ 3 months after IVIG administration Absolute CD4 T cell count ≥ 200/µL No evidence of GVHD Off immunosuppressive therapy for ≥ 3 months Careful assessment of risks and benefits

IVIG: intravenous immunoglobulins

disease in adult HSCT patients compared to the general population aged 18-65 years.[4,5] Furthermore, certain vaccine-preventable viruses have recently re-emerged in the general population, e.g. an outbreak of measles in a day care centre in spring 2011 and an outbreak of mumps among students in spring 2013 in Belgium.[6] The transplanted population is at a particularly increased risk for transmission of these infections, with possible complications such as pneumonia, encephalitis and disseminated disease with significant mortality. For instance, Kaplan et al. describe a case fatality rate of severe measles infections of 70% among oncology patients.[7,8] Therefore, prevention of infections in HSCT recipients is of major importance to improve their outcome. Prevention strategies include antibiotic prophylaxis, adequate diet, lifestyle adjustments and revaccination.

We present here the Belgian guidelines for vaccination after haematopoietic stem cell transplantation, based on available data in the literature and international guidelines, taking into account the availability of vaccines and, if applicable, their reimbursement in Belgium.

Vaccination guidelines

Pre-HSCT vaccination

In contrast to the setting of solid organ transplantation, pre-transplant vaccination is generally not recommended in HSCT because of the 'reset' of the immune system at the time of transplantation due to the conditioning regimen. An exception is made for the hepatitis B naive patient, receiving a graft from a hepatitis B positive donor (hepatitis B surface antigen (HbsAg) positive). In this case, vaccination should ideally start before HSCT and preferably prior to induction chemotherapy, at least for the initial two doses, as the response to vaccination has shown to be poor in patients immediately after therapy. A third dose should be given six months later, ideally also prior to the transplantation (but only if it is safe to postpone it).[4,9] Antibody titers are most often measured four weeks after the last dose.[10]

Vaccination of the donor

There is some evidence for a better immunity post-HSCT in the recipient when the donor has been vaccinated with tetanus toxoid, the pneumococcus vaccine and Haemophilus influenza type b conjugated vaccine before collection.[4] Furthermore, it has been suggested to vaccinate the donor for hepatitis B when the transplant recipient is both hepatitis B core antibody (HbcAb) and hepatitis B surface antibody (HbsAb) positive, to reduce the risk of reverse seroconversion (see also section on specific risk groups).[11] Because of practical difficulties and ethical issues, we make no recommendations regarding unrelated donor vaccination.[4,10] However, hepatitis B vaccination of a family donor could be proposed after appropriate information.

General vaccination scheme for the post-HSCT patient (Tables 2 and 3)

Before starting revaccination in the HSCT patient, some general conditions should be taken into account (*Table 1, box 1*). If these conditions are fulfilled, we recommend for all HSCT patients revaccination for Streptococcus pneumonia, Haemophilus influenza, diphteria, tetanus, pertussis, polio, hepatitis B and influenza, with dead or recombinant vaccines. For measles/mumps/rubella, a live attenuated vaccine is used. This therefore carries a

Table 2. Standard vaccinations for all HSCT recipients (auto/allo).

Organism	Vaccine	Timing start (Dose1)	Schedule	Booster	Remark/Follo Up/ Titer
Pneumococcus	Prevenar 13® (conj) Pneumo 23® (non-conj) (dead)	M3 or M6	Dose 1 (conj) Dose 1 + 1 or 2 M (conj)* Dose 1 + 2 or 4 M (conj)* Dose 1 + 8 or 10 M (non-conj, unless cGVHD/IS: conj)	Every 5 years in the general population; no data in SCT patients	Titers may be measured after vaccination (at least 1 month after 3rd of 4th dose) And after 2-3 years
Haemophilus influenzae **Diphteria/Tetanus/ Pertussis** **Polio** **Hepatitis B**	Infanrix Hexa® (DTP high dose) (dead)	M6 or M12	Dose 1 Dose 1 + 1M Dose 1 + 2M Dose 1 + 12M	Optional specific revaccination if non-protective titers	HBsAb titers may be checked after vaccination (1 month after the 3rd dose) Tetanus and polio Ab titers may be checked after vaccination if poor response is suspected
	Boostrix polio® (dead) (dTp + polio)	N/A	Dose 1 + 5Y	/	Cfr. general population; no data in SCT patients
	Boostrix® (dead) (dTp)	N/A	Dose 1+15Y	/	Cfr. general population; no data in SCT patients
	Tedivax pro adulto® (dT) (dead)	N/A	dose 1 + 25Y	Every 10Y	/
Measles/Mumps/ Rubella	Priorix® MMR Vaxpro® (**live** attenuated)	≥ M24	Dose 1 Dose 1 + 2M (for children < 9 years)	At 5Y in the general population; no data in SCT patients	Check titers before first vaccination (≥ 3 months after last dose IVIG/ FFP): vaccinate if titer not protective and/or if fertility is an issue. Additional conditions for live vaccines: see Table 1, Box 2 **Careful assessment of risks and benefits**

*M: month, M6: 6 months after HSCT, conj: conjugated vaccine, non-conj: non-conjugated vaccine, IS: immunosuppressive drugs, cGVHD: chronic graft-versus-host-disease, N/A: not applicable, IVIG: intravenous immunoglobulins, FFP: fresh frozen plasma. Allways take into account the general conditions for all vaccines (dead or alive): see table 1, box 1. * Interval between two pneumococcus vaccinations may be up to 2 months. (4) For influenza: see table 3*

potential risk of disease transmission, so vaccination should only be administered when titers are not protective and at certain additional conditions (*Table 1, box 2*).

Streptococcus pneumonia (*Table 2*)

Vaccination is started three or six months after transplantation (at the discretion of the centre: one possibility is to offer earlier (three months) vaccination to autologous HSCT recipients and later (six months) vaccination after allogeneic HSCT). Three doses of the conjugated vaccine (Prevenar 13®) are administered with an interval of one to two months, followed by the administration of the non-conjugated vaccine (Pneumo 23®) six months after the last dose.[4,10,12,13]

In one trial, non-inferiority was shown for the response rate to early (three months post-HSCT) versus late (nine months post-HSCT) vaccination. Starting early with vaccination offers an earlier protection, but may be associated with an earlier decline of the antibody titers during the second year of HSCT, despite booster vaccination with polysaccharide vaccine nine months after the first dose. In this case it may be of particular importance to measure the antibody titers after immunisation. A late immunisation offers better chances of an efficient and long-lasting immune response, but delays the protection in a patient group where the risk of invasive pneumococcal disease is already increased in the first six months.[12,14]

The conjugated vaccine is more immunogenic than the polysaccharide vaccine, especially in the first year post-transplantation, by stimulating T-cell dependent antibody responses. However, the conjugated vaccine has a narrower spectrum of protection with only thirteen

- albeit the most frequent - serotypes covered, compared to the 23 serotypes in the polysaccharide vaccine.[4,10] Because of the risk of an inadequate response, patients with GVHD and/or under immunosuppression at the time of the fourth dose, should receive the conjugated vaccine again.[4,10]

Titers can be checked at one month or later after the third or fourth dose of the pneumococcal vaccine.[4,10]

Two-three years after the first vaccination, antibody titers may be checked again: if non-protective, a booster vaccination can be given at that time. If protective, a booster vaccination is needed five years after the first vaccination. Thereafter, the booster vaccination is repeated every five years.[15]

Haemophilus influenza, diphtheria/tetanus/pertussis, polio, hepatitis B (*Table 2*)

We recommend starting vaccination six to twelve months after HSCT (possibly earlier after autologous than after allogeneic HSCT). Infanrix Hexa® consists of inactivated Haemophilus influenza type B, Bordetella pertussis antigen, high dose diphtheria anatoxin, inactivated poliomyelitis virus type I, II and III, hepatitis B virus antigen and tetanus anatoxin. Three doses are given with an interval of one month. A fourth dose is given one year after the start of vaccination.[4,10,13]

Because a low dose of diphtheria or pertussis antigens might lead to a poor response, it is recommended to use the high dose antigen vaccines.[13]

Booster vaccination with Boostrix polio® (low dose diphteria anatoxin and low dose pertussis antigen, tetanus anatoxin and poliomyelitis virus) is planned at five years post-transplantation. Booster vaccination with Boostrix® (same content, without poliomyelitis virus) is recommended ten years later, followed by Tedivax pro Adulto® (low dose diphtheria anatoxin and tetanus anatoxin, if >12 years) every ten years.

HbsAb titer may be checked one month after the third dose and revaccination is recommended if the patient has non-protective titers. Tetanus and polio antibody titers may be checked if poor response is suspected.

Measles/Mumps/Rubella (Priorix®, M.M.R. Vaxpro®) (*Table 2*)

Before immunisation with this live attenuated vaccine, titers should be checked (at least three months after the last dose of IVIG or fresh frozen plasma (FFP)): vaccination is recommended only in patients with non-protective titers. All additional conditions for vaccination with live vaccines should be met (*Table 1, box 2*).[13,16]

A second dose after a two month interval is administered in children younger than nine years. A booster vaccination is recommended at ten years in the general population, in HSCT patients there are no available data.

Influenza (Inflexal V®, Influvac S®, Agrippal®, Vaxigrip®, Alpha-rix®, Intanza®) (*Table 3*)

Start of vaccination is recommended as soon as possible during the flu season (which lasts from October till February) and at least four months after stem cell transplantation.[17]

We recommend using the inactivated subunit or split vaccines. The live intranasal influenza vaccine should not be administered because an inactivated form is available.[17]

Only one dose is necessary, except in children aged six months to nine years who are receiving influenza vaccination for the first time post-HSCT: they require two doses four weeks apart. Those who have received only one dose in the first year should receive two doses in the following year. Lifelong yearly renewal is necessary.[13]

Special situations

i. Vaccination for specific risk groups of SCT recipients (auto/allo) *(Table 4)*

There are some vaccines for which there are no or limited available data concerning their use (safety and/or immunogenicity) in HSCT patients, e.g. Neisseria meningitides type C, Human Papilloma Virus and hepatitis A. Our recommendations are based on the recommendations for the general population, as given by the Superior Health Council (SHC).[15]

Neisseria meningitides type A, C, W and Y

We recommend vaccination for patients in endemic areas or during an outbreak, and also for children and adolescents younger than eighteen years. Vaccination should start at least six to twelve months after transplantation. Two doses (three for children) of the conjugated quadrivalent vaccine (Menveo®, Nimenrix®) should be administered with an interval of one month. The only data available concerns the immunogenicity of the polysaccharide meningococcal vaccine (Meningitec®, Menjugate®, Neisvac-C®) in HSCT recipients with a HLA identical sibling donor.[18] There are no comparative studies in the context of HSCT, but the new conjugated vaccine is expected to be superior in generating a more stable immune response, compared to the polysaccharide based vaccine, as is true for pneumococcal and Hib vaccines.[4,10,13,19]

Human Papilloma Virus

All girls aged ten to thirteen years should be vaccinated, and females between 14-26 years preferably before they

Table 3. Influenza vaccinations for all HSCT recipients (auto/allo), close contacts & health care workers.

Organism	Vaccine	Who	When, start date	Dose	Booster	FU/titer	Risk for transmission
Influenza	inactivated vaccine Inflexal V® Influvac S® Agrippal® Vaxigrip® α-rix® Intanza® NO INTRANASAL INFLUENZA VACCINE !!!	**Patients**	≥ M4 During flu season (Oct-Feb)	1 dose*	Yearly renewal	N/A	N/A
		Close contacts	Before SCT: During flu season (Oct-Feb) 1st year post SCT: Beginning of flu season (October)	1 dose	Yearly renewal until patient stops IS	N/A	None
		Health-care workers	Beginning of flu season (October)	1 dose	Yearly renewal	N/A	None

*IS: immunosuppressive drugs, N/A: not applicable M: month, M4: 4 months after HSCT. Always take into account the general conditions for all vaccines (dead or alive): see table 1, box 1. * Children aged 6 months to <9 years who are receiving influenza vaccination for the first time require 2 doses and those who have received only one dose in the first year should receive 2 doses in the following year.*

become sexually active. In women who are already sexually active, vaccination is performed at discretion of the physician. The vaccination scheme starts six to twelve months after transplantation with the administration of three doses: either in a zero, one, six months schedule (Cervarix®), or a zero, two, six months schedule (Gardasil®). In addition, all female HSCT patients should be regularly screened for HPV by a gynaecologist.[13,19]

Hepatitis A (Havrix®, Epaxal®, Vaqta®)

Vaccination is recommended in patients with increased risk of infection and for complications in case of infection: people travelling to endemic areas, homosexual and bisexual men, liver transplant candidates, patients with chronic liver disease (including hepatitis B and/or C positive patients), patients with haemophilia, patients who have close contact with persons with active hepatitis A infection, personnel and residents of institutions for mentally disabled, children of migrants returning to their land of origin, people working in the food industry and close contacts of a recently adopted child from a country with a high prevalence of hepatitis A infections.[4,9,15,19] Vaccination should start six to twelve months after transplantation, with administration of two doses of the monovalent vaccine with an interval of six months.[4,13]

Hepatitis B in special cases (Engerix B®, Fendrix®, H Vaxpro®)

As noted above (see also section on pre-transplant vaccination), HBV-naive patients who receive stem cells from a HbsAg-positive donor should ideally be vaccinated prior to stem cell transplantation, preferably prior to chemotherapy. However, this vaccination will need to be repeated post-transplantation.

In case of HSCT in patients who are both HbcAb and HbsAb positive, with negative HbsAg, it is recommended to follow alanine amino transferase (ALT) regularly and HbsAb every three months post-HSCT. Elevation of ALT or reduction of the HbsAb titer could be a sign of reverse seroconversion (e.g. due to prolonged intake of immunosuppressive drugs for GVHD) and should prompt testing for HBV-DNA. If the polymerase chain reaction (PCR) is positive, the patient should be treated with antiviral therapy (e.g. lamivudine).[9,11,20] In case of a negative PCR, the patient should receive active immunisation as planned, in an attempt to restore protective levels of HbsAb.[9,11,20]

In case of the presence of HbcAb without presence of HbsAg or HbsAb, HBV DNA should be checked. If positive, antiviral treatment should be started. If negative, vaccination should be administered as planned.[9,11,20]

When HbsAg is positive, regardless of the other tests, antiviral treatment should be started. HBV DNA should be checked before, during and after therapy.[9,11,20]

There is no evidence regarding duration of antiviral treatment, but some reports suggest continuation of therapy until six months after autologous HSCT and six months after cessation of immunosuppressive drugs in case of allogeneic HSCT, because of the risk of (fatal) HBV reactivation after early withdrawal.[20-22] One could encounter problems with reimbursement of lamivudine in some specific circumstances (e.g. in case of positive HBV DNA but negative HbsAg).

The discussion about the prophylactic use of antivirals,

which antiviral therapy to choose and the associated reimbursement issues, is beyond the scope of this article.

ii. Travel vaccinations for SCT recipients (auto/allo) (*Table 5*)

When travelling to endemic areas, the same recommendations as for the general population should be followed, but for some vaccines specific recommendations exist for HSCT recipients.

For hepatitis A (Havrix®, Epaxal®, Vaqta®), polio (Imovax Polio®) and typhoid fever (Typhim®) vaccines (all dead), vaccination should start at least two weeks before travel to make sure that there is an adequate titer at departure, but at least six to twelve months after HSCT, to ensure adequate response to the vaccine.[4,10]

Hepatitis A vaccine consists of two doses with an interval of six months. For polio one dose is given, unless there was no primary revaccination post-HSCT: then full revaccination is needed (three doses with a monthly interval, followed by an additional dose twelve months after the first one). The vaccination for typhoid fever consists of one dose and gives protection for three years. After this time, the patient should receive a booster vaccination if the risk for typhoid fever still exists.

Because the vaccine for Yellow fever (Stamaril®) is live attenuated, administration is recommended at least two weeks before departure, but only when additional conditions for live vaccines are met (*Table 1, box 2*). It is a single dose vaccination that protects for ten years.[4,10] Careful assessment of risks and benefits should be ensured. If feasible, delaying departure should be encouraged.

Travellers at increased risk for rabies (Rabipur®, rabies vaccine Merieux HDCV®) (e.g. cycling tourists and travellers to remote areas for a long period) or people with potential occupational exposure (e.g. veterinarians and hunters) should be vaccinated at least three weeks before departure/exposure. There are no available data concerning the timing for start of vaccination after transplantation, but because it is a dead vaccine, we recommend starting the vaccination at six to twelve months after transplantation. Pre-exposure vaccination consists of three doses in four weeks (*Table 5*). No booster vaccination is needed, unless there is a non-protective titer (<0.5 IU/ml), measured at least ten days after the last dose.[4,10] After contact with rabies in vaccinated patients, only one dose of the vaccine should be administered, provided that the patient had a recent positive titer control or contact was within one month of preventive vaccination. If the titer is unknown, two doses are recommended, on day zero and day three. In unvaccinated travellers, post-exposure prophylaxis consists of the administration of anti-rabies immunoglobulines (20 IU/kg) as much as possible as a deep local injection in and around the wound, and the remainder as an injection in the arm. In addition, rabies vaccine is given in the contralateral arm on day zero, three, seven, fourteen and twenty eight. If there are no anti-rabies immunoglobulins available, one should be vaccinated with two doses on day zero, followed by a single dose on day seven and day twenty one, with monitoring of the titer on day thirty. If non-protective, a booster vaccination is needed.[15,23] In the setting of post-exposure prophylaxis, there is no B-cell count restriction and the vaccine can be administered at any time post-HSCT.[4,10]

iii. Not recommended

We do not recommend vaccination with the following live vaccines: BCG (Bacille Calmette Guérin), the oral polio vaccine, the intranasal influenza vaccine, the oral typhoid vaccine, and the varicella vaccine. Neither do we recommend vaccination with the cholera vaccine. Reasons for this are the availability of an effective, inactivated alternative, and/or the lack of data regarding safety and immunogenicity in HSCT patients.[4,10]

Family members, close contacts and health care workers (*Table 6*)

For family and close contacts recommendations for the general population should be followed, but some additional vaccinations (e.g. influenza, varicella) are recommended to reduce the risk of transmission of infections to the HSCT recipient. It is advisable to check if close contacts completed their vaccination scheme, according to the recommendations for the general population, including the booster doses. Furthermore, there are some specific issues to take into account:

For all dead vaccines there is no risk for transmission to the transplant patient. Therefore, it is recommended to always choose the dead inactivated alternative if available.

The use of a live attenuated vaccine such as the measles/mumps/rubella (MMR) vaccine (Priorix®, MMR Vaxpro®) and rotavirus vaccine (Rotarix®, Rotateq®), is not contraindicated for close contacts of HSCT recipients. However, when the vaccinated person develops a fever or rash after administration of the MMR vaccine, contact with transplant patients should be avoided, including visits to the HSCT unit. Concerning the rotavirus vaccine, there is evidence of excretion of the virus during

Table 4. Vaccinations for specific risk groups of HSCT recipients (auto/allo).

Organism	Vaccine	Risk groups	Timing start	Schedule	Booster	Remarks
Neisseria meningitides type C, A, W, Y	Nimenrix® Menveo® (conj-dead)	SHC recommendations: - Endemic areas or during outbreak - Children / adolescents ≤ 18Y	M6 or M12	Dose 1 Dose 1 + 1M Dose 1 + 2M (children)	N/A	
Human Papilloma Virus	Cervarix® Gardasil® (dead)	SHC recommendations: Women 14-26 Y, girls 10-13 Y (preferably before sexually activity; if already sexually active: at discretion of physician)	M6 or M12	Dose 1 Dose 1 + 1M (Cervarix) + 2M (Gardasil) Dose 1 + 6M	N/A	No data in HSCT patients
Hepatitis A	Havrix® Epaxal® Vaqta® (dead)	SHC recommendations: - Travel to endemic areas - Homosexual and bisexual men - Liver transplant candidates - Chronic liver disease (incl hep B/C) - Hemophilia - Contact with persons with hepatitis A - Personnel institutions for mentally disabled - Children of migrants returning to land of origin - People working in food industry - Close contacts of recently adopted child from country with high hep A prevalence	M6 or M12	Dose 1 Dose 1 + 6M	N/A	
Hepatitis B (special cases)	Engerix B® Fendrix® HBVaxpro® (dead)	HBV naïve patient receiving a HBsAg pos donor: - Vaccinate patient before HSCT - Revaccinate after HSCT as planned (table 1)	Pre HSCT	Dose 1 Dose 1 + 1M		Dose 1 + 6M before HSCT if HSCT can be delayed
			Post HSCT	See table 1		
		Pre-HSCT HBV exposed patient (HBcAb pos) **1. HBsAg neg, HBsAb pos : monitor ALT, HBsAb*** If ALT rises and/or HBsAb* declines: check PCR If PCR pos : anti-viral therapy ** If PCR neg : vaccinate patient as planned (table 1) **2. HBsAg neg, HBsAb neg :** Vaccinate donor pre HSCT, if possible Monitor PCR If pos, anti-viral therapy ** If neg, vacccinate patient **3. HBsAg pos** Vaccinate donor pre HSCT, if possible Anti-viral therapy (whatever PCR level) ** Monitor PCR : if neg, vaccinate patient	Post HSCT	See table 1		

M: month, conj: conjugated vaccine M6: 6 months after HSCT, Tx: transplantation, pt: patient, HB: hepatitis B, SHC: Superior Health Counsel;
** HBsAb are not evaluable in the 3 months following IV immunoglobulins; ** anti-viral therapy should last at least 6 months after autologous HSCT and 6 months after cessation of IS after allogeneic HSCT.*

fifteen to thirty days. Therefore, these children should not visit the transplantation unit for four weeks and transplant patients should not change diapers of these children for the same period. If this is not feasible, they should perform very careful hand hygiene.[4,10]

Some additional vaccinations, apart from the general vaccination scheme, are recommended for close contacts:

Influenza (*Table 3*)

Close contacts (except infants <6 months) should be vaccinated at least before stem cell transplantation (during the flu season (October to February)) and during the first year post-HSCT. Yearly renewal is necessary if the

Table 5. Travel vaccinations for HSCT recipients (auto/allo).

Organism	Vaccine	Risk groups	Condition(s) besides*	Timing start	Schedule	Booster	Comments
Hepatitis A	Havrix® Epaxal® Vaqta® (dead)	Before travel to endemic areas (SHC guidelines)	/	> 2 weeks before travel > M6 or M12	Dose 1 Dose 1 + 6M	N/A	
Polio	Imovax® (dead)	Before travel to endemic areas (SHC guidelines)	/	> 2 weeks before travel > M6 or M12	Dose 1	N/A	If no primary re-vaccination post-transplant : full revaccination as in Table 1
Typhoid fever	Typhim® (dead)	Before travel to endemic areas (SHC guidelines)	/	> 2 weeks before travel > M6 or M12	Dose 1	N/A Protective 3 years	
Yellow fever	Stamaril® (live attenuated)	Before travel to endemic areas (SHC guidelines)	conditions for live vaccines: see table 1, box 2	> 2 weeks before travel ≥ M24	Dose 1	N/A Protective 10 years	Carefully assess risk/benefit ratio
Rabies	Rabipur® Vaccin tegen rabies Merieux HDCV® (dead)	Preventive in patients with increased risk (SHC guidelines)	/	> 3 weeks before travel > M6 or M12	Dose 1 Dose 1 + 1W Dose 1 + 3W	Not necessary	
		After contact in vaccinated patients	No B cell count restriction	No time restriction	Dose 1 on D0 (Dose 2 on D3)	N/A	Restricted to one dose only if contact < 1M after vaccination or in case of a recent positive titer
		After contact in unvaccinated patients	No B cell count restriction	No time restriction	Ig on D0 Dose 1 on D0 Dose 2 on D3 Dose 3 on D7 Dose 4 on D14 Dose 5 on D28	N/A	If no Ig available: Two doses on D0, one dose on D3 and D7, and titer control on D30

*M: month, M6: 6 months after HSCT, D: day, W: week, N/A: not applicable, Ig: immunoglobulins. * General conditions for all vaccines (dead or alive): see table 1, box 1. SHC: Superior Health Council.*

patient is still taking immunosuppressive drugs. Healthcare workers should be vaccinated at the beginning of each flu season (October) with a yearly renewal. The dead inactivated vaccine should be used, the live attenuated intranasal vaccine is contra-indicated because of a possible transmission risk.[4] If a family member accidentally received the live vaccine, close contact should be avoided for seven days.[17]

General precautions, including good personal hygiene, frequent hand washing, covering mouth and nose when coughing or sneezing and safe disposal of oral and nasal secretions are also recommended. Education of patient and family pre-HSCT increases awareness of respiratory virus prevention strategies and household influenza vaccination, thereby reducing influenza risk after HSCT.[17]

Varicella (Provarivax®, Varilrix®)

In household members with a negative or uncertain history of varicella, serology should be checked. If negative, they should be vaccinated in order to protect the transplant patient from potential exposure to the wild type disease. The vaccination scheme should be finalised more than four weeks before the start of conditioning and more than six weeks before planned contact with the transplant patient. There is a risk for transmission

Table 6. Vaccinations for family members/close contacts/health-care workers.

Organism	Type of vaccine	Recommendation for use in general population	Risk for transmission to transplant recipient
Diphtheria/Tetanus/Pertussis	Dead	Routine vaccination is recommended for - children < 7 years : DTP - children > 7 years, adults: dTp	No
Polio	Dead	Routine vaccination is recommended for children. Routine revaccination (booster) not recommended for adults but inactivated polio vaccine should be used when polio vaccination is recommended	No with inactivated vaccine Yes in case of live vaccine (contra-indicated)
Haemophilus influenzae	Dead	Routine vaccination is recommended for children.	No
Hepatitis B	Dead	Routine vaccination is recommended for children as well as health-care workers and other persons at increased risk for hepatitis B or its adverse consequences	No
Hepatitis A	Dead	Routine vaccination is recommended for children and other persons at increased risk for hepatitis A or its adverse consequences	No
Measles/Mumps/Rubella	**Live** attenuated	Vaccination is recommended for all persons ≥ 12 months old, who are not pregnant or immune-compromised	No evidence but caution should be exercised (see text)
Neisseria meningitides type C	Dead	Routine vaccination is recommended for children.	No
Human Papilloma Virus	Dead	Routine vaccination is recommended for women 14-26 years old and girls 10-13 years old.	No
Rotavirus	**Live** attenuated	Vaccination not contraindicated in contacts of HSCT transplant recipients. Must be given before 12 weeks of age to be safe.	No evidence but caution should be exercised (see text)
Varicella	**Live** attenuated	Vaccination should be administered to all persons ≥ 12 months old, who are not pregnant or immune-compromised and who have a negative or uncertain history of varicella disease with a negative serological screen.	Yes for 42 days post-vaccination (in case of rash)

DTP: vaccine with high dose diphtheria anatoxin and pertussis antigen. dTp: vaccine with low dose diphtheria anatoxin and pertussis antigen. Adapted from Ljungman et al., 2009.

to the transplant patient in case of a rash, for 42 days after vaccination. In that case, contact with the transplant patient should be avoided until all lesions have dried out or disappeared.[4,10] For these reasons, it is generally not practical to vaccinate household members against varicella.

Risk of transmission also exists after vaccination with the live attenuated polio vaccine. Therefore, its use is contra-indicated in household members of a transplant patient. In case of erroneous administration of the live vaccine, close contact should be avoided during four to six weeks.[4] In Belgium, the oral live vaccine is no longer available, except for use in epidemics.[24]

Conclusion

Revaccination after HSCT is recommended because of the reset of the immune system of the patient, to protect them from vaccine-preventable diseases. Furthermore, re-emergence of these infections also poses a risk to the general population.

Time to start vaccination

Several factors influence the time to reconstitution of B- and T-cell immunity, necessary for an adequate response to vaccination. Therefore, the type of transplant (autologous versus allogeneic), the source of the transplanted cells (bone marrow, peripheral blood

stem cells or cord blood), the conditioning regimen (myeloablative versus reduced intensity), the manipulation of the graft (T-cell depleted, CD34 selected or unmanipulated), prevention and treatment strategies for GVHD, the underlying illness, comorbidities, etc., should be taken into account to decide on the optimal timing of revaccination.[19]

Generally, in the first one to three months after HSCT, the number of B- and T-cells is very low to unmeasurable. In the course of three to twelve months after HSCT the B-cell count rises to normal levels, but initially the new B-cells have a disturbed response to antigens, because of lack of CD4+ T helper-cells, necessary for isotype switching.[4,10]

After three months the number of T-cells starts to rise, mainly consisting of CD4+ T cells. The T-cells present in the first months after HSCT are mainly effector/memory T-cells, resulting from peripheral expansion from cells present in the graft, thus with narrow spectrum and directed against antigens encountered in the donor. T-cells newly generated from the infused haematopoietic stem cells and directed against new antigens in the patient, appear only after thymic function resumes, which depends on the patient's age, treatment pre-HSCT, presence of infections, etc., with a median time of six to twelve months after HSCT.[4,10]

Based on this information, start of revaccination is recommended at six months post-HSCT, when B-cells start reappearing. Because of low CD4+ T cell counts, the use of conjugated vaccines is preferred during the first year post-transplantation, to enhance the T-cell help in antibody responses.

An exception is made for influenza vaccination, which may be started earlier (from four months after transplantation), during the flu season, and for the pneumococcal vaccination, which may be started from three months after HSCT.[12,14,17]

Schedule in autologous and allogeneic HSCT

There is a difference in immune reconstitution after autologous versus allogeneic stem cell transplantation. The immunodeficiency is deeper and longer after allogeneic HSCT, due to the need for immunosuppressive drugs and possible GVHD. However, even after autologous stem cell transplantation there is a significant immunodeficiency, especially when the patient was heavily pre-treated for the underlying disease. Since there is little information available concerning the difference in response to vaccination, the vaccination scheme remains the same in different types of transplant (autologous versus allogeneic, myeloablative versus reduced intensity) or source of transplanted cells (cord blood, haploidentical donor, matched unrelated donor or matched related donor).[19] For example, it may be reasonable to delay pneumococcal vaccination to six months and other vaccines to twelve months post-HSCT after cord blood or haploidentical transplantation, in case of ongoing intense immunosuppression and/or active chronic GVHD.

General conditions

Some general conditions should be taken into account before starting vaccination (*Table 1*):

In case of aggressive disease, complete remission post-HSCT should be confirmed before revaccination. On the other hand, in case of more indolent disease, it is worth starting revaccination even if there is still (minimal) evidence of disease.

Furthermore, absolute B-cell count should be at least detectable and the administration of dead vaccines should be planned at least two weeks before or after administration of intravenous immunoglobulin (IVIG).

For live attenuated vaccines, there are a few additional conditions: the administration of live vaccines should be started at the earliest at 24 months post-transplantation and at least three months after administration of IVIG, the absolute CD4+ T-cell count should be >200/μL, there should be no evidence of chronic GVHD and the patient should be off immunosuppressive drugs for at least three months. Careful evaluation of risks and benefits should always be implemented.

It should be noted that GVHD or treatment thereof is not a reason to delay vaccination with dead vaccines, because of the increased risk for infection due to associated immunodeficiency, including a functional hyposplenism with increased risk for bacterial infections such as S. pneumonia and Haemophilus influenza. When vaccinating patients with active GVHD, it may be worthwhile to measure specific antibody levels before and after vaccination, to determine their level of protection and need for booster immunisations.[4,13]

If the patient is receiving >0.5 mg/kg prednisone and/or triple immunosuppressive therapy, vaccination may be temporarily postponed until immunosuppression is reduced to a double combination or prednisone <0.5 mg/kg in order to achieve a better immune response, but for no more than three months.[13]

In children, administration of dead vaccines should never be postponed, because of the high level of exposure to infections in day-care and schools.[13]

Adherence

Another important issue is adherence to the vaccination scheme. One retrospective study showed that 33% of the patients missed at least one vaccine set, and 26% received one set too late, despite the use of telephone reminder calls and vaccination cards.[25] Another interventional study showed that the rate of influenza vaccination in family members at the time of HSCT improved when a short educational session was organised for patients.[26] So, we recommend enhancing adherence by involving the patient by providing them with an overview of the planned vaccination schedule, by having a data manager or nurse coordinating the vaccination times and alerting the treating physician at the time of consultation.

Reimbursement

Today in Belgium, in the transplant setting, there is only reimbursement for the influenza vaccine. Based on the annihilation of previous vaccine immunity by the transplant procedure and the well-documented international guidelines, there is a really unmet need in this already financially challenged population for reimbursement of the whole vaccination program in transplant recipients.

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