Vaccination of Haematopoietic Stem Cell Transplant Recipients: Guidelines of the 2017 European Conference on Infections in Leukaemia (ECIL 7)

Companion paper 2/2

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Summary

Infection is a main concern after haematopoietic stem cell transplantation (HSCT) and a major cause of transplant-related mortality. Some of these infections are preventable by vaccination. Most HSCT recipients lose their immunity to many pathogens as soon as the first months after transplant, irrespective of the pre-transplant donor or recipient vaccinations. Vaccination with inactivated vaccines is safe after HSCT and is an effective way to reinstate protection to many pathogens, especially to those whose risk is especially increased by the transplant procedure, i.e. influenza virus and *Streptococcus pneumoniae*. The response to vaccines in transplant patients is usually lower than that in healthy individuals of the same age during the first months or years after transplant but improves over time to become close to normal from 2 to 3 years after transplant. However, as immunogenic vaccines have been found to induce a response in a significant proportion of the patients as early as three months after transplant, we do not recommend postponing some crucial vaccinations with inactivated vaccines until the patient has no graft-versus-host disease (GvHD) and no immunosuppressants, as patients with GvHD have higher risk of infection and are likely to benefit from vaccination. Another issue is that of providing HSCT recipients the same level of vaccine protection as healthy individuals of the same age in a given country as far as possible. Owing to the risk of vaccine-induced disease, the use of live attenuated vaccines should be limited to specific situations.

INTRODUCTION

Haematopoietic stem cell transplant (HSCT) recipients have a major risk of infections compared to healthy individuals of the same age. Some of these infections are life threatening but preventable by vaccination. This risk is due to complex humoral and cell-mediated deficiencies evolving over time, influenced by transplant procedures and prevention and treatment of Graft-versus-Host disease (GvHD) after allogeneic HSCT and drugs received for autologous HSCT. Specific antibody levels decrease for many pathogens over the first months after transplant, e.g. *S. pneumoniae*¹⁻⁴, *H. influenzae* B^{5,6}, or measles. Between 30% and 100% of the patients lose specific humoral immunity one year after transplant.⁷⁻¹¹

HSCT recipients are able to respond to most vaccines although to a lower extent than healthy individuals during the first months or years after transplant.¹²⁻¹⁴ The IDSA recommendation to consider HSCT recipients as ‘never vaccinated’¹⁵ highlighted the need to offer a full vaccination programme according to age and country recommendations, which take into account local epidemiology.

Several international guidelines, including recommendations for HSCT recipients, have been published.¹⁴⁻¹⁶ In 2017, ECIL 7 decided to provide an update on vaccination of all patients with haematological malignancies, including HSCT recipients.

METHODS

The methods used for developing guidelines are reported in the companion paper.¹⁷ The literature search was carried out with the following keywords: bone marrow or haematopoietic stem cell or peripheral blood stem cell (PBSCT) or umbilical cord blood transplantation (UCBT) AND immunisation, vaccination, vaccine, immune response, donor vaccination, AND/OR *S pneumoniae*, *H influenzae*, *N meningitidis*, tetanus, diphtheria, pertussis, influenza, B hepatitis, poliomyelitis, human

papillomavirus, varicella, zoster, measles, mumps, rubella, yellow fever, dengue, rotavirus, BCG, live-attenuated vaccines. The recommendations were graded according to the ESCMID (Appendix 1) ¹⁸.

RESULTS OF THE LITERATURE REVIEW AND RECOMMENDATIONS

ANTIBACTERIAL INACTIVATED VACCINES

Streptococcus pneumoniae

The ECIL group recommends 3 doses of pneumococcal conjugate vaccine (PCV) from 3 months after HSCT, followed 6 months later by either a 4th dose of PCV in case of GvHD, or one dose of pneumococcal 23-valent polysaccharide vaccine (PPSV23).

The risk of invasive pneumococcal disease (IPD) has been estimated to be 3.8–5 cases after autologous and 8.2–9 cases after allogeneic HSCT for 1,000 transplants, with a higher risk in case of chronic GvHD after allogeneic HSCT and total body irradiation (TBI) after autologous HSCT.^{19,20}

However, these 15-year old data do not reflect current procedures that rarely include TBI but often include maintenance therapies.

HSCT recipients have low specific antibody titres, especially IgG2 and IgG4, and serum opsonophagocytic activity (OPA).¹⁻⁴ Around 6 months after transplant, 85% of them are unprotected^{21,22}. Most patients are infected by vaccine serotypes.^{23,24}

After allogeneic HSCT, the response to PPSV23 is poor, in the range of 20–30% between 6 and 12 months, and 50% from 12 months.²⁵ It is impaired by chronic GvHD and steroids.^{1,26,27} However, when administered at 12 to 18 months after 3 PCV7 doses, PPSV23 induced a response in more than 80% of the patients, including in 42% of previous PCV non-responders.²⁷ Therefore, the administration of PPSV23 is recommended after 3 PCV13 doses to broaden the spectrum of vaccination, except in patients with GvHD in whom response is unlikely. PCV15 is currently under investigation.

In controlled studies of PCVs during the first year of allogeneic HSCT (Table 1), PCV was safe, with very rare severe adverse events (SAE), hypothetically related to PCV.^{21,22,28-30} The response to 3 doses of PCV was 64–98%^{21,22,28,30} and comparable when starting at 3 or at 9 months.²¹ Geometric mean concentrations (GMCs) of specific IgG correlated well with OPA.^{28,31} A fourth PCV13 dose given at 9–12 months still increased the GMCs.²⁸ Patients vaccinated at 3 months may have lower antibody titres at 24 months than those vaccinated at 9 months²¹, but with no difference 8–11 years later and no clear benefit of one PPSV23 dose given 2–11 years later.³² Uncontrolled studies in patients vaccinated after the first year showed consistent results.^{5,6,33,34}

After autologous PBSCT conditioned with BCNU, etoposide and melphalan, the response rate to PPSV23 at 11–12 months was 45%.³⁵ The response rate to 3 PCV7 doses given at 3, 6, and 12 months was higher than 60%.³⁶

Because the risk of IPD starts from the time of transplantation, especially in patients with GvHD, and the patients are able to respond early, we recommend starting vaccination from 3 months with 3 doses of PCV at 1-month interval, followed around 6 months later by either 1 dose of PPSV23, or by 1 dose of PCV in case of chronic GvHD (Table 2). Although there is no safety issue in administering 1 dose of PPSV23 after a fourth dose of PCV, the benefit to be expected is probably marginal in patients with GvHD. In patients with severe hypogammaglobulinemia (<3g/L), severe GvHD, or recent (<6 months) rituximab administration, the response may be low, and they may benefit from alternatives (i.e. antibacterials, immunoglobulins) to vaccination until improvement.

Given the lack of large data sets, no recommendation can be given for subsequent boosts. The assessment of antibody titres should help in defining the best individual option at a given time.

Haemophilus influenzae B (HiB)

The ECIL group recommends 3 doses of HiB vaccine at 1 month interval from 3 months after HSCT, or 3 doses of a combined Diphtheria-Tetanus-Pertussis-HiB vaccine from 6 months.

HiB may cause pneumonia, sinusitis, and bacteraemia early after transplantation^{37,38} owing to unprotective titres of capsular antibodies.^{6,39,40}

The response rate to HiB conjugate vaccines was 80–95%, after 2 or 3 doses^{6,41–44}, even when given from 4 months⁴⁰, after non-myeloablative HSCT⁵ or UCBT³⁴ and was hardly affected by GvHD.^{40,45–47} The benefit of pre-harvest vaccination reported in allogeneic marrow transplant recipients⁴¹ seems marginal for autologous PBSCT.⁴⁸

Considering the early onset of most HiB infections and that patients may respond early, we recommend starting vaccination (3 doses at 1-month interval) from 3 months (Table 2). Whether additional boosters are needed is unknown and the assessment of specific antibodies may inform this decision.

Given the widespread HiB vaccination of healthy children, nontypeable *H influenzae* (NTHi) infections are now predominant.⁴⁹ Data on *Hi* serotypes are warranted after HSCT and NTHi vaccines should be assessed in the future.

Neisseria meningitides

The ECIL group recommends meningococcal vaccination in accordance to country recommendations.

Although invasive meningococcal disease (IMD) has been reported after HSCT⁵⁰, there is a dearth of vaccine data. Between 8 and 20 months after transplant, 86–90%^{51,52} and 38–96%^{51,53} of the patients were unprotected for serogroups C and A.

Different types of vaccines exist in Europe: tetravalent (A, C, Y, W135) conjugate (MCV-4), monovalent C conjugate (MCV-C), and two anti-B vaccines (MenB). In children, 3 doses of MCV-4 administered from 12 months after autologous HSCT or 18 months after allogeneic HSCT provided a 100% response rate.⁵² One dose was poorly immunogenic.⁵³

Although the response to 2 doses of MenB was over 75% in other immunocompromised patients⁵⁴, studies after HSCT are lacking. Nevertheless, as serogroup B recently caused 74% of IMD in Europe⁵⁵, we recommend vaccination against serotypes B and C from 6 months (table 2).

Tetanus and diphtheria

The ECIL group recommends 3 doses of D-T vaccine at 1–2-months interval, from 6 months after HSCT.

Half of the patients lose their protection during the first year of transplantation, irrespective of the donor's and recipient's serology⁵⁶. The response to tetanus vaccine given from day 50, usually at 6–12 months, is 85–100% after 3 doses^{42,56-58}. It is slightly affected by GvHD^{42,57} or conditioning intensity⁵ but may be lower after UCBT.³⁴ The response is comparable after autologous HSCT, except in case of rituximab given before and/or after transplantation.^{44,59,60}

The response rate to diphtheria vaccine was 70–100% after 3 doses given from 3 months after allogeneic HSCT^{33,42,57,59} and 1.5–10 years after autologous HSCT.^{59,60}

Although the vaccine(s) containing high doses of diphtheria toxoid (DT) are not recommended for healthy adults owing to an increased risk of AE, these DT vaccines could provide better protection than low-dose toxoid (Td) vaccines after allogeneic HSCT⁵⁷ (table 2). Therefore, we recommend DT irrespective of age.

Bordetella pertussis

The ECIL group recommends to consider the addition of pertussis toxoid to each dose of D-T vaccine.

Despite the reappearance of pertussis in adults⁶¹, the data regarding whether pertussis causes severe infections after HSCT are limited. However, most HSCT recipients have decreased antibody titres^{34,60} and could be unprotected.⁶²⁻⁶⁵

All anti-pertussis vaccines are combined at least with tetanus-diphtheria. The vaccines licensed for children contain higher amounts of the pertussis toxoid (25 µg; DTaP) than those licensed for adults (2.5-8µg; Tdap). One dose of Tdap provides very low response rates.^{60,66} After 2 or 3 doses of Tdap in adults and of DTaP in children, a median of 17 months after UCBT, all children and 54% of the adults, with no GvHD, developed a ≥ 2 -fold rise in the antibody.³⁴ Although the response to pertussis vaccine

may be low and not persistent⁵⁷, we recommend this vaccination, especially to participate in maintaining herd immunity (table 2).

ANTIVIRAL INACTIVATED VACCINES

Inactivated influenza vaccine (IIV)

The ECIL group recommends one dose of seasonal IIV, yearly at the beginning of flu season, and as long as the patient is judged to be immunocompromised.

Influenza infection is frequent and may be severe in HSCT recipients. One-third of infected patients may develop lower respiratory tract disease, with high mortality rates despite antivirals⁶⁷⁻⁶⁹. The clinical efficacy of one dose of trivalent IIV has been shown in a cohort of 177 HSCT recipients vaccinated 6 months after transplantation.⁷⁰

The response rates were 10–40% within 6 months⁷¹⁻⁷³ and improved to 10–72% with the seasonal^{35,73-76}, and 37–84% with pandemic adjuvanted⁷⁷⁻⁷⁹ or non-adjuvanted⁸⁰ H1N1 vaccines after 6 months, to become close to the response of healthy individuals at 2 years.^{72,73,75,79,80} The response was negatively affected by lymphopenia^{72,81}, hypogammaglobulinemia^{79,81}, GvHD, immunosuppressants^{73,79,81}, and rituximab.⁸⁰ No safety issue was observed.

Most approaches failed to improve this response:

(1) An adjuvanted IIV was not more immunogenic than a non-adjuvanted vaccine after allogeneic HSCT.⁷³

(2) The benefit of 2 doses vs. one dose was suggested both for seasonal⁷² and H1N1 vaccines^{77-79,82} but not found in a randomised study after allogeneic HSCT.⁷⁵

(3) A high-dose (60µg) antigen trivalent IIV – not available in Europe – was more immunogenic but induced more injection-site reactions than a standard-dose (15 µg) vaccine after allogeneic HSCT⁸³.

(4) GM-CSF administered with the seasonal vaccine improved the response to influenza B but not to H1N1 or A/H3N2.⁷⁶

(5) Donor or recipient pre-transplant vaccination improved seroprotection during the first 2 months but not the response to later vaccination.⁷⁴

The clinical benefit and safety of IIV after HSCT largely support the vaccination (Table 2). A second dose might be beneficial in patients cumulating factors of poor response (GvHD, lymphopenia) or during outbreaks in patients vaccinated within 6 months of transplantation. HSCT recipients should benefit from additional measures (e.g. respiratory isolation, rapid diagnostic tests in case of symptoms, and post-exposure antivirals).⁸⁴

The intranasal influenza live-attenuated vaccine (LAV) is contra-indicated after HSCT.

Inactivated poliomyelitis vaccine (IPV)

The ECIL group recommends 3 doses of IPV given at 1–2-month interval from 6–12 months after HSCT. After HSCT, 30–100% of patients between 6–12 months lost their immunity to polio.^{85–88} Owing to the risk of post-vaccinal poliomyelitis with the oral LAV, only IPV should be used (DIII). The response to 3 doses of IPV given from 6 months was 80%-100%, affected slightly by GvHD^{33,42,57,58,86,89}, and long lasting, except in children transplanted before the age of 10 years (Table 2).⁹⁰

Hepatitis B virus (HBV) vaccine

The ECIL group recommends that patients who were negative for HBV before transplantation and patients who were vaccinated before transplant but lost their immunity at 6 months should be vaccinated from 6–12 months after HSCT according to country recommendation.

The ECIL group published guidelines for the management of viral hepatitis, including HBV, in 2016.⁹¹

There are three different goals of HBV vaccination after HSCT:

- a) To offer a similar protection as the healthy individuals according to country recommendations, even in patients vaccinated before transplant but who may lose their immunity
- b) To protect the recipient from getting HBV from an anti-HBc-positive donor
- c) To decrease the risk of reverse seroconversion in recipients previously HBV-infected

Although the donor can transfer his/her HBV immunity, and the recipient may have been vaccinated before the transplantation, half of the recipients lose seroprotection within 6 months^{92,93}, and 90% were unprotected at 5 years.⁹⁴

After 3 doses of HBV vaccine, started at a median of 23 months after allogeneic HSCT, seroconversion was 64%⁹³, impaired by age and chronic GvHD but not by T-cell depletion or rituximab given at a median of 16 months before. The benefit of an increased antigen dose (40–80 µg) is unknown after HSCT.

An anti-HBc positive donor can transmit HBV to the recipient, even if negative in nucleic-acid testing.⁹¹ In this case, the ECIL group recommended, on the basis of a retrospective study,⁹⁵ vaccinating the recipient before transplantation.⁹¹ Although not assessed after HSCT, an accelerated schedule of vaccination (day 0, 10, 21) may elicit a 70% response rate in healthy individuals (Table 2).⁹⁶ In previously HBV-infected recipients, in addition to antivirals⁹¹, vaccination might prevent reverse seroconversion.^{97,98}

Finally, a regular reassessment of anti-HBs titres is recommended from 6 months after HSCT, and 1–2 months after 3 vaccine doses. As the response is lower than in healthy individuals, non-responders (anti-HBs < 10 mIU/mL) should be identified to consider a second series later on, although its benefit is uncertain.

Human papillomavirus (HPV)

The ECIL group recommends to follow guidelines for general population in each country from 6-12 months after transplant.

HSCT recipients may develop HPV-associated tumours ⁹⁹, especially in case of chronic GvHD.¹⁰⁰ HPV vaccination is recommended for healthy adolescents or young adults to prevent HPV-related malignancies in most countries. Twenty previously unvaccinated children received 3 doses of the quadrivalent vaccine from 6–12 months after HSCT with only minor AE. The seroconversion rate was close to 100%.¹⁰¹ Although there is no large-scale data on vaccine efficacy after HSCT, no safety issues are expected ^{102,103} and HPV vaccination should be beneficial in the young patients (Table 2). Whether it is beneficial in older recipients remains to be assessed.

General issues on safety of inactivated vaccines after HSCT

Only prospective trials can properly assess AE and SAE. We mainly focused our safety review on pneumococcal and influenza vaccines and those assessed after HSCT in larger prospective trials. *After IIV*, mild injection-site reactions are common and may increase with higher dosage per shot ⁸³ but resolve quickly. In trials including healthy controls, there is no evidence that AE or SAE were more frequent after HSCT ^{79,82,104,105} and one study even suggested a decreased incidence of AE after intradermal injection of IIV as compared to healthy controls.¹⁰⁵

After anti-pneumococcal vaccination, AEs observed in HSCT recipients did not seem to be more frequent than in healthy individuals. In HSCT children, there were more local or systemic reactions after the third ²² or the fourth ²⁸ PCV dose.

In summary, AE or SAE after inactivated vaccines are not different in nature, severity, duration, or frequency in HSCT patients and healthy individuals and should not limit vaccination. Additionally, in prospective trials, there was no evidence that vaccination triggers or worsens GvHD.^{28,78}

LIVE-ATTENUATED VACCINES

LAVs are, in general, contraindicated in immunocompromised patients owing to the risk of vaccine-transmitted disease.¹⁰⁶ However, when there are no inactivated alternatives, they may be carefully considered based on the risk/benefit balance.

The ECIL group recommends varicella and MMR LAV from 24 months, only in seronegative patients with no GvHD, no immunosuppressants, no relapse, and no recent administration of immunoglobulins.

Varicella-zoster virus (VZV) vaccines

VZV infections may be life threatening after HSCT. The risks are primary varicella infection (chickenpox) in seronegative patients and shingles and postherpetic neuralgia in seropositive patients. Acyclovir/valacyclovir prophylaxis given for 1 year after allogeneic HSCT – longer in case of GvHD – and for 3–6 months after autologous HSCT is effective, cheap, and safe for preventing reactivation in seropositive patients.¹⁰⁷

At the ECIL 7 meeting, only LAVs against VZV were available: the varicella vaccines (LAVV), and the zoster vaccine (LAZV) which contains much higher titres of viruses than the LAVV. Fatal disseminated vaccine-induced VZV infections have been occasionally reported both with LAVV after HSCT¹⁰⁸ or intensive chemotherapy,¹⁰⁹ and with LAZV, even 6 months after stopping chemotherapy.¹¹⁰

Several observational studies with LAVV have been performed in seronegative HSCT recipients, with 1 to 3 doses given from 3¹¹¹ to 4–5 months¹¹² after autologous HSCT, and from 12-24 months¹¹³ in selected allogeneic HSCT recipients¹¹⁴ or for zoster prophylaxis in seropositive recipients.¹¹⁵ No SAE was reported. However, some patients developed vaccine-related varicella.^{112,114} The response rate was around 65%^{111,112,114} with some clinical protection, without a clear benefit of a second dose.¹¹¹⁻

¹¹⁴ This benefit may, however, be different in VZV seronegative or seropositive patients before transplantation. As there is no inactivated alternative, we recommend LAVV in carefully selected

seronegative patients for varicella prevention. Patients should be informed of the risk of varicella-like rash within three weeks, to receive antivirals if necessary.

Two retrospective studies were performed with the LAZV administered at a median of 21–27 months.^{116,117} The vaccine was safe and the studies suggested a reduced incidence of VZV infection^{116,117}. Additionally, a recent study, not available at time of ECIL 7, showed that LAVZ was safe when given from 24 months after autologous HSCT in myeloma patients receiving lenalidomide¹¹⁸, although 14% of the patients developed upper respiratory tract infections of unknown origin. Recently, two inactivated zoster vaccines have been developed. A subunit-adjuvanted zoster vaccine is approved for prevention of shingles in adults over 50 years.¹¹⁹ Autologous seropositive HSCT recipients who received 3 doses from day 50 developed good and persistent responses but without reduction of herpes zoster.¹²⁰ A heat-treated, zoster vaccine (V212) was shown to be poorly immunogenic after allogeneic HSCT¹²¹, but it reduced the incidence of herpes zoster vs. placebo after autologous HSCT¹²². This latter vaccine can be administered much earlier than LAVZ.

Given the close availability of inactivated vaccines and since antiviral prophylaxis is effective and safe, we consider that inactivated vaccines should be preferred to LAVZ. Additional data are needed in allogeneic HSCT.

Measles, Mumps, Rubella (MMR)

Although MMR vaccines are mostly combined, the concerns raised by each of these viruses are different. Measles may be life-threatening¹²³⁻¹²⁵ and the decreased coverage in healthy children led to outbreaks worldwide. Mumps or rubella infections are not life-threatening but a pregnant HSCT recipient may transmit rubella to her baby. The probability of becoming seronegative to measles, mumps and rubella 5 years after allogeneic HSCT is 60%, 73%, and 52%, respectively,⁸ and it is higher after vaccination than after natural infection^{7,8,10,124}. Several open studies assessed MMR vaccines (1

or 2 doses), mostly from 24 months after transplantation in children ^{7,33,34,52,57,70,126} and adults without GvHD and immunosuppressants.^{7,34,124} Vaccination was started earlier (9–18 months) during a Brazilian outbreak, including in patients receiving low-grade immunosuppression.¹²⁴ No SAE was reported. The response rates were 65–100% for measles, 50–87% for mumps, and 75–100% for rubella. In a regular setting, the group recommends that the vaccination be restricted to seronegative patients filling the conditions mentioned in table 3. In large community outbreaks, vaccination also without immunity testing or in seropositive individuals can be considered balancing the potential benefits and risks to the patient's situation including the time from transplant, age, and previous vaccination history. Patients with ongoing GVHD and/or immunosuppression should not be vaccinated.

Yellow fever (YF) vaccine

YF vaccination may be required for patients living or travelling in endemic areas. In healthy individuals, YF vaccine can cause a life-threatening disease.¹²⁷ After HSCT, the risk/benefit ratio of vaccination should be cautiously weighed. Patients should be discouraged from travelling in endemic areas during the first years after transplant. Some carefully selected patients (no immunosuppression for 2 years, no active GvHD, normal CD4 counts and IgG levels) were vaccinated at a median of 3 to 9 years after transplantation, with no SAE.¹²⁸⁻¹³⁰ Most patients responded. HSCT recipients who themselves, or whose donors, were vaccinated before transplant may retain protection years after transplant ^{129,131}, suggesting to test these patients before they travel to endemic areas.

Other LAVs

Rotavirus vaccines can lead to severe diarrhoea in immunocompromised infants ¹³² and are contraindicated after HSCT. BCG is also contraindicated owing to the risk of disseminated disease. There are no data on dengue or rabies vaccine after HSCT.

SPECIFIC ISSUES ANALYSED BY THE GROUP

Should we have different vaccination programmes after different HSCTs?

Although the infection risks are lower after autologous than allogeneic HSCT, the same revaccination programmes are generally proposed. However, most studies on autologous HSCT were done before the era of rituximab and not in myeloma patients representing a large proportion of today's autologous HSCT population. Vaccination schedules should be reassessed based on current transplant procedures. Two recent publications, not available at time of ECIL 7, show that vaccination with inactivated vaccines under lenalidomide therapy after autologous HSCT is safe ^{122,133} and efficient ¹³³.

Until 2000, most allogeneic HSCTs were transplanted from HLA-identical siblings with myeloablative conditioning. Nowadays, transplant cohorts are more heterogeneous, and some subgroups are not represented enough in studies to develop specific recommendations. However, GvHD remains the main driver of immune recovery ¹³⁴, but its negative impact, although documented in some vaccines, is marginal for the immunogenic ones. As patients with GvHD are at higher risk of infections, they might benefit more from vaccine protection, and prospective studies did not report worsening of GvHD after vaccination. On the other hand, the longer we wait after transplant, the better the vaccine response.^{72,73,75,79,80} Therefore, on the basis of a poor expected response in case of low CD4+ (< 200/cm) ⁷⁹ or CD19 + ⁵⁷ cell counts, some centres delay vaccination until the patient fulfils the biological criteria they consider as markers of full immune recovery. However, there are no data to support any specific lymphocyte level for starting vaccines, and delaying the vaccination knowing that the patient can respond well, especially to T-cell dependent vaccines, early after transplant ^{21,25,58} increases the at-risk period for the patient. Therefore, although a lower response can be sometimes expected, we recommend not delaying vaccination except in specific situations listed below.

Should some HSCT recipients be transiently or definitely excluded from vaccination programmes?

Patients with severe GvHD or hypogammaglobulinemia are usually excluded from vaccine studies because they are unlikely to respond. Although gammaglobulin titres <4 g/L decreased the response to PCV7, the response rate was still 38%²¹, suggesting a potential benefit. However, in case of severe hypogammaglobulinemia (< 3 g/L), alternatives should be considered until recovery. There are no data on patients receiving immunoglobulins.

Infused immunoglobulins could inhibit viral replication and consequently impair response to LAV.¹³⁵ In this case, even if the patient fulfils other precautionary criteria for LAV, these vaccines should not be administered at least 3 months and ideally 8 months after the last immunoglobulin infusion.¹³⁶ As the response to LAV can be impaired by circulating immunoglobulins, it is recommended that the vaccine response be checked in order to consider an additional dose.

Rituximab induces immediate and long-term B-cell depletion, with prolonged hypogammaglobulinemia in 20–30% of the patients.¹³⁷ Rituximab is widely used before and after autologous HSCT for B-cell lymphoma and in allogeneic HSCT for conditioning, EBV reactivation, or GvHD. Rituximab strongly impairs the vaccine response after allogeneic HSCT^{6,53,80} even as long as 28 months later⁵³ and in case of conjugate vaccines.⁶ Autologous HSCT recipients vaccinated 6–8 months after the last dose of rituximab demonstrated acceptable, although impaired, responses with T-cell dependent (e.g. tetanus, PCV), but not with T-cell independent, antigens (e.g. PPSV23).^{6,138} After autologous and allogeneic HSCTs, we recommend that vaccination be delayed at least for 6 months after the last dose of rituximab and the antibody response be assessed if necessary, as it is uncertain. Similar issues are expected with other anti-B monoclonal antibodies.

Should we assess individual vaccine responses in HSCT recipients?

Routine antibody titre assessment is futile when the expected response is close to 100% but can be useful to evaluate the need for certain vaccines (e.g. HBV at 6 months after transplant, MMR and LAVV at 24 months after transplant), to decide the need for vaccination or for a second dose or series in the presence of predictors of poor response (e.g. severe GVHD, rituximab), and to decide on booster administration during long-term follow-up (e.g. HiB at 5-10 years after the initial series, DTP every 3-5 years). Pneumococcal antibodies can be assessed at 24 months, although the practical consequences of such assessments – boost, or full revaccination program - are to be prospectively evaluated.

Should the donor be vaccinated before donation?

The donors should be vaccinated according to age and country recommendations for healthy individuals. Additional vaccination just before harvest is an appropriate strategy to improve the response of the recipient by transferring antigen-reacting T-cells (Table 4).¹³⁹ However, it raises feasibility and ethical issues when proposed only for the purpose of donation. Moreover, the benefit only exists for T-cell dependent vaccines^{30,42,140,141} and is transient.³⁰ Therefore, we do not recommend preharvest vaccinations, except for HBV vaccine in previously mentioned situations.⁹¹ LAV vaccines are contra-indicated four weeks before donation owing to the risk of vaccine-disease transmission even though the duration of vaccine-induced viremia is shorter for some LAVs.¹⁵

SPECIFIC CONSIDERATIONS FOR THE FAMILY AND CLOSE CONTACTS OF TRANSPLANT

RECIPIENTS

To avoid infection transmission to the patient, individuals in close contact with HSCT recipients should be either naturally immunised or vaccinated according to country recommendations for their age, especially against VZV and MMR, and additionally receive IIV yearly. These and other

recommendations, contraindications, and precautions for the family and close contacts are reported in Table 5.

Recommendations for vaccination of health-care workers in haematology wards are presented in the companion paper.¹⁷

AREAS FOR FUTURE RESEARCH

The diversity in transplant procedures is increasing and HSCT is expanding to many countries, which may have specific epidemiologies of diseases preventable by vaccination. The ECIL group clearly supports prospective studies and recommends that subgroups (e.g. haploidentical or UCBT recipients) be specifically assessed for their vaccine response. The impact of anti-B monoclonal antibodies before and after transplant should be further evaluated. The optimal long-term programme should also be explored, and new vaccines should be assessed. The use of combined vaccines should be studied, especially in children, to decrease the number of injections and visits.

CONCLUSION

HSCT recipients respond to vaccines. Inactivated vaccines after HSCT are safe and a rigorous vaccination programme should be offered to all allogeneic and autologous HSCT recipients. Postponing vaccination should be restricted to very specific situations. The programme should take in account the risks in a specific community. Vaccines may save lives and avoid unnecessary hospitalisations.

Contributors

CC and PL recruited the experts and compiled the recommendations. All authors were involved in the literature search, development of recommendations and conception of the manuscript. All authors revised the manuscript and gave final approval.

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Declaration of interests

CC has received grants from Merck and Astellas and has been a scientific adviser for Merck. RDB has received personal fees from Gilead and Merck. MM has been a scientific adviser for Biotest and has received payment for lectures and travel expenses from MSD, Janssen, Pfizer and Astellas, and has received travel fees from Gilead. TL has received grants from Gilead, and non-financial support and personal fees from Gilead, Astellas, MSD and Basilea. PL has received grants from Merck and Astellas and has been a scientific adviser for Merck. SC, HDL, SE, GG, CK and DE declare that they have no conflict of interests.

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Table 1: Main controlled studies assessing the efficacy of pneumococcal conjugate vaccines (PCV) during the first year after allogeneic haematopoietic stem cell transplant

Reference	Vaccine	No. Pts (evaluable) Age	Study design and immunisation schedule	Criteria for response	Percentage of responders and comments
Molrine et al. ³⁰	PCV7	96 (65) 2–64 y	Three doses at 3, 6, and 12 months (+/- donor vaccination by randomisation)	≥ 0.5 µg/mL for all 7 serotypes	At 13 months: 64–75% Benefit of donor vaccination for response to the first 2 doses, not for the third
Kumar et al. ¹⁴⁰	PCV7	64 (44) ≥ 18 y	Donor/recipient pairs randomised for either PPS23 or PCV7: 1 preharvest dose to the donor, 1 dose of the same vaccine to the recipient at 6 months. Assessment at 6 and 12 months for PCV7 antigen antibodies	≥ 0.35 µg/mL for ≥ 1 serotype	Better immunogenicity of PCV7 vs. PPSV23 At 6 months: 38.6% vs. 0% At 12 months: 90.9% vs. 55.6%
Meisel et al. ²²	PCV7	53 (43) 1–16 y	3 doses at 1-month interval from 6 to 10 months	≥ 0.5 µg/mL for all 7 serotypes	55.8% after 2 doses, 74.4% after 3 doses
Cordonnier et al. ²¹	PCV7	158 (114) 5–65 y	3 doses, at 1-month interval. Randomisation for starting early (3, 4, 5 months) or late (9, 10, 11 months) after HSCT	≥ 0.15 µg/mL for all 7 serotypes	Response after early vaccination was not inferior to late vaccination: 79% vs. 82%. Chronic GvHD and donor age impaired the response At 24 months after transplant: GMCs and response rates were lower in the early group
Cordonnier et al. ²⁸	PCV13	251 (207) 2–71 y	Open study: 3 doses, at 1-month interval, from 4 months, then a 4 th dose 6 months after the 3 rd dose	IgG GMFR and ≥ 0.35 µg/mL for all 13 serotypes	GMFR significantly increased from baseline to after the 3 rd dose: Response rate ≥ 0.35 µg/mL: 89.7%–98.0% Positive correlation between IgG GMCs and OPA GMTs The GMCs still increased after the 4 th dose No difference between myeloablative and non-myeloablative conditioning regimens

GMC: Geometric mean concentration
GMFR: Geometric mean fold rises
OPA: Opsonophagocytic activity
GMT: Geometric mean titres
PCV: Pneumococcal conjugate vaccine

Table 2: ECIL 7 recommendations for vaccination of HSCT recipients with inactivated vaccines

Vaccine	Recommendation and grading in allogeneic HSCT	Recommendation and grading in autologous HSCT	Paediatric specificities
13-valent pneumococcal conjugate vaccine (PCV13) (L*)	From 3 months after transplant: 3 doses of PCV13 (or subsequent, broader spectrum, conjugate vaccines) at 1-month interval (A I) . In case of chronic GVHD, considering the low response to PPSV23, an additional dose of PCV instead of a dose of PPSV23 is recommended 6 months after the 3 rd dose of PCV (B II u) .	Same initial schedule as for allogeneic HSCT: 3 doses of PCV13 given from 3 months after transplant, at 1-month interval (A I) .	The same schedule is recommended in children and adults. Children usually respond better than adults, close to healthy children ²² , but often develop vaccine-related fever and local reactions ²⁸ .
23-valent polysaccharide pneumococcal vaccine (PPSV23) (L)	At 12 months: If no chronic GVHD requiring immunosuppressors: 1 dose of PPSV23, not earlier than 8 weeks after the last PCV (B I) .	One dose of PPSV23 at 12 months after transplantation and not earlier than 8 weeks after the last PCV (B I) .	The same schedule is recommended for children and adults.
<i>H. influenzae B (HiB)</i> vaccine (L)	From 3 months after transplant: 3 doses at 1-month interval (B II r) . No preference on the type of vaccine (conjugated with tetanus-protein or diphtheria-protein). Alternatively, in order to give a combined vaccine and decrease the overall number of vaccine doses, administer 3 doses of a Diphtheria-Tetanus-Pertussis-HiB vaccine from 6 months (B II r) .	Same recommendation and same grading as for allogeneic HSCT.	The same schedule is recommended for children and adults. Children usually respond better than adults ⁶ .
<i>N. meningitidis</i> vaccines (L)	From 6 months after transplantation: at least 2 doses of either a mono- or tetravalent C vaccine (B II u) and meningococcal B vaccine	Same recommendation and grading as for allogeneic HSCT.	The same schedule is recommended for children and for adults. Children and adolescents are the main at-risk

	(B III) , in accordance with country recommendations for a given age and particularly for risk groups such as students living in campus, travellers, or soldiers		population.
Tetanus-Diphtheria vaccine (L)	From 6 months: 3 doses at 1–2-month interval (B II u) . DT vaccines should be preferred over Td vaccines both in children and adults (C III) Booster doses to be administered according to country recommendations.	Same recommendation and grading as for allogeneic HSCT.	The same schedule is recommended for children and for adults. Children usually respond better than adults.
Acellular pertussis vaccine (L)	The addition of pertussis toxoid to the Diphtheria-Tetanus vaccine, 3 doses at 1–2-month interval, should be considered (C III) . Although there is no specific study with DTaP in adult HSCT recipients, considering the poor response to Tdap, the DTaP that contains a higher dose of pertussis toxoid than the Tdap should be preferred both in children and adults (C III) .	Same recommendation and grading as for allogeneic HSCT.	The same schedule is recommended for children and for adults. Previously unvaccinated HSCT infants should be vaccinated as soon as possible. Children seem to respond better than adults.
Inactivated influenza vaccine (IIV) (C*)	From 6 months: annual seasonal IIV, 1 dose, at the beginning of flu season during the first years following transplant, at least until 6 months after stopping any immunosuppressor and as long as the patient is judged to be immunocompromised (A II r) or life-long (B II r) . A second dose given 3–4 weeks after the first one may be considered in patients with	From 6 months: annual seasonal IIV, 1 dose, at the beginning of flu season, at least as long as the patient is judged to be immunocompromised (B II r) . In the setting of a community outbreak, IIV can be given from 3 months after transplant. In that case, a second dose given 3–4 weeks	Children aged 6 months to 8 years, receiving IIV for the first time after transplantation should receive a second dose at least 4 weeks after the first dose (B II t) . For children older than 9 years, a 2 nd dose of vaccine after 3–4 weeks may be considered in patients with severe GVHD or low lymphocyte counts (B II

	<p>severe GVHD or low lymphocyte counts (B II r).</p> <p>In the setting of a community outbreak, IIV can be given from 3 months after transplantation. In that case, a second dose given 3–4 weeks later is likely to be beneficial (B II r).</p>	<p>later is likely to be beneficial (B II r).</p>	<p>r).</p>
Inactivated poliomyelitis vaccine (IPV) (L)	<p>From 6 to 12 months: 3 doses of IPV given at 1–2-month interval (B II u).</p> <p>Booster doses should be administered according to country recommendations.</p>	<p>Same recommendation and grading as for allogeneic HSCT.</p>	<p>The same schedule is recommended for children and for adults. Children usually respond better than adults. However, owing to a higher risk for losing polio immunity in the years after initial vaccination for patients transplanted before the age of 10 years, we recommend a regular assessment of anti-polio Ab titres to assess persistent immunity and consider boosters.</p>
Hepatitis B virus (HBV) vaccine (L)	<p><i>Before transplant:</i> HBV-negative patients for all markers transplanted with a graft from an anti-HBc positive donor should be vaccinated before transplantation if possible (B III) and may additionally receive anti-HBV immunoglobulins.</p> <p><i>After transplant, from 6 months:</i></p> <p>a) Patients who were negative for HBV before transplantation <i>and</i> patients who were vaccinated before transplant but lost their immunity at 6 months should be</p>	<p><i>After transplant, from 6 months:</i></p> <p>a) Patients who were negative for HBV before transplantation <i>and</i> patients who were vaccinated before transplant but lost their immunity at 6 months should be vaccinated according to country recommendation and age (3 doses: 0, 1, 6 mo, from 6–12 mo)</p> <p>(B II t).</p> <p>b) Patients infected with HBV before HSCT (HBsAg- and anti-HBc +) should</p>	<p>The same schedule is proposed for children and for adults, except that children should receive a standard paediatric dose (10 µg) of vaccine while adolescents should receive 20 µg of the vaccine according to the summary of product characteristics of each vaccine.</p>

	<p>vaccinated according to country recommendation (3 doses: 0, 1, 6 mo, from 6–12 mo)</p> <p>(B II t).</p> <p>b) Patients infected with HBV before HSCT (HBsAg- and anti-HBc+) should be assessed regularly for anti-HBs Ab titres and be vaccinated if they have unprotective titres (B III).</p> <p>If anti-HBs titres are <10 mIU/mL 1–2 months after the initial series of 3 vaccine doses, an additional series of 3 doses should be considered.</p>	<p>have anti-HBs Ab titres assessed regularly and be vaccinated if they have unprotective titres (B III).</p> <p>If anti-HBs titres are <10mIU/mL 1-2 months after the initial series of 3 vaccine doses, an additional series of 3 doses should be considered.</p>	
Human papillomavirus (HPV) vaccine (L)	<p>From 6-12 months: follow recommendations for general population in each country (BIIu)</p>	<p>Same recommendation and grading as for allogeneic HSCT.</p>	<p>Follow age recommendations for general population in each country</p>

*L: Guideline proposed on the basis of clinical endpoints. C: Guideline proposed on the basis of laboratory endpoints.

Table 3 : ECIL 7 recommendations for vaccination of HSCT recipients with live-attenuated vaccines (LAV)

Vaccine	Recommendation and grading for allogeneic HSCT	Recommendation and grading for autologous HSCT	Paediatric specificities
All LAV are contraindicated as long as the patient is considered severely immunocompromised.			
Varicella LAV (LAVV) (C*)	<p>LAVV is contraindicated in HSCT recipients with active GVHD, relapse of the underlying disease, or ongoing immunosuppression (D III).</p> <p>From at least 24 months: One dose of LAVV can be considered in VZV seronegative adult patients with no GvHD, no ongoing immunosuppression, no relapse of the underlying disease, and no treatment with immunoglobulins during the previous months** (B II r).</p> <p>The addition of a 2nd dose in adults may be considered in patients who were seronegative before HSCT or had no history of VZV infection.</p>	Same recommendation as after allogeneic HSCT.	Two doses (instead of 1 dose in adults) of LAVV can be considered in children meeting the same limitation criteria than in adults (B II r) . The interval between 2 doses should be the one recommended in the official label.
Zoster LAV	Not recommended (DIII)	Not recommended (DIII)	Not recommended (DIII)
Measles-mumps-rubella (MMR) (L*)	<p>From 24 months: HSCT recipients should have MMR Ab titres tested (B II u)</p> <p>Consider vaccination only in patients with no GvHD, no immunosuppression, no</p>	Same recommendation as after allogeneic HSCT.	Owing to a lower response in children, 2 doses – instead of one in adults – should be considered in children, at least 4 weeks apart.

	<p>relapse of the underlying disease, and treatment with immunoglobulins during the previous months**.</p> <p>Seronegative patients for measles should receive 1 dose of MMR (B II u).</p> <p>HSCT recipient women who are seronegative for rubella and of childbearing potential should receive 1 dose of MMR with the same precautions (C II u).</p> <p><i>In case of measles outbreak</i>, MMR vaccination could be considered from 12 months after transplantation in patients with low-grade immunosuppression (C III)</p>		
Yellow fever (L)	<p>YF vaccine should be considered cautiously only in patients with no active GvHD, no immunosuppressive drugs, and if travel to endemic area cannot be avoided, before 24 months (DIII) or from 24 months (CIII).</p>	<p>YF vaccine should be considered cautiously, if travel to endemic area cannot be avoided, before 24 months (DIII) or from 24 months (CIII).</p>	<p>Although there are no data in children, the same schedule is recommended for children and for adults.</p>

**L: Guideline proposed on the basis of clinical endpoints. C: Guideline proposed on the basis of laboratory endpoints.

**The interval between the last immunoglobulin administration and the administration of a varicella or MMR live-attenuated vaccine should be at least 3 months, ideally between 8 and 11 months.

Table 4 : Main data on donor immunisation before allogeneic HSCT donation.

Vaccine	Benefit of donor immunisation before donation on the post-transplant vaccine response of the recipient	References
PCV	Improved after early vaccination, no more significant at 12 months	29,30
PPSV23	No benefit	29,141
<i>H influenzae B</i>	Improves the response of early (d-1, d50) vaccination	141
<i>N meningitidis</i>	<i>Unknown</i>	
Tetanus-Diphtheria	Tetanus: Improves the response of early (d-1, d50) vaccination Diphtheria: Increases antibodies concentrations.	42,141
Acellular pertussis	<i>Unknown</i>	
Poliomyelitis	No benefit	42
Inactivated influenza	No difference in antibody levels after vaccination during the first 6 months after transplant No improved response when vaccinated at 6 months	74
Hepatitis B virus	Poor response to HBsAg with or without donor vaccination in Storek et al.	141,142

	Improved response to KLH (keyhole limpet hemocyanin) in Wimperis et al.	
Human papillomavirus	<i>Unknown</i>	

Table 5: ECIL 7 recommendations for family and close contacts of stem cell transplant recipients.

Vaccine	Recommendation	Grading
General recommendation	It is recommended that the family members and close contacts of HSCT recipients be immunised or vaccinated according to the age and country recommendation,	
Influenza inactivated vaccine (IIV)	It is recommended that family members and close contacts of HSCT recipients be vaccinated with IIV beginning the season before and first season after transplantation and annually as long as the patient is considered immunocompromised.	AII CIII
Contraindications or specific precautions		
Live-attenuated influenza vaccine	The nasal LAV influenza vaccine is contra-indicated in the close contacts of HSCT recipients during the first months of transplant or if the patient has GvHD.	BIII
Varicella or measles-mumps-rubella vaccine to a close contact of the patient	In case a close contact of an HSCT recipient needs LAV for varicella because he/she is seronegative, he/she should be separated from the patient in case of post-vaccine disease.	
Rotavirus vaccine in close infants	Within 4 weeks following rotavirus vaccination of infants, HSCT recipients should have no contact with the	

	stools or diapers of the children owing to the risk of contracting the vaccine virus.	
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