Vaccination and haematological malignancies 2

Vaccination of haemopoietic stem cell transplant recipients: guidelines of the 2017 European Conference on Infections in Leukaemia (ECIL 7)

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Infection is a main concern after haemopoietic 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 various 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 transplantation and is an effective way to reinstate protection from various pathogens (eg, influenza virus and *Streptococcus pneumoniae*), especially for pathogens whose risk of infection is increased by the transplant procedure. The response to vaccines in patients with transplants is usually lower than that in healthy individuals of the same age during the first months or years after transplant, but it improves over time to become close to normal 2–3 years after the procedure. However, because immunogenic vaccines have been found to induce a response in a substantial proportion of the patients as early as 3 months after transplant, we recommend to start crucial vaccinations with inactivated vaccines from 3 months after transplant, irrespectively of whether the patient has or has not developed graft-versus-host disease (GvHD) or received immunosuppressants. Patients with GvHD have higher risk of infection and are likely to benefit from vaccination. Another challenge is to provide HSCT recipients the same level of vaccine protection as healthy individuals of the same age in a given country. The use of live attenuated vaccines should be limited to specific situations because of the risk of vaccine-induced disease.

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Introduction

Recipients of haemopoietic stem cell transplant (HSCT) have an increased risk of infections compared with 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 that evolve over time, transplant procedures, and prevention and treatment of graft-versus-host disease (GvHD) after allogeneic HSCT and the administration of drugs for autologous HSCT. During the first months after transplantation, specific antibody amounts decrease for various pathogens, including *Streptococcus pneumoniae*,[1–4] *Haemophilus influenzae* type b,[5,6] and measles. Between 30% and 100% of the patients lose specific humoral immunity 1 year after transplantation.[7–11]

HSCT recipients can respond to most vaccines but to a lower extent than healthy individuals during the first months or years after transplantation.[12–14] The recommendation from the Infectious Diseases Society of America to consider HSCT recipients as never vaccinated[15] highlighted the need to offer a full vaccination programme according to age and country recommendations that take into account local epidemiology. Several international guidelines, including recommendations for HSCT recipients, have been published.[14–16] In 2017, the European Conference on Infections in Leukaemia (ECIL 7) decided to provide an update on vaccination of all patients with haematological malignancies, including HSCT recipients.

Guideline development overview

We provide the methods used for developing guidelines in the companion paper.[17] We did the literature search by using the following keywords: "bone marrow" OR "haemopoietic stem cell" OR "peripheral blood stem cell" OR "umbilical cord blood transplantation" 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". We graded the recommendations according to the European Society of Clinical Microbiology and Infectious Diseases (appendix).[18]

Antibacterial inactivated vaccines

Streptococcus pneumoniae

The ECIL group recommends three doses of pneumococcal conjugate vaccine (PCV) 1 month apart, from 3 months after HSCT, followed by a fourth dose of PCV in case of GvHD, or one dose of pneumococcal 23-valent polysaccharide vaccine (PPSV23) 6 months later.

The risk of invasive pneumococcal disease has been estimated to be 3·8–5·0 of 1000 transplant cases after autologous HSCT and 8·2–9·0 of 1000 transplant cases after allogeneic HSCT, and a higher risk is associated with chronic GvHD after allogeneic HSCT and with total body irradiation after autologous HSCT.[19,20] However,

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The European Conference on Infections in Leukaemia (ECIL) group, a joint venture of the Infectious Diseases Working Party of the European Society for Blood and Marrow transplantation (EBMT), the Infectious Diseases Group of the European Organisation for Research and Treatment of Cancer (EORTC), the European Leukaemia Net (ELN), and the Immunocompromised Host Society (ICHS)

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these 15-year-old data do not reflect current procedures that rarely include total body irradiation but often include maintenance therapies.

HSCT recipients have low specific antibody titres, especially immunoglobulin (Ig) G2 and IgG4 and serum opsonophagocytic activity.[1–4] About 6 months after transplantation, 85% of patients are unprotected.[21,22] Most patients are infected by vaccine serotypes.[23,24] After allogeneic HSCT, the response to PPSV23 is poor, ranging from 20% to 30% between 6 and 12 months, and 50% after 12 months after the procedure.[25] It is impaired by chronic GvHD and steroids.[1,26,27] However, when administered 12–18 months after three doses of PCV7, PPSV23 induced a response in more than 80% of the patients, and in 42% of patients who previously did not respond to PCV.[27] Therefore, the administration of PPSV23 is recommended after the administration of three doses of PCV13 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), the vaccine was safe, and rare severe adverse events (SAE) were hypothetically related to it.[21,22,28–30] The response to three doses of PCV was 64–98%[21,22,28,30] and comparable between patients who were vaccinated from 3 months and those who were vaccinated from 9 months after transplant.[21] Geometric mean concentrations of specific IgG correlated well with serum opsonophagocytic activity.[28,31] A fourth dose of PCV13 administered at 9–12 months after the procedure still increased the geometric mean concentrations.[28] Patients vaccinated 3 months after the procedure might have lower antibody titres at 24 months than those vaccinated after 9 months,[21] but with no difference 8–11 years after the transplant, and no clear benefit of one PPSV23 dose administered 2–11 years after.[32] Uncontrolled studies in patients vaccinated after the first year of HSCT showed consistent results.[5,6,33,34]

After autologous, peripheral blood stem-cell transplantation conditioned with carmustine, etoposide, and melphalan, the response rate to PPSV23 11–12 months after the procedure was 45%.[35] The response rate to three doses of PCV7 administered 3, 6, and 12 months after transplantation was higher than 60%.[36]

Because there is a risk of invasive pneumococcal disease infection from the time of transplantation, especially in patients with GvHD, and the patients are able to respond early, we recommend starting vaccination 3 months after transplantation with three doses of PCV at 1-month intervals, followed 6 months later by one dose of PPSV23, or one dose of PCV in case of chronic GvHD (table 2). Although there is no safety issue in administering one dose of PPSV23 after a fourth dose of PCV, the benefit is probably marginal in patients with GvHD. In patients with severe hypogammaglobulinaemia (<3 g/L), severe GvHD, or recent (<6 months) rituximab administration, the response might be low, and they might benefit from alternatives (ie, antibacterials and

	Vaccine	Number of patients (evaluable patients); age in years	Study design and immunisation schedule	Criteria for response	Percentage of patients who responded to treatment and comments
Molrine et al[30]	PCV7	96 (65); 2–64	Three doses of the vaccine were administered 3, 6, and 12 months after transplantation (positive or negative donor vaccination by randomisation)	≥0·5 µg/mL for all seven serotypes	13 months after the procedure the response was 64–75%; there was a benefit of donor vaccination for response to the first two doses, but not for the third
Kumar et al[29f]	PCV7	64 (44); ≥18	Donor and recipient pairs were randomised for either PPSV23 or PCV7 vaccination: one preharvest dose was administered to the donor and one dose of the same vaccine was administered to the recipient 6 months after the procedure; an assessment was done 6 and 12 months after the procedure for PCV7 antigen antibodies	≥0·35 µg/mL for one or more serotype	6 months after transplantation PCV7 had better immunogenicity (38·6%) than PPSV23 (0·0%); and 12 months after the procedure PCV7 immunogenicity was 90·9% and PPSV23's was 55·6%
Meisel et al[22]	PCV7	53 (43); 1–16	Three doses at 1-month intervals were administered 6–10 months after the procedure	≥0·5 µg/mL for all seven serotypes	55·8% immunogenicity after two doses and 74·4% after three doses
Cordonnier et al[21]	PCV7	158 (114); 5–65	Three doses at 1-month intervals were administered and patients were randomly assigned to two groups: those starting vaccination sooner after HSCT (3, 4, or 5 months) and those starting later (9, 10, or 11 months)	≥0·15 µg/mL for all seven serotypes	Response after early vaccination (79%) was non-inferior to late vaccination (82%); chronic GvHD and donor age impaired the response; 24 months after transplant the GMCs and response rates were lower in the earlier vaccinated group
Cordonnier et al[28]	PCV13	251 (207); 2–71	Three doses were administered at 1-month intervals, 4 months after transplantation, then a fourth dose was administered 6 months after the third dose	IgG GMFR and ≥0·35 µg/mL for all 13 serotypes	GFMR significantly increased from baseline after the third dose: response was ≥0·35 µg/mL in 89·7%–98·0% of patients; there was positive correlation between IgG GMCs and OPA GMTs; the GMCs still increased after the administration of the fourth dose and no difference was observed between myeloablative and non-myeloablative conditioning regimens

GMC=geometric mean concentration. GMFR=geometric mean fold rise. GvHD=graft versus host disease. OPA=opsonophagocytic activity. PCV=pneumococcal conjugate vaccine. HSCT=haematopoietic stem cell transplantation.

***Table 1*: Controlled studies assessing the efficacy of pneumococcal conjugate vaccines during the first year after allogeneic haemopoietic stem cell transplant**

	Recommendation and (grading) in allogeneic HSCT	Recommendation and grading in autologous HSCT	Paediatric specificities
PCV13*	From 3 months after transplantion three doses of PCV13 (or subsequent, broader spectrum, conjugate vaccines) are recommended at 1-month intervals (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 third dose of PCV is administered (B II u)	Same initial schedule as for allogeneic HSCT: three doses of PCV13 administered from 3 months after transplantation at 1-month intervals (A I)	The same schedule is recommended in children and adults; children with transplants usually have a similar response to healthy children,[22] and respond better than adults, but often develop vaccine-related fever and local reactions[28]
PPSV23*	12 months after the procedure, if the patient does not have chronic GvHD that requires immunosuppressors, then one dose of PPSV23, not earlier than 8 weeks after the last PCV is recommended (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
Hib vaccine*	From 3 months after transplant three doses at 1-month intervals are recommended (B II r); no preference on the type of vaccine (conjugated with tetanus-protein or diphtheria-protein). Alternatively, to decrease the overall number of vaccine doses, administer three doses of a combined diphtheria-tetanus-pertussis-Hib vaccine from 6 months after the transplantation (BIIr)	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]
Neisseria meningitidis vaccines*	From 6 months after transplantation at least two doses of either a monovalent or tetravalent C vaccine (B II u) and meningococcal B vaccine (B III), in accordance with country recommendations for a given age and particularly for at-risk groups such as students living in campus, travellers, or soldiers	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 population
Tetanus-diphtheria vaccine*	From 6 months after the transplant three doses at 1–2-month intervals (B II u); DT vaccines should be preferred over Td vaccines both in children and adults (C III); booster doses should 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*	The addition of pertussis toxoid to the diphtheria-tetanus vaccine, three doses at 1–2-month intervals, 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†	From 6 months after transplantation a seasonal IIV dose should be administered annually at the beginning of flu season, after the first years following transplant, and 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 administered 3–4 weeks after the first one could be considered in patients with severe GvHD or low lymphocyte counts (B II r); in the setting of a community outbreak, IIV can be administered 3 months after transplantation, in which case, a second dose administered 3–4 weeks later is likely to be beneficial (B II r)	From 6 months: annual seasonal IIV, 1 dose, at the beginning of influenza 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 administered 3 months after transplant, in which case, a second dose administered 3–4 weeks later is likely to be beneficial (B II r)	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 second dose of vaccine after 3–4 weeks could be considered in patients with severe GvHD or low lymphocyte counts (B II r)
IPV*	From 6 to 12 months: three doses of IPV are recommended to be administered at 1–2-month intervals (B II u); booster doses should 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; however, because of 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 antibody titres to assess persistent immunity and consider boosters
HBV vaccine*	Before transplant patients who are negative for all HBV markers that are transplanted with a graft from an anti-HBc positive donor should be vaccinated if possible (B III) and could additionally receive anti-HBV immunoglobulins; 6 months after transplantation 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 according to country recommendation (6–12 months after transplantation 3 doses should be administered 0, 1, and 6 months apart), (B II t); patients infected with HBV before HSCT (HBsAg negative and anti-HBc positive) should be assessed regularly for anti-HBs antibody titres and should be vaccinated if they have unprotective titres (B III); if anti-HBs titres are <10 mIU/mL 1–2 months after the initial series of three vaccine doses, an additional series of three doses should be considered	6 months after transplantation: patients who were negative for HBV before transplantation and patients who were vaccinated before transplantation but lost their immunity after 6 months should be vaccinated according to country recommendation and age (6–12 months after transplantation 3 doses should be administered 0, 1, and 6 months apart)(B II t); patients infected with HBV before HSCT (HBsAg negative and anti-HBc positive) should have anti-HBs antibody titres assessed regularly and be vaccinated if they have unprotective titres (B III); if anti-HBs titres are <10 mIU/mL 1–2 months after the initial series of three vaccine doses, an additional series of three doses should be considered	The same schedule is advised for children and for adults, except that children should receive a standard paediatric dose (10 µg) of vaccine and adolescents should receive 20 µg of the vaccine according to the summary of product characteristics of each vaccine
HPV vaccine	6–12 months after transplantation recommendations for the general population in each country should be followed (B II u)	Same recommendation and grading as for allogeneic HSCT	Follow age recommendations for general population in each country

aP=acellular vaccine. GvHD=graft-versus-host disease. HSCT=haemopoietic stem cell transplantation. PCV13=13-valent pneumococcal conjugate vaccine. PPSV23=23-valent polysaccharide pneumococcal vaccine. HPV=human papillomavirus. IPV=inactivated poliomyelitis vaccine. HBV=hepatitis B virus. Hib=*Haemophilus influenzae* type b. IIV=inactivated influenza vaccine. DT vaccines=diphtheria-tetanus vaccines containing high-doses diphtheria toxoid. Td vaccines=diphtheria-tetanus vaccines containing low-doses diphtheria toxoid. *Guideline proposed on the basis of laboratory endpoints. †Guideline proposed on the basis of clinical endpoints. For the evidence-based medicine grading system (A I, A II r, B I, B III, B II u, B II t, B II r, C III) see appendix.

Table 2: **ECIL 7 recommendations for vaccination of haemopoietic stem cell transplantation recipients with inactivated vaccines**

immunoglobulins) until their health improves. Based on the scarcity of large datasets, no recommendation can be given for subsequent boosts. The assessment of antibody titres should help in defining the best individual option at the time.

Haemophilus influenzae type b (Hib)

The ECIL group recommends three doses of Hib vaccine at 1-month intervals, from 3 months after HSCT, or three doses of a combined diphtheria-tetanus-pertussis-Hib vaccine from 6 months after HSCT.

Hib could cause pneumonia, sinusitis, and bacteraemia soon after transplantation[37,38] because of the unprotective titres of capsular antibodies.[6,39,40] The response to Hib conjugate vaccines was 80–95%, after two or three doses,[6,41–44] even when administered 4 months[40] after the procedure in non-myeloablative HSCT[5] or umbilical cord blood transplantation.[34] The response was hardly affected by GvHD.[40,45–47] The benefit of preharvest vaccination reported in recipients of an allogeneic marrow transplant[41] seemed marginal for autologous, peripheral blood stem-cell transplantation.[48]

Considering the early onset of most Hib infections and that patients could respond to treatment early, we recommend starting vaccination (three doses at 1-month intervals) 3 months after transplantation (table 2). Whether additional boosters are needed is unknown and the assessment of specific antibodies could inform this decision.

Because of widespread Hib vaccination of healthy children, non-typeable *H influenzae* (NTHi) infections are now predominant.[49] Data on *H influenzae* serotypes are warranted after HSCT, and NTHi vaccines should be assessed in the future.

Neisseria meningitides

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

Although invasive meningococcal disease has been reported after HSCT,[50] there are a dearth of data on the vaccines. Between 8 and 20 months after transplantation, 86–90% patients were unprotected for serogroup C[51,52] and 38–96% were unprotected for serogroups A.[51,53]

Different types of vaccines exist in Europe: tetravalent (A, C, Y, and W135), conjugate (MCV-4), monovalent C conjugate (MCV-C), and two anti-B vaccines (MenB). In children, three doses of MCV-4 administered 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 two doses of MenB was over 75% in other immunocompromised patients,[54] studies after HSCT administration are absent. Nevertheless, because serogroup B was responsible for 74% of invasive meningococcal disease cases in Europe between 2004 and 2014,[55] we recommend vaccination against serotypes B and C from 6 months after the procedure (table 2).

Diphtheria and tetanus

The ECIL group recommends three doses of diphtheria-tetanus vaccine at 1–2-months interval, from 6 months after HSCT.

Half of the patients lose their protection during the first year after transplantation, irrespective of the donor's and recipient's serology.[56] The response to tetanus vaccine usually administered at 6–12 months after the transplantation—but sometimes earlier from day 50—is 85–100% after three doses.[42,56–58] The response is slightly affected by GvHD[42,57] or conditioning intensity,[5] and could be lower after umbilical cord blood transplantation.[34] It is similar after autologous and allogeneic HSCT, except when rituximab is administered before or after transplantation.[44,59,60]

The response rate to diphtheria vaccine was 70–100% after three doses administered from 3 months after allogeneic HSCT[33,42,57,59] and 18 months to 10 years after autologous HSCT.[59,60] Although vaccines that contain high doses (DT) of diphtheria toxoid are not recommended for healthy adults because of an increased risk of adverse events, these vaccines could provide better protection than low-dose (dT) toxoid vaccines after allogeneic HSCT[57] (table 2). Therefore, we recommend DT vaccines for all ages.

Bordetella pertussis

The ECIL group recommends considering the addition of pertussis toxoid to each dose of the diphtheria-tetanus vaccine.

Despite the reappearance of pertussis in adults,[61] the data regarding whether pertussis causes severe infections after HSCT are scarce. 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 a tetanus-diphtheria vaccine. The vaccines licensed for administration to children contain higher amounts of the pertussis toxoid (25 µg, and are called DTaP) than those licensed for adults (2·5–8·0 µg, and are called Tdap). One dose of Tdap provides very low response rates.[60,66] After two or three doses of Tdap in adults and the same number of doses of DTap in children, approximately 17 months after umbilical cord blood transplantation, all the children and 54% of the adults with no GvHD, showed a fold-rise of at least two of the antibody titres when compared with baseline.[34] Although the response to pertussis vaccine could be low and not persistent,[57] we recommend this vaccination, especially to help 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 influenza season, and as long as the patient is assessed to be immunocompromised.

Influenza infection is frequent and could be severe in HSCT recipients. A third of infected patients might

develop lower respiratory tract disease, with high mortality despite antivirals.[67–69] The clinical protection offered by one dose of trivalent IIV was shown in a cohort of 177 HSCT recipients who were vaccinated 6 months after transplantation.[70] The response rates were 10–40% within 6 months of transplantation,[71–73] and after 6 months improved to 10–72% with the seasonal[35,73–76] and 37–84% with pandemic adjuvanted[77–79] or non-adjuvanted[80] H1N1 vaccines. The response rates become close to the response rates of healthy individuals from 2 years after transplantation.[72,73,75,79,80] The response was negatively affected by lymphopenia,[72,81] hypogammaglobulinaemia,[79,81] GvHD, immuno-suppressants,[73,79,81] and rituximab.[80] No safety issue was observed.

Most approaches did not find a way to improve this response: an adjuvanted IIV was not more immunogenic than a non-adjuvanted vaccine after allogeneic HSCT;[73] the benefit of two doses versus one dose was suggested both for seasonal[72] and H1N1 vaccines,[77–79,82] but not found in a randomised study after allogeneic HSCT;[75] a high-dose (60 µg) antigen trivalent IIV, which is not available in Europe, was more immunogenic but induced more injection-site reactions than a standard-dose (15 µg) vaccine after allogeneic HSCT;[83] granulocyte-macrophage colony-stimulating factor administered with the seasonal vaccine improved the response to influenza B but not to A/H1N1 or A/H3N2 types;[76] and 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 of patients (table 2). A second dose might be beneficial in patients that cumulate factors of poor response (GvHD, lymphopenia) or during outbreaks in patients vaccinated within 6 months of transplantation. HSCT recipients should benefit from additional measures (eg, respiratory isolation, rapid diagnostic tests in case of symptoms, and post-exposure antivirals).[84] The intranasal influenza live-attenuated vaccine (LAV) is contraindicated after HSCT.

Inactivated poliomyelitis vaccine

The ECIL group recommends three doses of inactivated poliomyelitis vaccine administered at 1–2 month intervals 6–12 months after HSCT.

Data shows that 6–12 months after HSCT, 30–100% of patients lost their immunity to polio.[85–88] Because of the risk of post-vaccinal poliomyelitis with the oral LAV, only inactivated poliomyelitis vaccine should be used (grading DIII). The response to three doses of the vaccine administered 6 months after the procedure was 80–100% and long lasting, except in children who had transplants aged 10 years or younger (table 2).[89] The response was affected slightly by GvHD.[33,42,57,58,86,90]

Hepatitis B virus (HBV) vaccine

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

The ECIL group published guidelines, in 2016, for the management of viral hepatitis, including HBV.[91] There are three different goals of HBV vaccination after HSCT: 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; to protect the recipient from getting HBV from an anti-HBc-positive donor; and to decrease the risk of reverse seroconversion in recipients previously infected with HBV. Although the donor can transfer his or her HBV immunity, and the recipient could have been vaccinated before the transplantation, half of the recipients lose seroprotection within 6 months of the procedure,[92,93] and 90% were unprotected at 5 years.[94]

After three doses of HBV vaccine, started at a median of 23 months after allogeneic HSCT, seroconversion was 64%,[93] and was impaired by patient age and chronic GvHD, but not by T-cell depletion or rituximab administered at a median of 16 months before vaccination. 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 he or she is 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, and 21) could elicit a 70% response rate in healthy individuals (table 2).[96] In previously HBV-infected recipients, in addition to antivirals,[91] vaccination might prevent reverse seroconversion.[97,98] Finally, a regular reassessment of anti-HBs titres is recommended 6 months after HSCT, and 1–2 months after three vaccine doses. Because the response in patients with transplants is lower than in healthy individuals, non-responders (anti-HBs <10 mIU/mL) should be advised to consider a second series of vaccinations later, although its benefit is uncertain.

Human papillomavirus

The ECIL group recommends following guidelines for the general population in each country 6–12 months after transplant.

HSCT recipients could develop human papillomavirus-associated tumours,[99] especially in cases of chronic GvHD.[100] Human papillomavirus vaccination is recommended for healthy adolescents or young adults in most countries to prevent human papillomavirus-related malignancies. 20 previously unvaccinated children received three doses of the quadrivalent vaccine 6–12 months after HSCT with only minor adverse events. The seroconversion rate was nearly 100%.[101] Although

there is no large-scale data on vaccine efficacy after HSCT, no safety issues are expected[102,103] and human papillomavirus vaccination should be beneficial in young patients (table 2). Whether it is beneficial in older recipients of transplantations remains to be assessed.

General issues on safety of inactivated vaccines after HSCT

Only prospective trials can properly assess adverse events 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 could increase with an increased dose per injection[83] but resolve quickly. In trials including healthy controls, there was no evidence that adverse events or SAE were more frequent after HSCT[79,82,104,105] and one study even suggested a decreased incidence of adverse events after intradermal injection of IIV when compared with healthy controls.[105]

After anti-pneumococcal vaccination, adverse events 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] dose of PCV.

In summary, adverse events and SAE after inactivated vaccines are not different in nature, severity, duration, or frequency in patients with HSCT and healthy individuals and should not prevent vaccination. Additionally, in prospective trials, there was no evidence that vaccination triggers or worsens GvHD.[28,78]

Live-attenuated vaccines

The ECIL group recommends varicella and measles, mumps, and rubella LAVs from 24 months after transplantations, only in seronegative patients with no GvHD, no immunosuppressants, no relapse, and no recent administration of immunoglobulins.

LAVs are, in general, contraindicated in immunocompromised patients because of the risk of vaccine-transmitted disease.[106] However, when there are no inactivated alternatives, they could be carefully considered on the basis of the risk and benefit balance.

Varicella-zoster virus (VZV) vaccines

VZV infections could be life threatening after HSCT. The risks are primary varicella infection (chickenpox) in seronegative patients and shingles and postherpetic neuralgia in seropositive patients. Acyclovir or valacyclovir prophylaxis administered 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 cases of vaccine-induced, disseminated VZV infections have been occasionally reported with LAVV after HSCT[108] or intensive chemotherapy,[109] and with LAZV, even 6 months after stopping chemotherapy.[110]

Several observational studies with LAVV have been done in seronegative HSCT recipients, with one to three doses administered 3 months[111] to 4–5 months[112] after autologous HSCT, and 12–24 months[113] after the procedure in selected allogeneic HSCT recipients,[114] 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 might, however, be different in VZV seronegative or seropositive patients before transplantation. Because 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 3 weeks, and to seek antivirals if necessary.

Two retrospective studies were done with the LAZV administered at a median of 21–27 months after transplantation.[116,117] The vaccine was safe and the studies suggested a reduced incidence of VZV infection.[116,117] Additionally, a study, which was not available at the time of ECIL 7, showed that LAVZ was safe when administered from 24 months after autologous HSCT in myeloma patients receiving lenalidomide,[118] 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 the age of 50 years.[119] Autologous seropositive HSCT recipients who received three doses from 50 days after the procedure developed good and persistent responses, but without reduction of herpes zoster.[120] A heat-treated, zoster vaccine was shown to be poorly immunogenic after allogeneic HSCT,[121] but it reduced the incidence of herpes zoster versus placebo after autologous HSCT.[122] This latter vaccine can be administered much earlier than LAVZ.

Because inactivated vaccines will be available soon and since antiviral prophylaxis is effective and safe, we consider that inactivated vaccines should be preferred to LAVZ. Additional data are needed on allogeneic HSCT.

Measles, mumps, and rubella

Although measles, mumps, and rubella vaccines are mostly combined, the concerns raised by each of these viruses are different. Measles could be life-threatening[123–125] and decreased vaccination in healthy children has led to outbreaks worldwide. Mumps or rubella infections are not life-threatening but a pregnant HSCT recipient could transmit rubella to her baby. The probability of becoming seronegative 5 years after allogeneic HSCT is 60% for measles, 73% for mumps, and 52% for rubella;[8] and it is higher after vaccination than after natural infection.[7,8,10,124] Several open studies assessed these vaccines (one or three doses), mostly 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. Outside the setting of an outbreak, the group recommends that the vaccination be restricted to seronegative patients that match the conditions mentioned in table 3. Also, in large community outbreaks, vaccination without immunity testing or in seropositive individuals can be considered to balance the potential benefits and risks to the patient's situation, including the time after transplantation, age, and previous vaccination history. Patients with ongoing GvHD or immunosuppression should not be vaccinated.

Yellow fever vaccine

Yellow fever vaccination might be required for patients living or travelling in endemic areas. In healthy individuals, a yellow fever 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, and normal CD4 counts and IgG levels) were vaccinated at a median of 3–9 years after transplantation, with no SAE.[128–130] Most patients responded. HSCT recipients who themselves, or whose donors, were vaccinated before transplant might retain protection years after transplant,[129,131] which suggests that these patients should be tested 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 because of the risk of disseminated disease. There are no data on dengue vaccine after HSCT.

Specific issues analysed by the group

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 who represent a large proportion of the autologous HSCT population.

	Recommendation and grading for allogeneic HSCT	Recommendation and grading for autologous HSCT	Paediatric specificities
LAVV*†	LAVV is contraindicated in HSCT recipients with active GvHD, a relapse of the underlying disease, or ongoing immunosuppression (D III); at least 24 months after transplantation 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); the addition of a second dose in adults could be considered in patients who were seronegative before HSCT or had no history of VZV infection	Same recommendation as after allogeneic HSCT	Two doses (instead of one dose in adults) of LAVV can be considered in children meeting the same limitation criteria as adults (B II r); label specific recommendations should be followed for the amount of time between administering the two doses
Zoster LAV†	Not recommended (D III)	Not recommended (D III)	Not recommended (D III)
MMR§	From 24 months after HSCT, recipients should have MMR antibody titres tested (B II u); consider vaccination only in patients with no GvHD, no immunosuppression, no relapse of the underlying disease, and treatment with immunoglobulins during the previous months‡; seronegative patients for measles should receive one dose of MMR (B II u); HSCT recipients who are women, seronegative for rubella, and of childbearing potential should receive one dose of MMR with the same precautions (C II u); in case of a measles outbreak, MMR vaccination could be considered 12 months after transplantation in patients with low-grade immunosuppression (C III)	Same recommendation as after allogeneic HSCT	Because of a lower response in children, two doses—instead of one in adults—should be considered in children, at least 4 weeks apart
Yellow fever§	Yellow fever vaccine should be considered cautiously and only administered to patients with no active GvHD and no immunosuppressive drugs, and if the patient cannot avoid traveling to endemic area before (DIII) or from 24 months (CIII) after the procedure	Yellow fever vaccine should be considered cautiously if the patient cannot avoid traveling to endemic area before (DIII) or from 24 months (CIII) after the procedure before (DIII) or from 24 months (CIII)" after the procedure	Although there are no data in children, the same schedule is recommended for children and for adults

HSCT=haemopoietic stem cell transplantation. LAVV=live attenuated varicella vaccine. LAV=live attenuated vaccine. GvHD=graft-versus-host disease. VZV=varicella-zoster virus. MMR=measles-mumps-rubella. *Guideline proposed on the basis of laboratory endpoints. †All LAV are contraindicated as long as the patient is considered severely immunocompromised. ‡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. For the evidence-based medicine grading system (B II u, B II r, C II u, C III, D III) see appendix. §Guideline proposed on the basis of clinical endpoints.

***Table 3*: ECIL 7 recommendations for vaccination of haematopoietic stem cell transplantation recipients with live-attenuated vaccines**

Vaccination schedules should be reassessed on the basis of current transplant procedures. Two publications,[122,133] which were not available at the time of ECIL 7, showed that vaccination with inactivated vaccines under lenalidomide therapy after autologous HSCT is safe and one of the studies[133] showed it was efficient. Until 2000, most allogeneic HSCTs were from HLA-identical siblings with myeloablative conditioning. Now, 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 effect, although documented in some vaccines, is marginal for the immunogenic ones. On one hand, because patients with GvHD are at a 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 a patient waits 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 cells per µL)[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 with the knowledge 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 to not delay vaccination except in specific situations listed below.

	Benefit of donor immunisation before donation to the post-transplant vaccine response of the recipient
PCV	Improved after early vaccination and the benefit was not maintained after 12 months of the procedure[29,30]
PPSV23	No benefit[29,141]
Haemophilus influenzae type b	Improved the response of early (d-1, d50) vaccination of the recipient [139]
Neisseria meningitidis	Unknown
Tetanus-diphtheria	Tetanus vaccine improved the response of early (d-1, d50) vaccination and diphtheria vaccine increased antibody concentrations[42,139]
Acellular pertussis	Unknown
Poliomyelitis	No benefit[42]
Inactivated influenza	No difference in antibody titres after vaccination during the first 6 months after transplant and response did not improve when the patient was vaccinated at least 6 months after the procedure[74]
Hepatitis B virus	Poor patient response to HBsAg with or without donor vaccination[139] and improved response to keyhole limpet hemocyanin[140]
Human papillomavirus	Unknown

PCV=pneumococcal conjugate vaccine. PPSV23= pneumococcal 23-valent polysaccharide vaccine

Table 4: **Main data on donor immunisation before allogeneic haematopoietic stem cell transplantation donation by vaccine**

	Recommendation	Grading
General recommendation	It is recommended that family members and close contacts of HSCT recipients be immunised or vaccinated according to the age and country recommendation	..
IIV	It is recommended that family members and close contacts of HSCT recipients be vaccinated with IIV at the start of autumn before transplantation and first season after, and annually as long as the patient is considered immunocompromised	A II t and C III
LAV influenza	The nasal LAV influenza vaccine is contraindicated in close contacts of HSCT recipients during the first months after transplantation or if the patient has GvHD	B III
Varicella or MMR vaccine to a close contact of the patient	In case a close contact of an HSCT recipient needs varicella or MMR LAV because he or she is seronegative, he or she should be seperated from the HSCT recipient, because of the risk of developing post-vaccine disease	..
Rotavirus vaccine in close infants	Within 4 weeks after rotavirus vaccination of infants, HSCT recipients should have no contact with the stools or diapers of the vaccinated infants because there is a risk of contracting the vaccine virus	..

IIV=influenza inactivated vaccine. LAV=live-attenuated vaccine. GvHD=graft-versus-host disease. MMR=measles-mumps-rubella. For the evidence-based medicine grading system (A II t, B III, C III) see appendix.

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

Transient or definite exclusion of HSCT recipients from vaccination programmes

Patients with severe GvHD or hypogammaglobulinaemia are usually excluded from vaccine studies because they are unlikely to respond. Although gammaglobulin titres lower than 4 g/L decreased the response to PCV7, the response rate was still 38%,[21] which suggests a potential benefit. However, in case of severe hypogammaglobulinaemia (<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] Because the response to LAV can be impaired by circulating immunoglobulins, it is recommended that the vaccine response be checked to consider an additional dose.

Rituximab induces immediate and long-term B-cell depletion, with prolonged hypogammaglobulinaemia 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, Epstein–Barr virus reactivation, or GvHD. Rituximab strongly impairs the vaccine response after allogeneic HSCT[6,53,80] even as long as 28 months later[53] and in case of conjugate vaccines.[6] Autologous HSCT recipients vaccinated 6–8 months after the last dose of rituximab showed acceptable, although impaired, responses with T-cell dependent (eg, tetanus and PCV), but not with T-cell

independent, antigens (eg, PPSV23).[6,138] After autologous and allogeneic HSCTs, we recommend that vaccination be delayed for at least 6 months after the last dose of rituximab, and the antibody response be assessed if necessary because it is uncertain. Similar issues are expected with other anti-B monoclonal antibodies.

Assessment of 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 some vaccines (eg, HBV 6 months after transplant, measles, mumps, rubella, and LAVV 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 (eg, severe GVHD or rituximab), and to decide on booster administration during long-term follow-up (eg, Hib 5–10 years after the initial series and DTP every 3–5 years). Pneumococcal antibodies can be assessed at 24 months, although the practical consequences of such assessments—boost, or full revaccination programme—are to be prospectively evaluated.

Donor vaccination 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 T cells that react to antigens (table 4).[141] 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[30,42,139,142] and is transient.[30] Therefore, we do not recommend preharvest vaccinations, except for HBV vaccine in previously mentioned situations.[91]

LAV vaccines are contraindicated 4 weeks before donation because of the risk of vaccine–disease transmission, even though the duration of vaccine-induced viraemia 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 naturally immunised or vaccinated according to country recommendations for their age, especially against VZV and measles, mumps, and rubella, and additionally receive IIV yearly. Table 5 summarises these and other recommendations, contraindications, and precautions for family and close contacts of patients. Recommendations for vaccination of health-care workers in haematology wards are presented in the companion paper.[17]

Areas for future research

Transplant procedures are becoming increasingly diverse, and HSCT is being done in more and more countries that might have specific diseases that could potentially be preventable by vaccination. The ECIL group supports prospective studies and recommends that patient subgroups (eg, recipients of haploidentical or umbilical cord blood transplants) be specifically assessed for their vaccine response. The effect 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 into account the risks in a specific community. Vaccines could 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.

Declaration of interests

MM has been a scientific adviser for Biotest and has received payment for lectures and travel expenses from MSD, Janssen, Pfizer, Astellas, and Gilead. RDB has received personal fees from Gilead and Merck. CC has received grants from Merck and Astellas and was a scientific adviser for Merck. 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 was a scientific adviser for Merck. All other authors declare no competing interest.

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