Guidelines for vaccination of patients with hematological malignancies and HSCT recipients

Final version Sept. 23, 2017

Mercure Sophia Antipolis Sophia Antipolis ♦ France
ECIL 7 Vaccine Group

Members

Catherine Cordonnier (France)
Simone Cesaro (Italy)
Hugues De Lavallade (UK)
Roberta Di Blasi (Italy)
Sigrun Einarsdottir (Sweden)
Dan Engelhard (Israel)
Giuseppe Gallo (Italy)
Per Ljungman (Sweden)
Malgorzata Mikulska (Italy)
Christina Rieger (Germany)

ECIL 7 meeting
Juan-les-Pins, France
Sept. 21-23, 2017
INTRODUCTION
Common issues to vaccination in hematology patients (1/2)

• An area often neglected by hematologists
• Few or no data with some vaccines
• Number of patients needed to show a clinical efficacy of vaccines in rare diseases: impossible to reach
• Efficacy mostly defined on biological parameters whose protective effect was established in healthy individuals. Clinical pertinence of such parameters unknown in immunocompromised pts
• Many hematological diseases = many different types of immunodeficiencies: difficult to transfer data from one population to another
• Treatments of hematological diseases fastly evolve
Common issues to vaccination in hematology patients (2/2)

• Lower vaccine response than healthy people of the same age range
• Few or no data on the durability of the response
• Live attenuated vaccines (LAV) contra-indicated, with some exceptions

• Timing is crucial
Main reasons to vaccinate hematology patients

• Higher risk than healthy individuals of the same age to acquire community infections (eg. Pneumococcal disease, Flu)
• Higher risk of infection-related hospitalization, respiratory failure, ICU stay, and death for most vaccine-preventable infections
• Risk that the infection delays or precludes the treatment of the underlying disease
• Decreased herd immunity in countries where vaccination is not mandatory

Many infections observed in hematology patients are vaccine-preventable

Vaccines may preclude - or at least decrease the severity of - the disease
Two different goals of vaccination in hematology patients

- To protect the patient against specific infections whose risk is clearly increased by the disease and/or the treatment procedures when compared to the healthy individuals
  - eg. *S pneumoniae* and HSCT, *Influenza infection*

- To offer him/her, as soon as possible, the same protection as healthy individuals for vaccines recommended in their country: individual and community benefit
ECIL 7 guidelines developed...

✓ For non-transplanted hematology patients (Part I):
  - by underlying disease

✓ For HSCT patients (Part II):
  - by type of vaccine

Outside the scope of this review: primary immune deficiencies, splenectomy, non-malignant hematological diseases
Grading system
(According to ESCMID)

<table>
<thead>
<tr>
<th>Strength of a recommendation</th>
<th>ECIL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade A</td>
<td>strongly supports a recommendation for use</td>
</tr>
<tr>
<td>Grade B</td>
<td>moderately supports a recommendation for use</td>
</tr>
<tr>
<td>Grade C</td>
<td>marginally supports a recommendation for use</td>
</tr>
<tr>
<td>Grade D</td>
<td>supports a recommendation against use</td>
</tr>
</tbody>
</table>

**Quality of Evidence**

<table>
<thead>
<tr>
<th>Level</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level I</td>
<td>Evidence from at least one properly designed randomized, controlled trial.</td>
</tr>
<tr>
<td>Level II*</td>
<td>Evidence from at least one well-designed clinical trial, without randomization; from cohort or case-controlled analytic studies (preferably from &gt;1 centre); from multiple time series; or from dramatic results of uncontrolled experiments</td>
</tr>
<tr>
<td>Level III</td>
<td>Evidence from opinions of respected authorities, based on clinical experience, descriptive case studies, or reports of expert committees</td>
</tr>
</tbody>
</table>

*Added index:
- r: Meta-analysis or systematic review of randomized controlled trials.
- t: Transferred evidence, that is, results from different patients’ cohorts, or similar immune-status situation.
- h: Comparator group is a historical control.
- u: Uncontrolled trial.
- a: Published abstract (presented at an international symposium or meeting).
Roadmap

HSCT

Catherine
Per
Sigrun

Allo  Auto

Non-HSCT

Hugues, Roberta
AML, MDS,
Chronic
myeloproliferative
disorders (CMD)

Malgorzata, Giuseppe
Lymphoproliferative
diseases (LPD):
myeloma, lymphoma,
CLL

Children ALL

Pediatric specificities: Simone, Dan

Side effects
Christina, Dan

Live vaccines
Simone, Giuseppe
Part I: Vaccination of non-transplanted patients with hematological malignancies

- I A: Myeloid diseases
- I B: Lymphoproliferative diseases
- I C: Children Acute lymphoblastic leukemia (ALL)

Part II: Vaccination in HSCT recipients
Part I A: Vaccination in patients with myeloid diseases

- Acute myeloid leukaemia (AML) and myelodysplastic syndrome (MDS)
- Chronic myeloid leukaemia (CML)
- Myeloproliferative disorders (MPDs)
Vaccination data in myeloid diseases

Important aspects:

• The effect of treatment is determinant on vaccine efficacy:
  – Standard intensive chemotherapy
  – Tyrosine Kinase Inhibitors (TKI) (CML)
  – JAK inhibitors (MPDs)

• Little data on vaccination in these groups of patients
Available influenza vaccines

**Inactivated (IIV),** usually trivalent (Trivalent inactivated vaccine: **TIV**), but possibly also quadrivalent (evaluable from the 2014-2015 season in some EU/EEA countries) or monovalent (e.g. against 2009 H1N1 pandemic strain), containing

- The whole virus
  - Non adjuvanted (Intramuscular, Intradermal)
  - Adjuvanted (with squalene, i.e. MF59, or AS03 - squalene and α-tocopherol, or aluminium phosphate gel)
  - Cell-based influenza vaccines which can be given to egg-allergic individuals (not available in all EU/EEA countries)
- Split-influenza virus products
- Subunit influenza products

**Live attenuated quadrivalent influenza vaccine (LAIIV)** for intranasal use, approved in the EU/EEA for children and adolescents (2-17 years of age) in 2011 (Fluenz tetra™).

THE LAIV is contra-indicated in HSCT recipients
(safety issue, no data in HSCT, and IIV alternatives exist)

All data presented in the next slides only concern IIVs
Vaccination data in adult patients with MDS

• No published data

• Median age of MDS patients is 75 years and as such, they should receive vaccination against influenza and pneumococcus

• However disease heterogeneity should be taken into account: for instance infections in CMML > RCMD (Refractory Cytopenia with Multilineage Dysplasia)
Vaccination in AML

Influenza
• Slightly increased incidence of influenza in comparison to the general population

HBV
• Acute HBV hepatitis has been associated with delays in chemotherapy
• In low HBV prevalence setting, there is very low risk of de novo HBV infection due to safe blood products
• Risk of de novo HBV infection exists in some high HBV prevalence countries due to high rates of horizontal transmission (blood transfusions, interventional procedures, etc.)

Other
• No sufficient data for VZV, MMR, DTP, meningococcus and pneumococcus in adults

Other vaccination data in AML: paediatric population, summary and impact on adult AML patients

- Loss of previous immunity is less pronounced in AML than in ALL children (in line with adult setting, e.g. tetanus)
- However, if revaccinated, both groups mount a satisfactory response once treatment is finished
- Extrapolation to adult population: revaccination of selected adult AML patients after completion of chemotherapy might be successful and may have clinical benefit, for example given low residual immunity to tetanus following AML chemotherapy

Chronic myeloid diseases
Infection incidence in CML patients on Tyrosine Kinase Inhibitors (TKI)

• CML patients in pre TKI era had an increased risk of respiratory and skin infections (Titmarsh 2014)

• TKIs further increase this risk, but precise data not available
  – Risk of reactivations of hepatitis B with TKIs have been repeatedly reported leading to a recommendation of the EMA to screen all patients for HBV before starting TKI
  – Case reports on dasatinib-induced opportunistic infection (Chang, IJID 2014)

• TKI treatment might lower the vaccine efficacy

• Response to pneumococcal vaccination was lower than in healthy controls
• Reponses to influenza vaccination (inactivated and adjuvanted) was similar to healthy controls

Myeloproliferative disorders (MPD) and ruxolitinib

- Data suggest no increased risk of infection in patients with MPDs in the pre-JAKi era

- Ruxolitinib is associated with an increased risk of infections, and in particular HZ and opportunistic infections

- JAKi treatment might lower the vaccine efficacy

- No data on the efficacy of vaccination in patients on JAKi
ECIL 7 guidelines on vaccination

Myeloid diseases: AML

- Indications based on age or comorbidities according to country recommendations should be taken into account
- Patients after the end of intensive chemotherapy: a single dose of inactivated influenza vaccine is recommended as long as considered immunocompromised (B IIu)
- In high HBV prevalence setting, where high risk of HBV transmission during CT is present, HBV vaccination, starting before and continuing during CT, can be performed, similar to what recommended in paediatric ALL (C II u)
- AML patients 3-6 months after the end of CT should be vaccinated according to country recommendations
  - Paediatric AML population should follow the recommendations for paediatric ALL patients
Indications based on age or comorbidities according to country recommendations should be taken into account.

Influenza vaccination is recommended in CML patients (B II u), although the precise risk is unknown and dual BCR-ABL/src inhibitors (dasatinib, bosutinib) might be more immunosuppressive. One dose seems sufficient to induce seroprotection.

CML patients should be vaccinated against pneumococcus (C II t).

Live vaccines are contraindicated in patients treated with ruxolitinib or TKIs (D III).
Part IB: Vaccination in patients with Lymphoproliferative diseases
Vaccination data in lymphoproliferative disorders (LPD): chronic LPD and ALL

Diseases
- Multiple myeloma (MM)
- Lymphoma (HD and NHL)
- Chronic lymphocytic leukemia (CLL)
- Acute lymphoblastic leukemia (ALL)

Particular aspects
- Use of anti CD-20 MoAbs
- High vs low intensity treatment for MM and lymphomas
- Novel drugs: e.g. bortezomib, carfilzomib, brentuximab, ibrutinib, idelalisib, lenalidomide
- Low probability of restoring long term immunity in diseases such as MM or CLL without allogeneic HSCT, but high probability after favourable response in diseases such as aggressive lymphomas (e. g. diffuse large B-cell lymphoma, ALL)
Multiple myeloma
Multiple myeloma and the risk of invasive pneumococcal disease (IPD)

- Increased risk of any bacterial infections (HR = 7.1; 95% CI 6.8-7), especially during the 1st year following diagnosis.
- The risk increased during the last decades (new treatments, autologous HSCT)
- Infections cause approx. 22% of all deaths in MM patients
  
  Blimark et al. 2015 Haematologica, Hsu et al. Medicine (Baltimore) 2015

- Patients with MM have the highest incidence of IPD compared to other LPD and controls (incidence /1000 person years)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Incidence /1000 Person Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myeloma</td>
<td>11 – 22</td>
</tr>
<tr>
<td>Any leukemia</td>
<td>4.1</td>
</tr>
<tr>
<td>CLL</td>
<td>4.3</td>
</tr>
<tr>
<td>Non-Hodgkin’s lymphoma</td>
<td>1.7</td>
</tr>
<tr>
<td>Hodgkin’s lymphoma</td>
<td>0.9</td>
</tr>
<tr>
<td>MGUS</td>
<td>0.12</td>
</tr>
<tr>
<td>General population</td>
<td>0.15</td>
</tr>
</tbody>
</table>

MM and pneumococcal vaccination, summary

**Response rate to PPSV23**: between 33-57%. However:
- Most patients off therapy or during plateau phase > not representative of current treatments

**Response rate to PCV**: a single study: **MM: 63% vs controls 100%**
- **Ab function test (OPA)**: MM: 8% vs controls: 55%
  - Karlsson Trials in Vaccinology 2013

**Response to vaccination variable**, possibly better on lenalidomide
- Noonan Clin Cancer Res 2012

**No safety issues**

**No data on the duration of immunity induced by vaccination**
MM and influenza vaccination, summary

Risk of influenza increased in MM: HR=6.1
  » Blimark et al. Haematologica 2015

Trivalent inactivated vaccine (TIV)

Seroconversion 0% to 83% (5/6 pts), most frequently approx. 20-25%*


Improving efficacy:

• No clear benefit of 2nd dose of TIV or of an adjuvanted vaccine


• Possible benefit of 2 doses of high dose or adjuvanted vaccine


No safety issues
MM and Haemophilus influenzae B (HiB) vaccination

• Unknown current risk of the HiB disease in MM

• Contradictory results on the rate of protective Abs vs. controls
  • Karlsson et al. CVI 2011; Nix et al. CVI 2012

• Response to HiB as healthy
  • Robertson Br J Cancer 2000
**MM and Herpes zoster (HZ)**

- **Increased risk of HZ infection: 4-14 fold**
  - Hansson et al. 2017 *Br J Cancer*; Blimark et al. 2015 *Haematologica*

- **Risk of HZ particularly high in patients treated with bortezomib**

- **No specific data on HZ vaccination in MM available**
  - Heat inactivated HZV, 4 doses, 30 days apart, randomized vs. placebo: 262 patients including **22 pts with MM** (7 no HSCT, 14 after ASCT, 1 after alloHSCT); immune response in IFN-γ ELISPOT was present in HM cohort
  - Mullane et al JID 2013
Lymphoma
Risk of infections in lymphoma

Very heterogenous disease

Increased risk of invasive pneumococcal disease: 5-10 fold


Increased risk of influenza

Increased risk of Herpes Zoster: 2-3.5 fold


HBV: In low endemicity settings de novo infections rare, while reactivation is more frequent, thus appropriate screening and prophylaxis or treatment should be provided

HPV: increased risk, particularly in case of HD or pelvic irradiation

Klosky et al. Cancer 2009
Pneumococcal vaccination and lymphoma

**PPSV23**
- Many data from splenectomised patients: good response (45%, 72%, 80%), similar to other patients undergoing splenectomy, if vaccinated before CT
- Titres waned at 3 years > revaccination at 2 years might be beneficial

**PCV**
- Better response to conjugate HiB than polysaccharide vaccine to PPSV23
- No data in lymphoma with PCV7 or PCV13
- The benefit of the conjugated vaccine in this population is expected
Response to influenza vaccination in lymphoma, summary of 15 studies

- **Response to TIV highly variable (3%-95%, in median approx. 30%*), lower than controls**
  

- **Similar response to TIV and an adjuvanted vaccine**
  

- **Possible benefit of a 2nd dose, particularly of an adjuvanted vaccine**
  

- **Not affected by chemotherapy, but no clear data on high intensity regimens**
  

- **Response strongly impaired by rituximab (ongoing and at least during the previous 6-10 months): no response at all reported in most studies (See next)**
  
Role of rituximab on the immune response to vaccination in lymphoma 1/2

Most data on influenza vaccination

- **During rituximab**
  - Response approx. 0
    - even if rituximab used in monotherapy
    - even in case of 2 doses or adjuvanted vaccine


- **After rituximab therapy**
  - Within **6 months after last rituximab**: very low response (0-29%)
  - No response in 7 pts treated with rituximab within the previous **10 months**

  *De Lavallade et al. Haematologica 2011*

  - Best response in a study of 31 pts with a median of **29 months** (7-65) between rituximab and TIV: **3-29%**

  *Bedognetti et al. J Immunol. 2011*
Role of rituximab on the immune response to vaccination in lymphoma 2/2

No data of the duration of response after pre-rituximab vaccination

Few data on other vaccines in CLD receiving rituximab
- **PPSV23**: 1/9 response when given at 6-12 mo after rituximab
- **Act-HiB**: 5/9 response when given at 6-12 mo after rituximab
  
  *Svensson et al. 2011*

In small series, some studies suggest that *rituximab could mainly affect the response to primary* antigens and not or to lower extent to recall antigens


However, in all studies with healthy controls, the response to recall antigens remain always lower than the one of the controls

CLL
Risk of infections in CLL

• In a recent cohort of 263 pts, mainly treated with novel drugs, 72% had an infectious complications and infections were responsible for 38% of deaths

  *Williams et al. Leuk Lymph 2017*

• Historically, higher rate of *pneumococcal* and *HiB* infections and inverse correlation between IgG levels and the incidence and severity of infections

• Higher rate of *HZ*

• Suboptimal responses to vaccines due to
  – impaired antibody production
  – defects in antigen presentation
  – higher plasma histamine levels (> studies of vaccination with concomitant ranitidine which blocks the histamine type-2 receptors)
Pneumococcal vaccination in CLL, summary

Response to PPSV23:
• Poor, ranging from 0% to 21%
• Always lower than controls
• Better in early stage disease
• No benefit of ranitidine or of GM-CSF

Response to PCV: better
  – PCV7: 20-47%, better in early stage disease (Sinisalo et al. Vaccine 2007)
  – PCV13: 58% in patients naïve of any treatment (Pasiarski et al. PLOS One 2014)
  – Poor in case of ibrutinib, but very experienced pts (Andrick BJH 2017)

With both vaccines: clinical protection and duration of the response unknown
Influenza vaccination in CLL, summary

Response to TIV was low in two studies: 5-30%; but as high as 72%-95% in a single study, which included, among others, 60 CLL patients, mainly treatment naïve


Little benefit of 2nd dose of TIV but good response to 2 doses of adjuvanted vaccine, particularly in early stage CLL


Poor response (8%-26%) to TIV in patients treated with ibrutinib, even in case of high dose TIV

Sun JAMA Oncology 2016; Douglas Haematologica 2017
CLL and response to other vaccines

**HiB:**
- Response rate variable 21-92%
  
  Jurlander 1995; Hartkamp 2001; Sinisalo 2001; Sinisalo 2002; Van der Velden 2007

- 52% in a recent study, better with ranitidine vs. 28% without
  
  van der Velden 2007

- Better response associated with younger age, early-stage disease and normal Ig levels
  
  Hartkamp 2001; Sinisalo 2001; Sinisalo 2002

**Heat inactivated HZ vaccine, no data specifically for CLL:**
Two studies of 4 doses in a mixed cohort of patients with HM (27 and 12 with CLL) elicited specific T-cell responses n IFN gamma ELISPOT assays

  Mullane et al. 2013; Parrino et al. 2017
ECIL 7 guidelines for vaccination of patients with CLD (1/2)

*myeloma, lymphoma, CLL*

Comments

• Inactive vaccines are safe but might not be effective, especially in case of
  • severe hypogammaglobulinemia
  • current or previous, even > 12 months before, treatment with rituximab
• In particular, vaccination is futile in patients who are receiving or have received within the previous 6 months rituximab, as they do not respond. Similar negative impact is expected with other B-cell MoAbs.
• All these patients should benefit from other protective measures, especially during CT and in the following year: droplet precautions, antiviral prophylaxis, Ig, household vaccination, etc.
• After the active phase of treatment (i.e. during maintenance or plateau) or within 3-6 months after the end of treatment, the vaccine history should be individually reviewed in order to plan the vaccination program and apply the country recommendations for inactivated vaccines according to the patient’s age and comorbidities.
  – Abs titres (e.g. tetanus, HBV) assessed 3-6 months after the end of chemotherapy or > 6 months after the end of rituximab treatment can help in designing a tailored program
ECIL 7 guidelines for vaccination of patients with CLD (myeloma, lymphoma, CLL) (2/2)

<table>
<thead>
<tr>
<th>Vaccine and population</th>
<th>Timing</th>
<th>ECIL 7 recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pneumococcal</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCV13 and PPSV23 (at least 8 weeks after PCV) in CLD</td>
<td>if possible at diagnosis, or during maintenance or plateau phase</td>
<td>B II u, t</td>
</tr>
<tr>
<td><strong>Influenza</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inactivated^</td>
<td>Annually, as long as considered immunocompromised</td>
<td>A II u</td>
</tr>
<tr>
<td>Influenza vaccination should be postponed in patients who are receiving or have received during the previous 6 months <strong>anti-CD20 Abs</strong> due to the absence of response</td>
<td>B II u</td>
<td></td>
</tr>
<tr>
<td><strong>HPV</strong> In lymphoma survivors</td>
<td>As in healthy population</td>
<td>B II t</td>
</tr>
<tr>
<td><strong>Live-attenuated vaccines (LAV)</strong></td>
<td></td>
<td>D III</td>
</tr>
<tr>
<td>Do not administer as long as considered immunocompromised, usually at least 3 months after the end of CT or at least 6 months from rituximab</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Protective response is not expected during high intensity chemotherapy or within 6 months from the end of rituximab administration; ^ Better response might be obtained administering a 2nd dose and/or using an adjuvanted* or high dose vaccine**; *Data from monovalent pandemic vaccine; no data from regular adjuvanted vaccine. **Unavailable in Europe; One dose unless specified otherwise
Areas of research

- MDS - no data > collaborative/multicentric research projects should be encouraged
- MPD - no data on vaccine efficacy > collaborative/multicentric research projects should be encouraged

- Pneumococcal vaccination:
  - Duration of protection
  - Benefit of > 1 dose of PCV
  - Need for PPSV23 after PCV, and 5-year PPSV23 booster

- Any inactivated vaccine:
  - Vaccine response during treatment with new drugs
  - Identification of parameters to predict high probability of immunological response
  - Optimal timing of vaccination after anti-CD20 therapy

- Role of HPV vaccination after oral-neck or pelvic irradiation

- Efficacy of new inactivated HZ vaccines (heat inactivated and recombinant)
Part IC: Vaccination in Pediatric ALL
Issues in vaccination in pediatric ALL

✓ Increased risk of
  ✓ Influenza: incidence relatively low, but higher morbidity and mortality, and a delay of CT
  ✓ IPD over 10 fold than healthy population
  ✓ VZV

✓ Risk of losing long term immunity after CT (a need for booster in previously vaccinated patients)
  ✓ Chemotherapy variably reduces seropositivity rates
  ✓ In a systematic review: protective titres after chemotherapy
    ✓ 17-98% for diphtheria
    ✓ 27-82% for *Bordetella pertussis*
    ✓ 20-98% for tetanus
    ✓ 62-100% for poliomyelitis
    ✓ 35-100% for HiB
    ✓ 29-92% for mumps, 29-60% for measles, 72-92% for rubella


CT, chemotherapy
Response to influenza vaccination

Inactivated influenza vaccine is safe and might reduce respiratory infections and hospitalization in children with leukemia or lymphoma

Cheuk DK 2011 Cochrane Database Syst Rev

Wide range of response to vaccination with TIV during maintenance: H1N1 22% - 72%; H3N2 34% - 88%; B 35% - 88%


No benefit of high dose or adjuvanted vaccine vs TID

Hakim H 2016 Vaccine; McManus M 2014 Pediatr Blood Cancer

Response rate lower than in healthy controls

Porter CC 2004 Pediatr Blood Cancer

Adverse events: only mild (mostly local)
Pneumococcal vaccination in pediatric ALL

✓ Seropositivity rates after vaccination during (mainly maintenance) chemotherapy:

PCV 7, 2 doses: 86%-100% (depending on serotypes) [7]
PCV 10, 1 dose: 33%-89% (depending on serotypes) [1]
PCV 13, 1 dose (50% pts with ALL): 46%-87% (depending on serotypes) [6]

✓ Seropositivity rates after vaccination post-chemotherapy:

PCV 13, 1 dose: 64%-100% (depending on serotypes) [6]

1- Crawford 2015 Vaccine Reports; 2- Lehrnbecher 2011 British J Haematol
3- Patel SR 2010 BMJ; 4- Ridgway 1993 Leukemia and lymphoma
5- Wong 2010 Epidemiol Infect; 6- Hung TY 2017 Cancer; 7- Cheng FW 2010 Arch Dis Child
HBV infection and vaccination

✓ Countries with high prevalence of HBV
  ✓ High incidence of de novo HBV infection in, mainly related to hospitalization (unsafe transfusions, in-hospital transmission,...) [1]
  ✓ HBV infection results in delaying full CT course and a reduction of doses with higher mortality rates (7-40%) [2]

✓ In the setting with low risk of HBV transmission, the reactivation of chronic HBV infection is the main risk and should be prevented pharmacologically

DTP, HiB, IPV, meningococcus

DTP
✓ Seroconversion rate is lower in case of vaccination during maintenance compared to post-CT
✓ Seroconversion rate post-CT: diphtheria 71%-96%, tetanus 90 - 100%, pertussis 69%

HiB
✓ Comparable seroconversion rate with vaccination during maintenance or 3 months after the end of CT
✓ Seroconversion rate post-CT: 87% – 100%

Poliomyelitis
✓ Seroconversion rate post-CT: 68-100%

Meningococcus
✓ Response to MenC (conjugated vaccine) 6 months post-CT: 12-96%

HPV vaccination

Cancer survivor women are at higher risk of HPV related complications

There are no study on HPV vaccination in ALL patients

James L. Klosky 2009 Cancer
VZV infection and vaccination in ALL patients

- Higher incidence and severity of VZV infections
- 41% of VZV infections occur during maintenance therapy
- In low income countries - fatality risk of VZV reported of 3.4% - 10%
- Seroconversion rate:
  - During maintenance: 1 dose: 19%-54%; 2 doses: 94%
  - Post CT: 1 dose 39.6%; no data for 2 doses
- Vaccination was effective during maintenance, but it requires suspension of CT 1 week before and 1 week after, or longer in case of post-vaccination rash (which occurred up to 33% of patients)
- Recent data from 35.128 ALL children: 20 fatal cases (only 4 during maintenance CT), including 1 death attributed to varicella vaccination

MMR in pediatric ALL

Measles:
• High risk of severe complications in oncology pts (deaths reported) [1];
• Outbreak in hematological pts is associated with high mortality and morbidity [3];
• No treatment or preventive measure available

Mumps:
• Few data available,
• Mild infection reported in ALL pts [2]

Rubella:
• Almost no data available,
• 1 case report of persistent rubella infection in pt vaccinated during maintenance [4]

ECIL 7 guidelines for vaccination of children with ALL INDUCTION and REINDUCTION PHASES

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Timing and doses</th>
<th>ECIL 7 recommendation</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>In the setting of high HBV prevalence and high risk of acquiring HBV infection during CT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HBV in HBsAb and HBcAb seronegative patients</td>
<td>Double dose</td>
<td>B II u</td>
<td>Different schedules of 3-5 doses can be used</td>
</tr>
<tr>
<td>Co-administration of HBV specific HBlg might improve protection</td>
<td></td>
<td>C II u</td>
<td></td>
</tr>
<tr>
<td>All live vaccines (including VZV) are contraindicated</td>
<td></td>
<td>D II u</td>
<td></td>
</tr>
</tbody>
</table>

^ Better response might be obtained administering a 2nd dose and/or using an adjuvanted* or high dose vaccine**
*Data from monovalent pandemic vaccine; no data from regular adjuvanted vaccine. **Unavailable in Europe
One dose unless specified otherwise
## ECIL 7 guidelines for vaccination of children with ALL MAINTENANCE THERAPY

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Timing and doses</th>
<th>ECIL 7 recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inactivated vaccines are feasible but suboptimal response might be present &gt; most vaccinations should be postponed to 3-6 months after the end of CT in order to achieve better and longer lasting protection</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inactivated influenza vaccine</td>
<td>Yearly</td>
<td>A II u, t for dose</td>
</tr>
<tr>
<td></td>
<td>2 doses if ≤ 9 years</td>
<td></td>
</tr>
<tr>
<td>PCV13</td>
<td>1 dose</td>
<td>B II u</td>
</tr>
<tr>
<td>VZV</td>
<td>CT suspended for at least 1 week before and after, longer if vaccine-related rash</td>
<td>C II u</td>
</tr>
<tr>
<td>Postpone VZV vaccination to 3-6 months after CT, and provide alternative protective measures during maintenance therapy (acyclovir, isolation, vaccination of household contacts, etc.), in consideration of the potential risk of ALL relapse</td>
<td>A III</td>
<td></td>
</tr>
<tr>
<td>Live vaccines other than VZV are contraindicated</td>
<td></td>
<td>D II u</td>
</tr>
</tbody>
</table>
ECIL 7 guidelines for vaccination of children with ALL 3-6 MONTHS FROM THE END OF CHEMOTHERAPY

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Dose</th>
<th>ECIL 7 recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inactivated influenza</td>
<td>From the end of maintenance CT and as long as considered immunocompromised</td>
<td>B II u</td>
</tr>
<tr>
<td>Patients fully vaccinated before ALL diagnosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DTaP, IPV, HiB</td>
<td>Irrespective of Ab titres* 1 dose **</td>
<td>A II u</td>
</tr>
<tr>
<td>HBV</td>
<td>Irrespective of Ab titres* 1 dose according to country recommendations</td>
<td>A II u</td>
</tr>
<tr>
<td>PCV13</td>
<td>1 dose</td>
<td>A II u</td>
</tr>
<tr>
<td>MenC/ACWY</td>
<td>1 dose according to country recommendations</td>
<td>B III</td>
</tr>
<tr>
<td>MenB</td>
<td>1 dose according to country recommendations</td>
<td>C III</td>
</tr>
<tr>
<td>HPV</td>
<td>According to country recommendations</td>
<td>B III</td>
</tr>
<tr>
<td>VZV in seronegative patients</td>
<td>2 doses (or 2° only if seronegative 4 weeks after 1st)</td>
<td>A II u</td>
</tr>
<tr>
<td>MMR</td>
<td>Irrespective of Ab titres or when seronegative 1 dose in previously vaccinated</td>
<td>A II u</td>
</tr>
<tr>
<td>Patients not vaccinated before CT should be revaccinated with full courses, according to country’s recommendations</td>
<td></td>
<td>A II u</td>
</tr>
</tbody>
</table>

*Titres may decline over time; ** In high risk patients, suboptimal response to 1 dose might occur
Areas of research on vaccination in children ALL

- Vaccination schedules in children who did not complete the full course of primary vaccination cycles: full revaccination or boosting?

- The possible role of inactivated VZV or inactivated HZ vaccines

- The role of PPSV23
Part I: Vaccination of non-transplanted patients with hematological malignancies

- I A: Myeloid diseases
- I B: Lymphoproliferative diseases
- I C: Children Acute lymphoblastic leukemia (ALL)

Part II: Vaccination in HSCT recipients
ANTIBACTERIAL VACCINES
AFTER HSCT
Streptococcus pneumoniae
Invasive pneumococcal disease (IPD) after HSCT

Mainly pneumonia and bacteremia, 21 - 57% occurring during the first 12 months after transplant
Mortality rate after HSCT # 11-22%

The risk correlates with the decrease of specific Abs (IgG, especially IgG2 and IgG4, and IgM) levels and opsonic activity (OPA) after HSCT.

Although HSCT recipients are at higher risk after Allo than after Auto, all HSCT patients are at risk.
Main risk factors:
- After allo: chronic GVHD
- After auto: total body irradiation (TBI)

There is no data about the present risk of IPD in autologous HSCT with actual conditioning without TBI, or in those receiving post-transplant maintenance treatment

Antipneumococcal vaccines available

- **23-valent polysaccharidic (PS) vaccine (PPSV23, Pneumo23®)**
  - Poorly immunogenic, T-cell independent response, no boost effect

- **13-valent (replacing the previous 7-valent (2001-2010)) conjugate vaccine (PCV 13, Prevenar®)**
  - Highly immunogenic, due to the conjugation of each PS to a protein carrier (diphtheria CRM197 protein) which confers a T-cell dependence to the immune response, and consequently a stronger, longer-lasting Ab response, and a boost effect

- **10-valent pneumococcal non-typeable H influenzae protein D vaccine (PHiD-CDn, Synflorix®) available in some countries**
PPSV23 after allogeneic HSCT

• The immune response to PPSV23 alone is poor, (<55%) even when given from 12 months, and especially in case of chronic GVHD or ongoing steroids (Gandhi et al. BMT 2001; Kumar et al. CID 2007)

• The response to one dose given at 8 or at 20 months after allogeneic HSCT is not different (Parkkali T et al. BMT 1996)

• However, when given at 12 or 18 months after 3 doses of PCV, the response rate to specific PPSV23 antigens is in the range of 83-89% and additionally increases the response to the PCV antigens (Cordonnier C et al. Vaccine 2010)
<table>
<thead>
<tr>
<th>Reference</th>
<th>Vaccine</th>
<th>No. Pts (No. evaluable pts)</th>
<th>Immunization schedule</th>
<th>Definition of response</th>
<th>% of responders and comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Molrine Blood 2003</td>
<td>PCV7</td>
<td>96 (65)</td>
<td>3 doses at 3, 6, 12 mo (+/- donor (D) vaccination)</td>
<td>≥0.5 µg/mL for all 7 serotypes</td>
<td>At 13 months: 64-75% Benefit of D vaccination for the response to the first 2 doses, not for the 3rd</td>
</tr>
<tr>
<td>Kumar CID 2007</td>
<td>PCV7</td>
<td>64 (44)</td>
<td>1 dose of either PPV23 or PCV7 at 6 mo (1 dose of PPV23 or PCV7 to the D), assessed at 12 mo</td>
<td>≥0.35 µg/mL for ≥1 serotype</td>
<td>38.6% after PCV7 0% after PPV23 Better immunogenicity of PCV7 vs PPV23</td>
</tr>
<tr>
<td>Meisel Blood 2007</td>
<td>PCV7</td>
<td>53 ped. (43)</td>
<td>3 doses at 1 mo. interval from 6-10 mo</td>
<td>≥0.5 µg/mL for all 7 serotypes</td>
<td>74%</td>
</tr>
<tr>
<td>Cordonnier CID 2009</td>
<td>PCV7</td>
<td>158 (114)</td>
<td>3 doses: Early (3, 4, 5 mo.) or Late (9, 10, 11 mo) after HSCT</td>
<td>≥0.15µg/mL &lt; 0.5 µg/mL for all 7 serotypes</td>
<td>79 (E) vs 82 (L) % 56 (E) vs 54 (L) % Early not inferior to late</td>
</tr>
<tr>
<td>Cordonnier CID 2015</td>
<td>PCV13</td>
<td>251 (207)</td>
<td>3 doses from 4 mo, then a 4th dose at 9 mo.</td>
<td>IgG GMFR and &gt; 0.35 µg/mL for all 13 serotypes</td>
<td>89.7%–98.0% No † between MA and non-MA conditioning regimens</td>
</tr>
</tbody>
</table>

GMFR: Geometric Mean Fold Rise; MA: myeloablative
Main conclusions about pneumococcal vaccination after HSCT

• Poor response to the PPSV23 during the 1st year of transplant, especially in patients with GVHD and/or receiving steroids

• The PCV is much more immunogenic than the PPSV23 (Kumar et al. CID 2007)

• The PCV should always be administered before the PPSV23:
  – because a previous exposure to PS may induce hyporesponsiveness to subsequent administration of the conjugate vaccine including the same antigens
  – because the immune response of HSCT patients is much better and much earlier after PCV than after PPSV23

• The administration of the PPSV23 after 3 doses of PCV:
  – Increases the serotype coverage
  – Allows a significant number of previously non-responder patients to respond
Main conclusions about pneumococcal vaccination after HSCT

• Response rates to PCV are in the range of 54-98% after 3 doses over the first 12 months after transplant
• Intervals of 1 month between each PCV dose provides a regular increase of the Ab titers
• Early vaccination (from 3 months, 3 x PCV) is not inferior to late (from 9 months) vaccination after allogeneic HSCT. **Considering the risk of IPD starts early after transplant, it is crucial to achieve protective Ab titers as soon as possible. Therefore, an early vaccination is recommended.**

• No large data on long-term duration of immunity

*Meisel R Blood 2007, Cordonnier CID 2009, Cordonnier CID 2015*
Pneumococcal vaccination

ECIL 7 guidelines for allogeneic HSCT recipients

From 3 months after transplant
3 doses of PCV13 at 1 month interval

A 4th dose given 6 months after the 3rd one can be considered

in case of GVHD

At 12 months:

- 1 dose of PPSV23 * if no GVHD

* No earlier than 8 weeks after the last PCV

No large data to support recommendations after the initial program

The assessment of Ab titers to the main conjugate and PS vaccine serotypes may help in defining the best option at a given time for a patient
Pneumococcal vaccination

ECIL7 guidelines for autologous HSCT recipients (1/1)

From 3 months after transplant

3 doses of PCV13 at 1 month interval  B III

At 12 months:

1 dose of PPSV23  B III

No large data to support recommendations after the initial program

The assessment of Ab titers to the main conjugate and PS vaccine serotypes may help in defining the best option at a given time for a patient
Pneumococcal vaccination
Pediatric specificities

• Pediatric patients respond better than adults

• Their responses are close to those of healthy children (Meisel et al. Blood 2007)

• More post-vaccine fever, more local reactions than adults (Cordonnier et al. CID 2015)

• Same schedule recommended for children and adults
Haemophilus influenzae B
Immune response to Hib vaccination after allogeneic HSCT

• Although the subclass Ig response is different, the overall response to 1 dose of Hib-conjugate was not different at 6-8 or at 18-20 months (Parkkali T et al. BMT 1996; Parkkali T et al. BMT 1999)

• The response rates (#85%) to 2 doses starting between 4-9 months or between 10-17 months were not different (Barra et al. JID 1992)

• After 3 doses given over the first 2 years, the response rate varied between 47-81% (Molrine et al. Blood 1996; Parkkali et al. BMT 2007)

• A 3rd dose increases the GMCs of specific Abs (Molrine et al. Blood 1996, Parkkali et al. BMT 2007)
Immune response to Hib vaccination after allogeneic HSCT

- The Hib conjugate vaccines are highly immunogenic after HSCT
- GVHD seems to have a low impact on the immune response
- High immune responses are observed with young donors and in young recipients.
- Hib conjugate vaccines are safe after HSCT: No SAE reported
Anti-Hib vaccination

ECIL 7 guidelines for HSCT recipients

The same schedule is recommended after allogeneic or autologous HSCT.

Considering the timing of Hib infections after transplant and that patients can respond to the vaccine from 3 months, it is recommended to give **3 doses of conjugate vaccine at 1 month interval from 3 months after transplant**.

In order to give a combined vaccine and decrease the overall number of vaccine doses, an alternative is to give 3 doses of a DTP-Hib vaccine from 6 months.

Although there is no prospective comparison, the type of the conjugated protein (tetanus vs diphtheria) does not seem to impact on the response in HSCT patients.

The optimal subsequent anti-Hib vaccination program after the 3 initial doses after transplant remains to be determined.

*The assessment of specific Ab titers may help in defining the best option at a given time and at an individual level.*
Hib vaccination

Pediatric specificities

• Better vaccine response than in adults (Pao et al. BBMT 2008)

• Same schedule recommended for children and adults
Neisseria meningitidis
Meningogoccal vaccination after HSCT
Data on vaccine response

- **Available data**: only in children or young adults

- **After 1 dose of MCV-4 given** a median time of 2.3 (0.6-5.2) y after transplant: (retrospective study, 46 allo-HSCT aged 9-25y), only 65% responded either to the 4 (15%) or ≥ 1 (31-56%) serogroup. In the 16 non-responders, a second dose elicited a response in 8 of them (*Malher MB BBMT 2012*)

- **After 3 doses of MCV-C given** at 1 month interval: (prospective trial, 23 patients aged 2-17y) from 12 (auto) or 18 months (allo) after transplant, the response rate was 100% both in auto- and allogeneic HSCT recipients (*Patel SR CID 2007*)

- No data on the MenB vaccines after HSCT so far
Vaccination with Meningo vaccines is recommended, regardless of any previous vaccination, from 6 months after transplant, at least 2 doses, in accordance with country recommendations and local prevalence for the healthy population for a given age and particularly for risk groups such as students living in campus, travellers or soldiers:

- with either a Men-C or a tetravalent vaccine

AND

- with a Men-B vaccine
Meningococcal vaccination
Pediatric specificities

• Main population at risk

• Guidelines based on the pediatric population

• Same recommendations in adults and in children
Tetanus vaccine after HSCT

• 3 doses are needed (Ljungman et al. JID 1990). Excellent tolerance, no SAE.

• Excellent response (85-100%) after 3 doses given at 1-2 months interval from 6-12 months.

• Comparable response after Allo (Ljungman et al. JID 1990; Parkkali et al. BMT 1997; Parkkali et al. BMT 2007; Inaba et al. BJH 2012) or Auto HSCT (Vance et al. BMT 1998), except in NHL patients who had received Rituximab before and/or after Auto (Small T et al. BBMT 2009)

• Comparable responses after RIC (Meerveld-Eggink et al. BBMT 2009) or cord blood transplant when vaccinated at 7-45 months (Shah et al. BBMT 2015)

• No difference in response when vaccinated early (6, 8, 14 months) or late (18, 20, 26 months) (Parkkali et al. BMT 1997)

• Responses are not or only weakly affected by GVHD
Diphtheria vaccine after HSCT

• 3 doses are needed (Parkkali et al. BMT 2007). Excellent tolerance, no SAE.

• Excellent response (70-100%) to 3 doses given at 1-2 months interval from 6-12 months after Allo (Parkkali et al. BMT 2007; Olkinuora et al. Acta Pediatr 2012; Inaba et al. BBMT 2012)

• Limited data after Auto HSCT (Nordoy et al BMT 2001; Small T et al. BBMT 2009)

• No specific data after RIC

• Response after cord blood in the same range as BM or PBSC when vaccinated at 7-45 months (Shah et al. BBMT 2015)

• Responses are not or only weakly affected by GVHD

• A trend for lower long-term immunity with Td than with DT in allogeneic HSCT children and young adults (Inaba et al BJH 2012)
Diphtheria-Tetanus vaccination

**ECIL 7 guidelines for allogeneic and autologous HSCT recipients**

- 3 doses at 1-2 months interval from 6 months, both for allogeneic and autologous HSCT  
  B II u

- Prefer DT to Td both in children and adults  
  C III

- Boost doses to administer according to country recommendations
DT vaccination

Pediatric specificities

• Better response in children than in adults

• Same recommendation in adults and in children
Bordetella pertussis
# Main data on pertussis vaccination after HSCT

<table>
<thead>
<tr>
<th>Reference</th>
<th>Vaccine (Pertussis Toxoid content/µg)</th>
<th>No. evaluable patients Type of HSCT (age range)</th>
<th>Immunization schedule</th>
<th>Definition of response</th>
<th>% of responders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Papadopoulos Blood 2008 (Abstract ASH)</td>
<td>Tdap (2.5)</td>
<td>41 pts ALLO (1) (10-64y)</td>
<td>1 dose, at a median of 4.5 y post-transplant</td>
<td>&gt; 2 fold Ab titers from pre-vaccine titers</td>
<td>7/41 (17%)</td>
</tr>
<tr>
<td>Small BBMT 2009</td>
<td>Tdap (2.5)</td>
<td>28 pts AUTO (2) (20-73y)</td>
<td>1 dose, at a median of 4.5 y post-transplant</td>
<td>«</td>
<td>2/28 (7%)</td>
</tr>
<tr>
<td>Inaba BJH 2012</td>
<td>DTaP (25)</td>
<td>30 children ALLO ≤ 7 y evaluable for long-term FU with 3 Ab assessments</td>
<td>3 doses planned at 12, 15 and 18 months (4)</td>
<td>EIA index values &gt; 1.19</td>
<td>Each of the 3 doses increased Ab titers At 5 years post-HSCT: only 5/16 (31%) were protected</td>
</tr>
<tr>
<td>Shah BBMT 2016</td>
<td>Tdap (8) in adults DTaP (25) in children</td>
<td>63 pts ALLO Cord Blood (0.9-64)</td>
<td>2 or 3 doses at 1 month interval, started at a median of 17 (range: 7-45) months (3)</td>
<td>Seroconversion in a seroneg patient or &gt;2 fold rise Ab titer</td>
<td>Children (n=16): 100% Adults (n= 44): 54%</td>
</tr>
</tbody>
</table>

(1) 59% of the patients were transplanted with T-cell depleted grafts  
(2) 84% of the patients had received Rituximab before and/or after autologous HSCT  
(3) Vaccination was post-poned in case of chronic GVHD, CD4 <200/µL and IgG <5g/L  
(4) Vaccination was post-poned in case of chronic GVHD
Pertussis vaccination
ECIL 7 guidelines for allogeneic and autologous HSCT recipients

• *The vaccination mainly aims at avoiding pertussis transmission by HSCT patients in the community*

• The addition of pertussis toxoid to the tetanus-diphtheria vaccine (*recommended as BII*), 3 doses at 1-2 month interval from 6 to 12 months, should be considered after transplant

  **CIII**

• Although there is no specific study with DTaP in adult HSCT recipients, considering the poor response to Tdap, **the DTaP** which contains a higher dose of PT than the Tdap *should be preferred both in children and adults*

  **CIII**
Pertussis vaccination
Pediatric specificities

• Response significantly better in children than in adults (Shah et al. BBMT 2016)

• Previously unvaccinated HSCT infants should be vaccinated as soon as possible

• Same recommendations in older children and in adults
ANTIVIRAL VACCINES AFTER HSCT

- Influenza
- Poliomyelitis
- Hepatitis B
- Human papillomavirus (HPV)

- Varicella-zoster virus (VZV)
- Measles-mumps-rubella (MMR)

*In purple: Live attenuated vaccines (LAV)*
Influenza after HSCT

- Morbidity and mortality
- H1N1-pandemic: 6% mortality in HSCT recipients
- Pneumonia=main complication of influenza, 29-33% of HSCT-recipients with influenza acquire pneumonia.
- Mortality rate of Flu pneumonia after HSCT: 6-28%

*Ljungman et al 2011, Nichols et al 2004*
Inactivated influenza vaccine in HSCT patients

Summary

- One study shows the clinical efficacy of 1 dose of TIV in HSCT pts vaccinated more than 6 months after transplant (Machado et al. BMT 2005)
- Response rates to 1 dose given > 6 mo.: 10-74% for TIV, 44-64% for H1N1
- Response improves with time after transplant
- No clear benefit of adjuvanted vs. non adjuvanted vaccines
- Conflicting data exist on the benefit of a 2nd dose
- There is marginal benefit of GM-CSF and of high-dose of antigen
- Transient (early) benefit of pretransplant donor or recipient vaccination
Predictors of poor immune response to IIV after HSCT

- Low lymphocyte counts at vaccination \((\text{Engelhard 2011, Fukatsu 2016})\)
- Low IgG, IgA or IgM at vaccination \((\text{Fukatsu 2016, Mohty 2011})\)
- Chronic GVHD \((\text{Fukatsu 2017})\)
- Use of calcineurin inhibitors or other immunosuppressive drugs \((\text{Mohty 2011, Natori 2017})\)
- Use of rituximab last 12 months \((\text{Issa, 2011})\)
- Local vaccine reaction associated with better immune response \((\text{Gelinck, 2009})\)
ECIL 7 guidelines for seasonal inactivated influenza vaccination (IIV) in HSCT-recipients

- **In allogeneic HSCT recipients**: Annual seasonal IIV, 1 dose, at the beginning of flu season in all patients > 6 months after transplant and pursued during the first years following transplant, at least until 6 months after stopping any IS and:
  - as long as the patient is judged to be immunosuppressed
  - Or life-long

- **In autologous HSCT-recipients**: Annual seasonal inactivated influenza vaccination, 1 dose, at the beginning of flu season in all patients > 6 months after transplant, at least as long as the patient is judged to be immunosuppressed

- **In children > 9 y and in adults**, a **2nd dose of vaccine** after 3-4 weeks may have a marginal benefit and should preferably be considered in patients with severe GVHD or low lymphocyte counts

- **In the setting of a community outbreak**: IIV can be given both to allo- and auto-HSCT-recipients, from 3 months after transplant. In that case, considering waning of immunity over time, a 2nd dose is likely to be beneficial
Influenza vaccination of HSCT recipients
Pediatric specificities

- Children 6 months through 8 years, receiving influenza vaccination for the first time after transplant should receive a second dose at least 4 weeks after the first dose

B II
Main data of the literature on Inactivated Polio Vaccine

- Vaccination equally immunogenic when started at 6 or 18 months after alloSCT (Parkkali 1997). Well tolerated, no SAE reported
- More limited data after Auto HSCT (Nordoy BMT 2001; Small T BBMT 2009)
- No specific data after RIC
- Response after cord blood in the same range of those of other stem cell sources when vaccinated at 7-45 months (Shah et al. BBMT 2015)
- Response not or only weakly affected by GVHD (Parkkali 1997)
- Long-term immunity well retained, except in children (<10y at time of transplant) (Ljungman 2004)
- Small benefit of donor vaccination (Parkkali 2007)
ECIL guidelines for polio vaccination of HSCT recipients

• 3 doses of inactivated polio vaccine at 1-2 months interval, starting from 6-12 months post HSCT

• Oral polio vaccine should not be given after HSCT
Poliovirus inactivated vaccination

Pediatric specificities

• Better response in children than in adults

• Higher risk for loosing immunity in the years after initial vaccination if transplanted before 10 years old
  => Regular Polio-Ab assessment may be useful in children

• Same recommendations in children and in adults
Hepatitis B virus vaccination (3/3)

Before transplant:
Donor anti-HBc+ for Recipient all negative: Pt vaccination if possible  
Additional antiHBV immunoglobulins may be combined with vaccination

After transplant:
- Pts who were all negative before transplant and patients who were vaccinated before transplant but lost their immunity at 6 mo. should be vaccinated according to country recommendation and age (3 doses: 0, 1, 6 mo, from 6-12 months)
- Pts previously infected with HBV before HSCT (AntiHBc +) should be followed for antiHBs and be vaccinated if they have unprotective titers in order to prevent reverse seroconversion

After vaccination, HSCT recipients may be assessed for antiHBs titers between 1-2 months after the 1st series of 3 doses. If antiHBs< 10mIU/mL: an additional series of 3 doses should be considered but the benefit of a 2nd series is uncertain
HPV and HSCT

Savani et al, BBMT, 2008
35 female allo-pts,
Cervical cytology testing 45-163 months after transplant
43% had abnormal cytology
34% had HPV-related squamous intraepithelial lesions (high-grade: 20%)
Highest risk in chronic GVHD

HPV vaccine and HSCT

MacIntyre et al. Vaccine 2016
59 immunocompromised children (5-18y) including 20 HSCT recipients
3 doses of quadrivalent vaccine from 6 months after transplant, within 2-6 months
Seroconversion rate after 3 doses: 89 to 100% according to type
ECIL-guidelines for HPV-vaccination in HSCT-recipients

• Follow recommendations for general population in each country from 6-12 months after transplant

No specific safety issue expected in this patient population
Side effects of inactivated vaccines
Conclusions for HSCT recipients

Vaccinations are safe in HSCT pts: No evidence that side effects of vaccines after HSCT are increased compared to healthy controls or to donors

Most AE (local reactions, myalgia, fever, fatigue) quickly resolved

Most SAE not related to vaccines

No evidence that vaccination triggers or worsens GVHD after allogeneic HSCT Engelhard et al. Vaccine 2011
Risk of Varicella-Zoster infections in HSCT patients

- VZV infections may be severe, even life-threatening, after HSCT, and require hospitalization
- Risk of primary varicella infection (chickenpox) in seronegative patients
- High risk of zoster infection (VZV reactivation/shingles) in previously seropositive patients (23-59%), especially:
  - during the 1st year, and persistent thereafter
  - in patients with GVHD
- High risk of postherpetic neuralgia (35%) in this population (Onazawa M, BBMT 2009)
Vaccines for VZV infections

VACCINES COMMERCIALY AVAILABLE:

• **Live attenuated VARICELLA vaccines** (LAVV): low-titer VZV-vaccine (#10\(^3\)PFU), indicated in healthy individuals for:
  – Vaccination of individuals > 12 mo or recent (3 days) exposure to varicella (Varivax®): 2 doses at ≥1 mo. interval
  – Vaccination of seroneg adolescents and adults (> 13 y): (Varilrix ®)2 doses at 6 w interval

• **Additionally:** LAV combining Measles, Mumps, Rubella, and Varicella

• **Live attenuated ZOSTER vaccine**: high-titer VZV-vaccine (>19x10\(^3\)PFU), indicated in sero + healthy individuals of > 50 y for:
  – Prevention of zoster
  – Prevention of zoster-related post-herpetic neuralgia

VACCINES NOT YET COMMERCIALLY AVAILABLE:

• Adjuvanted VZV-subunit vaccine (*submitted to FDA and EMA approval*)
• Inactivated VZV-vaccine (V212)

PFU: Plaque-forming unit
Severe adverse events following varicella or zoster LAV

Fatal disseminated VZV infections due to the vaccine strain have been reported in HSCT patients after live attenuated varicella vaccine, even when vaccinated several years after HSCT (Bhalla CID 2015), and in non-transplanted, hematology patients under chemotherapy (Schrauder A, Lancet 2007) or in primary immunodeficient children (Leung, Hum Vaccine Immunother 2014)

Fatal disseminated zoster infections have been reported after live attenuated zoster vaccine, both in HSCT recipients and in other, non-transplanted hematology patients (Curtis KK, J Gen Intern Med 2008) even in pts whose CT had been stopped 6 months before (Costa, BMJ case report 2015)

The timing (> 24 mo after transplant) is not a sufficient condition to use LAAV in HSCT patients. Other conditions are required.
Inactivated Zoster vaccine (ZVIN, V212) in Autologous HSCT

A phase III, double-blind, randomized, placebo-controlled, multicenter clinical trial to study safety, tolerability, efficacy and immunogenicity of inactivated VZV-vaccine(ZVIN) in recipients of autologous HSCT

- 4 doses (1st within 30 days before auto-HSCT, dose 2-4: d30, 60, 90 post HSCT)
- 3 randomization groups:
  - ZVIN (n=560)
  - ZVIN high antigen (n=160)
  - Placebo (n=564)

Results

- Herpes zoster(HZ) significantly reduced with ZVIN vs. placebo
  42/538 (7.8%) vs 113/535 (21%) (p<.0001)

- SAE, and vaccine-related SAEs: Similar between ZVIN and placebo group (32.9% vs 32.7%, and 0.8% vs 0.9%, respectively)

Cornely A et al. Abstracts EBMT 2017
Main conclusions on VZV-vaccination in HSCT recipients

• Antiviral prophylaxis (Acyclovir/valacyclovir) is still the primary mode of prevention: effective, cheap and safe. It should be given for at least one year after allogeneic HSCT and for 3-6 months after autologous HSCT.


• **New inactivated zoster vaccine (V212)**(not yet commercially available): safe in HSCT recipients
  - promising data in auto-HSCT (*Cornely*, *EBMT abstract 2017, paper not published*): clinically efficient in reducing zoster
  - but poorly immunogenic in allo-HSCT recipients (*Mullane* 2013)
ECIL-guidelines for VZV-vaccination after HSCT

- Live-attenuated Varicella vaccine (LAVV) is contraindicated in HSCT-recipients with active GVHD, relapse of the underlying disease, or ongoing immunosuppression
  
  \[ \text{DIII} \]

- 1 dose (adults) of LAVV can be considered in a clinically well, seronegative patient > 24 months after transplant, no GVHD, no IS, no relapse of the underlying disease, and no Ig since at least 8 months
  
  \[ \text{BIIr} \]

- The addition of a 2\textsuperscript{nd} dose in adults may be considered in patients who were seronegative before HSCT or had no history of VZV infection

- Live-attenuated Zoster vaccine is not recommended in HSCT-recipients
  
  \[ \text{DIII} \]
Pediatric specificities on live-attenuated Varicella Vaccine

• Two doses (instead of 1 dose in adults) of LAVV can be considered in children meeting the same limitation criteria than in adults

• The interval between 2 doses should be the one recommended in the official label
Measles, Mumps, Rubella

**Measles after HSCT**: often severe, pneumonia, encephalitis, possibly fatal

**Mumps**: No severe morbidity reported after transplant

**Rubella**: No severe morbidity reported. The main goal of vaccination is to *prevent vertical transmission* in fertile women

Probability to be seronegative at 5 years after allo: **60%, 73% and 52%**, for measles, mumps and rubella, respectively (*Ljungman Blood 1994*)

High risk in pts with previous aGVHD or vaccination prior to HSCT instead of natural infection (*Ljungman BMT 2004*)

**Only live-attenuated vaccines available:**
Measles (alone), measles+mumps, measles+rubella, MMR, MMR+LAVV (varicella)
ECIL-guidelines for MMR vaccination

• HSCT recipients should be tested for MMR Ab titers from **24 months** after transplant

• Seronegative patients for measles should receive 1 dose of MMR from 24 mo. after transplant, if no GVHD, no IS, no relapse of the underlying disease, and no IG since at least 8 months

• Seronegative women for Rubella and of childbearing potential should receive 1 dose of MMR with the same precautions

• In case of measles outbreak, MMR could be considered from 12 mo. after transplant in patients with low grade IS

**Pediatric specificities**

• Lower response in children - -> Consider 2 doses in children, with an interval of at least 4 weeks
Rituximab and vaccination after HSCT

**AUTOLOGOUS SCT:** Ritux given for maintenance after Auto: acceptable – although impaired – vaccine response with T-cell dependent (ie. Tetanus, PCV, HiB) antigens but not with T-cell independent Ags (ie. PPSV23) when vaccinated > 6-8 months after last dose of Ritux (Horwitz Blood 2004, Pao BBMT 2008)

**ALLOGENEIC HSCT:**
- Very limited data
- Ritux greatly impairs the vaccine response, even when vaccine given 28 mo. after last dose (Issa BBMT 2011, Malher BBMT 2012, Roll Infection 2012, Shah BBMT 2015)

**ECIL GUIDELINE:**
- HSCT who have received Ritux from transplant should have their vaccine program delayed at least more than 6 months after the last dose
- Ab response is uncertain even with T-cell dependent vaccine. Specific Ab assessment after vaccination can be helpful
  
  Similar issues are expected with other anti-B MoAbs.
Specific questions on Recipient vaccination

• Non-severe, controlled GVHD has limited effects on the response to most vaccines and should not delay starting vaccination

• Assessment of individual Abs is encouraged after most vaccines, especially in patients who are likely to have a suboptimal response (severe GVHD, Rituximab)
Summary ECIL 7 guidelines for vaccination in adult ALLOGENEIC HSCT recipients (I/II)

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>3-6 mo.</th>
<th>6-12 mo.</th>
<th>12-24</th>
<th>&gt; 24 mo.</th>
<th>Grading</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCV</td>
<td>3 doses</td>
<td></td>
<td></td>
<td></td>
<td>AI</td>
</tr>
<tr>
<td>HiB</td>
<td>3 doses</td>
<td></td>
<td></td>
<td></td>
<td>BIIr</td>
</tr>
<tr>
<td>HiB</td>
<td></td>
<td>A 4th dose if GVHD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HiB</td>
<td></td>
<td>Or 3 doses of DTP-HiB combined vaccine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PPSV23</td>
<td></td>
<td>1 dose at 12 mo if no GVHD</td>
<td></td>
<td></td>
<td>BI</td>
</tr>
<tr>
<td>DTpolio + pertussis</td>
<td></td>
<td>3 doses from 6-12 mo</td>
<td></td>
<td></td>
<td>BII u  CIII</td>
</tr>
<tr>
<td>MenC MCV4</td>
<td></td>
<td>&gt;2 doses</td>
<td></td>
<td></td>
<td>CR</td>
</tr>
<tr>
<td>Men B</td>
<td></td>
<td>2 doses</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**CR**: According to country recommendation and age
<table>
<thead>
<tr>
<th>Vaccine</th>
<th>3-6 mo.</th>
<th>6-12 mo.</th>
<th>12-24</th>
<th>&gt; 24 mo.</th>
<th>Grading</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inact. influenza</td>
<td></td>
<td>At the beginning of Flu season</td>
<td></td>
<td></td>
<td>1 dose:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>All r</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2 doses:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>BII r</td>
</tr>
<tr>
<td>HPV</td>
<td></td>
<td>No. doses according to official label</td>
<td></td>
<td></td>
<td>CR BIIu</td>
</tr>
<tr>
<td>HBV</td>
<td></td>
<td>In pts all neg for HBV before HSCT <em>and</em> in pts vaccinated before HSCT but with antiHBs&lt;10IU/L</td>
<td></td>
<td></td>
<td>CR BII t</td>
</tr>
<tr>
<td>«</td>
<td></td>
<td>In pts previously infected and antiHBS &lt;10IU/L</td>
<td></td>
<td></td>
<td>BIII</td>
</tr>
<tr>
<td>Varicella LAV</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MMR</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*CR: According to country recommendation and age*
Summary ECIL 7 guidelines for vaccination in adult AUTOLOGOUS HSCT recipients (I/II)

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>3-6 mo.</th>
<th>6-12 mo.</th>
<th>12-24</th>
<th>&gt; 24 mo.</th>
<th>Grading</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCV</td>
<td>3 doses</td>
<td></td>
<td></td>
<td></td>
<td>BIII</td>
</tr>
<tr>
<td>HiB</td>
<td>3 doses</td>
<td></td>
<td></td>
<td></td>
<td>BII r</td>
</tr>
<tr>
<td>HiB</td>
<td></td>
<td>Or 3 doses of DTP-HiB combined vaccine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PPSV23</td>
<td></td>
<td></td>
<td>1 dose at 12 mo</td>
<td></td>
<td>BIII</td>
</tr>
<tr>
<td>DTpolio + pertussis</td>
<td></td>
<td></td>
<td>3 doses from 6-12 mo</td>
<td></td>
<td>BII u CIII</td>
</tr>
<tr>
<td>MenC or MCV4 Men B</td>
<td></td>
<td></td>
<td>&gt;2 doses</td>
<td></td>
<td>CR BIIu BIII</td>
</tr>
</tbody>
</table>

**Note:** CR: According to country recommendation and age.
<table>
<thead>
<tr>
<th>Vaccine</th>
<th>3-6 mo.</th>
<th>6-12 mo.</th>
<th>12-24</th>
<th>&gt; 24 mo.</th>
<th>Grading</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inact. influenza</td>
<td></td>
<td>At the beginning of Flu season</td>
<td></td>
<td></td>
<td>1 dose: All r</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2 doses: BII r</td>
</tr>
<tr>
<td>HPV</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>CR BIIu</td>
</tr>
<tr>
<td>HBV</td>
<td></td>
<td>In pts all neg for HBV before HSCT and</td>
<td></td>
<td></td>
<td>CR BII t</td>
</tr>
<tr>
<td></td>
<td></td>
<td>vaccinated before HSCT but with</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>antiHBs&lt;10IU/L</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>«</td>
<td></td>
<td>In pts previously infected and antiHBS&lt;10IU/L</td>
<td></td>
<td></td>
<td>BIII</td>
</tr>
<tr>
<td>VZV</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>BII r</td>
</tr>
<tr>
<td>MMR</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>BII u</td>
</tr>
</tbody>
</table>

**GRADING:**
- **CR:** According to country recommendation and age
- **BII r:** Both recommendations are required
- **BII u:** Only one recommendation is required
- **BIII:** No further recommendations

**NOTE:** The table outlines the ECIL 7 guidelines for vaccination in adult AUTOLOGOUS HSCT recipients (II/II). The recommendations vary based on the type of vaccine and the time frame after HSCT.
DONOR VACCINATION
# Benefit of donor vaccination before harvest on the recipient response to inactivated vaccines

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Benefit</th>
<th>Comments</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tetanus</td>
<td>Yes</td>
<td>Improves the response of early (d-1, d50) R vaccination</td>
<td>Storek 2004</td>
</tr>
<tr>
<td>Diphtheria</td>
<td>Yes</td>
<td>Improves the Ab concentrations</td>
<td>Storek 2004, Parkkali 2007</td>
</tr>
<tr>
<td>Polio</td>
<td>No</td>
<td>Good response in the group with no D vaccination</td>
<td>Parkkali 2007</td>
</tr>
<tr>
<td>Pertussis</td>
<td>Unknown</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PPV23</td>
<td>No</td>
<td></td>
<td>Storek 2004, Kumar 2007</td>
</tr>
<tr>
<td>PCV</td>
<td>Yes</td>
<td>Improved after early vaccination, no more significant at 12 months</td>
<td>Molrine 2003, Kumar 2007</td>
</tr>
<tr>
<td>Hib</td>
<td>Yes</td>
<td>Improves the response of early (d-1, d50) R vaccination</td>
<td>Storek 2004</td>
</tr>
<tr>
<td>Influenza</td>
<td>No</td>
<td>No difference on Flu Abs of the R during the first 6 months after transplant. No improved response of the R when vaccinated at 6 months</td>
<td>Ambati 2015</td>
</tr>
<tr>
<td>HBV</td>
<td>Conflicting results</td>
<td>Poor response to HBsAg with or without D vaccination in Storek et al. Improved response to KLH in Wimperis et al.</td>
<td>Storek 2004, Wimperis 1990</td>
</tr>
</tbody>
</table>
Donor vaccination
LAV to avoid before harvest

LAV should be avoided before harvest, due to the risk of transmitting the pathogen with the graft.

All these vaccines (MMR, VZV, yellow fever, LAV flu vaccine) are contra-indicated in the donor in the weeks preceding donation.

Although the duration of vaccine-induced viremia is shorter for some of these vaccines, excluding any LAV 4 weeks before stem cell harvest should reasonably exclude any risk of transmission (Rubin et al. CID 2014)
Vaccination of the healthcare personnel in the hematology ward

ECIL 7 guidelines

- Hospital staff working with immunocompromised patients should receive inactivated influenza vaccine (IIV) annually

- Hospital staff working with hematology or HSCT patients should be vaccinated according to the country recommendations and additionally to the hospital guidelines

- Care holders who are seronegative for Measles or for VZV should be vaccinated. In case of post-vaccine rash, they should avoid any contact with immunocompromised patients
Vaccination of household members of HSCT recipients
ECIL 7 guidelines

Individuals who live with HSCT recipients should be either immunized or vaccinated according to their age and country recommendations, especially for VZV and MMR

Individuals who live with HSCT recipients should receive inactivated influenza vaccine (IIV):
- beginning season before transplant and first season after transplant AIII
- and annually as long as the patient is judged to be severely immunosuppressed CIII

The live attenuated influenza vaccine (LAIV) should not be used in individuals living with a HSCT recipient in the first months of transplant or with GVHD. BIII

Infants 2-7 months in close contacts with HSCT recipients should be vaccinated for rotavirus but the HSCT recipient should have no contact with the stools or diapers of the vaccinated children for 4 weeks following vaccination
Areas of research on vaccination in HSCT

✓ Early vaccination programs in specific HSCT populations:
  - Cordblood, Haplo

✓ Predictors of the very poor response to vaccine (in order to develop alternatives)

✓ Optimal timing to vaccinate SCT patients after rituximab

✓ Efficacy and safety of combined vaccines

✓ Need for long-term immunization programs

✓ New vaccines to be assessed in this very specific population

✓ LAV for traveler HSCT recipients
These slides are open for public consultation until November 1st, 2017

Any comment, question, suggestion, should be sent by @mail to

catherine.cordonnier@aphp.fr

by Nov 2, 2017