Vaccinations For Paediatric Patients Treated With Standard-Dose Chemotherapy And Haemopoietic Stem Cell Transplantation (HSCT) Recipients

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VACCINATIONS FOR PAEDIATRIC PATIENTS TREATED WITH STANDARD-DOSE CHEMOTHERAPY AND HAEMOPOIETIC STEM CELL TRANSPLANTATION (HSCT) RECIPIENTS

Most children with cancer are immunocompromised. The cancer itself may cause a variable degree of immunosuppression but it is the cytotoxic anti-cancer therapy that is the main contributor. The majority of children with cancer are treated with standard-dose chemotherapy but children with high-risk haematological malignancy, children with certain solid tumors and children with disease relapse require high dose chemotherapy +/- radiotherapy followed by haematopoietic stem cell transplant (HSCT). These different forms of treatment have different influences on the immune system and the degree of immunodeficiency. Immune alteration is reflected by decreases in neutrophils, lymphocytes, immunoglobulin levels and specific antibodies against previous vaccinations.

Most of the vaccine-preventable diseases are now fortunately rare. However, the risk for some remains significant, in part due to increases in migration and travel. Furthermore they can be associated with high morbidity and mortality, particularly in immunocompromised patients. In view of the secondary immunodeficiency of children treated for cancer, particularly HSCT recipients, and their improved long-term survival after completion of treatment, it is important to ensure that they are protected against vaccine-preventable diseases. This can be achieved by optimising the vaccination strategy in children during chemotherapy and by re-vaccination of children after completion of chemotherapy. In view of the diversity of malignant diseases and their treatment protocols, it would be difficult to propose different vaccination schedules for each disease. Rather it is sensible to divide into children treated with standard-dose chemotherapy and children treated with high-dose chemotherapy (+/- radiation) followed by allogeneic or autologous HSCT.
VACCINATIONS FOR PAEDIATRIC PATIENTS TREATED WITH STANDARD-DOSE CHEMOTHERAPY

Different cancers require treatment with different combinations of chemotherapy agents. Therapy for a single disease is risk-stratified based on patient factors, extent of disease and tumour biology, so there may be variation in intensity of therapy for a single disease type. Therapy regimens that include agents such as cyclophosphamide, purine nucleoside analogues or corticosteroids are immunosuppressive; they particularly have an effect on lymphocyte function. Some treatment regimens include radiation therapy; there are few data on the influence of radiotherapy on immunosuppression. If radiation therapy involves the spleen it may cause functional hyposplenia or asplenia which increases susceptibility to infections with polysaccharide encapsulated bacteria.

Depending on the treatment regimen, B- and T-lymphocyte levels decrease during treatment; with an increase in number occurring one month after completion of chemotherapy. Total B- and T-lymphocytes usually recover fully quantitatively and functionally six months after completion of chemotherapy, although in some cases recovery may take up to one year.

There are published studies demonstrating a reduction in immunity to vaccine antigens such as *Haemophilus influenzae* type b (Hib), Meningococcus C (Men C), tetanus, polio, measles and pneumococcus serotypes; and protective antibody responses have been demonstrated to these antigens with a vaccination regimen beginning 6 months after completion of treatment. However, there are no published data in this group of patients on immunity to, or immune response to, newer vaccines such as Human Papilloma Virus vaccine (HPV).

There is a reduction in vaccine-antigen specific antibody concentrations after completion of chemotherapy. It is therefore wise to follow the same vaccination recommendations for all patients treated with standard-dose chemotherapy.

**General Principles:**

- Avoid administration of all live vaccines to patients on chemotherapy and within 6 months following completion of chemotherapy.
- Avoid administration of live vaccines, except MMR (Measles/Mumps/Rubella), VZV (Varicella Zoster Virus), LAIV (Live attenuated Influenza vaccine) and Rotavirus vaccines, to siblings of patients on chemotherapy (or within 6 months following completion of chemotherapy).
- VZV vaccine should be offered to healthy susceptible siblings and other family members of patients receiving chemotherapy.
- Inactivated Influenza vaccine should be offered to all patients receiving chemotherapy or are within 6 months of completion of chemotherapy.
- Update primary health care records if vaccination takes place in hospital

**Vaccinations for patients receiving standard-dose chemotherapy (or within 6 months of completion)**

Consider following the timing and content of the routine childhood vaccination programme, using only non-live vaccines provided the child’s general condition is stable and is expected to stay so for 3 weeks from vaccination. Avoid vaccination during the period the patient is receiving steroids (the immune response will be suboptimal) or the patient is neutropaenic (defined as neutrophil count <0.5).

Inactivated influenza vaccine is recommended annually in the autumn for all patients on chemotherapy or within 6 months of its completion. The live attenuated intranasal vaccine should not be given to this group of patients.

**Vaccination schedule for patients beginning 6 months after completion of standard-dose Chemotherapy**

For children age less than 10 years give Diphtheria, Tetanus, acellular Pertussis, IPV, Hib-conjugate (DTaP/IPV/Hib) [Pediaccel®].

AND Meningococcal C-conjugate vaccine (Men C) [NeisVac® or Menjugate®]
Or Men ACWY-conjugate vaccine [Menveo®] for children at additional risk because of splenic dysfunction or asplenia or underlying complement deficiency

For children age 10 years and over give dTaP/IPV (Repevax) and Hib/Men C (Menitorix). For children at additional risk because of splenic dysfunction or asplenia or underlying complement deficiency also give Men ACWY-conjugate vaccine [Menveo®].

- 13-valent Pneumococcal conjugate vaccine (PCV13) [Prevenar 13®]
- Meningococcal B vaccine [Bexsero]
- MMR [Priorix® or MMRVaxPRO®]: If patient only received 1 dose of MMR prior to starting chemotherapy then should receive 2 doses of MMR after completion of chemotherapy. The 2nd dose should be given 6 months after the 1st dose. The 2nd dose can be given 3 months after the 1st dose or can be considered even earlier (1 month after 1st dose) in measles outbreak situations.
- Human Papilloma Virus vaccine (HPV) for eligible girls [Gardasil®]: Girls that did not start or complete the course of HPV vaccination should be given 2 doses of HPV vaccine at 6 and 12
months after completion of chemotherapy. Girls who have not had their first dose of HPV vaccine by the time they are 15 years old should be offered the three dose schedule. For girls that did complete the course, a booster dose should be given.

Subsequent routine booster doses will not be necessary if scheduled to be given within one year of the above booster doses.

BCG Vaccine: If patient has previously had BCG and is considered to be at high risk of tuberculosis: perform mantoux test and if negative, re-vaccinate. If patient has not previously had BCG vaccinate according to local policy.

**Vaccination of close contacts of patients receiving standard-dose chemotherapy (or within 6 months of completion)**

The following live vaccines can be administered to siblings/ close family contacts of patients on chemotherapy or within 6 months following completion of chemotherapy.

- MMR Vaccine should be given to contacts as per the national vaccination schedule.

- VZV vaccine (Varivax®) should be offered to healthy susceptible siblings (and adult family members who are VZV seronegative) of VZV seronegative patients. There is theoretical risk of transmitting the attenuated vaccine virus to a susceptible individual; as a precautionary measure, any person who develops a vesicular rash after receiving VZV vaccine should avoid direct contact with the patient until the rash is dry and crusted.

- Shingles vaccine (Zostavax®): Is offered to adults aged 70-79 years old, so the patient’s grandparents may be offered this vaccine. Rarely the transmission of vaccine virus may occur between those vaccinated who develop a varicella-like rash and susceptible contacts. As a precautionary measure, any person who develops a vesicular rash after receiving Zostavax® should avoid direct contact with the patient until the rash is dry and crusted.

- Rotavirus vaccine (Rotarix®): Is given to infants aged 6-24 weeks. Rotarix should not be given to the patient but can be given to siblings. There is potential for transmission from the infant to immunocompromised contacts through the faecal-oral route for at least 14 days post-vaccination. However, vaccination of the infant will offer protection to household contacts from wild-type rotavirus disease and outweigh any risk from transmission of vaccine virus to any immunocompromised close contacts. Good personal hygiene should be observed following administration of Rotarix.

- Influenza vaccine: Consideration should also be given to giving influenza vaccine to
household contacts. There is a theoretical potential for transmission of live attenuated influenza virus from LAIV to immunocompromised contacts for one to two weeks following vaccination.

**Travel Abroad**
Live vaccines such as BCG, VZV, MMR, LAIV, rotavirus, oral typhoid and yellow fever should be avoided during chemotherapy and for 6 months after completion of chemotherapy.
HSCT recipients are profoundly immunosuppressed for several months, even years after transplantation. Immune reconstitution after HSCT occurs in a well-defined manner. The various components of the new immune system develop and mature at different rates and this dictates the timing and type of specific infections as well as the response to different antigens. Immune reconstitution after autologous HSCT occurs faster than allogeneic HSCT. Innate immune function recovers earlier than adaptive immune function; innate immune function recovers weeks to months after transplantation. A prolonged immune deficiency arises from a deficiency of the more specialized functions of the adaptive immune system, in particular, the reconstitution of CD4+-lymphocytes. B-lymphocyte numbers can recover three-months after transplant in recipients without chronic-GvHD, full functional recovery takes longer. Immunoglobulin levels start normalising six-months after transplant; IgG2 subclass is the last to recover. T-lymphocyte recovery is via thymic-independent and thymic-dependent pathways; recovery of naïve CD4+-T-lymphocytes is particularly slow and is influenced by recipient age and chronic-GvHD. T-lymphocyte genesis is evident 6-12 months after transplant.

Immunity to vaccine preventable diseases declines after HSCT; there are published reports showing a significant proportion of HSCT recipients to be susceptible to pathogens against which they had been successfully immunised prior to transplantation. There are few published reports on the incidence of vaccine-preventable diseases in HSCT recipients, the available reports show an increased incidence and/ or morbidity and mortality for pneumococcal disease, varicella, measles and influenza [Winston et al., 1979; Feldman et al., 1987; Sheridan et al., 1990; Kaplan et al., 1992; Hoyle and Goldman. 1994; Schutze et al., 2001; Engelhard et al., 2002; Machado et al., 2005]. By the nature of immunosuppression present after HSCT it would be expected that HSCT recipients have a particularly increased risk of infections with polysaccharide-encapsulated bacteria. There are published studies demonstrating an increased incidence of pneumococcal disease but there no data on the incidence of Hib or Men C infections in HSCT recipients [Winston et al., 1979; Sheridan et al., 1990; Hoyle and Goldman. 1994; Schutze et al., 2001; Engelhard et al., 2002]. Children with leukaemia have a higher incidence of Hib disease so this is also likely to be true for HSCT recipients [Feldman et al., 1990].

A number of factors have an influence on immunity to vaccine antigens, and immunogenicity of vaccines in HSCT recipients; type of transplant, time lapse after transplant, chronic-GvHD, recipient age, the number of vaccine doses, and the actual vaccine. Time lapse after transplantation [Witherspoon et al., 1981; Avanzini et al., 1995; Parkkali et al., 1997a; Parkkali et al., 1997b], and the number of vaccine doses are important determinants of immune response [Ljungman et al., 1990; Ljungman et al., 1991; Li Volti et al., 1994; Guinan et al., 1994].

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It is not only of importance to the HSCT recipient to be protected against vaccine preventable diseases, particularly with increases in migration and travel, but also to maintain herd immunity. Therefore re-vaccination of HSCT recipients is indicated. There are few studies in this area on which to base vaccination recommendations and guidelines are therefore often based on expert opinion, and a limited number of published studies. This was the basis of the Royal College of Paediatics and Child Health (RCPCH) guidelines, published in 2002. Since the publication of the RCPCH guideline further vaccine studies in HSCT recipients have been published.

There is a reduction of tetanus and diphtheria immunity after HSCT. Two to three vaccine doses are needed to elicit protective responses. As diphtheria toxoid is a combined vaccine preparation with tetanus toxoid, its timing and number of doses can be in accordance with the tetanus schedule. Pertussis vaccine is combined with diphtheria and tetanus toxoids as part of the DTaP vaccine. The correlation between antibody concentrations and clinical efficacy of the pertussis vaccine have not been clearly established, sufficient data are not available on immunity to, and immune responses to pertussis vaccine in HSCT recipients.

The level of immunity to each poliovirus-serotype declines after HSCT. The few available studies indicate that three-doses of IPV are needed to elicit protective antibody responses, which can potentially be administered from six-months after transplant.

Studies suggest that a single dose of MMR given 1-2 years after HSCT does not induce long-lasting immunity to measles, primarily due to primary vaccine failure; this has also been demonstrated in healthy subjects. There is one UK based publication looking at re-vaccination of HSCT recipients with two doses of MMR as per the RCPCH schedule; this demonstrated all recipients achieved protective antibody against measles after the second dose. Machado et al, demonstrated that measles vaccine can be safely and effectively administered to HSCT recipients 9-18 months after transplant.

It would be ideal to re-vaccinate with the polysaccharide-protein conjugate vaccines as early as an immune response can be mounted. In general this is from 6 to 18 months after transplant. Studies indicate that at least two doses of Hib-conjugate and Men C-conjugate vaccine are needed to induce protective responses in HSCT recipients. Recent studies looking at pneumococcal-conjugate vaccination in HSCT recipients show that protective antibody responses can be elicited as early as 3 months after transplantation (IKAST and EBMT IDWP01 trials).
The aim in HSCT recipients is to commence re-vaccination as soon as it is safe and as soon as a protective immune response can be achieved. Potentially this would be once the patient is off immunosuppressive therapy. In most published studies, however, vaccination schedules have been started ≥12 months after HSCT.

- All children should be considered for re-vaccination after allogeneic or autologous HSCT.
- In comparison to recipients of allogeneic HSCT, autologous HSCT recipients are less immune suppressed. However, both transplant types follow the same vaccination schedule content.
- The use of live vaccines is potentially dangerous until the child has been off all immunosuppressive treatment for at least 12 months and has no evidence of active chronic GvHD.
- Chronic GvHD and its treatment cause immune suppression, therefore these patients are at high risk of infectious complications.
- In view of the difficulty in predicting the extent of immune suppression and immune recovery, a pragmatic approach is to recommend re-vaccination of all recipients of allogeneic and autologous HSCT:

Re-Vaccination should commence:

- 12 months after any HSCT (BMT Team can review this on case by case basis)
  Normal serum immunoglobulins, CD4 count >15% and / or >300 x 10^6/L

Providing that:

- No evidence of active chronic GVHD
- Off all immunosuppressive treatment for at least 6 months, and for at least 12 months for live vaccines
- Off IVIg for at least 3 months

NB. In infants who have undergone allogeneic HSCT for primary immunodeficiency it may be appropriate to start vaccination earlier than specified above.
## Re-Vaccination schedule for HSCT Recipients

<table>
<thead>
<tr>
<th>Time after HSCT</th>
<th>Age under 10 years</th>
<th>Vaccine</th>
<th>Age 10 years and over</th>
<th>Vaccine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Every autumn (start 6 months after transplant)</td>
<td>Inactivated influenza¹</td>
<td>Inactivated influenza¹</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 Months</td>
<td>DTaP / IPV / Hib² (Pediacel) PCV13 Men B</td>
<td>dTaP / IPV² (Repevax) Hib / Men C (Menitorix) PCV13 Men B HPV³</td>
<td></td>
<td></td>
</tr>
<tr>
<td>13 Months</td>
<td>DTaP / IPV / Hib² (Pediacel) Men C</td>
<td>dTaP / IPV² (Repevax)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>14 Months</td>
<td>DTaP / IPV / Hib² (Pediacel) PCV13 Men B</td>
<td>dTaP / IPV² (Repevax) Hib / Men C (Menitorix) PCV13 Men B</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18 Months</td>
<td>MMR⁴</td>
<td>MMR⁴</td>
<td></td>
<td></td>
</tr>
<tr>
<td>24 Months</td>
<td>MMR⁵ Men ACWY Men B PCV13 or PnPS23</td>
<td>MMR⁵ Men ACWY Men B PCV13 or PnPS23</td>
<td></td>
<td></td>
</tr>
<tr>
<td>48 Months</td>
<td>DTaP / IPV (Infanrix-IPV) Hib / Men C (Menitorix)</td>
<td>dTaP / IPV (Repevax) Hib / Men C (Menitorix)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>School leaver booster</td>
<td>dT / IPV Men ACWY</td>
<td>dT / IPV Men ACWY</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

¹The intranasal live-attenuated influenza vaccine should not be used in post-HSCT patients. Note that the immune response to influenza vaccine is not optimal during the first 6 months after HSCT, which is the period of greatest risk; therefore vaccination should be offered to family members and hospital staff.

²Can be given as Pediacel (for <10 years age at administration) or Repevax (for ≥10 years age)

³HPV vaccine should be offered to girls ≥12 years old: 2 doses of HPV vaccine (Gardasil) should be given at 0 and 6 months from starting re-vaccination. If patient is aged 15 years and over, 3 doses recommended at 0,1, 6 months from starting re-vaccination.

⁴1st dose of MMR should be given at 18 months provided patient is at least 12 months off all immunosuppressive treatment and fulfills criteria as above.

⁵The 2nd dose of MMR is usually given 6 months after the 1st dose, but can be given 3 months after the 1st or even earlier (1 month after 1st dose) in outbreak situations.

[DTaP = Diphtheria/ Tetanus/ acellular Pertussis, dTaP = Low dose Diphtheria/ Tetanus/ acellular Pertussis, Hib = H.influenzae b conjugate, HPV = Human papillomavirus, IPV = Inactivated polio virus, Men B = Meningococcal B conjugate, Men C = Meningococcal C conjugate, Men ACWY = Meningococcal ACWY conjugate, MMR = Measles/Mumps/Rubella, PCV13 = 13 valent Pneumococcal conjugate, PnPS 23 = 23 valent pneumococcal polysaccharide]
Other Vaccines

Hepatitis B vaccine, travel vaccines and BCG vaccine may be considered for individual cases (after discussion with the transplant team). There is little data about the safety and effectiveness of the BCG vaccine in HSCT recipients. Its use is not recommended unless there is a clear case of need such as travel to or residence in an area with a high incidence of tuberculosis (greater than 40/100,000 per year), and provided the patient has no active chronic-GvHD and there is evidence of immune function recovery (such as normal serum immunoglobulin concentrations, recovery of lymphocyte function and CD4-lymphocyte numbers). Prior to administering BCG, particularly in patients that have previously had BCG, a tuberculin skin test should be done.

Vaccines contraindicated for HSCT Recipients

- BCG (except in specific circumstances – as above and only after discussion with BMT or immunology consultant)
- Rotavirus
- Intranasal live attenuated Influenza vaccine
- VZV vaccine
- Yellow fever
- Live attenuated Typhoid vaccine

Vaccination of close contacts of HSCT Recipients

The following live vaccines can be administered to siblings / close family contacts of HSCT recipients: MMR, VZV, Shingles vaccine (Zostavax®) and Rotavirus vaccines.

- MMR Vaccine should be given to contacts as per the national vaccination schedule.
- VZV vaccine (Varivax®) should be offered to healthy susceptible siblings (and adult family members who are VZV seronegative) of VZV seronegative patients. There is theoretical risk of transmitting the attenuated vaccine virus to a susceptible individual; as a precautionary measure, any person who develops a vesicular rash after receiving VZV vaccine should avoid direct contact with the patient until the rash is dry and crusted.
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References:


Hoyle C, Goldman (1994). Life-threatening infections occurring more than 3 months after BMT. 18 UK Bone Marrow Transplant Teams. Bone Marrow Transplant; 14: 247-252.


