03 Immunisation of Immunocompromised Persons

In some circumstances, advice in these guidelines may differ from that in the Summary of Product Characteristics (SmPC). When this occurs, the recommendations in these guidelines, which are based on current expert advice from NIAC, should be followed.

This chapter has the following sections:

Introduction

This chapter outlines basic principles and makes recommendations regarding immunisation of those whose immune system has been impaired by disease or treatment. Recommendations are also made regarding immunisation of contacts of immunocompromised patients (household contacts and health care workers) who may also require additional vaccines (e.g. influenza, pertussis), to help protect the patient (the cocooning principle).

Chapter 3 Immunisation of Immunocompromised Persons

Immunocompromise, or immunodeficiency, can be classified as primary or secondary.

Primary immunodeficiencies are inherited and include conditions with an absence or deficiency of cellular and/or humoral components that provide immunity. Examples include diseases such as Severe Combined Immune Deficiency (SCID) and X-linked agammaglobulinaemia.

Secondary (acquired) immunodeficiency is associated with loss or qualitative deficiency in cellular and/or humoral immune components occurring as a result of a disease or its therapy. Examples include HIV infection, haematologic malignancies, acquired asplenia and hyposplenia, and treatment with immunosuppressive drugs or radiation.

The degree of immunocompromise can vary significantly and this, along with the risk of acquiring a vaccine preventable infection, should be taken into account when considering immuniastion.

Assessing the safety and effectiveness of vaccines for conditions associated with primary or secondary immunodeficiency is challenging, especially when new therapeutic modalities are being used and information about the safety and effectiveness of vaccines has not been fully characterised in persons receiving these drugs. Deciding whether particular vaccines are indicated is complicated. Consultation with an appropriate specialist may be necessary

With some exceptions, live vaccines should be avoided during systemic immunosuppressive therapy. An individualised patient approach may be necessary, taking into account the underlying disease, the patient's medications, the pathogenicity and replication capacity of the vaccine strain, the risk of infection, and the availability of appropriate treatments. If a live vaccine is indicated, the appropriate specialist should be consulted.

General Principles of Immunisation of Immunocompromised Persons

Immunocompromised persons are at increased risk from vaccine preventable diseases (VPD) and should receive appropriate vaccines.

The degree of immunocompromise can vary from mild to profound and this, along with risk of VPD, should be taken into account when considering vaccination.

Live vaccines should not be given to immunocompromised persons, with some important exceptions (see text).

Non-live vaccines are safe to use. However, depending on the degree of immunocompromise, recipients may not develop an adequate protective response.

A review of immunisation status and administration of required vaccines should be an integral part of the assessment before and after immunosuppressive treatment and transplantation.

Live virus vaccines should not be given to donors less than four weeks prior to organ donation.

For complex cases, relevant specialist advice should be sought from an appropriate physician.

Further details about individual vaccines can be found in the specific chapters.

Asplenia and hyposplenia

Asplenia includes both functional and anatomic asplenia. Hyposplenia (the reduction of splenic function encountered in various pathological conditions) is difficult to identify and quantify. It is variably associated with a number of conditions, including chronic liver disease, coeliac disease, graft versus host disease, HIV/AIDS, inflammatory bowel disease, lymphoma, nephrotic syndrome, rheumatologic diseases, sickle cell disease, and thalassaemia. It can be accompanied, to a varying extent, by all pathological findings encountered in patients with asplenia.

Individuals with asplenia or hyposplenia are at increased risk of fulminant sepsis from encapsulated polysaccharide bacteria, particularly *Strep.*

pneumoniae but also *H. influenza* and *N.meningitidis*. They have a higher mortality rate (40%–70%) from meningococcal disease than healthy populations. There is no measurable degree of hyposplenia that correlates with an increased risk of sepsis.

For these reasons, in addition to routine vaccines, the following vaccines are recommended for those with asplenia and should be considered for those with conditions that can be associated with hyposplenia:- PCV13, PPV23, Hib, MenACWY, MenB and annual influenza vaccines (see Table 3.1).

Recommendations

For those requiring splenectomy, vaccination should be completed at least 2 weeks and preferably 4 weeks or more before surgery. In the case of emergency splenectomy, or if immunisation was not completed pre operatively, vaccination can be commenced 2 weeks post operatively. In addition to routine vaccines in the national schedule the following should be given to those with asplenia or hyposplenia.

Table 3.1. Additional vaccines for those with asplenia or hyposplenia

	Age at diagnosis		
Vaccine	**<12 months**	**12-23 months**	**24 months and older**
MenACWY [1]	2 doses 2 months apart; booster aged ≥12 months, then every 5 years	2 doses 2 months apart; booster every 5 years	2 doses 2 months apart; booster every 5 years
MenB			If unvaccinated, 2 doses 1 month apart.
PCV13		1 dose, ≥2 months after 13 month dose	1 dose ≥ 2 months after previous dose. If unvaccinated, 2 doses 2 months apart
Hib		1 dose ≥ 2 months after 13 month dose. If unvaccinated, 2 doses 2 months apart	
PPV23			1 – 3 doses[2] 1st dose at least 2 months after PCV13 2nd dose 5 years later. Final dose at ≥65 years
Inactivated Influenza	Annually from 6 months of age If aged <9 years, 2 doses 4 weeks apart in the first season of receipt		

[1] Can be given instead of routine MenC at 6 months

[2] See Chapter 16

Cancer patients

Chemotherapy regimens vary significantly in intensity depending on the disease risk group and an individual's response. Patients on treatment for haematologic malignancies are likely to be more immunosuppressed than those on treatment for solid tumours.

The risks of VPDs in cancer patients vary depending on exposure, vaccination history and the degree of immunosuppression. The effectiveness of vaccination varies depending on disease stage and degree of immunosuppression. Vaccination should be avoided during periods of intense chemotherapy as vaccine responses are likely to be very poor.

Live vaccines

With some exceptions, live vaccines should not be given to cancer patients receiving chemotherapy. In some situations however the benefits of a live vaccine can outweigh potential associated risk, e.g. varicella - susceptible* leukaemia patients in remission and post chemotherapy can benefit from varicella vaccine.

Non-live vaccines

Patients receiving chemotherapy, immunotherapy (including checkpoint inhibitors) or radiation therapy can receive non-live vaccines if not contraindicated (see Recommendations below). If non-live vaccines are given during chemotherapy, there may be a suboptimal immune response; the vaccines should be re-administered when immune function has recovered.

Patients on *combination* checkpoint inhibitors (e.g. ipilumumab plus nivolumab) ***should not*** receive any vaccines.

Reimmunisation after chemotherapy

Children treated with standard chemotherapy regimens should be offered a booster of each age appropriate vaccine in the routine childhood immunisation schedule 6 months after completion of treatment.

For **adults**, re-administration of vaccines given prior to chemotherapy is generally not necessary except when chemotherapy has been followed by haematopoietic stem cell transplantation (HSCT); (see Transplantation section below).

* Those without laboratory evidence of immunity or documented prior vaccination

Recommendations
When possible, complete recommended immunisation at least 2 weeks prior to chemotherapy, as the immune response may be reduced if vaccines are received during treatment.

Vaccines should not be administered during times of severe neutropenia (absolute neutrophil count Change to $<0.5 \times 10^9$/L), to avoid causing an acute febrile episode.

If non-live vaccines are given during chemotherapy, they should be readministered after recovery of immunocompetence, generally after three months following treatment.

Vaccines should be given on the opposite side if radiation therapy involves an arm or hemithorax.

Non-live vaccines:

- **Hib vaccine** is not routinely recommended for adult cancer patients unless undergoing HSCT (see Table 3.1).

- **Inactivated influenza vaccine** is recommended annually for most cancer patients.

  If it has not been given 2 weeks or more before commencing treatment, it should be given during chemotherapy. However, the response to the vaccine may be blunted. A second vaccine is recommended in the same influenza season, a minimum of 4 weeks following a course of chemotherapy, if the lymphocyte count is $\geq 1.0 \times 10^9$/L (see Chapter 11, Table 11.1).

  Patients on **combination** checkpoint inhibitors (e.g. ipilumumab plus nivolumab) ***should not*** receive any influenza vaccines, because of a significant increased incidence of immune-related adverse reactions.

  Families and care providers of patients with cancer should be encouraged to receive an inactivated influenza vaccine, preferably before treatment treatment is started.

  In a small number of people receiving Ipilimumab or combination checkpoint inhibitor therapy, fatal immune related adverse events (irAEs) occurred after receipt of an influenza vaccination. The theoretical risk that any event that stimulates the immune system could trigger the onset of irAEs means a possible role of influenza vaccination cannot be discounted.

  There are currently no international consensus statements on the use of influenza vaccines in people receiving combination immune checkpoint inhibitor treatment.

Until further evidence emerges, patients on combination checkpoint inhibitors (e.g. ipilumumab plus nivolumab) should not receive any influenza vaccines, because of a potential association with immune-related adverse reactions.

- **Pneumococcal vaccine** is recommended for all cancer patients who are under hospital supervision
  - For those who have never received PCV13 or PPV23, a single dose of PCV13 is recommended, followed by PPV23 after ≥2 months.
  - For patients who have received 1 or more doses of PPV23, a single dose of PCV13 is recommended, at least 12 months after the PPV23.
  - Those who have received PCV7 should be given PCV13 and PPV23 (see Chapter 16).
  - Booster doses of PPV23 are recommended, the first at least 5 years after the initial dose if still immunosuppressed, and when ≥65 years of age.

- **Zoster vaccine**: If available, *Shingrix*® is recommended for patients 50 years and older with haematologic malignancies and solid tumours, as they are at increased risk of developing herpes zoster (shingles). Patients with Hodgkin's disease are at particularly high risk, with rates approaching 30% during illness or its treatment.

- Other non-live vaccines including **HAV, HBV, HPV, MenACWY, MenB, polio and Tdap** should be considered (see relevant chapters).

Live vaccines.

With some exceptions, cancer patients should not receive live vaccines.

- **BCG vaccine** for TB prophylaxis is not recommended.
- **MMR vaccine** may be given to patients with leukaemia or lymphoma who are in remission and have been off chemotherapy for 6 months, when there is high risk of measles or mumps infection. The minimum interval post chemotherapy for administration of MMR is 3 months.
- **Varicella vaccine** may be given to susceptible persons (negative varicella serology) with leukaemia, lymphoma or other malignancies who are in remission, who are off chemotherapy for a minimum of 3 (ideally 6) months, and who are at high risk for severe or complicated varicella. The vaccine should be given only under specialist supervision and with an appropriate protocol in place for the management of vaccine virus infection, which may occur in up to 20% of cases.
- **Zoster vaccine:** *Shingrix*® (non-live vaccine) is recommended prior to starting immunosuppressive therapy in individuals 50 years of age and older (see Chapter 23). If *Shingrix*® is not available *Zostavax*® (live vaccine) may be used.

If there is uncertainty about the level of immunosuppression, or concern regarding the safety of a live vaccine, vaccination should be withheld and advice sought from the treating physician and/or an immunisation specialist.

Corticosteroid therapy

Neither the dose nor duration of systemic corticosteroids that cause immunosuppression, nor the duration of altered immunity following cessation of therapy are well defined. The degree of associated immunosuppression depends on the dose and duration of steroid use. Recovery of immune competence depends on the dose, frequency of administration (daily or alternate day) and duration of therapy.

Daily receipt of high dose corticosteroids is immunosuppressive. The following doses of prednisolone (or equivalent dose of other glucocorticoid) are likely to be immunosuppressive:

- Adults and children ≥10kg:

  ≥40 mg/day for more than 1 week,
  or
  ≥20 mg/day for 2 weeks or longer

- Children < 10 kg:
  2mg/kg/day for 2 weeks or longer

The timing of immunisation following steroid therapy is influenced by the expected degree of immunosuppression and the urgency of vaccination.

It is generally accepted that live virus vaccines can be given from 3 months after cessation of high dose steroid therapy, with some experts recommending their administration as soon as 1 month after cessation.

If there is uncertainty about the level of immunosuppression, or concern regarding the safety of administration of a live vaccine, vaccination should be withheld and advice sought from the treating physician and/or an immunisation specialist.

Recommendations

- When possible complete age appropriate immunisation prior to high dose steroid therapy.
- **Non-live vaccines** can safely be given to patients receiving steroids, but protective responses may be blunted. If there is concern, re- immunisation 1 to 3 months post steroid therapy is recommended.
- **Live vaccines** should not be given to patients receiving potentially immunosuppressive steroid therapy.

- **Live vaccines** should be deferred for a minimum of 1 month, and where circumstances permit 3 months, after stopping high dose steroid therapy.
- Defer BCG vaccine for a minimum of 3 and ideally ≥6 months after stopping high dose corticosteroid therapy.
- Defer neonatal BCG vaccine until ≥3 months of age for infants born to mothers who received high dose steroid therapy for two weeks or more in the second or third trimester.
- There are no contraindications to using live vaccines if steroid treatment is:
  - short term (<7days) irrespective of dose
  - long term (≥2 weeks) < 20mg/day of prednisolone or equivalent (<2mg/kg/day in children <10kg)
  - long-term, alternate-day treatment with short-acting preparations
  - maintenance physiologic doses (replacement therapy)
  - topical (skin or eyes) or by inhalation
  - intra-articular, bursal, or tendon injection
  - fludrocortisone ≤300 micrograms/day

HIV

People with HIV infection should generally receive all recommended and some additional vaccines (see Table 3.3). The immunisation schedule depends on a patient's age, the type of vaccine (live or non-live) and the level of immunocompromise. For those severely immunosuppressed, live viral vaccines should be delayed until immune recovery. BCG is contraindicated regardless of CD4 count due to the risk of disseminated BCG infection.

Recommendations

Children

All standard childhood vaccinations may be given to HIV-infected or exposed children, although certain live viral vaccines (such as rotavirus, varicella,MMR) should only be given to individuals with a CD4 cell count ≥15% (see Table 3.2). BCG is contraindicated in all HIV infected children and deferred in HIV exposed infants pending determination of infection risk. HIV infection is an indication for MenACWY vaccination in infants and children.

Non-live vaccines can be given to all HIV infected children, even those significantly immunocompromised (see Table 3.3). However, as responses may be suboptimal, revaccination after recovery of immune function is recommended. If antiretroviral treatment is being initiated, delay vaccination until the child has had 6 months of undetectable viraemia and the CD4 count is ≥15%, to optimize the vaccine response. The decision to delay vaccination must be balanced against the urgency of attaining protection.

Table 3.2 CD4 counts indicative of severe immunocompromise

If aged:	%CD4 per µl	CD4 count (x10⁶/L)
< 1 year	<15%	<750
1 - 5 years	<15%	<500
≥ 6 years	<15%	<200

Live vaccines

For specific recommendations see Table 3.3.

BCG is contraindicated.

Varicella vaccine is recommended for HIV infected children ≥12 months without serological evidence of immunity to VZV who have either asymptomatic or mildly symptomatic HIV infection and CD4 count ≥15%.

Table 3.3. Sample Vaccination Schedule for HIV exposed and HIV infected children

	HIV exposed	HIV infected
Birth	Hep B	Hep B
2, 4 and 6 months	Routine recommended vaccines (may give MenACWY instead of MenC)	
Annually (from 6 months of age)		Inactivated influenza vaccine (if < 9 years of age, 2 doses 4 weeks apart at first receipt)
8 months		MenACWY (if not already received)
12 months	Routine recommended vaccines *plus* Hepatitis A vaccine if HCV or HBV infected	
	MMR	MMR (if on treatment and CD4 count ≥ 15%)-see Table 3.3
13 months	Routine recommended vaccines	
15 months		Varicella (if CD4 count is ≥15%) MenACWY
18 months		Varicella (if CD4 count is ≥15%)
24 months		PPV23
4 – 5 years	Routine recommended vaccines	
4 – 5 years	MMR	MMR (if on treatment and CD4 count ≥ 15%)
12 years	HPV4 or 9*(girls), 2 doses	HPV4 or 9* **(girls and boys), 3 doses**
11-14 years	Routine recommended vaccines	

*HPV9 preferred.

Adults
Detailed information on the immunisation of HIV infected adults can be found at www.bhiva.org.

Hepatitis A: Give monovalent Hepatitis A vaccine to susceptible HIV-infected persons in at risk groups (see chapter 8)

- For those with CD4 count ≥ 350 /μL, 2 doses at 0 and 6 months.
- For those with CD4 count <350 /μL, 3 doses at 0, 1 and 6 months.
- Boost every 10 years for those with ongoing exposure risk.

Hepatitis B: Give to susceptible patients (HBsAg negative, HBcAb negative, HBsAb negative).

Four doses of Fendrix® at 0, 1, 2 and 6 months or 3 doses of HBVaxPro40® at 0, 1 and 6 months should be used.

The HBsAb level should be measured 2 months after completion of the vaccine schedule; if the HBsAb level is <10mIU/ml, a booster dose should be considered.

HPV4 or HPV9: HPV9 should be used where available.
A 3 dose schedule at 0, 2 and 6 months is recommended for all HIV infected female patients age < 25 years, and all HIV infected or non-infected MSMs aged < 45 years.

Inactivated influenza: Give annually.

Meningococcal: HIV infected adults should be given MenB, two doses one month apart and MenACWY vaccines, two doses at least 2 months apart.

MMR (seronegative individuals):
- If CD4 count ≥200 x 10^6/L: 2 doses 1 month apart.
- If CD4 count <200 x 10^6/L, MMR is contraindicated.

Pertussis: HIV infected adults who meet general indications for pertussis vaccine (see Chapter 15), including pregnant females, should be offered one Tdap vaccine, with a Tdap boster 10 years later and a Td booster every 10 years.

Pneumococcal:
- PCV13: All HIV infected adults should receive one dose of PCV13 irrespective of CD4 count, ART use, and viral load, unless they already received PCV13.

- PPV23: HIV infected adults should receive one dose of PPV23, ≥2 months after PCV13.

Tetanus: HIV infected adults who meet general indications for tetanus vaccine (see Chapter 21), including HIV infected pregnant females, should receive one dose of Tdap/IPV.

Varicella (seronegative individuals):
If CD4 count is ≥200 x 10_6/L give 2 doses 3 months apart.
If CD4 count is <200 x 10_6/L varicella vaccine is contraindicated.

Yellow fever vaccine can be given to HIV infected persons who are not immunocompromised (i.e. with CD4+ counts ≥200 per µL). Vaccination of those with evidence of immunocompromise where risk of yellow fever virus exposure is unavoidable should be considered on a case-by-case basis with the person's treating clinician.

Immunocompetent household contacts of immunocompromised persons

Optmising vaccination of family members and household contacts (cocooning strategy) may provide indirect protection for those for whom vaccination either does not provide adequate protection or is inappropriate.

Optional vaccines to reduce household transmission include influenza, MMR, pertussis, rotavirus, and varicella vaccines (seronegative persons only).

Families and care providers of patients with cancer should be encouraged to receive an inactivated influenza vaccine, preferably before treatment treatment is started.

When household contacts of immunocompromised individuals receive rotavirus vaccine, careful hand washing by household members should be used to minimize the risk of transmission of vaccine virus. This includes after assisting a child with toileting, changing a nappy, before food preparation, and before direct contact with the immunocompromised person.

If a varicella vaccine-associated rash developes in an immunocompetent individual, post exposure prophylaxis should be considered for the immunocompromised contact. Similarly, transmission of VZV can occur following direct contact with herpes zoster lesions, resulting in chickenpox in contacts who are susceptible to VZV. Therefore individuals at high risk of severe complications from varicella infection should be assessed for the need for post exposure management with varicella zoster immunoglobulin.

Immunomodulatory treatment

Immunomodulatory treatment includes biological disease modifying anti-inflammatory drugs (bDMARDs) such as azathioprine, cyclophosphamide,

cyclosporine, hydroxychloroquine, leflunomide, methotrexate, mycophenolic acid preparations, sirolimus and tacrolimus, in addition to biologics, such as TNFα blocking agents (adalimumab, etanercept, infliximab), and others including abatacept, anakinra, ecolizumab, rituximab and tocilizumab.

Patients with Immune Mediated Inflammatory Diseases (IMIDs), including auto-immune inflammatory rheumatic diseases, are at increased risk of VPDs because of the underlying disease process and/or the effects of treatment. Increasingly, combination therapy with a number of agents with different targets in immune activation pathways are used and can result in very significant immunosuppression.

Non-live vaccines: When possible, recommended vaccination should be completed at least 2 weeks before commencing imunomodulators. Patients receiving *long-term* immunosuppressive therapy may have mildly impaired immune responses to vaccines, but post vaccination antibody titres are usually sufficient to provide protection for the majority of immunised individuals. Severely reduced immunogenicity can occur from treatment with abatacept, methotrexate (>0.4 mg/kg/week), methotrexate and TNF inhibitor combination therapy, and particularly rituximab.

Patients on eculizumab (Soliris®), a terminal complement inhibitor are at very high risk of meningococcal disease due to strains that do not normally cause disease but are frequently carried asymptomatically in the nasopharynx. These are usually non-groupable strains. Vaccination offers limited or possibly no protection against these strains but will protect against those commonly associated with invasive disease.

Use of topical calcineurin inhibitors (TCIs, e.g., tacrolimus and pimecrolimus) for atopic dermatitis in otherwise healthy children/adults does not result in significant systemic absorption or immunosuppression. The immunogenicity of non-live vaccines in patients being treated with TCIs is likely to be satisfactory. At standard dosing, there are no immediate safety concerns for use of live viral vaccines in patients receiving TCIs.

Live vaccines: these should not be given to patients receiving immunosuppressive therapy.

Recommendations
When possible complete age appropriate immunisation prior to therapy. In addition, MenACWY, MenB, PCV followed by PPV23 ≥2 months later, and annual influenza vaccine should be given.

Non-live vaccines may safely be administered during short or medium term immunosuppressive therapy. However, as the immune response may be suboptimal, if such vaccines are given ≤ 2 weeks prior to or during therapy they should be repeated ≥6 months after treatment if immune competence is restored.

MenACWY and MenB vaccines should be given to those on eculizumab (Soliris®), a terminal complement inhibitor.

Live vaccines should be given at least one month before the start or restart of immunotherapy when off other immunosuppressive therapy. Varicella (if non-immune) and age-appropriate zoster vaccines are recommended.

Long term low dose corticosteroid therapy (≤20mg prednisolone per day for >14 days) either alone or in combination with low dose non-biological oral immune modulating drugs (e.g. methotrexate ≤0.4 mg/kg/week, azathioprine ≤3.0mg/kg/ day or 6-mercaptopurine ≤1.5mg/kg/day) is not considered sufficiently immunosuppressive to contraindicate live vaccines in most circumstances and these patients can generally receive live vaccines. However as data on yellow fever vaccine data is limited, a cautious approach is recommended, and specialist advice should be sought in these circumstances. Specialist advice should be sought for other immunosuppressing treatment regimes.

All vaccines (live and non-live) can safely be given to patients being treated with topical calcineural inhibitors (e.g. tacrolimus).

Vaccination after cessation of immunosuppressing treatment
The safe time intervals for the administration of live vaccines after cessation of immunosuppressive/immunomodulatory drugs vary depending on the pharmacokinetic and pharmacodynamic features of the drugs. There is no strong evidence on which to base recommendations for timing of vaccination following cessation of immunosuppressant therapy. Decisions should be made taking into account the likely degree and the duration of immunosuppression. Some medications have a relatively short duration of action (e.g. etanercept) whereas with others (e.g. rituximab) the effects can last for months after discontinuation of therapy. Therefore, whenever possible, recommended vaccines should be administered at least 4 weeks prior to rituximab therapy.

Live vaccines should be delayed for at least:

- 4 weeks after etanercept treatment, and 6 months after other TNF inhibitors (infliximab, adalimumab)
- 4–12 weeks after methotrexate treatment of >0.4 mg/kg/week. There is no need to delay varicella or zoster vaccines if the patient is on methotrexate ≤0.4 mg/ kg/week)
- 6 to 12 months after rituximab (if possible, live vaccines should be delayed until the B cell count returns to normal)
- 2 years after leflunomide.

Interferon therapy is not a contraindication to live vaccines. However, to avoid the potential for drug side effects being confused with a vaccine reaction, deferral of vaccination until after treatment is completed may be prudent.

Infants of mothers receiving immunosuppressive medication
Certain immunosuppressive medications given during pregnancy for management of a medical condition (e.g. biological disease modifying anti-rheumatic drugs [bDMARDs]) may cross the placenta and be detectable in the infant, particularly if given during the third trimester. In this setting, administration of BCG vaccine in the first six months of life is contraindicated.

- There are little data available regarding the use of rotavirus vaccines in infants of mothers who received immunosuppressive therapy in pregnancy. In general, given the current prevalence of rotavirus infection, the risks associated with wild type infection exceed potential risks associated with the vaccine. Infants of women treated with corticosteroids in pregnancy or corticosteroids and low dose methotrexate can receive rotavirus vaccine.
- If immunosuppression is anticipated to be moderate or severe, rotavirus vaccine should be deferred until the infant is 4 and 6 months of age. Moderate or major immunosuppression may occur in mothers with severe rheumatoid arthritis or inflammatory bowel disease receiving bDMARDs, and in renal transplant recipients. If in doubt, consult the supervising specialist.

Primary Immunodeficiency

Non-live vaccines are recommended, but may not be efficacious.

Live vaccines are generally not recommended for children with primary immunodeficiency. However, for some conditions, particularly those with restricted defects, they are safe and effective, and are recommended (Table 3.4). When in doubt, expert advice should be sought.

Table 3.4. Vaccinations for children with primary immunodeficiency

Condition	RoutineNon-live Vaccines	Routine Live Vaccines	Additional Vaccines	Contraindicated Vaccines
Ataxia Telangiectasia	Yes	No	Inactivated influenza, MenACWY, MenB	All live vaccines
Bruton agammaglobulinaemia (X linked agammlobulinaemia, XLA)[1]	Yes	Consider MMR	MenACWY, MenB. Consider varicella	BCG[2] Live typhoid vaccine, Yellow fever
Chronic/cyclic neutropoenia	Yes	Yes	Inactivated influenza, MenACWY, MenB	None
Chronic granulomatous disease (CGD)	Yes	Yes except BCG	Inactivated influenza, MenACWY, MenB	BCG[2] Live typhoid vaccine
Chronic mucocutaneous candidiasis (APECED syndrome)	Yes	For some, discuss with relevant specialist	Inactivated influenza, MenACWY, MenB	BCG[2] Live typhoid vaccine, Yellow fever
Complement deficiency	Yes	Yes	Inactivated influenza MenACWY, MenB PPV23 at ≥2 years, ≥2 months after PCV	None
Common variable immunodeficiency (CVID) & other immunoglobulin deficiencies except isolated IgA deficiency[1] IgG subclass deficiency[1]	Yes	For some; discuss with relevant specialist	Inactivated influenza, MenACWY MenB. PPV23 at ≥2 years, ≥2 months after PCV	BCG[2] Live typhoid vaccine, Yellow fever
DiGeorge syndrome (22q11 deletion)[3]	Yes	Rotavirus; MMR if CD4 count > 400 10^6/L	Inactivated influenza, MenACWY, MenB	BCG[2] Live typhoid vaccine Yellow fever
Down syndrome	Yes	Yes	Inactivated influenza, PCV13, PPV23,	None
Fanconi's anaemia	Yes	Yes	Inactivated influenza, HPV[4] from 1 year of age MenACWY, MenB, varicella	None
Isolated IgA or IgG subclass deficiency[1]	Yes	Yes	Inactivated influenza Can receive MenACWY, MenB and varicella	Yellow fever
SCID[5]	Yes	No	MenACWY, MenB	All live vaccines
Wiskott Aldrich Syndrome	Yes	No	Inactivated influenza, MenACWY, MenB	All live vaccines

1 All vaccines are likely to be effective but immune response may be suboptimal
2 Often have received BCG prior to diagnosis. Main groups at risk for BCG related complications include SCID, CGD and advanced HIV infection.
3 Effectiveness depends on degree of iimmunosuppression. Most children with DiGeorge syndrome have efficient immune systems
4 As soon as diagnosis is made, due to significant increased risk of head, neck, oropharyngeal and anogenital squamous cell carcinoma
5 Severe combined immunodeficiency syndrome

Transplantation

Haematopoietic Stem Cell Transplant (HSCT)

Almost all HSCT recipients experience a prolonged period of humoral and cell-mediated immunosuppression following transplantation. The degree of immunosuppression and the rate of recovery of immune competence depend on age at transplantation, underlying diagnosis, type of transplant, intensity and duration of immunsuppressing treatment before and after transplantation, and levels of numeric or functional immune reconstitution. HSCT recipients are at increased risk of infection during the period of immunosuppression.

Allogeneic HSCT recipients experience profound immunosuppression in the early post-transplant period but relatively normal immunity after 1 to 2 years if they are off immunosuppressive medication and free of graft-versus-host disease (GVHD). GVHD generally does not occur.

All HSCT recipients should be viewed as "never immunised" and require re-immunisation post-transplant because the pre-transplant ablation of haematopoietic cells in the bone marrow eliminates the person's immune memory. Immunity after transplant must be at least partially reconstituted for a vaccine to mount a clinically significant response. B cell counts recover by 6 months after autologous and by 9 months after allogenic HSCT. In general, T cells capable of responding to new antigens are generated 6 to 12 months after transplant, earlier in young children and later in adults. The CD4 count provides a reasonable guide to recovery of the T cell immune system.

Non-live vaccines can generally be initiated 6 to 12 months after HSCT. However, depending on degree of immunosuppression, vaccine responses may be suboptimal. Because B-cell immune reconstitution is highly variable after HSCT in patients with primary immunodeficiencies, vaccination is delayed until there is robust evidence of functional B-cell recovery.

Vaccination should be deferred for 3 months after receiving immunoglobulin (IVIG).

Live vaccines should be deferred for at least 2 years after HSCT and only given if there is no GVHD or ongoing immunosuppressive treatment, and the CD4 count is > 400 $x10^6$/L and IgM > 0.5g/L. Expert discussion is recommended.

Recommendations

Non-live vaccines can generally be given from 6 months post-transplant (1 year if transplant was for primary immunodeficiency). Given the high risk of pneumococcal disease in the post-transplant patient, PCV13 vaccination may be given as early as 3 months post-transplant. However, depending on degree of immunosuppression, vaccine response may be suboptimal. In this case a second PCV13 dose at least 6 months post transplant and at least 2 months after the first dose may be given.

Live vaccines (MMR, varicella) should be deferred for at least 2 years post-transplant. BCG is not indicated post- transplant.

Post vaccination serology testing of HSCT patients may be considered every 5 years to assess immunity to HBV, measles, tetanus, diphtheria and polio.

Children who received a HSCT should start a complete revaccination programme 6 to 12 months after the procedure (18 months for recipients of a transplant from an unrelated donor).

Table 3.5 outlines a sample schedule that can be tailored for different scenarios, but recommended minimum intervals between vaccines must be observed (see Chapter 2). Anti-HBs antibody level should be tested 2 months after completion of HBV vaccination, and non-responders may need high-dose HBV (see Chapter 9)

Table 3.5. Sample vaccination schedule following HSCT*

	Vaccines	
Months post transplant	**Age**	
	< 10 years	**≥ 10 years**
6 months*	6 in 1, PCV13	Tdap/IPV + PCV13 + Hib
7 months	MenACWY, MenB	MenACWY, MenB, Hep B
8 months	6 in 1, PCV13	Tdap/IPV, PCV13, Hib
9 months	MenACWY, MenB	MenACWY, MenB, Hep B
10 months	6 in, PCV13	Tdap/IPV, PCV13, Hib
11 months	MenACWY	MenACWY
12 months	PPV23 and/or PCV[1]	
12 months		HPV[2]
14 months		HPV, Hep B[3]
18 months		HPV
24 months	MMR[4] (2 doses, 1 month apart)	
> 24 months	Consider varicella vaccine[5]	
Annual	Inactivated influenza, initiate 6 months post transplant, 2 doses four weeks apart then 1 dose annually	
> 4 years post transplant	DTaP/IPV, (3 years after 3rd 6 in 1) Tdap 10 years later	Tdap/IPV (≥3 years after 3rd DTaP/IPV) Tdap 10 years later

* *Delay for 12 months if transplant was for primary immunodeficiency*

[1] For patients with chronic graft versus host disease (GVHD) substitute a fourth dose of PCV13 for PPV23, as patients with GVHD are unlikely to mount protective responses to polysaccharide vaccines. PPV23 can be given after resolution of GVHD and at least 2 months following PCV13.

[2] For females up to 45 and males up to 26 years.

[3] Test for anti-HBs antibody 2 months after completion of HBV vaccination. A second three-dose Hepatitis B vaccination course is recommended for non-responders.

[4] If no GVHD or immunosuppression

[5] If VZV vaccine seronegative, and no GVHD or immunosuppression.

Solid organ transplant (SOT) candidates and recipients

The risk of acquiring infection and the reduced ability of vaccines to prevent infection are directly related to the degree of immunosuppression. The greater the degree of immunosuppression, the less likely the patient is to respond to vaccines. Factors contributing to immunosuppression include the underlying disease (e.g. renal or hepatic insufficiency), the presence of allograft rejection, and the immunosuppressive therapy administered after transplantation.

Although certain vaccines provide some protection, an adequate vaccine response cannot be assumed. Protection of the immunocompromised patient may require the use of vaccines and/or passive immunisation (i.e. intravenous immunoglobulin) as well as adjunctive measures, such as antiviral drug prophylaxis during influenza A outbreaks.

Recommendations

Pre transplant *(children and adults)*

Ideally, all non-immune SOT candidates should be immunised with recommended routine vaccines prior to transplantation and as early in the course of disease as possible, because vaccine response may be reduced in people with organ failure pre-transplant. Also, vaccines are generally more immunogenic if given pre-transplantation because the immunosuppressive medications given after transplant to prevent and treat rejection may reduce the vaccine response.

Live vaccines, *except BCG*, can be given pre-transplant. They should be given at least 1 month before transplant, but not to those receiving immunosuppressive therapy.

- MMR vaccine can be given from 6 months of age and should be given early if transplant before 13 months of age is anticipated.
- Varicella vaccine should be given to seronegative patients from 12 months of age (see Chapter 23).
- Live zoster vaccine (Zostavax®) may be given to transplant candidates aged ≥50 years if non-live vaccine (Shingrix®) is not available.

BCG vaccine should not be given pre transplant.

Non-live vaccines: immunisation should be completed at least 2 weeks prior to transplant as a protective immune response is unlikely to be produced if vaccines given after this time.

- All age-appropriate immunisation should when possible be completed prior to therapy (see Chapter 2, Table 2.3). The minimum intervals are given in Chapter 2.
- Hepatitis A vaccine should be considered in all seronegative organ transplantation candidates, particularly liver transplantation candidates.
- Hepatitis B vaccine is recommended for patients who are anti–HBs negative. The 3-dose HBV vaccine series (0, 1, and 6 months) is recommended, although the third dose may be given post-transplantation if the transplantation occurs in the interim.
- Hib vaccine should be considered for lung transplant candidates.

- HPV vaccine is recommended for males and females in the appropriate age groups, because of the increased risk of anogenital HPV-associated neoplasia in SOT recipients.
- Inactivated influenza vaccine is recommended for all candidates from 6 months of age.
- MenB and MenACWY vaccines are indicated for those at increased risk (see Chapter 13).
- PCV13 and PPV23 vaccines should be given if not previously received.
- Tdap should be given to those aged over 10, at least 10 years after a previous dose.
- Zoster vaccine (Shingrix®) should be given to those aged ≥50 years

Post transplant *(see Table 3.6):*
SOT recipients generally receive lifelong immunosuppressive treatment, which varies depending on the organ transplanted. The degree of immunosuppression is greatest in the first 3 to 6 months post-transplant, but a significant degree of immunosuppression persists indefinitely. A minority of transplant recipients who experience chronic rejection, persistent organ dysfunction, or chronic infections, remain profoundly immunosuppressed. In general, vaccination should not be re-initiated until 3 to 6 months post-transplant when baseline immunosuppressive levels are attained.

SOT recipients are at risk of severe illness or death due to influenza. They are also at increased risk of invasive pneumococcal disease, *H. influenza* type b disease and complications of HPV and varicella infection.

Live vaccines, if indicated, should if possible be given at least 4 weeks prior to transplant. They are generally not given post-transplant as these patients are likely to remain on immunosuppressive therapy. BCG should never be given post SOT.

Non-live vaccines can be given from 6 months post-transplant. If immunisation is not completed pre-transplant, the course should be completed post-transplant.
- Those who received non-live vaccines <2 weeks prior to transplant should be re-immunised, starting 6 months post-transplant.
- Patients aged 6 months and older should receive annual inactivated influenza vaccination see Chapter 11).

Table 3.6 Vaccines for SOT candidates and recipients aged ≥10 years.

Vaccine	Pre-SOT	Post-SOT, if immunisation not completed pre transplant
Hep A (if seronegative)	Yes	Yes
Hep B (if HBsAg negative & anti-HBs<100miu/L)	Yes (i.e. HBVAXPRO40® or Fendrix®)	Yes
Hib (consider for lung transplant)	Yes	Yes
HPV	Yes	Yes
Inactivated influenza (annual)	Yes	Yes
MenACWY (if at increased risk)	Yes	Yes
MenB (if at increased risk)	Yes	Yes
MMR (unless laboratory evidence of immunity to each antigen or documented prior vaccination)	Yes (complete at least 1 month prior to transplant)	**No**
PCV13	Yes	Yes
PPV23 (at least 2 months post PCV)	Yes	Yes
Tdap **or** **Tdap/IPV**	Yes, if not received within 10 years Use if not fully immunised with IPV	Yes, if not received within 10 years Use if not fully immunised with IPV
Varicella (unless seropositive or documented prior vaccination)	Yes (complete at least 1 month prior to transplant)	**No**
Zoster (Shingrix®is preferred)	Yes if > 50 yrs	**No**

All require annual inactivated influenza vaccine from 6 months of age (2 doses 4 weeks apart in the first season of receipt)

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