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.

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3.1 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).

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 immunisation. 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.

An individualised approach is necessary, taking into account the underlying condition, the patient's medications, the risk of infection and the availability of appropriate treatments. With some exceptions, live vaccines should be avoided during systemic immunosuppressive therapy. Consultation with an appropriate specialist may be necessary.

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 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.

3.2 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 may be considered for those with conditions that can be associated with hyposplenia:- PCV13, PPV23, Hib, MenACWY, MenB and annual influenza vaccines (Table 3.1).

Recommendations

For those requiring splenectomy, vaccination should be completed at least two weeks and preferably four weeks or more before surgery. In the case of emergency splenectomy, or if immunisation was not completed pre operatively, vaccination can be commenced two weeks post operatively. In addition to routine vaccines recommended 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] Chapter 16

3.3 Cancer patients

Chemotherapy and radiotherapy 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 vaccine preventable diseases (VPDs) in cancer patients vary depending on exposure, vaccination history, and 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.

When possible, all indicated vaccines should be given at least two weeks before initiation of chemotherapy, radiation or splenectomy, and before treatment with other immunosuppressive drugs.

Live vaccines

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

* Those without laboratory evidence of immunity or documented prior vaccination

Non-live vaccines

Patients receiving chemotherapy, immunotherapy (including a single checkpoint inhibitor) or radiation therapy can receive non-live vaccines if not contraindicated (see Recommendations below). As there may be a suboptimal immune response; booster doses should be given six months after treatment has stopped (Table 3.2), when immune function has recovered.

Recommendations

When practicable, complete recommended immunisation at least two and preferably four weeks prior to chemotherapy, as the immune response may be reduced if vaccines are received during treatment.

Cancer patients with severe neutropoenia (absolute neutrophil count <0.5 $\times 10^9$/L) should not receive **any** vaccines, to avoid an acute vaccine-related febrile episode. This does not apply to children with primary autoimmune neutropoenia.

Patients on combination checkpoint inhibitors should not receive **any** vaccines because of a significant increased incidence of immune-related adverse reactions.

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

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

Re-immunisation after chemotherapy:
Children treated with standard chemotherapy regimens should be offered a booster of each age appropriate vaccine in the routine childhood immunisation schedule six months after completion of treatment, except MenC vaccine which should be replaced with MenACWY vaccine as well as a dose of PPV23 vaccine (Table 3.2).

Table 3.2. Booster vaccine schedule[1] for children beginning six months after completion of standard-dose chemotherapy

Visit	Interval	Age[1]		
		<5 years	5-9 years	10 -17 years
1		6in1 + MenACWY + MenB	6in1 + MenB + COVID-19	Tdap/IPV[2] + MenB + COVID-19
2	4 weeks	MMR[3] + PCV13	MMR[3] + PCV13 + MenACWY	MMR[3] + PCV13 + MenACWY
3	8 weeks	PPV23	PPV23	PPV23 + HPV

[1] If child did not receive full vaccination schedule prior to treatment, complete the age-appropriate catch-up vaccination schedule (including COVID-19 vaccine). For those who completed the course, a booster dose should be given

[2] If Tdap/IPV is not available, give Tdap followed by Td/IPV ≥28 days apart

[3] If child did not receive 2 doses of MMR prior to chemotherapy, give 2 doses of MMR ≥28 days apart.

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 Section 3.10).

Non-live vaccines

- *COVID-19 vaccine.* Give primary course followed by an additional dose four months later and booster doses (see Chapter 5a).
- *Hib vaccine* is not routinely recommended for adult cancer patients unless undergoing HSCT (Table 3.9).
- *Inactivated influenza vaccine* is recommended annually for most cancer patients. If it has not been given two weeks or more before commencing treatment, it should be given during chemotherapy if the lymphocyte count is ≥1.0 x10^9/L. However, the response to the vaccine may be blunted. A second dose should be given at least four weeks after completion of chemotherapy, and at least four weeks after the first dose (Chapter 11, Table 11.1).

  Note: Patients on combination checkpoint inhibitors should not receive any influenza vaccines, because of a potential association with immune-related

adverse reactions.

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

- *Pneumococcal vaccine* is recommended for all cancer patients who are under hospital supervision
  - For those who have never received PCV13 or PPV23 vaccines, a single dose of PCV13 vaccine is recommended, followed by PPV23 vaccine after ≥2 months
  - For patients who have received one or more doses of PPV23 vaccine, a single dose of PCV13 vaccine is recommended, at least 12 months after the PPV23 vaccine
  - Those who have received PCV7 vaccine should be given PCV13 vaccine and PPV23 vaccine (Chapter 16)
  - If PCV13 or PPV23 vaccine has been given during chemotherapy or radiotherapy, revaccination ≥3 months after treatment is recommended
  - Booster doses of PPV23 vaccine are recommended, the first at least five years after the initial dose if still immunosuppressed, and when aged 65 years or older (need to leave 5 years since last dose).
- *Zoster vaccine*: *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 contraindicated.
- *MMR vaccine* may be given to patients with leukaemia or lymphoma who are in remission and have been off chemotherapy for six months (three months if there is high risk of measles or mumps infection).
- *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 three (ideally six) 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: Zostavax* is contraindicated in immunocompromised patients due to the risk of disseminated herpes zoster infection.

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 a relevant specialist.

3.4 Chronic kidney disease, dialysis and renal transplant

Infections are a leading cause of morbidity and mortality among patients with chronic kidney disease (CKD). Vaccines can help protect against some of the most common infections to which patients with CKD are exposed.

In addition to routine recommended age-appropriate vaccines including influenza and COIVD-19, additional vaccination against pneumococcal infection and Hepatitis B infection (in those predicted to require future haemodialysis or transplant) are recommended.

Fifty to 60% of those with end stage kidney disease develop antibodies following HBV vaccination. Increased response rates have been reported to vaccines specially formulated for use in patients with chronic renal failure. Patients with chronic kidney disease (CKD), predicted to require renal transplant, should receive HBV vaccine before dialysis or transplant. All patients on dialysis should be given HBV vaccination course as soon as possible.

Children should have received HBV vaccine as part of the primary immunisation series. Anti-HBs levels should be checked and a full course administered (as per Table 9.2) if <10 mIU/ml. Based on adult experience, vaccination with a higher dosage of antigen (two doses of Engerix Paediatric 10mcg) may improve the immune response (Table 3.3). Serological testing is recommended two months following vaccination.

Three vaccines for patients with renal insufficiency (including pre-dialysis and dialysis patients) are licensed. All are adjuvanted recombinant DNA vaccines. Fendrix (20mcg) is indicated from the age of 15 years onwards and Engerix B and HBVAXPRO 40 are indicated from 16 years of age for active immunisation against HBV infection (Table 3.3). When feasible, the same manufacturer's vaccines should be used to complete the series. Post vaccine Anti-HBs titres should be checked two months after the vaccination course.

Table 3.3: Hepatitis B vaccines for chronic kidney disease, dialysis and renal transplant patients

Not all listed vaccines may be available in Ireland

Age (years)	Vaccine	Dose	Schedule (months)
0 to ≤15	Engerix B (10mcg)	20mcg (2x10mcgs at different sites)	0, 1, 6 or 0, 1, 2, 12[1]
≥15	Fendrix	20mcg	0, 1, 2, 6
≥16	Engerix B (20mcg)	40mcg (2x20mcgs at different sites)	0, 1, 2, 6
	HBVAXPRO 40	40mcg	0, 1, 2, 6

[1]Accelerated course

Additional doses of vaccine may be needed to ensure a protective anti-HBs level ≥ 10 mIU/ml (Table 3.4).

Table 3.4: Post vaccination testing for chronic kidney disease including those on dialysis

Anti HBs (mIU/ml)	Interpretation and management	Follow Up
≥10	Adequate response	Re-check anti-HBs annually If anti-HBs < 10 mIU/ml, give booster dose of vaccine
<10	Non-response Repeat vaccination course (different brand) Check anti-HBs two months later: • If anti-HBs ≥10 mIU/ml, adequate response • If anti-HBs < 10 mIU/ml, non-responder	Test for HBsAg three monthly while on dialysis

3.5 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 one week,
  or
  ≥20 mg/day for two weeks or longer

- Children <10 kg:
  2mg/kg/day for two 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 three months after cessation of high dose steroid therapy, with some experts recommending their administration as soon as one 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 a relevant 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 one to three 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 one month, and where circumstances permit three months, after stopping high dose steroid therapy.
- Defer BCG vaccine for a minimum of three and ideally six months or more after stopping high dose corticosteroid therapy.
- Defer neonatal BCG vaccine until aged three months or older 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

3.6 HIV

People living with HIV should generally receive all recommended and some additional vaccines (Table 3.6). 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 vaccine 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 positive 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% (Table 3.5). BCG vaccine is contraindicated in all HIV positive 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 positive children, even those significantly immunocompromised (Table 3.6). 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 six 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 3.5 CD4 counts indicative of severe immunocompromise

If aged:	%CD4	CD4 count (x 10^6/L)
< 1 year	<15%	<750
1 - 5 years	<15%	<500
≥ 6 years	<15%	<200

Live vaccines
For specific recommendations see Table 3.6.

BCG vaccine is contraindicated.

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

Table 3.6. Sample Vaccination Schedule for HIV exposed and HIV infected children

	HIV exposed	HIV positive
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 3.5)
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	HPV9 1 dose	HPV9 3 doses
11-14 years	Routine recommended vaccines	

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

COVID-19 vaccine: Give primary course followed by an additional dose four months later and booster doses (Chapter 5a).

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

- For those with CD4 count ≥350 x 10^6/L, two doses at 0 and 6 months.
- For those with CD4 count <350 x 10^6/L, three doses at 0, 1 and 6 months.
- Boost every 10 years for those with ongoing exposure risk.

HIV positive individuals should be screened for evidence of HBV infection or immunity. Non-immune individuals (HBsAg negative, HBcAb negative, HBsAb negative) aged 15 years and older are recommended to receive HBV vaccination as follows:

- Engerix B 20 mcg, two doses at separate sites (total 40 µg) at 0, 1, 2 and 6 months, **or**
- HBVAXPRO40 at 0, 1, 2, and 6 months, **or**
- Fendrix 0, 1, 2, and 6 months.

An ultra-rapid vaccination course (**standard-dose** at 0, 7 and 28 days) may be considered in patients with CD4 cell counts >500 x 10^6/L, if there is an imperative need to ensure rapid completion of vaccination and/or where compliance with a full course is doubtful. High-dose vaccination should not be used in this schedule due lack of safety data.

If Fendrix or HBVAXPRO 40 are not available, four doses of Engerix B 1ml at two sites may be given to those aged 16 years and older at 0, 1, 2 and 6 months.

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

HPV9 vaccine: HPV9 should be used where available.
A three dose schedule at 0, 2 and 6 months is recommended for all HIV positive males and females age ≤26 years and all HIV positive MSM age ≤45 years.

Inactivated influenza vaccine: Give annually.

Meningococcal vaccine: HIV positive adults should be given MenACWY vaccines, two doses at least 2 months apart and MenB vaccine two doses one month apart should be considered in those with additional risks.

MMR vaccine: (seronegative individuals):
- If CD4 count ≥200 x 10^6/L, two doses at least 28 days apart.
- If CD4 count <200 x 10^6/L, MMR vaccine is contraindicated.

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

Pneumococcal vaccine:

- PCV13 vaccine: All HIV positive adults should receive one dose of PCV13 vaccine irrespective of CD4 count, ART use, and viral load, unless they already received PCV13 vaccine.
- PPV23 vaccine: HIV positive adults should receive one dose of PPV23 vaccine, ≥2 months after PCV13 vaccine.

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

Varicella vaccine: (seronegative individuals):

If CD4 count is ≥200 x 10^6/L, give two doses three months apart.

If CD4 count is <200 x 10^6/L, varicella vaccine is contraindicated.

Zoster vaccine: Consider including Shingrix vaccine for >50 years who are HIV positive.

Yellow fever vaccine: may be given to HIV positive persons who are not immunocompromised (i.e. with CD4+ counts ≥200 x 10^6/L). 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.

3.7 Immunocompetent household contacts of immunocompromised persons

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

Additional vaccines to reduce household transmission may include influenza, MMR, pertussis, and varicella or zoster vaccines (seronegative persons only).

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

The rotavirus vaccine virus may be found in stools for up to 28 days after the first and up to 15 days after the second dose. 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 an infant with toileting, changing a nappy, before food preparation, and before direct contact with the immunocompromised person.

If a varicella vaccine-associated rash develops 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 management post exposure.

3.8 Immunomodulatory treatment

Acquired immunodeficiency can be caused by treatment including biological disease modifying drugs, cancer chemotherapy and long-term steroid treatment.

Immunomodulatory treatment includes disease modifying anti-inflammatory drugs (DMARDs) 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 iInflammatory diseases (IMIDs), including autoimmune 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.

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.

When considering vaccinating people who are about to start, are receiving or have received immunomodulatory treatment, it is important to review:

- the mechanism of action of the treatment and duration of its effect on the immune system
- the consequence of using combination therapies which can contribute to the nature, extent and duration of immunocompromise, e.g., corticosteroids with other immunosuppressive treatments such as disease-modifying anti-rheumatoid drugs (DMARDS)
- the anticipated duration of immunocompromise due to the disease or treatment
- the underlying disease
- the interval since completing treatment.

The degree of immunosuppression and the interval until immune reconstitution vary with the type and intensity of immunosuppressive therapy, radiation therapy, underlying disease, and other factors. Therefore, it may not be possible to make a definitive recommendation for an interval after cessation of immunosuppressive therapy when non-live vaccines can be administered effectively or when live vaccines can be administered safely and effectively.

If there is uncertainty about the severity of immunocompromise and whether it is safe to receive a vaccine, do not vaccinate. Seek expert advice from the treating physician.

See Table 3.7 for immunimodulatory and immunosuppressing treatment requiring deferral of live vaccination.

Table 3.7 Immunomodulatory and immunosuppressing treatment requiring deferral of live vaccination

Those who are receiving or have received treatment in the previous six months	Immunosuppressive therapy for a solid organ transplant
	Immunosuppressive chemotherapy or radiotherapy for any indication
	Rituximab, leflunomide
Those who are receiving or have received treatment in the previous three months (*this is not a comprehensive list*)	Targeted therapy for autoimmune disease e.g., • JAK inhibitors • Biologic immune modulators including: ◦ B-cell targeted therapies ◦ monoclonal tumour necrosis factor inhibitors (TNFi) ◦ T-cell co-stimulation modulators ◦ soluble TNF receptors ◦ interleukin (IL)-1, IL-6, IL-17/23 inhibitors
	Non-biological oral immune modulating drugs e.g., • methotrexate ≥0.4 mg/kg/week • azathioprine ≥3.0mg/kg/day • 6-mercaptopurine ≥1.5mg/kg/day • mycophenolate >1g/day
	Certain combination therapies at individual doses lower than stated above, including: • on prednisolone ≥7.5 mg per day with other immunosuppressants (other than hydroxychloroquine or sulfasalazine) • methotrexate (any dose) with leflunomide
Those who are receiving or have received treatment in the previous three months	Prednisolone or its equivalent: Adults and children weighing ≥10kg: • ≥40mg/day for more than one week, or • ≥20mg/day for two weeks or longer Children <10 kg: • 2mg/kg/day for two weeks or longer

Recommendations

Ideally, recommended live vaccines should be administered at least four weeks prior to commencing immunomodulatory treatment, and non-live vaccines at least two weeks prior to treatment. In addition, MenACWY, MenB (in those with additional risks), PCV followed by PPV23 > 2 months later and annual influenza vaccines should be given.

Non-live vaccines may safely be administered during short or medium term immunosuppressing therapy. However, as the immune response may be suboptimal, if such vaccines are given two weeks or less prior to or during therapy they should be repeated six or more months after treatment if immune competence is restored.

COVID-19 vaccine: Give primary course followed by an additional dose four months later and booster doses (Chapter 5a).

MenACWY and MenB vaccines should be given to those on complement inhibitors such as eculizumab (Solliris) or ravulizumab (Ultomiris).

Live vaccines should be given at least four weeks 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 immunosuppressing to contraindicate live vaccines in most circumstances and these patients can generally receive live vaccines. However as data on yellow fever vaccine are 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).

Table 3.8. Vaccinations for children with primary immunodeficiency

Condition	Routine Non-live Vaccines	Routine Live Vaccines	Additional Vaccines	Contraindicated Vaccines
Ataxia Telangiectasia	Yes	No	Inactivated influenza, MenACWY	All live vaccines
Bruton agammaglobulinaemia (X linked agammlobulinaemia, XLA)[1]	Yes	Consider MMR	MenACWY. Consider varicella	BCG[2] Live typhoid vaccine, Yellow fever
Chronic/cyclic neutropoenia	Yes	Yes	Inactivated influenza, MenACWY	None
Chronic granulomatous disease (CGD)	Yes	Yes except BCG	Inactivated influenza, MenACWY	BCG[2] Live typhoid vaccine
Chronic mucocutaneous candidiasis (APECED syndrome)	Yes	For some, discuss with relevant specialist	Inactivated influenza, MenACWY	BCG[2] Live typhoid vaccine, Yellow fever
Complement deficiency	Yes	Yes	Inactivated influenza MenACWY. MenB (if not vaccinated), 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 (if not vaccinated).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 > $400x10^6$/L	Inactivated influenza, MenACWY	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, varicella	None
Isolated IgA or IgG subclass deficiency[1]	Yes	Yes	Inactivated influenza Can receive MenACWY and varicella	Yellow fever
SCID[5]	Yes	No	MenACWY	All live vaccines
Wiskott Aldrich Syndrome	Yes	No	Inactivated influenza, MenACWY	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

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 immunosuppressing medication
Some immunosuppressants given during pregnancy e.g., biologic DMARDS, may cross the placenta particularly if given during the third trimester. In this setting, administration of BCG vaccine in the first 12 months of life is contraindicated.

- There are little data available regarding the use of rotavirus vaccines in infants of mothers who received immunosuppressants 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 four and six 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.

  Infants of mothers receiving infliximab or other biologic therapies throughout the pregnancy and/or during breastfeeding, should not receive live vaccines such as rotavirus vaccine. Consideration may be given to administration of rotavirus vaccine to a non-breastfeeding infant if maternal infliximab use did not extend beyond the first trimester.

3.9 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 3.8). When in doubt, advice from a relevant specialist should be sought.

Children with primary autoimmune neutropoenia may receive all recommended live and non-live vaccines unless contraindicated.

3.10 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 one to two years if they are off immunosuppressive medication and free of graft-versus-host disease (GVHD).

All HSCT recipients should be viewed as "never immunised" and require re-immunisation post-transplant because pre-transplant ablation of haematopoietic cells in the bone marrow eliminates 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 six months after autologous HSCT and by nine months after allogenic HSCT. In general, T cells capable of responding to new antigens are generated 6-12 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 6-12 months after HSCT. However, depending on the degree of immunosuppression, vaccine responses may be suboptimal. Because B-cell immune reconstitution is highly variable after HSCT in patients with primary immunodeficiencies, vaccination should be delayed until there is robust evidence of functional B-cell recovery (generally 12 months).

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

Live vaccines should be deferred for at least two 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. Discussion with a relevant specialist is recommended.

Recommendations

Non-live vaccines can generally be given from six months post-transplant (one 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 three months post-transplant. However, depending on the degree of immunosuppression, vaccine response may be suboptimal. In this case a second PCV13 dose at least six months post transplant and at least two months after the first dose may be given.

A primary course of COVID-19 vaccine is recommended for those listed for or within 12 months of a transplant followed by an additional dose four months later and booster doses (Chapter 5a).

Live vaccines (MMR, varicella) should be deferred for at least two years post-transplant. BCG vaccine is contraindicated post-transplant.

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

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

Table 3.9 outlines a suggested schedule that can be tailored for different scenarios, but recommended minimum intervals between vaccines must be observed (Chapter 2). Anti-HBs antibody level should be tested two months after completion of HBV vaccination, and non-responders may need high-dose HBV vaccine (Chapter 9).

Table 3.9. Suggested vaccination schedule following HSCT*

Months post transplant	Vaccines	
	Age	
	< 10 years	≥ 10 years
6 months*	6 in 1, PCV13	Tdap/IPV[1]+ 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[2]	
12 months		HPV[3]
14 months		HPV, Hep B[4]
18 months		HPV
24 months	MMR[5] (2 doses, 1 month apart)	
> 24 months	Consider varicella vaccine[6]	
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[7] Tdap 10 years later

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

[1] If Tdap/IPV is unavailable and less than 14 years, replace with TDaP/IPV. If 14 years and older give Tdap, followed by Td/IPV at 8, 10 and 12 months. There may be increased reactogenicity due to four tetanus containing vaccines in a short time.

[2] 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.

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

[4] 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.

[5] If no GVHD or immunosuppression

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

[7] If Tdap/IPV is unavailable, give Td/IPV 5 years after primary course

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 immunosuppressants 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 receive 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 immunosuppressants 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 one month before transplant, but not to those receiving immunosuppressive therapy.

- *MMR vaccine* can be given from six 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 (Chapter 23).

Non-live vaccines: immunisation should be completed at least two weeks and preferably more than 4 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 (Chapter 2, Table 2.3). The minimum intervals are given in Chapter 2.
- *COVID-19 vaccine* should be given as recommended in Chapter 5a.
- *Hepatitis A vaccine* should be considered in all seronegative organ transplantation candidates, particularly liver transplant candidates.
- *Hepatitis B vaccine* is recommended for patients who are anti-HBs negative (section 3.4).
- *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. Include 3 doses through age 26 years (Chapter 10).

- *Inactivated influenza vaccine* is recommended for all candidates from six months of age.
- *MenB and MenACWY vaccine*s are indicated for those at increased risk (Chapter 13).
- *PCV13 and PPV23 vaccines* should be given if not previously received.
- *Tdap vaccine* 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 ≥18 years at increased risk of herpes zoster (shingles).

Post transplant *(Table 3.10):*
SOT recipients generally receive lifelong immunosuppressants, which vary depending on the organ transplanted. The degree of immunosuppression is greatest in the first 3-6 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 3-6 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 four 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 six months post-transplant. If immunisation is not completed pre-transplant, the course should be completed post-transplant.
- Those who received non-live vaccines less than two weeks prior to transplant should be re-immunised, starting six months post-transplant.
- Patients aged six months and older should receive annual inactivated influenza vaccination (Chapter 11).
- A primary course of COVID-19 vaccine is recommended (if not already received) followed by an additional dose four months later and booster doses (Chapter 5a).

Table 3.10 Vaccines for SOT candidates and recipients aged ≥10 years.

Vaccine	Pre-SOT	Post-SOT, if immunisation not completed pre transplant
COVID-19*	Yes	Yes
Hep A (if seronegative and at increased risk)	Yes	Yes
Hep B (if HBsAg negative & anti-HBs<10miu/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	Yes, if not received within	Yes, if not received
or	10 years	within 10 years
Tdap/IPV**	Use if not fully immunised with IPV	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 ≥18 years	Yes, if ≥18 years

* for those aged 5 and older

**If Tdap/IPV is unavailable, see Table 2.4a

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

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