

Immunisation of the Immunocompromised Child

Best Practice Statement

February 2002



IMMUNISATION OF THE IMMUNOCOMPROMISED CHILD

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This Statement will be reviewed and updated (as appropriate) at least every 12 months. The next review is planned for February 2003, unless required earlier.

How to use this Best Practice Statement

This Best Practice Statement includes a general introduction and a summary of important principles underlying the immunisation of immunodeficient children and adolescents; specific recommendations concerning their immunisation are outlined in Sections 1 to 7. Each section has the same layout, including background information, general principles, and detailed recommendations (listed as bullet points and highlighted within boxes for clarity). Many of the sections incorporate additional recommendations concerning passive immunisation. Sections 2 and 3 also include further specific information for particular patient groups. Section 8 provides information about specific vaccines.

NB It is important to read the section entitled “General principles for all immunodeficient children and adolescents” (page 6) before referring to individual sections of the Statement.

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Introduction

Immunisation works because the intact immune system's complex network of lymphocytes and effector cells generates memory and specificity. Immune dysfunction due to disease or the treatment of disease affects different elements of the immune system to varying degrees, and this in turn determines the effectiveness and safety of specific vaccines. Some immunocompromised children and adolescents at particular risk of certain infections will benefit from extra immunisations. Advances in medical care (eg the increasing success of both chemotherapy and transplantation in a variety of conditions, the development of highly active anti-retroviral treatment in HIV), together with greater use of immunosuppressive treatment for inflammatory diseases, have resulted in greatly increased numbers of immunocompromised children and adolescents whose immunisation schedule needs to be carefully considered.

Seven groups of conditions and treatments need to be considered:

- 1) Primary immunodeficiency.
- 2) Standard chemotherapy* for leukaemia and solid tumours.
- 3) Intensive chemotherapy* and haemopoietic stem cell transplantation / rescue (allogeneic or autologous; bone marrow, or peripheral blood, or umbilical cord blood).
- 4) Solid organ transplantation.
- 5) Inflammatory disease being treated with immunosuppressive therapy.
- 6) HIV infection.
- 7) Other conditions, including hyposplenism, malnutrition and chronic disease, nephrotic syndrome, and children born prematurely.

* In this statement, "intensive" chemotherapy is defined as that which is followed by allogeneic or autologous haemopoietic stem cell transplantation (or rescue); all other chemotherapy is defined as "standard".

Unfortunately, there are only a few published reports of controlled studies (constituting level 2 evidence¹) on which to base recommendations for immunising specific groups of immunocompromised children. Therefore, except where referenced otherwise, this Best Practice Statement uses evidence from expert committee opinions and reports, and the clinical experience and practice of respected authorities (level 4 evidence). Overall, the statement can be considered to provide grade C and sometimes B, recommendations.¹

There is a clear and important need for further research in immunocompromised children concerning immunisation in general, and specific vaccines in particular. The Working Party anticipates that the publication of this Statement will act as a stimulus for audit of current and recommended practices, and that this will in turn promote research.

Although the Working Party did not consider it appropriate to create patient and parent information sheets on a national basis, the recommendations provide a template for the local production of such documents.

Abbreviations

AIDS	Acquired immunodeficiency syndrome
BCG	Bacille Calmette Guerin (TB vaccine)
BMT	Bone marrow transplantation / rescue
CGD	Chronic granulomatous disease
CID	Combined immunodeficiency
CVID	Common variable immunodeficiency
DT	Diphtheria-tetanus vaccine
DTP	Diphtheria-tetanus-pertussis vaccine
Hib	Haemophilus influenzae type b (vaccine)
HIV	Human immunodeficiency virus
HSCT	Haemopoietic stem cell transplantation / rescue (BMT, PBSCT, umbilical cord blood transplantation)
Ig	Immunoglobulin
IVIg	Intravenous immunoglobulin
IPV	Inactivated polio vaccine
MeningoC	Meningococcal Group C conjugated vaccine
MMR	Measles, mumps, rubella vaccine
NIG	Human normal immunoglobulin
OPV	Oral polio vaccine
PBSCT	Peripheral blood stem cell transplantation / rescue
PID	Primary immunodeficiency
SCID	Severe combined immunodeficiency
ZIG	Zoster immunoglobulin

General principles for all immunodeficient children and adolescents

- It cannot be overemphasised that vaccinations which may benefit these patients should be given and not avoided, so long as each vaccine being delivered is safe. However, there are many scenarios where there is little convincing evidence for efficacy, and current practice is based on clinical experience rather than published research. Further study is necessary in many aspects of immunisation in immunocompromised children.
- There are certain situations where live vaccines are clearly not safe and should be avoided (eg BCG in patients with SCID).
- Routine measurement of specific antibody concentrations to guide immunisation decisions is not recommended because the levels are often very difficult to interpret.
- In general, vaccines are not likely to be beneficial whilst the patient is on Ig replacement treatment. Therefore, vaccine administration generally should be deferred until at least 3 months after cessation of such treatment.
- Primary health care records should be updated if immunisations are undertaken in the hospital setting.

Certain general principles relate to immunisation of siblings or other close contacts:

- Avoid administration of live vaccines (except MMR and BCG) to siblings of immunocompromised patients. Live OPV can be transmitted from person to person. Where there is a recommendation that OPV should not be used and that IPV should be used instead in an immunocompromised patient, the same principle should be applied to all household and other close contacts. However, MMR can be given because transmission of these vaccine viruses has not been reported. Indeed, it is strongly recommended that siblings should be given MMR to reduce the patient's risk of exposure to wild measles.
- Patients should avoid close physical contact with children vaccinated with OPV for approximately 4-6 weeks following administration, although it is not suggested that children should be kept away from school for this period. If contact is unavoidable (eg within the household when OPV has been given inadvertently), rigorous handwashing and hygiene (eg using separate towels) must be practised for this period of time.

1 Primary immunodeficiency (PID)

Children with inherited defects of immunity are at increased risk of frequent and severe infection. Therefore, they require the maximum protection possible from both active and (where appropriate) passive immunisation.

1.1 General Principles

- Only rarely is immunity so compromised that active immunisation is totally ineffective and inappropriate.
- Certain live vaccines may pose risks to some of these children.
- Subgroups of primary immunodeficiencies need to be considered separately:

NB See general principles relating to immunisation of siblings or other close contacts (page 6).

1.1.1 Group 1 - Severe

- Severe and other combined immunodeficiencies (SCID, CID)
- di George syndrome*
- Wiskott Aldrich Syndrome*
- Ataxia telangiectasia*
- Leukocyte adhesion deficiency
- Hyper IgM syndrome (CD40 ligand deficiency)
- Chronic mucocutaneous candidiasis (APECED syndrome)
- Hyper IgE (“Job’s”) syndrome*
- Familial erythrophagocytic lymphohistiocytosis (FEL)
- X linked agammaglobulinaemia
- Common variable immunodeficiency (CVID)*

The phenotypic severity of some of these conditions (indicated by asterisks in Table) is variable, so the immunisations used will not be standard. However, in general, such patients will not be given live vaccines, although some can be given MMR safely and some will have been given OPV and / or MMR without ill effects prior to the diagnosis of immunodeficiency. The value of active immunisation is controversial in some of these disorders particularly when Ig replacement is being used. When immunisation is performed, monitoring of antibody responses may be undertaken if interpretation is not rendered impossible by Ig treatment. Since vaccines induce both humoral and cell-mediated immunity, they may be of value in children with severe but specific defects of antibody production (such as X-linked agammaglobulinaemia). The use of varicella zoster vaccine in seronegative family members may provide indirect protection for patients with severe PID. Some children with severe PID may be managed by HSCT (see section 3 for re-immunisation post-HSCT).

1.1.2 Group 2 - Moderate

- IgA deficiency and/or most IgG subclass deficiencies
- Failure of antibody production to specific vaccines

These children, although usually judged not to require Ig replacement therapy, are often given long term antibiotic prophylaxis. They are not known to be at risk from commonly used live vaccines, and indeed many will have been given both OPV and MMR, and some BCG, prior to diagnosis. Nevertheless, IPV can be used instead of OPV, and MMR should not be withheld routinely. Additional vaccines, including pneumococcal and influenza vaccines, should usually be given, as should BCG where local policies suggest its use.

1.1.3 Group 3 – Non specific

- Chronic neutropenia
- Chronic granulomatous disease (CGD)
- Complement deficiency diseases
- Other opsonisation defects

Children with these disorders are not at enhanced risk from live vaccines (except for BCG in CGD). Therefore, with this exception, all routine vaccines should be given. Additionally, they should receive pneumococcal and influenza vaccines, and in the case of complement deficiencies, meningococcal A, C, Y, W135 vaccine also. However, patients with CGD should not be given BCG because of the reported risk of disseminated BCGosis.

1.1.4 Group 4 – Undiagnosed predisposition to infection

- Clinical impression of increased susceptibility to infection without demonstrable abnormalities on standard immunological tests.

Children thought clinically to be unusually prone to infections but in whom available investigations fail either to permit a specific immunological diagnosis, or to reveal an alternative explanation such as cystic fibrosis, should be given all routine vaccines, as well as pneumococcal and influenza vaccines as deemed appropriate. Antibody responses to vaccines often form part of the diagnostic investigation of such cases.

1.2 Recommendations for immunisation of children with PID

Group 1 – Severe

- Seek specialist advice. Requirements will vary between patients.
- A few will be given no vaccines. Many will receive non-live vaccines only (eg Diphtheria, Tetanus, Pertussis, Hib, MeningoC).
- Use IPV instead of OPV.
- Avoid BCG.
- Some patients can safely be given MMR.
- Consider giving varicella zoster vaccine to seronegative family members to provide indirect protection.

Group 2 – Moderate

- All routine vaccines should be given (Diphtheria, Tetanus, Pertussis, Polio, Hib, MeningoC, MMR) *as per* universal childhood immunisation schedule.
- IPV may be used instead of OPV.
- Give conjugate pneumococcal vaccine initially, followed by polysaccharide pneumococcal vaccine once the child is 2 years old² (see section 8.6).
 - If child under 24 months age, give 3 doses of conjugate vaccine at monthly intervals, followed by one dose of polysaccharide vaccine at 2 years age.
 - If child over 24 months age, give 2 doses conjugate vaccine at monthly intervals, followed by one dose of polysaccharide vaccine.
- Give influenza vaccine annually in autumn from age of 6 months.
- Can receive BCG when indicated.

Group 3 – Non-specific

- All routine vaccines should be given (Diphtheria, Tetanus, Pertussis, Polio, Hib, MeningoC, MMR) *as per* universal childhood immunisation schedule.
- OPV can be used.
- Give conjugate pneumococcal vaccine initially, followed by polysaccharide pneumococcal vaccine (see schedule outlined above for Group 2).
- Give influenza vaccine annually in autumn from age of 6 months.
- For complement defects – give polysaccharide meningococcal A,C,Y,W135 vaccine.
- Can receive BCG when indicated, except in patients with CGD.

Group 4 – Undiagnosed

- All routine vaccines should be given (Diphtheria, Tetanus, Pertussis, Polio, Hib, MeningoC, MMR) *as per* universal childhood immunisation schedule.
- OPV can be used.
- Give conjugate pneumococcal vaccine initially, followed by polysaccharide pneumococcal vaccine (see schedule outlined above for Group 2).
- Give influenza vaccine annually in autumn from age of 6 months.
- Can receive BCG when indicated.

1.3 Recommendations for passive immunisation of children with PID

Many children with severe (group 1) and some with moderate (group 2) PID receive regular treatment with intravenous or subcutaneous pooled Ig.

- Children with severe PID may also require specific passive protection following known exposure to varicella zoster or measles (see section 2.4 for further details).
- Specialist advice should be sought in all such cases.

2 Standard chemotherapy for leukaemia and solid tumours

The degree of compromise of immune function during and after treatment for malignant disease in childhood is determined by:

- the nature of the disease,
- the degree and nature of treatment-induced immuno- and myelosuppression, and
- whether the spleen has been irradiated or removed.

In most contemporary treatment regimens, chemotherapy is the principle cause of the immunocompromised state, but in some situations other treatment modalities (eg radiotherapy, monoclonal antibodies), as well as the underlying malignancy (eg Hodgkin's disease), may contribute to immunosuppression.

2.1 General principles

- Avoid all live vaccines (but see section below on varicella zoster vaccine) in patients actively receiving treatment, and for 6 months following cessation of treatment. This includes OPV, MMR, BCG, oral typhoid and yellow fever vaccines. IPV should be administered in place of OPV.

NB See general principles relating to immunisation of siblings or other close contacts (page 6). These precautions apply during, and for 6 months following cessation of, treatment.

2.2 Recommendations for immunisation of children treated with standard chemotherapy

2.2.1 Immunisation during and until six months after completion of treatment

- During treatment, administration of non-live vaccines (ie IPV rather than OPV) may be considered, following the content and timing of the universal childhood immunisation schedule as closely as possible, provided that the child's general condition is stable (ie free from infection and major organ toxicity) and is expected to stay so for 3 weeks from immunisation. Although it is likely that responses will be suboptimal, some patients may achieve protective antibody levels. This may be important, for example, if the patient is at higher than usual risk of tetanus exposure.
- Influenza vaccine is recommended annually in autumn for all patients receiving chemotherapy, and for those still within 6 months of completion of chemotherapy.

2.2.2 Immunisation six months and later after completion of treatment

- At 6 months following completion of treatment, administer an additional booster of diphtheria, tetanus, acellular pertussis, IPV, Hib, MeningoC and MMR. Subsequent routine booster doses (eg pre-school) will not be necessary if they are scheduled to be given within one year of this additional dose.

- If patient has previously had BCG, and is considered to be in a high risk group for tuberculosis, check tuberculin test and if negative, revaccinate. If patient has not previously had BCG, immunise according to local policy. Ensure that primary health care team is informed.
 - High risk groups for tuberculosis are:
- Families with an ethnic minority background from a country with an incidence of tuberculosis of greater than 40 per 100,000 per year.
- Patients travelling for over a month to a country with an incidence of tuberculosis of greater than 40 per 100,000 per year.
- Household contact or prolonged close contact with an individual with tuberculosis.

2.3 Other specific vaccines

• **Varicella Zoster:** Routine administration is not practised currently in the United Kingdom, and many oncologists and haematologists have concerns about interrupting treatment to allow its administration. Therefore, the routine use of varicella zoster vaccine is not recommended at the current time, although its use may be considered appropriate in individual patients after careful assessment of potential benefits and disadvantages. A license for the live attenuated vaccine is expected to be granted during 2002. In the meantime, if considered appropriate, it is possible to obtain the vaccine on a named patient basis for administration to individual patients, provided that a) the lymphocyte count is $>0.7 \times 10^9/l$, b) immunosuppressive therapy is withheld for 1 week prior to and 1 week after the first dose, and c) no steroids are given for the following 2 weeks. There are published studies concerning administration in leukaemic patients in continuous remission for over a year,³ and in solid tumour patients.⁴ Cases of varicella zoster are reported after immunisation - these may be treated with aciclovir given intravenously if clinically severe. Steps should be taken to culture the virus and establish whether it is vaccine or wild type (see section 8.10). The use of varicella zoster vaccine in seronegative family members may be considered as a means of providing indirect protection for susceptible patients during, and for six months after completion of, standard chemotherapy.

2.4 Recommendations for passive immunisation of children treated with standard chemotherapy

This is applicable for all patients on active treatment, or within 6 months of completion of therapy.

2.4.1 *Passive immunisation after measles contact*

- Contact requires action regardless of antibody status.⁵
- Children who have significant contact (play or direct contact for more than 15 minutes, on ward or in household) with an individual with virologically confirmed measles during the infectious period from up to 5 days prior to, to 4 days after, the onset of the rash require passive immunisation. Every effort should be made to confirm the diagnosis of measles in the index case, but this may not always be possible. Local availability will determine which investigations are used for confirmation of the diagnosis. In the event of contact with clinically diagnosed but virologically unproven measles, passive immunisation may be warranted if the clinical diagnosis seems plausible.

- If less than 14 days (most effective if within 72 hours) from contact, in view of the potential severity of measles infection in these patients, give either intramuscular human normal Ig (NIG) or (especially if thrombocytopenic) intravenous Ig (IVIg). The protection lasts approximately 4 weeks.
- NIG dose:
 - Under 1 year age 250 mg
 - 1-2 years age 500 mg
 - Over 2 years age 750 mg
- IVIg (standard dose) 0.4g/kg

2.4.2 Passive immunisation after varicella zoster contact

- The clinical history of past infection and the current antibody status should be ascertained prior to commencement of chemotherapy and prior to administration of blood products. Routine retesting of initially antibody positive patients is not recommended since standard EIA assays do not provide clinically helpful information about the degree of protection.
- Significant contact with an individual with chickenpox (play or direct contact for more than 15 minutes, on ward or in household), during the infectious period from 2 days prior to onset of rash, until crusting of all vesicles, or with herpes zoster (direct contact with exposed lesions only) requires one of the following prophylactic treatments in varicella antibody negative patients:

Either

- Aciclovir is widely prescribed as a prophylactic agent in this setting. However, there is relatively little supportive clinical literature.⁶
- High dose oral aciclovir from 7 – 21 days following the initial contact.
- Aciclovir dose:
 - Under 2 years age 200 mg four times daily
 - 2-6 years age 400 mg four times daily
 - Over 6 years age 800 mg four times daily

Or

- If less than 72 hours from contact, give intramuscular zoster immunoglobulin (ZIG) (may attenuate infection if administered up to 10 days post exposure) or (especially if thrombocytopenic) IVIg. The protection lasts approximately 4 weeks.
- ZIG dose:
 - Under 5 years age 250 mg
 - 5-10 years age 500 mg
 - Over 10 years age 750 mg
- IVIg (standard dose) 0.4g/kg

- Whichever method of prophylaxis is used, the patient and family should be instructed to contact the specialist unit immediately if any suspicious skin lesions develop so that early treatment with intravenous aciclovir may be considered.

3 Intensive chemotherapy and haemopoietic stem cell transplantation / rescue (HSCT)

Following HSCT, the degree and kinetics of immune function recovery is determined by:

- the original disease,
- the type of conditioning regimen,
- whether autologous or allogeneic haemopoietic stem cells were used, and the source of these stem cells (bone marrow, peripheral blood, umbilical cord blood),
- the degree of HLA disparity between allogeneic donor and recipient (particularly the use of an unrelated or mismatched related donor),
- whether T cell depletion (*in vivo* or *in vitro*) was performed,
- the engraftment status,
- the time elapsed since transplantation, and
- the presence or absence of chronic GVHD and of continued immunosuppressive treatment.

Although there are many published studies concerning immunisation after HSCT, interpretation of their findings is complicated by considerable heterogeneity in patients and donors, and also by inclusion of patients with chronic GVHD, and of those receiving immunosuppressive treatment, in some studies. Although some publications have only included patients immunised relatively late (eg 2 years) after allogeneic HSCT, this statement (in common with guidelines suggested by many BMT groups) recommends earlier immunisation provided that the patient has been off all immunosuppressive treatment for a specified period (see section 3.2.1 below).

It is assumed that all intensive chemotherapy is followed by HSCT, so separate recommendations for intensive chemotherapy alone are not presented.

3.1 General principles

NB See general principles relating to immunisation of siblings or other close contacts (page 6). These precautions apply until the patient is at least 12 months post-HSCT and has been off all immunosuppressive treatment for at least 12 months, and has no evidence of active GVHD.

3.1.1 Allogeneic HSCT

- It should be assumed that all children are at very considerable risk of losing their natural or immunisation-derived protective antibodies against a wide variety of potentially preventable infectious diseases. Although debate continues over whether they will remain immunologically naive, or alternatively acquire the donor's immunity, without re-immunisation, it is likely that individual children will differ in this respect (see section 3 above).

However, in general:

- All children who have received an allogeneic HSCT should be considered for a re-immunisation programme.
- In view of the difficulty of predicting the extent of immune recovery in individual children and in interpreting specific antibody levels, a pragmatic approach is to recommend re-immunisation of all recipients of allogeneic HSCT, starting at the times stated in section 3.2.1.

- The use of live vaccines is potentially dangerous until the child has been off all immunosuppressive treatment for at least 12 months and has no evidence of active chronic GVHD.
- Chronic GVHD and its treatment both cause considerable and often prolonged immunosuppression. Therefore, these children respond poorly to immunisation, and the administration of live vaccines is potentially dangerous. However, they are at high risk of infectious complications due to their immunosuppressed condition, and the use of non-live vaccines is recommended if the patient is not receiving IVIg, even if it is considered that the response may be sub-optimal.

3.1.2 Autologous HSCT

- In comparison to those children who have received an allogeneic HSCT, the frequency and severity of loss of immunity appears to be lower in children who have received an autologous HSCT. Nevertheless, for example, about 70% of patients may become seronegative to tetanus after autologous HSCT, and 50% after autologous PBSCT.⁷

Therefore, in general:

- All children who have received an autologous HSCT should be considered for a re-immunisation programme.
- In view of the difficulty of predicting the extent of immune recovery in individual children and in interpreting specific antibody levels, a pragmatic approach is to recommend re-immunisation of all recipients of autologous HSCT, starting 1 year post-HSCT.

3.1.3 Specific antibody measurements

Routine measurement of specific antibody levels is rarely helpful, and is not recommended except in the context of research studies.

3.2 Recommendations for immunisation of children after HSCT

3.2.1 Re-immunisation of allogeneic HSCT recipients

- Re-immunisation should commence:
 - 12 months after a HLA-identical sibling donor allogeneic or a syngeneic HSCT.
 - 18 months after any other allogeneic HSCT.
- Providing that:
 - there is no evidence of active chronic GVHD, and
 - the child has been off all immunosuppressive treatment (eg steroids, cyclosporin A) for at least 6 months (12 months before administering any live vaccines), and
 - the child has been off IVIg for at least 3 months.
- However, in patients with chronic GVHD not receiving IVIg, consider the use of non-live vaccines – see section 3.1.1 above.
- In some instances, it may be appropriate for infants who have undergone allogeneic HSCT for primary immunodeficiency in supraregional units to start immunisation at earlier time points post-HSCT than those specified above. However, this should only be instigated under specialist advice from the supraregional unit.

HLA-identical sibling donor allogeneic or syngeneic HSCT

- At 12 months post-HSCT, administer
 - Diphtheria, tetanus, acellular pertussis – 3 doses at monthly intervals.⁸⁻¹⁰
 - IPV - 3 doses at monthly intervals.^{9,11-13}
 - Hib - 3 doses at monthly intervals.^{10,14}
 - MeningoC - 3 doses at monthly intervals.¹⁵
- At 15 months post-HSCT, administer:
 - Pneumococcal vaccine – give conjugate vaccine initially, followed by polysaccharide vaccine once the child is 24 months post-HSCT^{2,16} (see section 8.6).
 - If child under 24 months age, give 3 doses of conjugate vaccine at monthly intervals (NB polysaccharide vaccine to follow later – see below).
 - If child over 24 months age, give 2 doses conjugate vaccine at monthly intervals (NB polysaccharide vaccine to follow later – see below).
- At 18 and 24 months post-HSCT, administer:
 - MMR (providing that at least 12 months off all immunosuppressive treatment)^{17,18} – these 2 doses should usually be given with a minimum 6 month interval, but the 2nd dose can be given 4 weeks after the 1st in the event of a measles outbreak.
- At 24 months post-HSCT, administer:
 - Polysaccharide pneumococcal vaccine (see above and section 8.6) – 1 dose.
- Every autumn, administer:
 - Influenza vaccine¹⁹ (for as long as the patient remains clinically immunocompromised or is considered to be at increased risk from influenza virus infection).

Any other allogeneic HSCT

- Re-immunisation schedule as above, but starting and continuing 6 months later (ie starting at 18 months post-HSCT).

3.2.2 Re-immunisation of autologous HSCT recipients

- Re-immunisation programme should commence 1 year after an autologous HSCT.
- The schedule is identical to that for “HLA-identical sibling donor allogeneic or syngeneic HSCT” (see above).

3.3 Other active immunisations

There is a lack of evidence about the safety (or otherwise) of BCG immunisation after HSCT because tuberculosis is relatively uncommon in those countries in which most HSCT procedures are performed. Therefore its use should be avoided unless there is a clear case of need (eg travel to or residence in a country with a high incidence of TB [greater than 40 per 100,000 per year]), and there is good evidence of immune function recovery (no history of serious infections, satisfactory serum immunoglobulin concentrations, CD4 lymphocyte numbers and lymphocyte function with no evidence of chronic GVHD).

3.4 Recommendations for wounds likely to engender a risk of tetanus in children after HSCT

- Patients suffering wounds likely to engender a risk of tetanus, and who have not been reimmunised yet, should be considered non-immune and should receive a first dose of tetanus vaccine.
- Tetanus immunoglobulin (250–500 units intramuscularly) should also be given, along with wound toilet and prophylactic antibiotics (intravenous benzylpenicillin or co-amoxiclav).

3.5 Adoptive immunotherapy (pre-harvest donor immunisation)

- There is preliminary evidence that donor immunisation with conjugate Hib vaccine, performed before bone marrow harvest, may enhance and accelerate recovery of specific anti-Hib antibodies in the recipient after allogeneic HSCT.²⁰ However, the practical and ethical implications of this procedure limit its usefulness since most donors for paediatric patients undergoing allogeneic HSCT are either children themselves or are unrelated. More evidence of benefit is required before pre-harvest donor immunisation can be generally recommended.
- A parallel study suggested the possible benefit of immunisation with conjugate Hib vaccine before bone marrow harvest in autologous BMT patients.²¹ However, although pre-harvest immunisation is likely to be more feasible and acceptable in the autologous setting, there is insufficient evidence of benefit to justify its recommendation at present.
- More studies of immunisation before stem cell harvest, particularly as a means of achieving adoptive immunotherapy in allogeneic HSCTs, are required.

3.6 Recommendations for passive immunisation after HSCT in children

3.6.1 Measles and varicella zoster

- Significant contact with measles or with varicella zoster virus infection requires treatment as outlined in section 2.4.1 and 2.4.2, regardless of antibody status pre-HSCT.
- This recommendation is applicable for all allogeneic and autologous HSCT patients until at least 1 year post-HSCT (18 months post-HSCT from non-sibling and mismatched related donors or from unrelated allogeneic donors), and at least 12 months off all immunosuppressive treatment.

3.6.2 Intravenous immunoglobulin

- IVIg is used by many BMT centres for prophylaxis against CMV in allogeneic HSCT patients who are CMV IgG positive pre-HSCT, or whose donor is CMV IgG positive.^{22,23}
- IVIg may also be used in patients with chronic GVHD receiving long-term immunosuppressive treatment.

- Doses of IVIg used for these indications vary, but typically 0.4 - 0.6 g/kg is given every 1-4 weeks.

3.7 Hyposplenism due to total body irradiation

Patients who have received total body irradiation (TBI) are assumed to have functional hyposplenism. Lifelong antibiotic prophylaxis (usually with phenoxymethylpenicillin) is recom-

mended in these patients (see section 7.1).

3.8 Varicella zoster vaccination of seronegative family members

The use of varicella zoster vaccine in seronegative family members may be considered as a means of providing indirect protection for HSCT recipients until at least 12 months post-HSCT, and until the patient has been off all immunosuppressive treatment for at least 12 months, and has no evidence of active GVHD.

4 Solid organ transplantation

Most children undergoing solid organ transplantation will have commenced, and many completed, the primary immunisation schedule. However, after transplantation, these children are usually on long term immunosuppression. Therefore, most do not have another opportunity for optimal immunisation once a transplant has been performed. There are few published studies of vaccination specifically in children undergoing solid organ transplantation, so it is possible only to propose a few important general principles and recommendations.

4.1 General principles

- Before solid organ transplantation, children should be up to date with routine primary immunisations.
- After solid organ transplantation, children receiving chronic immunosuppressive treatment should be given non-live vaccines normally according to the universal childhood immunisation schedule, but should not receive live vaccines.

NB See general principles relating to immunisation of siblings or other close contacts (page 6). These precautions apply whilst the child is receiving immunosuppressive treatment following solid organ transplantation.

4.2 Recommendations for immunisation of children treated by solid organ transplantation

4.2.1 Immunisation before transplantation

- Ensure that the child is fully up to date with routine primary and (where relevant) booster immunisations.
- Varicella zoster vaccine should be given in non-immune patients.
- Children undergoing haemodialysis whilst awaiting renal transplantation should be given hepatitis B vaccine if they have not already received it.

4.2.2 Immunisation after transplantation

- The routine childhood immunisation schedule should continue to be followed with the exception of live vaccines.
 - Pneumococcal vaccine should be given²⁴ – administer conjugate vaccine initially, followed by polysaccharide vaccine once the child is 2 years old² (see section 8.6).
 - If child under 24 months age, give 3 doses of conjugate vaccine at monthly intervals, followed by one dose of polysaccharide vaccine at 2 years of age.
 - If child over 24 months age, give 2 doses conjugate vaccine at monthly intervals, followed by one dose of polysaccharide vaccine.
- Influenza vaccine should be given annually in autumn.²⁴
- Consider giving varicella zoster vaccine to seronegative family members to provide indirect protection for susceptible patients.

4.3 Recommendations for passive immunisation in children after solid organ transplantation

- Passive protection against measles with NIG (see section 2.4.1) is recommended in the event of significant contact, regardless of antibody status. Although there is no specific evidence basis for this practice in this patient group, and contact with measles has been very rare in recent years, it is considered that the potential consequences of measles infection in all immunocompromised children merit prophylaxis.
- Passive protection against chickenpox (or herpes zoster) with ZIG and/or aciclovir (see section 2.4.2) should be given in the event of significant contact in non-immune patients.

5 Inflammatory disease being treated with systemic corticosteroids and/or other immunosuppressive drugs

Several inflammatory diseases, such as inflammatory bowel disease and juvenile idiopathic arthritis, may be treated with pharmacological doses of systemic corticosteroids and/or other immunosuppressive drugs. The dose and duration of systemic steroid treatment that results in significant immunosuppression is usually considered to be prednisolone 2 mg/kg/day for more than one week, or 1 mg/kg/day for more than one month (or equivalent doses of other steroids). The statements below apply to this group of children, as well as to those given additional or alternative immunosuppressive drugs, such as azathioprine, cyclosporin A, methotrexate, and other newer agents (eg mycophenolate mofetil, TNF blocking agents) who may suffer further impairment of immune function.

5.1 General principles

- Children with inflammatory diseases treated with immunosuppressive treatment, including systemic corticosteroids, should be given non-live vaccines normally according to the universal childhood immunisation schedule, but should not receive live vaccines.
- Although there are theoretical anxieties that immunisations may exacerbate the underlying disease in children with certain inflammatory diseases, such as juvenile idiopathic arthritis, there is no convincing evidence to support these concerns

NB See general principles relating to immunisation of siblings or other close contacts (page 6). These precautions apply whilst the child is receiving immunosuppressive treatment, and for 3 months (steroids) or 6 months (other immunosuppressive treatment) after its completion.

5.2 Recommendations for immunisation of children with inflammatory disease being treated with immunosuppressive drugs

- If circumstances permit, varicella zoster antibody status should be checked prior to starting immunosuppressive treatment; where appropriate, varicella zoster vaccine should be given at this time.
- Similarly, if circumstances permit, pneumococcal vaccine should be given prior to starting immunosuppressive treatment. If this is not possible, it should still be given whilst the child is on immunosuppressive treatment unless it is anticipated that this treatment is likely to be discontinued permanently in the next 6 months. Administer conjugate vaccine initially, followed by polysaccharide vaccine once the child is 2 years old² (see section 8.6).
 - If child under 24 months age, give 3 doses of conjugate vaccine at monthly intervals, followed by 1 dose of polysaccharide vaccine at 2 years of age.
 - If child over 24 months age, give 2 doses conjugate vaccine at monthly intervals, followed by 1 dose of polysaccharide vaccine.
- The routine childhood immunisation schedule should be followed with the exception (in general) of live vaccines.
- Live vaccines may be given once the child has been off steroid treatment for more than 3 months, and off other or combination immunosuppressive treatment for more than 6 months.
- Influenza vaccine should be given annually in autumn.
- Consider giving varicella zoster vaccine to seronegative family members to provide indirect protection for susceptible patients.

5.3 Recommendations for passive immunisation during immunosuppressive treatment for inflammatory disease in children

- Passive protection against measles with NIG should be given in the event of significant contact, regardless of antibody status (see Sections 2.4.1 and 4.3).
- Passive protection against chickenpox (or herpes zoster) with ZIG and/or aciclovir should be given in the event of significant contact in non-immune patients (see Section 2.4.2).

6 HIV infection

Children with HIV infection have mostly acquired their infection by vertical transmission. Initially, it may not be clear whether or not the child is infected. Infected children may maintain immunocompetence for a prolonged period or may progress rapidly to AIDS. The degree of immunosuppression present can be classified according to criteria produced by the Centers for Disease Control (see table).²⁵

CD4 count / μ L (%)

Age	< 12 months	1 -5 years	6-12 years
No suppression	≥ 1500 (≥ 25)	≥ 1000 ($\geq 15-24$)	≥ 500 (≥ 25)
Moderate suppression	750 -1499 (15-24)	500 -999 (15 - 24)	200 - 499 (15-24)
Severe suppression	< 750 (<15)	< 500 (<15)	< 200 (<15)

The use of highly active anti-retroviral therapy (HAART) regimens can restore a considerable degree of immunocompetence even in the most severely compromised patients. In general, vaccines will produce a poor immune response in severely immunocompromised patients. If HAART is being considered in such cases then it may be wise to defer vaccination until some immune competence has been restored. Alternatively, in those patients already immunised, repeating the vaccinations after introduction of HAART should be considered.

The use of live vaccines in this group of patients is potentially problematic and decisions on their use need to be taken in the light of the risks of developing the disease. In severely immunocompromised patients, disseminated BCGosis has followed immunisation with BCG and extremely rare cases of vaccine associated paralytic poliomyelitis have been described. In the latter case there is also a risk to other immunocompromised individuals in the household. MMR has been used widely in HIV-infected children but there has been a recent single case report of vaccine strain measles pneumonitis following immunisation in a severely immunocompromised adolescent.²⁶

6.1 General principles

- In the UK, most infants born to HIV-infected mothers are not given BCG but are followed up closely. In developing countries where the risk of exposure to TB is higher the vaccine is used.
- IPV should be used instead of OPV in children with HIV infection.

NB See general principles relating to immunisation of siblings or other close contacts (page 6).

6.2 Recommendations for immunisation of children with HIV infection

- The routine childhood immunisation schedule is followed normally except that IPV is given instead of OPV and MMR is not given while the child has a severe degree of immunosuppression as judged by the CD4 lymphocyte count (see Table - Section 6).

- If the child's HIV status proves to be non-infected, BCG should be given since there is a high risk of exposure to tuberculosis in a household with at least one other HIV-infected individual.
- If the family is returning soon to a country with a high incidence of tuberculosis (greater than 40 per 100,000 per year), and the child will not be followed up closely, BCG should be given at birth (*as per* WHO policy for developing countries).
- Influenza vaccine will produce a response in most HIV infected children who are not severely immunodeficient and should be given annually in autumn after the age of 6 months.
- Conjugate pneumococcal vaccine has yet to be fully evaluated in this group of patients but is potentially very useful and should be considered. Administer conjugate vaccine initially, followed by polysaccharide vaccine once the child is 2 years old² (see section 8.6).
 - If child under 24 months age, give 3 doses of conjugate vaccine at monthly intervals, followed by 1 dose of polysaccharide vaccine at 2 years of age.
 - If child over 24 months age, give 2 doses conjugate vaccine at monthly intervals, followed by 1 dose of polysaccharide vaccine.

6.3 Recommendations for passive immunisation in children with HIV infection

- Passive protection against measles with NIG should be given in the event of significant contact (see Sections 2.4.1). This should be given regardless of antibody status and regardless of the degree of immunosuppression.
- Passive protection against chickenpox (or herpes zoster) with ZIG and/or aciclovir should be given in the event of significant contact in non-immune patients who have immunosuppression of moderate or severe degree as judged by CD4 count (see Table in Section 6). See also Section 2.4.2.

7 Other conditions

7.1 Sickle cell disease and other causes of hyposplenism

Children with absent spleens or reduced splenic function, including those with sickle cell disease and coeliac disease, are not at any increased risk from viral infection, nor from live vaccines. However, overwhelming pneumococcal infection is a significant risk for these patients, whilst invasive Hib infection (even after the age of 5 years) and meningococcal infection may occur. Re-immunisation may be deemed necessary, based on specific antibody titres, but clear recommendations can not be made. Lifelong antibiotic prophylaxis (usually with phenoxymethylpenicillin) is recommended in these patients, but they and their families should be made aware that penicillin-resistant strains of *Streptococcus pneumoniae* are commoner in some parts of the world. A low threshold for seeking urgent medical attention should be advised in the event of febrile or severe illness whilst abroad in these patients.

7.1.1 Recommendations for immunisation of children with sickle cell disease and other causes of hyposplenism

- The routine childhood immunisation schedule, including live vaccines, should be followed normally.
- Influenza vaccination should be advised annually in autumn since it reduces the risk of serious secondary bacterial infection.
- Pneumococcal vaccine should be given - administer conjugate vaccine initially, followed by polysaccharide vaccine once the child is 2 years old² (see section 8.6).
 - If child under 24 months age, give 3 doses of conjugate vaccine at monthly intervals, followed by 1 dose of polysaccharide vaccine at 2 years of age.
 - If child over 24 months age, give 2 doses conjugate vaccine at monthly intervals, followed by 1 dose of polysaccharide vaccine.
- If an elective splenectomy is planned, it is important to ensure that the child is up to date with Hib and meningococcal C conjugate vaccinations, and has received pneumococcal vaccination, as far in advance as possible.

7.2 Malnutrition and chronic disease

Although very important globally, chronic malnutrition is a rare cause of impaired immune responses to infections and vaccines in the UK. However, children with chronic diseases in which inadequate nutrition may occur, such as cystic fibrosis, may be at greater risk of infection.

7.2.1 Recommendations for immunisation of children with malnutrition and chronic disease

- The routine childhood immunisation schedule, including live vaccines, is followed normally.
- Additional protection with pneumococcal vaccine should be offered - administer conjugate vaccine initially, followed by polysaccharide vaccine once the child is 2 years old² (see section 8.6).
 - If child under 12 months age, give 3 doses of conjugate vaccine at monthly intervals, followed by 1 dose of polysaccharide vaccine at 2 years of age.
 - If child over 12 months age, give 1 dose conjugate vaccine, followed by 1 dose of polysaccharide vaccine after 2nd birthday.
- Influenza immunisation should be given annually in autumn.

7.3 Nephrotic syndrome

Children with the nephrotic syndrome are at increased risk of pneumococcal infection, and also often receive corticosteroids or other immunosuppressive treatment (see section 5.2 and 5.3 for recommendations for children receiving such treatment).

7.3.1 Recommendations for immunisation of children with nephrotic syndrome

- Children with the nephrotic syndrome should receive pneumococcal vaccine – administer conjugate vaccine initially, followed by polysaccharide vaccine once the child is 2 years old² (see section 8.6).
 - If child under 12 months age, give 3 doses of conjugate vaccine at monthly intervals, followed by 1 dose of polysaccharide vaccine at 2 years of age.
 - If child over 12 months age, give 1 dose conjugate vaccine, followed by 1 dose of polysaccharide vaccine after 2nd birthday.

7.3.2 Recommendations for passive immunisation in children with nephrotic syndrome

- Except when in remission, children with nephrotic syndrome need passive protection in the event of significant contact with chickenpox (or herpes zoster) or measles (see sections 2.4.1 and 2.4.2).

7.4 Children born prematurely

Children born prematurely respond appropriately to most immunisations, but there is some evidence that a minority may fail to respond adequately to Hib and hepatitis B immunisations.

7.4.1 Recommendations for immunisation of children born prematurely

- All routine childhood immunisations should be given and should be scheduled on the basis of the child's actual date of birth, with no allowance being made for prematurity.
- More studies of immunisation are needed in premature infants, especially those treated with corticosteroids.

8 Specific Vaccines

8.1 Diphtheria and Tetanus (DT) (non-live)

These are non-live protein antigens which are highly immunogenic. The only children who should not be given them are those deemed totally unable to mount antibody responses and who are passively protected with Ig. Give adult preparation (low dose diphtheria, ("dT") in children over >10 years of age.

8.2 Pertussis (P or aP) (non-live)

Children in the UK receive 3 doses during the first year of life. Whole cell vaccine is most commonly used in infancy, although acellular vaccine (aP) may be used as sometimes the supply of whole cell vaccine is interrupted. A booster dose, combined with DT, was introduced as standard in October 2001. It is important that acellular vaccine is used in children older than 1 year, as the whole cell vaccine frequently causes adverse effects. Pertussis vaccine should generally be used in all immunocompromised children, since it still frequently circulates in the community. Even patients with poor antibody production can nevertheless mount cell-mediated responses. Immunodeficient children who have not completed a primary course of 3 doses, or who have lost immunity due to HSCT, should be fully re-immunised with the acellular vaccine. Others, including older children, should receive a single dose of acellular vaccine.

8.3 Poliomyelitis (OPV and IPV) (live and non-live)

A trivalent live oral vaccine (OPV) is used in the UK universal childhood schedule at present, except in situations of supply shortage. Cases of paralytic polio due to the vaccine are seen very rarely in normal children but are a serious problem in children with major defects in specific immunity.²⁷ An inactivated injectable trivalent vaccine (IPV) of comparable immunogenicity is licensed in the UK and is used for routine immunisation in many other countries. It can be given combined with DTP/Hib. In children with specific severe or moderate immunodeficiencies, who require polio immunisation, this vaccine is the logical choice.

8.4 Haemophilus influenzae type b (Hib) (non-live)

Several protein-conjugated capsular polysaccharide vaccines are licensed and available in the UK and can be given combined with DTP. Despite the reduced prevalence of disease due to this organism since the introduction in the UK of universal immunisation in 1992, it is still of major concern in immunodeficient children. The vaccine is likely to be immunogenic and of some protective value in most immunocompromised children. Immunodeficient children who have not completed a primary course of 3 doses, or who have lost immunity due to HSCT, should be fully re-immunised.

8.5 Combined Measles, Mumps and Rubella (MMR) (live)

This trivalent live virus vaccine poses theoretical risks to children with severe specific immunodeficiency which have to be weighed against the risks of contracting the wild-type illnesses. Unlike OPV, cases of vaccine-induced severe disease are virtually unknown. In practice the vaccine is not usually given knowingly to many severely immunocompromised

children. Those receiving Ig are likely to be protected passively. Herd immunity effects will go some way towards protecting the remainder. Withholding the vaccine from patients with moderate or non-specific immunodeficiency is not necessary. A second dose of MMR vaccine is recommended in children undergoing primary immunisation or re-immunisation post-HSCT, in line with the universal childhood immunisation schedule.

8.6 Pneumococcus (non-live)

Until recently the only available vaccine was a non-live 23-valent capsular polysaccharide vaccine that is poorly immunogenic, and thus of very little value, in normal children under 2 years of age and in other children with poor antibody production. In 2001 the first of a new generation of conjugate pneumococcal vaccines received a European license and can now be obtained in the UK. It is 7-valent – providing protection against serotypes responsible for about 75% of invasive disease. Children at enhanced risk of pneumococcal infection should normally be immunised initially with the conjugate vaccine (1, 2 or 3 doses depending on age and severity of risk; see individual sections above and a recent review²⁹ for detailed recommendations). This should be followed later by a dose of the polysaccharide vaccine in order to derive some protection against the 16 serotypes not included in the conjugate vaccine. The latter immunisation should not normally be given until at least 2 years of age. Immunisation against pneumococcus may sometimes be omitted in severely immunodeficient children on Ig treatment. Routine booster doses of pneumococcal vaccine are not currently recommended. The recommendations made in this Best Practice Statement are similar to the current Department of Health guidelines, although the former recommend use in children over 2 years of age (unlike the latter), and there are minor differences in the number of doses suggested for some age groups.

8.7 Meningococcus (non-live)

There is no vaccine currently available against Group B, the commonest strain in the UK. A bivalent polysaccharide vaccine against groups A and C has been available for some time and used in the management of group C outbreaks. A quadrivalent polysaccharide vaccine (A,C,Y,W135) is available on a named patient basis only. Like pneumococcal polysaccharide vaccine, these vaccines are poorly immunogenic in children under 2 years of age and in other immunocompromised children, in whom they are not widely used. However, they have a defined role in rare cases of complement component deficiency, where A,C,Y,W135 vaccine is used. Furthermore, A,C vaccine is advisable in immunocompromised children likely to travel to areas of endemic and epidemic group A infection, especially sub-Saharan Africa. Recently highly immunogenic protein-conjugated group C vaccines have been developed which were included in the universal childhood immunisation schedule in 1999. It is suggested that children undergoing re-immunisation post-HSCT receive 3 doses, since they are considered to be potentially immunologically naive. Other immunocompromised children should receive 3 doses in infancy or one dose if older than 1 year of age. Routine booster doses of meningococcal vaccines are not currently recommended.

8.8 Influenza A and B (non-live)

Several non-live combined influenza A and B vaccines are manufactured each year. Live attenuated nasal vaccine is under development but is not currently available. Influenza may cause severe illness in immunocompromised children and also predispose to secondary bacterial infections. These vaccines should therefore be given widely each autumn in these patient

populations and to their family contacts and care-givers.

8.9 Tuberculosis (BCG) (live)

This live bacterial vaccine is thought to provide protection against severe childhood infection if given in infancy. It must not be given to infants suspected to have immunodeficiency (although its routine use is policy in third world countries regardless of HIV status). Its use later in childhood is contra-indicated in patients with severe inherited defects of specific immunity or CGD,²⁸ during and for 6 months after standard chemotherapy, or after HSCT (but see section 3.3). Otherwise it should only be used as according to local policy which varies in different parts of the UK.

8.10 Varicella Zoster (live)

A live vaccine has been available for some time (OKA strain) and licensure in the UK is expected soon. Meantime it can be obtained on a named patient basis from the manufacturers (Glaxo Smith Kline and Aventis Pasteur MSD) for selected cases such as organ transplant recipients, some individual children with malignant disease. There is also a case for using this vaccine in seronegative family members of children with severe cell-mediated immunodeficiency and others at risk, as a way of providing indirect protection for the patients at risk. Additionally, some units have instituted a policy of giving this vaccine to seronegative health care professionals who care for immunodeficient children. Although the vaccine can occasionally induce a mild form of varicella (either generalised or at the injection site), the vaccine virus is highly sensitive to aciclovir which can therefore be used if there are clinical concerns in immunocompromised recipients. In cases where the degree of immunocompromise is judged to put the patient at high risk, or where the child is significantly unwell with widespread infection (eg more than 50 lesions), aciclovir should be administered intravenously. It is important to attempt to isolate the virus from lesions and to arrange testing to determine whether it is vaccine or wild type – as a significant proportion of cases of suspected VZV infection are not VZV and many post-vaccine cases are due to VZV wild type infection

8.11 Hepatitis B (non-live)

This recombinant protein vaccine is now given routinely to infants in many countries, but not in the UK at present. It can be used safely in immunodeficient children, but should only be given to seronegative high-risk cases such as children born to hepatitis B surface antigen positive mothers (these infants may also require passive immunisation), children who have close household contacts who are or are likely to be cases or carriers of hepatitis B, and children with chronic renal failure likely to require dialysis or transplantation.

8.12 Travel vaccines

Non-live vaccines (hepatitis A, cholera, rabies, typhoid Vi polysaccharide) are safe and should generally be used as indicated. They may be administered after HSCT if clinically indicated, or required for travel purposes, although the response may be suboptimal if given before the recommended time for starting the re-immunisation programme (see sections 3.2.1 and 3.2.2). The response to typhoid Vi polysaccharide vaccine is likely to be suboptimal if given to children less than 2 years of age, or earlier than 2 years post-HSCT. Live vaccines, (eg yellow fever, live oral typhoid vaccine) carry potential risks for severely immunocompromised patients and should only be used under specialist guidance in such cases.

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