IMMUNISATION OF THE IMMUNOCOMPROMISED CHILD: A CLINICIAN'S UPDATE

Running title:

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Abstract

Immunocompromised children have a higher risk of developing infections and associated higher rates of mortality and morbidity. Although this group could benefit the most from vaccine administration, specific considerations regarding immunisations are required. This review is a summary of the vaccines that are relevant to the immunocompromised host, covering both live and non-live vaccines. Burden of disease, safety, immunogenicity/effectiveness and specific recommendations for each vaccine are described as well as specific guidelines from different organisations.

Key words: immunocompromised, vaccines, children, immunogenicity, safety, recommendations

Introduction

Children who are at increased risk of infections, either due to an impaired immune system or underlying chronic illness, require specific consideration when it comes to immunisation. These individuals potentially stand to benefit most from vaccine administration, but often have sub-optimal responses or may be more likely to suffer adverse effects, particularly from live vaccines. As new vaccines become available and the epidemiology of vaccine-preventable diseases evolves, it is increasingly important for all those caring for children to

be up to date with the recent changes in these guidelines, changing the traditional low uptake of additional immunisations in high risk groups (1).

Accordingly this review will focus on new developments in the field of active immunization in immunocompromised and 'at-risk' children, including those with primary immunodeficiencies and those on immunosuppressive therapy (Table 1).

Specific vaccines with relevance to the immunocompromised host

Live vaccines

Guidelines regarding the use live vaccines in the immunocompromised host are evolving. Long considered an absolute contra-indication, a more nuanced approach has emerged. This reflects the need to balance the degree of immunosuppression, the risk of natural exposure and the availability of non-live alternatives. Such decisions should therefore be made on a case by case basis, considering the current health status as well as the type of immunodeficiency.

Rotavirus

The rotavirus vaccine is an oral live vaccine available in two different versions; a monovalent vaccine licensed as a two dose schedule and a pentavalent version with a three doses schedule (2),(3).

Burden of disease

Despite evidence of herd-immunity in populations with high immunisation rates, it remains likely that immunocompromised children in such countries will be exposed to this virus, albeit potentially at an older age than in a non-immunised population (4),(5).

Although there are relatively few data on the clinical outcome in immunocompromised children with rotavirus infection, an observational study in 28 paediatric oncology patients receiving intensive chemotherapy showed the mean length of hospital stay in children with confirmed rotavirus infection was 12.6 days (+/-2.3 days), significantly longer than matched children without rotavirus infection (5.0 days+/-1.5 days.) These children also required higher rates of parental nutrition or tube feeding ($p<0.001$) (6) than non-infected patients. Reports of rotavirus infection in paediatric liver transplant recipients also emphasise the severity of illness in solid organ transplant recipients (7),(8).

Safety

There have been three case reports of infants with Severe Combined Immunodeficiency (SCID) with a "vaccine associated disease" following rotavirus immunization (9). The main symptoms cited were severe diarrhoea and dehydration after immunisation. In all of the cases, nucleic acid isolated from stools using RT-PCR analysis showed amplification of the rotavirus vaccine strains, with prolonged shedding when compared with healthy children (9).

By contrast, a double blind study of 100 Human immunodeficiency virus (HIV)-infected mildly or a-symptomatic infants, who were randomised 1:1 to receive human rotavirus RIX4414 strain vaccine or placebo, showed that the vaccine was well tolerated, with symptoms occurring at a similar frequency in both groups (10). The peak and duration of vaccine virus shedding was similar to that reported in healthy infants, although there was one case with prolonged shedding that resolved between day 56 and 70 (10).

Immunogenicity/effectiveness

Although no data are available on the efficacy of rotavirus immunisation in immunocompromised children, the above study showed that the vaccine was immunogenic in HIV-infected infants, with 57% of vaccine recipients achieving the threshold of 20 U/mL serum antirotavirus IgA compared with 18% in controls (10).

Recommendations

In summary this vaccine should be avoided in infants with SCID, but is recommended for infants with HIV infection (11). Although of uncertain efficacy and safety in infants with other immunocompromising conditions, the majority of the children are likely to benefit, by potentially avoiding the severe outcome associated with a natural rotavirus infection is this population (2),(6,7).

Varicella

Two monovalent varicella vaccines are available, both of which are contain the live attenuated 'OKA' strain. The vaccines are licensed from 12 months of age and two doses are normally administrated at least four to eight weeks apart (3). The vaccine strain is susceptible to aciclovir and, unique amongst immunisations, establishes a latent infection in the recipient.

Burden of disease

In countries without routine immunisation exposure is almost inevitable. The risk of devastating varicella infections in immunocompromised children is well documented, with hospitalisation rates in HIV positive children on highly active antiretroviral treatment (HAART) 16 times higher than the general population in the UK (and 150 times higher if not on treatment) (12). For children on anti-tumor necrosis factor (TNF) immunosuppressive treatment the hospitalisation rate due to shingles and varicella was 32 and 26 cases per 100 000 patients respectively, considerably higher than rates of 3.4 and 1.9 (respectively) in the general paediatric population (13).

Accordingly varicella seronegative immunocompromised children frequently receive administration of immunoglobulin or aciclovir prophylaxis following natural exposure, adding to the burden of their underlying disease (14).

Safety

A cohort of 97 HIV positive children who were varicella-zoster virus (VZV) naïve and had a CD4+ percentage of ≥15% and a CD4+ T cell count ≥ 200 cells/uL were immunised with two doses of live varicella vaccine three months apart (15). The vaccine was well tolerated, with a breakthrough rash reported in two patients following the first vaccine dose and one after the second dose. Systemic adverse events were identified in 12% of the subjects, but no serious adverse events considered to be related to the vaccine were reported (15).

The breakthrough rash after the varicella vaccine was also reported in three out of 25 paediatric rheumatology patients receiving treatment methotrexate +/-corticosteroids, however no severe adverse reactions were reported in the 40 days following immunization (16).

A multicenter retrospective cohort study in children with DiGeorge Syndrome, a congenital disorder characterized by a cellular immune deficiency, showed that in cases with mild-to-moderate immunosuppression varicella vaccine is well tolerated and only one unspecified rash was described (17).

By contrast, amongst children receiving maintenance chemotherapy for leukaemia (immunised in the middle of a two weeks 'window' off treatment), rashes were observed in 36% of children following the first dose of vaccine, 10% of whom transmitted the vaccine virus to siblings (18). Although the rash was not considered to be severe, it was extensive and in 3% of the cases continued to evolve for up to six weeks (18). There are also case reports of fatalities following dissemination of the varicella vaccine virus in a four year old girl immunised five weeks previously during a two week window off maintenance chemotherapy for leukaemia, and reactivation of the virus in a 47 year old man with a non-Hodgkin's

lymphoma (19).

Immunogenicity/effectiveness

A retrospective study in HIV positive children, showed two doses of varicella vaccine to have an effectiveness of 82% (95% CI, 24-99%) against varicella and 100% (95% CI, 67-100%), against herpes zoster (20). Two (3%) vaccinated children developed breakthrough varicella at 3.9 and 4.7 years after one and two vaccine doses. Among 65 vaccinated children receiving HAART none developed zoster in contrast to 15/60 unvaccinated children ($p<0.01$).

In a study by Pileggi et al enrolling children with rheumatologic conditions receiving immunosuppressive treatment, two cases of varicella (out of 25) were identified after one dose of the varicella vaccine during the follow-up period (median 32 months) (16). The same study showed that positive VZV- IgG titers four to six weeks after vaccination were reached in 50% of the previous seronegative patients and in 72.2% of the controls (healthy children). One year after immunisation the titers remained positive in 80% of the patients that previously seroconverted (16).

In the study described above, in which 191 children in remission from leukaemia were immunised with varicella vaccine, 18% developed varicella disease after household exposure, compared to 90% in historical controls (18).

Recommendations

The varicella vaccine is currently recommended for varicella seronegative HIV positive patients with CD4 counts of more than 15%, preferably three months after immune reconstitution (2,11). Similarly, children with DiGeorge syndrome can receive the varicella vaccine if they have adequate CD4 counts (17).

For children who are varicella seronegative and are due to commence immunosuppressive medication, it is recommended that the varicella vaccine is administered three to four weeks before commencing treatment. According to European league against rheumatism (EULAR) guidelines, more studies are required before recommendations on primary vaccinations with live attenuated vaccines can be made while on low-dose immunosuppressive therapy (21). However, use of the varicella vaccine in children on high dose immunosuppressants is clearly contra-indicated.

In children with leukemia, it is recommended that immunisation should be deferred until they are in remission, three months after chemotherapy with evidence of recovery of cell mediated immunity (22).

It is also recommended that family members of all immunosuppressed children who are not themselves immune to varicella should be immunized (16).

Influenza

Live influenza vaccines have been shown to be more effective in healthy children than inactivated vaccines, but they are only licensed for children above two years of age and their use in immunocompromised children has the potential to cause influenza like illness (23).

Burden of disease

As a major cause of global mortality and morbidity in children, influenza infections are known particularly to affect children with underlying medical conditions (24). Of the 70 UK children that died during the influenza A H1N1 pandemic, 64% had a co-morbidity, none of whom had been immunized (24),(25).

During 2009-2010 influenza A H1N1 pandemic in the UK, a childhood mortality rate of six per million population was reported. Of these, 64% had a severe pre-existing disorder (26). In 2014-2015, 22% of the confirmed influenza cases in the UK were children and 27% of these had an underlying condition (27).

Safety

Clinical studies of live attenuated influenza vaccine (LAIV) have been performed in HIV infected children and also in a small number of mild to moderately immunocompromised children with cancer. None of these studies demonstrated any serious safety concerns following LAIV administration (28),(29).

Immunogenicity

Two hundred and forty three HIV infected children receiving antiretroviral treatment were randomised either to receive intranasal live influenza vaccine or an intramuscular inactivated vaccine (30). The antibody responses to both of the vaccines were similar to those reported in healthy children (30). In a small pilot study, seroresponses to LAIV were demonstrated in some children receiving chemotherapy for cancer (29).

Recommendations

The use of the intranasal live vaccine is recommended for 2 to 18 year olds with stable HIV infection receiving antiretroviral therapy in the UK (3),(11) but not in the USA (31), where it is recommended these children/adolescents receive the inactivated vaccine. The UK guidelines also recommend use of LAIV in 'at-risk' children who are receiving topical/inhaled corticosteroids or low-dose systemic corticosteroids (3).

The inactivated influenza vaccine is recommended for children on high doses of immunosuppressants, on chemotherapy or with T or B cell immunodeficiency, and in all children in clinical risk groups under two years of age (3).

Immunisation of contacts

Immunisation of household and close contacts of 'at risk' children is encouraged to reduce the risk of transmitting wild-type virus (32). In the UK guidelines this applies to those who expect to share living accommodation on most of the days over the winter and for whom close contact is unavoidable (3). Influenza vaccine should also be offered to social care workers and health professionals in contact with such patients (3).

Immunising close contacts with LAIV raises the theoretical risk of exposing the immunocompromised patient to the vaccine virus and subsequent 'vaccine type' influenza infection (3). In a study in which 197 healthy children attending day care were randomised to receive either LAIV or placebo, 80% of the 98 vaccine recipients shed at least one vaccine strain (mean 7.6 days). One unimmunised child developed mild respiratory symptoms associated with isolation of the vaccine strain virus, giving a probability of vaccine strain transmission of 0.58% (95% CI, 0-1.7%) (32).

Accordingly, 2013 Infectious Diseases Society of America (ISDA) and UK guidelines recommend that close contacts of severely immunocompromised patients (e.g. patients with SCID or within two months of a hematopoietic stem cell transplant or with graft *vs* host disease should receive the inactivated, rather than live, influenza vaccine (3),(22)). Casual contacts (e.g. at school) may receive the LAIV vaccine as per usual indications.

Measles/MMR (measles, mumps, rubella)

Burden of disease

In high-income countries with a high immunisation uptake the incidence of these infections and associated mortality rates are low, but recent outbreaks have demonstrated the potential for measles exposure from isolated outbreaks in discrete areas with historically low levels of immunisation (33).

Given the potential of immunisation with the live measles vaccine to prevent overwhelming natural infection in children with acquired immune deficiency syndrome (AIDS), the use of measles vaccines in HIV positive children with relative immunocompetence is the most well studied example of giving a live vaccine in an immunocompromised population, and was the subject of a WHO global advisory committee report (34).

Safety

No serious adverse reactions were reported in HIV positive children with a CD4 count of > 15% who received a primary or booster dose of vaccine whilst on anti-retroviral treatment (35), while administration of measles vaccine nine to eighteen months post bone marrow transplant was also shown to be safe with no severe or moderate adverse reactions (36).

Immunogenicity/effectiveness

HIV infected children may develop a sub-optimal response to the primary measles immunisation and lack long-term protective antibody titers (37). Of 29 children on

antiretroviral treatment previously immunised with one or two doses of measles vaccine only 10 (34.5%) had detectable anti-measles antibody, compared with 6/37 (16.2%) unvaccinated HIV infected children in the same study. Eight to 12 weeks after immunisation in the overall population, 93.3% had positive measles antibodies (37).

A retrospective study by Zignol et al. showed a loss of previously detectable measles specific serum antibodies in 25% of 92 children successfully treated for solid organ or haematological malignancy (38). In a study with 51 patients who had received a bone marrow transplant at least nine months prior to vaccination (53% under immunosuppressive drugs), nine were found to be non-immune to measles at the time of vaccination (77.7% under immunosuppression); all nine seroconverted after vaccination.

Recommendations

Similar to the varicella vaccine, the MMR vaccine is recommended in HIV infected children or those with DiGeorge syndrome whose CD4 count is more than 15% (11),(17). The vaccine should otherwise be avoided for all T cell and combined T and B cell immunodeficiencies; the vaccine may be safe in those with B cell immunodeficiencies but is unlikely to be of benefit if these patients are receiving immunoglobulin replacement (2).

Children who are to receive immunosuppressive medication should have primary immunisation prior to commencement of treatment if possible.

Non-live vaccines

In general, immunocompromised children should receive all the routine non-live vaccines, although they may require additional doses and in specific cases additional non-live vaccines**.**

Meningococcus

Vaccines against *Neisseria meningitidis* serogroups A, C, W and Y are based on the respective capsular group-specific polysaccharide antigens, either as 'plain' polysaccharide vaccines (poorly immunogenic in children under two years of age), or with the polysaccharide antigens conjugated to a protein carrier. It is the latter, 'conjugate', vaccines that are generally recommended for use in children, formulated either as monovalent (capsular groups A and C) or multivalent vaccines (e.g. MenACWY).

Vaccines developed to protect against serogroup B meningococcus, by contrast, target subcapsular proteins, and recently a Meningitis B (MenB) vaccine (Bexsero®) has been licensed for use in infants and older children/adolescents in Europe and elsewhere (39), while this vaccine and another vaccine (Trumenba®) are licensed for use in adolescents in the USA (40),(41) with European licensure expected for the latter in the near future.

Burden of disease

Increased susceptibility to meningococcal disease is primarily seen in individuals with deficits in the complement cascade (42), in particular those who lack the ability to activate C3 and thereby or otherwise to create the membrane attack complex that is the functional endpoint of the classical, lectin and alternative complement pathways (43).

Although rare (estimated prevalence of 0.03% in Caucasian population), individuals with a complement deficiency in the alternative pathway, C3 or in the late pathway components (C5, C6, C7, C8, C9) have a 5000-10000 fold increase risk of meningococcal disease when compared with healthy individuals (43),(44), with 40 – 50% of these individuals experiencing recurrent meningococcal disease (43).

Complement deficiencies can also be acquired, such as in patients receiving the monoclonal antibody Eculizumab, which acts as a terminal complement pathway inhibitor and is used to treat certain types of auto-immune disease (35,45). An efficacy study in which 195 patients with paroxysmal nocturnal haemoglubinuria received Eculizumab described two cases of meningococcal invasive disease over a 66 month period, resulting in an infection rate of 0.42 per 100 patient-years (46).

Immunogenicity and effectiveness

The most direct, albeit observational, evidence of the ability of meningococcal vaccines to provide protection to patients with complement deficiencies comes from a study of 45 patients diagnosed with late complement component deficiency, 31 (69%) of whom were immunised with the meningococcal ACWY plain polysaccharide vaccine. In the three to

eight year follow-up period, episodes of meningococcal disease were reported in 19% of the vaccinated population, compared with 43% among unvaccinated patients (47). No studies of the immunogenicity or effectiveness of meningococcal conjugate or sub-capsular-protein vaccines in complement deficient individuals have yet been published, although such a study has recently been completed (Clinical trials.gov NCT02141516).

Studies of the monovalent conjugate MenC vaccine in asplenic adults (48), of conjugate MenACWY vaccines in patients post bone marrow transplant (49) and of patients with HIV infection (50) have been conducted, all showing a general trend towards reduced immunogenicity compared with healthy controls.

Recommendations

The current recommendation is to vaccinate all children with congenital or acquired complement deficiency or asplenia with MenB and MenACWY vaccines. The immunization schedules (adapted according to the age at diagnosis) and are shown in Table 2.

Pneumococcus

Vaccines against *Streptococcus pneumoniae* are based on the capsular polysaccharides, which can either be presented in a 'plain polysaccharide' vaccine (PPV, containing purified capsular polysaccharides from 23 pneumococcal capsular types (PPV23)) or conjugated to

carrier proteins, as for example the 10-valent (PCV10) and 13-valent pneumococcal conjugate vaccines (PCV13) currently available.

Burden of disease

Children with a broad range of co-morbidities are at an increased risk of invasive pneumococcal disease (IPD). Examples include untreated HIV infected children in the UK and Ireland who were more than 150 times more likely than uninfected children to suffer invasive pneumococcal disease (IPD) (a risk that remained 16.7 higher even once commenced on HAART) (12).

A national surveillance study conducted in England and Wales between 2009 and 2011 found that 29.3% of children less than five years of age who developed IPD also had a co-morbidity, the two most common of which were an immunodeficiency (33.9%) and chronic respiratory disease (31.5%) (51).

However, the introduction of routine childhood immunisation with pneumococcal conjugate vaccines has contributed to a large reduction in morbidity and mortality of IPD in the general population and, by direct protection and herd immunity, in 'at-risk' children. A large and growing proportion of residual IPD cases are caused by serotypes not contained in the PCV10 or PCV13 vaccines making the administration of additional conjugate vaccine doses to at-risk individuals progressively less effective and cost-effective over time.

Immunogenicity and effectiveness

A literature review of 58 trials on immunogenicity of PCV in populations with a higher risk of IPD, provided re-assuring data on the immunogenicity of the 7-valent pneumococcal conjugate vaccine (PCV7) in immunocompromised, asplenic and HIV infected children, although functional responses in the latter group were lower than in HIV seronegative children (52). Children undergoing stem cell transplantation also benefit from the vaccine, but in children who had a history of solid organ transplantation, the immunogenicity of PCV7 varied according to the organ (52). The immunogenicity of PCV13 in at risk groups has been less well studied, although 48 children and adolescents with perinatally acquired HIV infection mounted a robust immune response to this vaccine which persisted for the majority of the serotypes beyond six months (53).

Although there are no randomized studies of pure polysaccharide pneumococcal vaccines in high-risk groups showing benefit (and one conducted in Uganda in adults with HIV infection which suggested increased rates of pneumococcal disease in vaccine recipients), PPV23 is still widely recommended both for adults and children at high risk of IPD. During 2010-2011, 124 children with co-morbidities were identified in a national survey in England and Wales with IPD, of whom only 26.6% had received PPV23 (54). After adjusting for age, sex, year of diagnosis and previous PCV7 vaccination, the development of IPD due to PPV specific serotypes was not associated with prior PPV23 vaccination (adjusted odds ratio 1.09 (95%CI 0.36-3.32) (54) raising doubts about the effectiveness, as well as the uptake, of this vaccine in at-risk children.

When repeated doses of PPV23 are given at short intervals, hypo-responsiveness (reduced seroresponses) to some vaccine serotypes may be observed. If PPV23 is given to a child who has previously received PCV7, the antibody responses against the majority of the PCV serotypes are higher than in an unprimed child although subsequent responses to further doses of PPV23 may once again be lower (55).

Recommendations

In an era of widespread use of PCV, the majority of 'at-risk' children will have already received these vaccines in infancy, and all except older children will have received either a 10 or 13 valent vaccine. While it is important to ensure that at risk children have received routinely recommended pneumococcal conjugate vaccines, cost-effectiveness analyses in the UK argue against offering additional doses of PCV13 to most 'at-risk' children, with the exception of children recovering from bone marrow transplant, with haematological malignancies or primary immunodeficiencies.

The use of PPV23 in 'at-risk' children is controversial, and is not included in CHIVA guidelines for immunization of HIV infected children (11).

Immunisations schedules for specific conditions

While the discussions above focus on vaccines of particular relevance, immunisation guidelines will, appropriately, usually be developed with a 'condition-specific' focus e.g. for

children experiencing asplenia, splenic dysfunction, complement deficiency, HIV and children receiving immunosuppressive treatment and chemotherapy. A summary of the general principles for differing conditions and immunisations is given in Table 3, however, the specifics of these guidelines will differ between different countries according to their routine immunisation schedules and local epidemiology.

Examples of condition- and region- specific guidelines included here are those for children with complement deficiencies or asplenia (Table 2).

Further information on these guidelines, and additional regional specific guidelines are available at the following locations:

Asplenia, splenic dysfunction and complement deficiency:

- *UK guidelines:*

  Immunisations against the disease: the Green Book(3), Available from: https://www.gov.uk/government/collections/immunisation-against-infectious-disease-the-green-book

- *USA guidelines:*

  Infectious Disease Society of America (IDSA): Clinical Practice Guideline of the Vaccination of the Immunocompromised Host 2013(22); Available from: http://cid.oxfordjournals.org/lookup/doi/10.1093/cid/cit684

HIV:

- *UK guidelines (CHIVA)*

Children's HIV association (CHIVA): CHIVA Vaccination of HIV infected Children 2015(11); Available from: http://www.chiva.org.uk/guidelines/immunisation/

- *USA guidelines:*

  Infectious Disease Society of America (IDSA): Clinical Practice Guideline of the Vaccination of the Immunocompromised Host 2013 (22); Available from: http://cid.oxfordjournals.org/lookup/doi/10.1093/cid/cit684

Vaccination for children receiving chemotherapy and Bone Marrow Transplantation

- *UK guidelines*

  Children's Cancer and Leukaemia Group (CCLG) guidelines: Vaccinations for Paediatrics Patients Treated with Standard-Dose Chemotherapy and Haematopoietic Stem Cell Transplantation (HSCT) Recipients. CCLG guidelines. 2014(56)

- *European Union guidelines*

  European Society for Blood and Marrow transplantation: EBMT-EHS Handbook 2012(57). Available from: https://www.ebmt.org/Contents/Resources/Library/EBMTESHhandbook/Pages/EBMT-ESH-handbook.aspx

- *USA guidelines*

  Infectious Disease Society of America (IDSA): Clinical Practice Guideline of the Vaccination of the Immunocompromised Host 2013 (22); Available from: http://cid.oxfordjournals.org/lookup/doi/10.1093/cid/cit684

Summary

Immunisations have the potential to provide protection to immunocompromised children who are at increased risk of developing infections associated with high morbidity and mortality rates. However, special considerations for this population are required regarding both live and non-live vaccines. Importantly, the uptake of additional vaccines in immunocompromised children is known to be low, increasing the need for constant update and awareness in the medical community. No vaccine works while it is on the shelf, and it is incumbent on all paediatricians to be mindful of the immunisation status of at-risk children, and to ensure they are receiving optimal vaccine induced protection.

Conflicts of interest

MDS is an investigator for clinical trials sponsored and funded by vaccine manufacturers, but receives no personal financial benefit from this role. The remaining authors declare no conflicts of interest.

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References

1. Pebody RG, Hippisley-Cox J, Harcourt S, Pringle M, Painter M, Smith G. Uptake of pneumococcal polysaccharide vaccine in at-risk populations in England and Wales 1999-2005. Epidemiol Infect. 2008;136(3):360–9.

2. Shingadia D, Sharland M CA et al. Manual of Childhood Infections, The blue book, 3 edition, Oxford University Press 2011. 2011.

3. Salisbury D, Ramsay M NK. Immunisation against infectious disease: the green book, Public Health England. BMJ (Clinical research ed.). 2013.

4. Public Health England. PHE Weekly National Norovirus and Rotavirus Report. 2015;(January 2016):1–9.

5. World Health Organization. Weekly epidemiological record Relevé épidémiologique hebdomadaire. Wkly Epidemiol Rec 2013;(5):49–64.

6. Rayani A, Bode U, Habas E, Fleischhack G, Engelhart S, Exner M, et al. Rotavirus infections in paediatric oncology patients: a matched-pairs analysis. Scand J Gastroenterol 2007;42(1):81–7.

7. Fitts SW, Green M, Reyes J, Nour B, Tzakis AG, Kocoshis SA. Clinical features of nosocomial rotavirus infection in pediatric liver transplant recipients. Clin Transplant 1995 Jun;9(3 Pt 1):201–4.

8. Cui H, Bai S, Huo Z, Li J, Sun J, An X. A cluster of rotavirus enteritis in pediatric liver recipients. Transpl Infect Dis. 2015;17(3):477–80.

9. Patel NC, Hertel PM, Estes MK, de la Morena M, Petru AM, Noroski LM, et al. Vaccine-acquired rotavirus in infants with severe combined immunodeficiency. N Engl J Med 2010 Jan 28;362(4):314–9.

10. Steele AD, Madhi SA, Louw CE, Bos P, Tumbo JM, Werner CM, et al. Safety, Reactogenicity, and Immunogenicity of Human Rotavirus Vaccine RIX4414 in Human Immunodeficiency Virus-positive Infants in South Africa. Pediatr Infect Dis J . 2011;30(2):125–30.

11. CHIVA. Vaccination of HIV infected children (UK schedule , 2015). 2015 accessed on http://www.chiva.org.uk/

12. Payne H, Chb MB, Judd A, Donegan K. Incidence of Pneumococcal and Varicella Disease in HIV-infected Children and Adolescents in the United Kingdom. 2015;34(2):149–54.

13. Garcia-Doval I, Perez-Zafrilla B, Descalzo MA, Rosello R, Hernandez M V., Gomez-Reino JJ, et al. Incidence and risk of hospitalisation due to shingles and chickenpox in patients with rheumatic diseases treated with TNF antagonists. Ann Rheum Dis. 2010;69(10):1751–5.

14. Roderick M, Finn A, A V R. Chickenpox in the immunocompromised child. Arch Dis Child. 2012;97(7):587–9.

15. Levin MJ, Gershon A a, Weinberg A, Song L-Y, Fentin T, Nowak B. Administration of live varicella vaccine to HIV-infected children with current or past significant depression of CD4(+) T cells. J Infect Dis. 2006;194:247–55.

16. Pileggi GS, de Souza CBS, Ferriani VPL. Safety and immunogenicity of varicella vaccine in patients with juvenile rheumatic diseases receiving methotrexate and corticosteroids. Arthritis Care Res 2010;62(7):1034–9.

17. Hofstetter a M, Jakob K, Klein NP, Dekker CL, Edwards KM, Halsey N a, et al. Live Vaccine Use and Safety in DiGeorge Syndrome. Pediatrics. 2014;133(4):e946–54.

18. Gershon AA, Steinberg SP, Gelb L, Galasso G, Borkowsky W, LaRussa P, et al. Live attenuated varicella vaccine. Efficacy for children with leukemia in remission. Jama 1984;252(3):355–62.

19. Bhalla P, Forrest GN, Gershon M, Zhou Y, Chen J, LaRussa P, et al. Disseminated, Persistent, and Fatal Infection Due to the Vaccine Strain of Varicella-Zoster Virus in an Adult Following Stem Cell Transplantation. Clin Infect Dis 2014;60:1068–74.

20. Son M, Shapiro ED, LaRussa P, Neu N, Michalik DE, Meglin M, et al. Effectiveness of varicella vaccine in children infected with HIV. J Infect Dis. 2010;201(12):1806–10.

21. Heijstek MW, Ott de Bruin LM, Bijl M, Borrow R, van der Klis F, Kone-Paut I, et al. EULAR recommendations for vaccination in paediatric patients with rheumatic diseases. Ann Rheum Dis. 2011;70(10):1704–12.

22. Rubin LG, Levin MJ, Ljungman P, Davies EG, Avery R, Tomblyn M, et al. 2013 IDSA Clinical Practice Guideline for Vaccination of the Immunocompromised Host. Clin Infect Dis. 2014;58(3):e44–100.

23. Ambrose CS, Levin MJ, Belshe RB. The relative efficacy of trivalent live attenuated and inactivated influenza vaccines in children and adults. Influenza Other Respi Viruses. 2011;5(2):67–75.

24. Lozano R, Naghavi M, Foreman K, Lim S, Shibuya K, Aboyans V, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet 2012;380(9859):2095–128.

25. Thompson WW, Shay DK, Weintraub E, Brammer L, Cox N, Anderson LJ. and Respiratory Syncytial Virus in the United States. 2014;289(2):179–86.

26. Sachedina N, Donaldson LJ. Paediatric mortality related to pandemic influenza A H1N1 infection in England: an observational population-based study. Lancet 2010;376(9755):1846–52.

27. Public Health England. Surveillance of influenza and other respiratory viruses in the United Kingdom : Winter 2013/14. 2014;29.

28. Tennis P, Toback SL, Andrews E, McQuay LJ, Ambrose CS. A postmarketing evaluation of the frequency of use and safety of live attenuated influenza vaccine use in nonrecommended children younger than 5 years. Vaccine 2011;29(31):4947–52.

29. Halasa N, Englund J a, Nachman S, Weinberg G a, Huber VC, Allison K, et al. Safety of live attenuated influenza vaccine in mild to moderately immunocompromised children with cancer. Vaccine 2011;29(24):4110–5.

30. Levin MJ, Song L-Y, Fenton T, Nachman S, Patterson J, Walker R, et al. Shedding of live vaccine virus, comparative safety, and influenza-specific antibody responses after administration of live attenuated and inactivated trivalent influenza vaccines to HIV-infected children. Vaccine. 2008 Aug 5;26(33):4210–7.

31. National CDC, Diseases R. Flu Vaccination : Who Should Do It , Who Should Not. :241332.

32. Vesikari T, Karvonen A, Korhonen T et al. A Randomized, Double-Blind Study of the Safety, Transmissibility and Phenotypic and Genotypic Stability of Cold-Adapted Influenza Virus Vaccine. Pediatr Infect Dis J 2006;25(7):590–5.

33. Shakoor S, Mir F, Zaidi AKM, Zafar A. Hospital preparedness in community measles outbreaks challenges and recommendations for low-resource settings. Emerging Health Threats J 2015, 8:24173.

34. Global advisory committe on vaccine safety, report of meeting held 17-18 June 2009. WHO Wkly Epidemiol Rec. 2009;84(32):325–32.

35. Legendre CM, Licht C, Muus P, Greenbaum L a, Babu S, Bedrosian C, et al. Terminal complement inhibitor eculizumab in atypical hemolytic-uremic syndrome. N Engl J Med 2013;368(23):2169–81.

36. Machado CM, de Souza V a UF, Sumita LM, da Rocha IF, Dulley FL, Pannuti CS. Early measles vaccination in bone marrow transplant recipients. Bone Marrow Transplant. 2005;35(8):787–91.

37. Seth A, Deepa S, Dutta R, Chandra J. Evaluation of Immune Response to Measles Component of MMR Vaccine in Children with HIV Infection Receiving Antiretroviral Therapy. Pediatr Infect Dis J 2016, 31(1):e8-e11

38. Zignol M, Peracchi M, Tridello G, Pillon M, Fregonese F, D'Elia R, et al. Assessment of humoral immunity to poliomyelitis, tetanus, hepatitis B, measles, rubella, and mumps in children after chemotherapy. Cancer 2004;101(3):635–41.

39. European Medicines Agency Bexsero Assessment report. 2012;44(November):1–102.

40. Food and Drug Administration Trumenba product information 2014;1–10. Accessed on: http://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm421020.htm

41. Food and Drug Administration Bexsero product information 2015;1–11. Accessed on: http://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm431374.htm

42. Lewis L a., Vu DM, Vasudhev S, Shaughnessy J, Granoff DM, Ram S. Factor h-

dependent alternative pathway inhibition mediated by porin B contributes to virulence of Neisseria meningitidis. MBio. 2013;4(5):1–9.

43. Fijen C a, Kuijper EJ, Drogari-Apiranthitou M, Van Leeuwen Y, Daha MR, Dankert J. Protection against meningococcal serogroup ACYW disease in complement-deficient individuals vaccinated with the tetravalent meningococcal capsular polysaccharide vaccine. Clin Exp Immunol 1998;114(3):362–9.

44. Figueroa JE, Densen P. Infectious diseases associated with complement deficiencies. Clinical Microbiology Reviews. 1991. 4(3):359-95 .

45. Lewis LA, Ram S. Meningococcal disease and the complement system. Virulence. 2014;5(1):98–126.

46. Hillmen P, Muus P, Röth A, Elebute MO, Risitano AM, Schrezenmeier H, et al. Long-term safety and efficacy of sustained eculizumab treatment in patients with paroxysmal nocturnal haemoglobinuria. Br J Haematol 2013;162(1):62–73.

47. Platonov AE, Vershinina IV, Kuijper EJ, Borrow R, Kayhty H. Long term effects of vaccination of patients deficient in a late complement component with a tetravalent meningococcal polysaccharide vaccine. Vaccine 2003;21(27-30):4437–47.

48. Balmer P, Falconer M, McDonald P, Andrews N, Fuller E, Riley C, et al. Immune Response to Meningococcal Serogroup C Conjugate Vaccine in Asplenic Individuals. Infect Immun. 2004;72(1):332–7.

49. Mahler MB, Taur Y, Jean R, Kernan NA, Prockop SE, Small TN. Safety and Immunogenicity of the Tetravalent Protein-Conjugated Meningococcal Vaccine (MCV4) in Recipients of Related and Unrelated Allogeneic Hematopoietic Stem Cell Transplantation. Biol Blood Marrow Transplant 2012;18(1):145–9.

50. Lujan-Zilbermann J, Warshaw MG, Williams PL, Spector S a., Decker MD, Abzug MJ, et al. Immunogenicity and safety of 1 vs 2 doses of quadrivalent meningococcal conjugate vaccine in youth infected with human immunodeficiency virus. J Pediatr. 2012;161(4):676–81.

51. Ladhani SN, Slack MPE, Andrews NJ, Waight PA, Borrow R, Miller E. Invasive pneumococcal disease after routine pneumococcal conjugate vaccination in children, England and Wales. Emerg Infect Dis. 2013;19(1):61–8.

52. Fletcher MA, Balmer P, Bonnet E, Dartois N. PCVs in individuals at increased risk of pneumococcal disease: a literature review. Expert Rev Vaccines 2015;14(7):975–1030.

53. Bamford A, Kelleher P, Lyall H, Haston M, Zancolli M, Goldblatt D, et al. Serological response to 13-valent pneumococBamford, A., Kelleher, P., Lyall, H., Haston, M., Zancolli, M., Goldblatt, D., & Kampmann, B. (2014). Serological response to 13-valent pneumococcal conjugate vaccine in children and adolescents with perinatally . Aids 2014;28(14):2033–43.

54. Ladhani SN, Andrews NJ, Waight P, Borrow R, Slack MPE, Miller E. Invasive pneumococcal disease, comorbidities, and polysaccharide vaccine use in children aged 5-15 years in England and Wales. Clin Infect Dis. 2014;58(4):517–25.

55. Borrow R, Heath PT, Siegrist C-A. Use of pneumococcal polysaccharide vaccine in children. Curr Opin Infect Dis 2012;25(3):292–303.

56. Children's Cancer and Leukaemia Group. Vaccinations for Paediatric Patients Treated With Standard-Dose Chemotherapy and Haematopoietic Stem Cell Transplantation (HSCT) Recipients. 2014;(September 2014):1–22.

57. Mensa J, Carreras E. Chapter 12 - Infections after HSCT. EBMT-ESH Handbook 2012,

196-215

Table captions

Table 1 Secondary immunodeficiency due to immunosuppressive medication

Table 2 Recommendations for Men B and Men ACWY vaccines in immunocompromised children (asplenia, splenic dysfunction, complement disorders)

Table 3 Vaccine recommendations for specific conditions

Table 1 Secondary immunodeficiency due to immunosuppressive medication

Secondary immunodeficiency due to immunosuppressive medication
1. Glucocorticoids - High dose glucocorticoids pulse therapy (> 2mg/kg/day or >20 mg per day for 2 weeks) 2. Non-biological immunosuppressants (also known as DMARDS) -Methotrexate: >15 mg/m2/week -Cyclosporine: > 2.5 mg/kg/day -Azathioprine: 1-3 mg/kg/day -Cyclophosphamide: 0.5-2.0 mg/kg/day -Leflunomide: 0.25-0.5 mg/kg/day -6-mercaptopurine: 1.5 mg/kg/day 3.Biological agents (any dose considered immunossupressive): -Infliximab (Anti-TNF α) -Rituximab (Anti B cell activity) -Abatacept (reduced T cell activation) -Tocilizumab (Anti IL-6) -Eculizumab (reduced complement activation)

Adapted from: Heijstek M et al. Ann Rheum Dis 2011.

Table 2 Recommendations for Men B and Men ACWY vaccines in immunocompromised children (asplenia, splenic dysfunction, complement disorders)

<table>
<tr><th>UK recommendations*</th><th>US recommendations **</th></tr>
<tr><td rowspan="3">Diagnosed under 6 months
- Men B: 2,3 and 4 months with routine immunisations or 3 doses with one month intervals, with a booster at 14 months
- Men C and ACWY:
o Men C naïve patients should receive 2 doses of Men ACWY 1 month apart.
o If 1 dose of MenC has been given, give a dose of MenACWY at least one month later.
o Booster doses:
▪ 12 months (Hib/MenC)
▪ 14 months (MenACWY)
▪ 24 months (Hib/MenC)

Diagnosed 6-11 months
- Men B: 2 doses with at least 2 months interval; booster after 2nd birthday
- Men C and ACWY:
o Men C naive children should receive 2 doses of Men ACWY 1 month apart
o If 1 dose of MenC has been given, give a dose of MenACWY at least one month later.
o Booster doses:
▪ 12 months (Hib/MenC)
▪ 14 months (MenACWY)
▪ 24 months (Hib/MenC)

Diagnosed 12-23 months
- Men B: 2 doses with at least 2 months interval; Booster 12-23 months after primary course
- Men C and ACWY:
o Booster doses:
▪ 12 months (Hib/MenC)
▪ 14 months (MenACWY)
▪ 24 months (Hib/MenC)</td><td rowspan="3">Men B**:
Age >9 years old:
Bexsero ® 2 doses at least 1 month apart; Trumenba® 3 doses (2nd dose 2 months after the first and 3rd dose 6 months after the first

Men C and ACWY#:
Age 6 weeks-18 months
- Men C: 4 doses of Hib/Men C administered at 2,4, 6 and 12-15 months or if

Age > 9 months:
- Men ACWY: as an alternative to the first scheme 2 primary doses of ACWY should be administered 3 months apart if age between 9-23 months and with 2 months apart if >24 months old

*Adapted from: Salisbury D, Ramsay M NK. Immunisation against infectious disease: the green book, Public Health England. 2013. Chapter 7: 49-56; **Adapted from: CDC: Meningococcal:Who needs to be vaccinated? October 2015; #Adapted from: Rubin LG et al. 2013 IDSA Clinical Practice Guideline for Vaccination of the Immunocompromised Host. Clin Infect D 2014</td></tr>
</table>

Table 3 Vaccine recommendations for specific conditions

Recommended

Uncertain safety or effectiveness

Contraindicated

Not recommended

		Primary immunodeficiencies						Acquired immunodeficiencies					Other						
		Combined B/T cell deficiency	B cell deficiency	(Minor) antibody deficiency	Reduced T cell numbers	Phagocytic cell deficiencies	Complement deficiency	HIV infection	High-dose immunosuppressive medication[i]	Chemotherapy for malignancy	Haematopoietic stem cell transplantation	Solid organ transplantation	Hyposplenia & (functional) asplenia	Nephrotic syndrome	Renal failure, chronic renal disease & dialysis	Chronic liver disease	Cyanotic heart disease & heart failure	Cystic fibrosis, bronchiectasis & home ventilation	Premature infants
'Routine' inactivated vaccines		a	a					f	j	n	p	q							v
Live vaccines	MMR, Rotavirus, BCG		c		d	e		g	k	o	p	q		s					v
	Varicella Zoster Vaccine				d			h	m	m	m	r		s			u		
'Additional' inactivated vaccines[b]		PCV	PCV	PCV	PCV	PCV	Men ACWY MenB PCV	PCV HepB	PCV (ACWY & MenB)[n]	PCV		r	Men ACWY MenB PCV	PCV	PCV HepB	PCV HepA/B	PCV	PCV	
Influenza vaccine (annual) (IAV- inactivated vaccine, live – live attenuated)		IAV Flu	IAV Flu	Live Flu	IAV Flu	Live Flu		Live Flu[h]	IAV Flu	IAV Flu	IAV Flu	IAV Flu		Live/ IAV Flu[t]	Live Flu	Live Flu	Live Flu	Live Flu	Live Flu
Vaccines for household contacts		VZV Flu	VZV Flu	VZV Flu	VZV Flu	VZV Flu			VZV Flu	VZV Flu	VZV Flu	VZV Flu		VZV Flu	Flu	Flu	Flu	Flu	Flu

a) Effectiveness doubtful, especially for children on immunoglobulin replacement therapy
b) If ≥2 years old and PCV not previously administered give 2 doses (2 to 5 years old) or 1 dose (≥5 years) if recommended by local guidelines
c) Safety uncertain and effective immune response unlikely, therefore generally not indicated
d) Safe when given to DiGeorge syndrome patients ≥12 months with CD4 ≥15% and normal PHA (mitogen) response
e) Avoid BCG and other live bacterial vaccines (e.g. oral typhoid)
f) If HAART indicated, delay vaccination until both viral load <50 cp/ml and CD4 ≥15% for 6 months

g) Rotavirus safe, MMR only if CD4 ≥15% (or CD4 ≥750 cells/mm3 [<12 mo], CD4 ≥500 cells/mm3 [1 - 5 years], CD4 ≥200 cells/mm3 [> 6 years]), avoid BCG
h) Only if CD4 ≥15% (or CD4 ≥750 cells/mm3 [<12 mo], CD4 ≥500 cells/mm3 [1 - 5 years], CD4 ≥200 cells/mm3 [> 6 years])
i) Considered as 'high dose': Glucocorticoids as pulse therapy or >2 mg/kg/d or 20mg/d for >2 weeks; on non-biological immunosuppressants (Methotrexate >15 mg/m2/week; Cyclosporine >2.5/mg/d; Sulphosalazine 40 mg/kg/d to 2 g/d; Azathioprine 1-3 mg/kg/d; Cyclophosphamide 0.5-2 mg/kg/d; Leflunomide 0.25-0.5 mg/kg/d; 6-Mercaptopurine >1.5 mg/kg/d); biological agents (e.g. Infliximab, Rituximab, Abatacept, Tocilizumab, Eculizumab, ...) at any dose within the last 6 months
j) If child not up to date with vaccines, catch-up immunisations should ideally be given before commencing immunosuppressants
k) Avoid all live vaccines for 6 months after treatment
l) Only for children on Eculizumab due to increased risk of meningococcal disease given central role of C5 (bound by eculizumab) in complement cascade
m) If possible, check VZV serology prior to commencing treatment/transplant and administer the varicella vaccine to sero-negative children at least 4 weeks before
n) Safe but should not be administered during induction or consolidation therapy because lack of immune response; administer a booster dose of all routine vaccines (except Rotavirus) at 6 months following completion of chemotherapy
o) Avoid in patients on treatment and for 6 months following cessation of treatment
p) Conditioning therapy before transplantation removes the humoral immune memory; vaccination as per routine schedule if not immunosuppressed prior to HSCT (should be completed >4 weeks before HSCT). Dependent upon local guidelines re-immunisation should begin 6 -12 months (inactivated vaccines) or 18 to 24 months (live vaccines) after transplant. This should be delayed if immunosuppressive drugs within 6 mo (12 mo for live vaccines), or IVIG has been used within 3 months, or evidence of GvHD.
q) Vaccination as per schedule (including adolescent immunisations and MMR) should be given whenever possible >4 weeks prior to transplant; avoid live vaccine after transplant
r) Hepatitis B and VZV vaccine to be given >4 weeks prior to transplant
s) Give MMR and VZV during remission when off steroids for 3 mo or off other immunosuppressants for 6 mo; if on Rituximab immunise as per specific guidance
t) Live attenuated influenza vaccine only if not on high-dose immunosuppressants
u) If on aspirin, consider VZV vaccination in children >12 mo to decrease risk of Reye's syndrome
v) Administer at the chronological age (even if on steroid therapy for CLD), particular attention to timely routine booster doses; rotavirus vaccination should be given even if still in NICU (standard infection control measure apply)