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UNIT NO. 4

VACCINATIONS IN INFANTS AND CHILDREN

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ABSTRACT

We have effective vaccines against some of the common and dangerous infections in children. Most of these vaccines have a high safety profile. Vaccines available for routine immunisations belong to different categories. Live viral vaccines are highly effective and provides a good protective effect against the infections caused by those viruses. Conjugate and toxoid bacterial vaccines are also very effective. An overview of all the recommended childhood vaccines, along with their dosing schedule and specific contraindications are discussed. We have looked at situations where vaccinations should be delayed or avoided. Catch up vaccination recommendations for missed or delayed vaccinations are briefly discussed.

Keywords: Vaccinations, Conjugate vaccines, Live attenuated vaccines, Inactivated vaccines, missed vaccinations, delayed vaccinations

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INTRODUCTION

Vaccinating children is an integral part of paediatric & family medicine practice. This article will review the routine childhood vaccination schedule, contraindications and precautions to immunisation, and common special considerations in immunisation including catch-up schedules for unimmunised and partially immunised children. The National Childhood Immunisation Program (NCIP) in Singapore covers vaccination against TB, hepatitis B, diphtheria, pertussis and tetanus, poliomyelitis, haemophilus influenzae type b, measles, mumps and rubella, pneumococcal disease and human papillomavirus.[1] Only vaccinations against diphtheria and measles are compulsory by law.[2] There are a few more optional vaccines like rotaviral vaccine, varicella vaccine, hepatitis A vaccine, influenza vaccine and meningococcal vaccine.

GENERAL PRINCIPLES

Early childhood vaccines are one of the best ways to protect children from serious diseases that can be potentially dangerous for infants and children. Standard recommended intervals should be followed for all routine vaccinations. But minimal intervals may be used to "catch up" children with delayed immunisations[3] or if there is concern that a child may not return for vaccinations. When immunisation is delayed, there is no need to repeat the doses already given.

If vaccines are administered too early, the dose should be repeated at the recommended minimum age. Guidelines say that vaccines given within a grace period of four or fewer days below the minimum interval may be accepted as valid.[4] Most vaccines may be administered simultaneously, but when live vaccines are not given simultaneously, administrations should be separated by at least four weeks.[4] Evidence related to the interchangeability of brands for vaccinations is limited.[4] The same product should be used for repeat doses if possible but may consider substitution if the same brand is not available.

Vaccines should not be administered in the presence of a true contraindication. Only one contraindication is common to all vaccines- anaphylaxis to a previous dose or vaccine component. During a moderate-severe acute illness, immunisation is generally deferred.[5] However, vaccines may be given if the benefit outweighs the risk. In these situations, immunisation may resume as soon as the acute illness resolves.[5] Deferring vaccines in the absence of true contraindications (e.g. minor acute illness) is an important reason for delayed or missed immunisation.

Chronic high dose corticosteroids, chemotherapeutic agents, and biologic therapies for autoimmune disease are all contraindications for live virus vaccines such as varicella and measles-mumps-rubella (MMR). Prednisolone > 2 mg/kg, or > 20 mg/day for children who weigh >10 kg, when administered for ≥ two weeks, is immunosuppressive.[6] Current guidelines recommend that live virus vaccines should not be given until three months after immunosuppressive therapy has stopped.[7] Immunosuppressive therapy should not be started until one month after live virus vaccines have been given.[7]

CONJUGATE VACCINES

The advent of conjugate vaccine technology for polysaccharide vaccines has been very useful in improving the protection of children younger than two years of age as well as immunocompromised individuals. Bacterial polysaccharides, which are poorly immunogenic in younger children, are conjugated to carrier proteins (typically capsular or outer membrane antigens). These proteins improve immune response by triggering T-cell-dependent immunity to polysaccharides, thereby strengthening immune memory. The pneumococcal, meningococcal and haemophilus influenza type b vaccines are available as conjugate vaccines.

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Haemophilus Influenzae Type B (Hib) Vaccine

Haemophilus influenzae type b (Hib) was a leading cause of bacteremia, meningitis, cellulitis, and epiglottitis in the pre-vaccine era. Hib vaccines are prepared from the purified capsule of Haemophilus influenzae type b. Hib vaccine is given in three doses between two to six months old, with a booster at 18 months of age.[2]

Pneumococcal Conjugate Vaccine

Pneumococcal diseases (otitis media, pneumonia, sepsis, meningitis) are caused by more than 90 serotypes of Streptococcus pneumoniae (pneumococci). Pneumococcal vaccine (PCV13) is directed against 13 common serotypes that cause these diseases. The conjugate vaccine contains purified capsular polysaccharides of Streptococcus pneumoniae. PCV13 is given in two doses, four weeks apart between two to six months old, with a booster at 12 months of age.[2]

Meningococcal Conjugate Vaccines

There are two quadrivalent conjugate meningococcal vaccines available - Menactra [MCV4-D] and Menveo [MCV4-CRM]. They protect against meningococcal strains A/C/Y and W-135. Nearly 75 percent of meningococcal infections in children 11 years and older involve these strains. Two doses of MCV4 separated by 8 to 12 weeks are recommended for children (2 years of age and older) with immunodeficiency and adolescents (11 years of age or older) with human immunodeficiency virus (HIV) infection. Only MCV4-D is approved for infants two to nine months old at increased risk of meningococcal disease; either conjugate vaccine may be administered to infants and children older than nine months. Children with functional or anatomic asplenia, including sickle cell disease, should not receive MCV4-D until after two years of age due to immune interference with pneumococcal conjugate vaccine (PCV13).[8]

LIVE ATTENUATED VACCINES

Live attenuated vaccines include vaccines against measles, mumps and rubella (MMR), varicella, oral polio and rotavirus. Live vaccines generally induce stronger mucosal immunity than inactivated vaccines. Viral replication occurs after live viral vaccines, so they are generally contraindicated in immunocompromised patients, in pregnancy, and after receiving intravenous immunoglobulins (up to 11 months, depending on the dose of immunoglobulin received).

Measles, Mumps and Rubella (MMR) Vaccine

The MMR vaccine contains live-attenuated measles and mumps viruses, prepared in chicken embryo cell cultures.[9] It also contains live-attenuated rubella virus, prepared in human diploid lung fibroblasts.[9] MMR vaccine and varicella vaccine are available as a combined vaccine -MMRV vaccine.[9] Two doses of MMR and varicella are given in childhood (at 12 months and 15-18 months of age).[2] The minimum interval between doses is 28 days for MMR and varicella vaccines given at 13 years of age or older and three months for children younger than 13 years of age.[3] Immunisation may be started by administering the trivalent MMR and monovalent varicella vaccines separately (but simultaneously) or MMRV to children younger than 13 years. Because MMRV is associated with a higher risk of febrile seizures than MMR, children with a personal or family history of seizure should generally be immunised with MMR and varicella separately for the first dose. MMR and Varicella vaccine is contraindicated in individuals with neomycin or gelatin allergy. The MMR vaccine may cause a mild or inapparent, noncommunicable infection.[9] The rubella component may cause painful joint swelling, usually in adults.[9] Egg allergy is not a contraindication for MMR vaccination.[10]

Poliovirus Vaccine

Poliomyelitis is an acute paralytic disease caused by three poliovirus serotypes.[11] There are two types of polio vaccines – Inactivated Poliovirus Vaccine (IPV) and Oral Polio Vaccine (OPV). Inactivated poliovirus vaccine (IPV) contains a mixture of formalin-inactivated poliovirus types 1, 2, and 3. IPV may contain trace amounts of streptomycin, neomycin, and polymyxin B.[12] Oral Polio Vaccine is a live attenuated vaccine. Poliovirus vaccine is given in three primary doses between two to six months age: with boosters at 18 months and between 10 – 11 years old.[2] IPV is given for three primary doses and the first booster dose at 18 months of age.[2] OPV is given for the fifth and final dose at 10-11 years of age.[2]

Rotavirus Vaccine

Rotavirus vaccines are live viral vaccines, and there are two vaccines licensed for use in infants. Rotateq (RV5) is a pentavalent reassortant virus from human and bovine origin that expresses human serotypes G1, G2, G3, G4, and P[8].[13] Rotarix (RV1) is an attenuated human virus of the G1P[8] strain which protects against non G1 serotypes on the basis of their common P[8] antigen.[13] Rotavirus vaccine helps in prevention of acute diarrheal disease due to rotavirus infection in healthy infants. The vaccine is administered orally as two-dose (Rotarix) or three-dose (Rotateq) schedule.[14] The first dose should not be administered after 14 weeks and six days of age, and the final dose should not be administered after eight months of age, even if the series is incomplete.[14] Rotavirus vaccine is contraindicated in patients with a history of intussusception due to increased risk of recurrence and in patients with severe combined immunodeficiency.[14]

Tuberculosis Vaccine

Tuberculosis vaccine (BCG) is given at birth as a single intradermal dose. It is a live attenuated vaccine prepared from strains of Mycobacterium bovis. The vaccine helps in reducing the risk of serious complications of tuberculosis disease in children – miliary and meningeal tuberculosis. Healthy infants from birth to two months of age may be given BCG vaccine without tuberculin skin test (TST) or Mantoux test. For infants two to six months of age, an individual assessment of the risks and benefits of TST prior to BCG vaccination is indicated.[15]

For infants over six months of age, administer BCG vaccine only if TST is negative.[15]

NONCONJUGATE INACTIVATED VACCINES

Hepatitis B Vaccine

Hepatitis B vaccine is composed of recombinant DNA-produced hepatitis B surface antigen (HBsAg). Hepatitis B vaccine is given at birth, with the subsequent doses given at one month of age and five to six months of age.[2] These can also be given as part of the combination 6-in-1 vaccine. The hepatitis B vaccine dose is 0.5 mL IM up to age 20 years or 1 mL IM for adults (≥ 20years). If people are not vaccinated or not completely vaccinated, the missing doses should be given to complete the 3-dose hepatitis B series. The second dose is given one month after the first dose; the third dose is given ≥ two months after the second dose (and ≥ four months after the first dose).

Hepatitis A Vaccine

Hepatitis A vaccine is a single-antigen inactivated vaccine. It is prepared from formalin-inactivated, cell culture-derived hepatitis A virus. The hepatitis A vaccine dose is 0.5 mL IM up to age 18 years or 1 mL IM for adults (>18years).[16] Children are given a two-dose series, first dose given after the age 12 months and the second dose is given 6 to 12 months after the first dose.[16]

Diphtheria, Tetanus & Pertussis Vaccine (DTaP & Tdap)[17]

Diphtheria (D) vaccine contains toxoids prepared from Corynebacterium diphtheriae. Tetanus (T) vaccine contains toxoids prepared from Clostridium tetani. Acellular (a) pertussis (P) vaccine contains semipurified or purified components of inactivated subunits of Bordetella pertussis.[17] Whole-cell pertussis vaccine is no longer available in Singapore because of concerns about adverse effects. There are two preparations of the acellular vaccine: Diphtheria-Tetanus-acellular Pertussis (DTaP) for children < seven years and Tetanus-diphtheria-pertussis (Tdap) for children > seven years and adults. Tdap contains lower doses of diphtheria and pertussis components (indicated by the lower-case d and p). Diphtheria, Tetanus, and Pertussis vaccines (DTaP) are given in three doses between two to six months old.[2] Two boosters are given at 18 months (DTaP) and between 10 and 11 years old (Tdap).[2]

Influenza Vaccine

Vaccination is the most effective way to prevent infection and severe outcomes caused by influenza viruses. There are two types of influenza vaccine. The first is the commonly used inactivated vaccine which contains killed virus that is given as an injection. The second type is the live, attenuated intranasal influenza vaccine (LAIV) that is given as a nasal spray. Quadrivalent vaccines (QIV) provide coverage against two influenza A virus strains and two influenza B virus strains; the traditional trivalent vaccines (TIV) provide coverage against two influenza A virus strains and only one influenza B virus strain.[18] Trivalent vaccines are gradually being superseded by quadrivalent vaccines. Inactivated influenza vaccine (IIV) can be given to all children ≥ six months and pregnant women. Children below nine years old taking flu vaccine for the first time or without two prior doses of flu vaccine need two doses.[19] Historically, influenza vaccine has had 50-60 percent efficacy against infection with influenza A viruses and 70 percent efficacy against influenza B viruses.[20]

Human Papilloma Virus (HPV) Vaccine

Human Papilloma Virus (HPV) infection is the most common sexually transmitted infection. Approximately 40 types of human papillomaviruses infect humans, predominantly through sexual contact. The latest available HPV vaccine is the 9-valent Human Papilloma Virus (9vHPV) vaccine. This vaccine protects against the most common HPV types, which cause 90 percent of cervical, vaginal, vulvar, anal, and penile cancers.[21] This vaccine also prevents HPV types that cause genital warts in both males and females.[21] The HPV vaccine is routinely recommended for both males and females.[21] The 9vHPV vaccine is recommended from ages 9 through 26 for females and ages 9 through 21 for males.[21] The 9vHPV vaccine is a two-dose series if the first dose is given prior to the fifteenth birthday.[21] The second dose should be 6 -12 months after the first dose.[21] If the first dose is given on or after the fifteenth birthday, two additional doses should be administered to complete the series (0, 1-2 months, and 6 months).[21] The national school-based HPV vaccination programme is offered free to secondary school students.[22] Two doses of the HPV vaccine are administered to female students in the target schools during Secondary 1 (13 years old) and Secondary 2 (14 years old).[22] Observation for 15 minutes following vaccination is advised due to an association with syncope. Patients who began a series with 4vHPV may complete the series with 9vHPV.[21] Repeat vaccination with 9vHPV is not recommended in patients who have completed three-dose courses of 2vHPV or 4vHPV vaccines.[21] Among women who have not been previously infected with a vaccine targeted HPV type, 2vHPV, and 4vHPV have over 95 percent efficacy in preventing cervical pre-cancers caused by HPV16 and HPV18.[21]

CONCLUSION

Despite the great success of the national childhood immunisation programme, gaps in coverage remain, and vaccine-preventable diseases continue to occur. The childhood immunisation schedule is clearly written and easy to follow. Although serious adverse reactions to immunisations are not common, clinicians must be well-versed to deal with these situations and should be aware of specific adverse reactions and contraindications for each vaccine.

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LEARNING POINTS

- **Vaccinations protect children from serious diseases that can be potentially dangerous.**
- **Live viral vaccines are highly effective in preventing the disease.**
- **Conjugation of polysaccharide antigens like pneumococcal, haemophilus influenzae and meningococcal antigens have made them highly immunogenic even in younger children.**
- **Acute minor illnesses are not considered contraindications for any vaccination.**
- **Delayed or missed vaccinations should be administered at the earliest possible opportunity.**
- **Some vaccines have specific contraindications - either absolute or relative.**

Table 1. National Childhood Immunisation Schedule, Singapore[2]

Vaccination against	Birth	1 Month	3 Months	4 Months	5 Months	6 Months	12 Months	15 Months	18 Months	10-11 Years
Tuberculosis	BCG									
Hepatitis B	HepB (D1)	HepB (D2)			HepB (D3)					
Diphtheria, Tetanus, Pertussis			DTaP (D1)	DTaP (D2)	DTaP (D3)				DTaP (B1)	Tdap (B2)
Poliovirus			IPV (D1)	IPV (D2)	IPV (D3)				IPV (B1)	OPV (B2)
Haemophilus influenzae type b			Hib (D1)	Hib (D2)	Hib (D3)				Hib (B1)	
Measles, Mumps, Rubella							MMR (D1)	MMR (D2)		
Pneumococcal Disease			PCV (D1)		PCV (D2)		PCV (B1)			
Human Papillomavirus	Recommended for females 9 to 26 years									

Table 2. Lower age limit and minimum interval between doses of vaccines[23]

Vaccine	Lower age limit	Minimum interval between doses 1 and 2 (weeks)	Minimum interval between doses 2 and 3 (weeks)	Minimum interval between doses 3 and 4 (weeks)
DTP	6 weeks	4	4	4
Polio	0	4	4	4
Hib (PRP-OMP)	6 weeks	4	52	--
Hib (PRP-T)	6 weeks	4	4	52
Hepatitis B	0	4	8	8
MMR	9 months	4	--	--
MenCCV	6 weeks	8	8	--
PCV	6 weeks	4	4	--
Rotavirus (Rotarix®)	6 weeks	4	--	--
Rotavirus (RotaTeq®)	6 weeks	4	4	--
Varicella (Varilrix®)	9 months	4	--	--
Varicella (Varivax®)	12 months	4	--	--

DTP, diphtheria–tetanus–pertussis; Hib, Haemophilus influenzae type b; MenCCV, meningococcal C conjugate; MMR, measles–mumps–rubella; PCV, pneumococcal conjugate (7-, 10- or 13-valent); polio, poliomyelitis; PRP-OMP, polyribosylribitol phosphate-outer membrane protein conjugate; PRP-T, polyribosylribitol phosphate conjugated with Tetanus toxoid.