UNIT NO. 2B

CHILDHOOD VACCINES

Dr Chong Chia Yin

ABSTRACT

Vaccination in children is to protect children against infectious diseases and the ultimate goal is the eradication of these diseases. Besides the routine childhood vaccines, new optional vaccines are described in this article, e.g. pneumococcal conjugate vaccines, human papillomavirus vaccine, and rotavirus vaccines. Combination vaccines have the ability to reduce the number of injections and, at the same time, improve parents' compliance. Although vaccines can be reactogenic and produce mostly temporary side effects, e.g. fever and injection site pain, the myth of autism being caused by MMR vaccines should be forever dispelled and parents should be given the correct advice to proceed with MMR vaccination in order to avoid measles outbreaks.

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INTRODUCTION

The ultimate goal of immunisation is the eradication of a disease; the immediate goal is prevention of a disease in individuals or groups. The global eradication of smallpox in 1977 and elimination of poliomyelitis from the developed world in 1990s serve as models for fulfilling the promise of disease control through immunisation. Since the start of the World Health Organization's (WHO) Global Eradication of Polio Initiative, the worldwide incidence of polio has decreased from 350,000 cases in 1988 to just over 5,000 cases in 1999. Vaccines have been developed for many diseases, including measles, tetanus, pertussis (whooping cough), poliomyelitis and diphtheria. However, at least two million children die each year from vaccine-preventable diseases.

Vaccines provide several advantages over treating a disease including:

Antibiotics often work too slowly in avoiding the damaging effects of a disease. Infectious agents also can develop resistance to antibiotic treatments. According to the WHO, resistance to antibiotics is a crisis for health care at the dawn of the 21st century.

If immunisation is to be an effective means of controlling infectious disease, then at least 80% of the whole population and 80% of the newborns have to be successfully vaccinated. This is the condition for creating heard immunity which occurs when a large proportion of the population is vaccinated against a particular microbe, which in turn makes the odds of infection among unvaccinated individuals low.

CHONG CHIA YIN, Head & Senior Consultant, Paediatric Medicine, Infectious Diseases Services, KK Women's & Children's Hospital

Vaccines prevent the spread of a disease to others. This is an added economic advantage because fewer people miss school or work. After providing adequate nutrition, there is no more efficient expenditure of health funds than on immunisation.

THE IMMUNE SYSTEM AND VACCINES

Immunisation works by preparing the immune system to attack the infection by building a "memory" of a pathogen. This memory allows the immune system to later "recognise" a pathogen and fend-off infection.

Active immunisation involves administration of all or part of a microorganism or modified product of that microorganism, e.g. toxoid, a purified antigen or an antigen produced by genetic engineering to evoke an immune response that mimics that of natural infection, without putting the person at risk for infection. Vaccine incorporating an intact infectious agent may be live-attenuated (weakened, e.g. measles, varicella) or killed (inactivated, e.g. influenza, hepatitis A). Many viral vaccines are live-attenuated. Although active, infection with viral replication ensures after administration of these vaccines, usually little or no host reaction occurs. Other vaccines are killed components, subunit (purified protein) or inactivated toxins, or are conjugated chemically to immunologically active proteins, e.g. tetanus toxoid, nontoxic variant of mutant diptheria toxoid, or meningococcal outer membrane protein complex. Viruses and bacteria that are killed are not capable of replicating in the host; therefore, these vaccines must contain a sufficient antigenic mass to stimulate a desired response. Maintenance of long-lasting immunity may require periodic administration of booster doses. Inactivated vaccines may not elicit the range of immunologic response provided by live-attenuated agents.

Passive immunisation involves administration of preformed antibody to a recipient. This is indicated only in specific circumstances for prevention or amelioration of infectious disease, e.g. when suffering from an immunodeficiency or for post-exposure prophylaxis. These products include immune globulin and are not further discussed in this module.

Milestones in the development of vaccines

Late 1700s. Edward Jenner developed the first vaccine against smallpox after observing that milkmaids who had acquired cowpox never got smallpox. In an experiment, Jenner took fluid from a sore of a woman with cowpox and injected it into a healthy boy, whom he later exposed to smallpox. The boy

stayed healthy. Jenner reasoned that he could protect humans from smallpox by inoculating them with the cowpox material from cows (L. vaccinus). The world's first attempt at vaccination had succeeded.

1880. Louis Pasteur first created attenuated vaccines, which use weakened forms of the pathogen. He introduced this process of inducing protective immunity as "vaccination" when he showed, in 1881, that sheep and cows vaccinated with the baccilli of anthrax became immune to the disease. At the same time, Salmon and Smith developed the first "dead" vaccines made from a heat-killed sample of an infectious agent.

1970. Subunit or acellular vaccines, which contain only a portion or single cell of an organism, were introduced.

1980s. The first glycoconjugate vaccines (combining bacterial capsular saccharides with protein carriers) to prevent *Haemophilus influenzae* type b (Hib) disease in infants and toddlers were introduced.

Constituents in a vaccine

The main constituents of vaccines include the following:

Active immunising antigens.
Some vaccines consist of a single antigen, e.g. tetanus and diptheria toxoid. Others contain multiple antigens that vary in chemical composition and numbers, e.g. acellular pertussis components, Haemophilus influenzae type b, and pneumococcal products. Such vaccines produce both humoral and cellular-mediate responses to ensure long-term protection.

Conjugating agents
Carrier proteins of proven immunologic potential, e.g. tetanus toxoid, nontoxic variant of diptheria toxin, and outer membrane protein complex of meningococcus, are combined to less immunogenic polysaccharide antigens, e.g. Hib and Pneumococcus. This enhances the type and magnitude of immune responses, especially in persons with immature immune systems, particularly children younger than 2 years old.

Suspending fluid
This is commonly sterile water for injection or saline solution or a complex tissue-culture fluid. This fluid may contain proteins or other constituents derived from the medium or system in which the vaccine is produced, e.g. gelatin, egg antigens or cell-culture derived antigens.

Preservatives, stabilisers, antimicrobial agents
Trace amounts of thimerosal (<0.5 mcg/0.25 ml of vaccines), other chemicals and antibiotics, e.g neomycin and streptomycin, may be included in vaccines to prevent bacterial growth or stabilise an antigen.

Adjuvants
An aluminium salt is commonly used to increase immune response and to prolong the stimulatory effect, e.g. for vaccines with killed organism such as hepatitis B, diptheria and tetanus toxoids.

VACCINE ADMINISTRATION

DTaP/Tdap/Td, Hib, inactivated influenza, hepatitis A, hepatitis B, pneumococcal conjugate, meningococcal conjugate, and HPV vaccines are administered IM. MMR, MMRV, meningococcal polysaccharide, and varicella vaccines are administered SQ. Rotavirus vaccine is given orally. With the exception of vaccines against rabies and hepatitis B, vaccines that have not been administered via the recommended route should be considered valid. In cases of doubt, the product circular should be consulted.

Site selection. The site for IM injection varies by age. For children up to the age of 18 months and often beyond, the anterolateral thigh is preferred. The deltoid muscle may be used for older children and adults. With the exception of immunoglobulin injection, the buttocks should not be used as an injection site because the gluteal site is covered by a large layer of subcutaneous fat and because of the possibility of damaging the sciatic nerve. Preferred SQ injection sites include the fatty outer aspect of the thigh or triceps area of the upper arm.

Injection technique. Proper injection technique requires rapid insertion of the needle through the skin after a brief warning to the patient. The limb should be relaxed and placed firmly against an immovable object. Aspiration on the plunger is NOT required prior to injection because there are no large blood vessels at the recommended injection sites. When multiple vaccines are administered, separate sites should be used if possible, especially if one of the vaccines contains DTaP. Injection sites in the limb should be spaced at least one to two inches apart if the same limb is used.

For IM injection, the skin is entered at a 90° angle. Some recommend a Z-shaped track, created by sliding the stretched skin over the muscle before injection. To avoid leaving any portion of an IM vaccine in fatty tissue, the syringe plunger should not be depressed when the needle is withdrawn. Subcutaneous injection are given at 45° angle into the anterolateral aspect of the thigh, or upper triceps by inserting the needle in a pinched up fold of skin and subcutaneous tissue. Subcutaneous administration of hepatitis B vaccine results in decreased immunogenicity compared to IM injection, therefore this vaccine should not be given subcutaneously.

Vaccine containing adjuvants, e.g. aluminium, must be injected deep into the muscle mass. They should not be injected subcutanously or intracutaneously because they can cause local irritation, inflammation, granuloma formation and tissue necrosis.

Table 1: Vaccines administration

Vaccines	Injection Route	Needle Size	Patient Characteristics (inches)	Needle Length	Administration Site
DTap, DT	IM	22-25 gauge	Very small or preterm infants	5/8	Anterolateral thigh
Hepatitis A			Neonate to toddler (12-18 months)	7/8-1	Anterolateral thigh
Hepatitis B			Toddler (12-18 months) to older child (36 months)	7/8-1.25	Anterolateral thigh
Hib					or deltoid
HPV			Older child (>38 months) to adolescent (18 years)	7/8-1.5	Deltoid or
Influenza inactivated					Anterolateral thigh
Meningcoccal conjugate			Adolescents and adults by sex and weight		
vaccine			Female/male <60 kg	5/8-1	Deltoid
Pneumococcal conjugate			Male 60-120 kg	1-1.5	
vaccine			Male >129 kg	1.5-2	
Pneumoccal			Female 60-90 kg	1.1.5	
polysaccharide vaccine*			Female >90kg	1.5-2	
Rabies vaccine					
IPV*	SQ	23-25 gauge		5/8-3/4	Fat of anterolateral
MMR, MMRV					thigh or upper arm
Meningcoccal					
polysaccharide vaccine					
Pneumococcal					
polyscaaharide vaccine*					
Varicella vaccine					
Zoster vaccine					
Rotavirus vaccine	Oral				
Influenza virus, live	Intranasal				Intranasal: 1/2 dose
					in each nostril

DTaP = diphteria, tetanus, acellular pertussis; DT = diphteria, tetanus (pediatric); Hib = Haemophilus influenzae type b conjugated; HPV = human papillomavirus; IM = intramuscular; IPV = inactivated poliovirus vaccine; MMR = measles, mumps, rubella; MMRV = measles, mumps, rubella, varicella; SQ = subcutaneous.
**IPV and pneumococcal polysaccharide vaccine can be given either IM or SQ; most authorities recommend the SQ route for IPV, IM route for PPV.*

Autism and Vaccines

There is no link between autism and the measles-mumps-rubella (MMR) vaccine or the vaccine preservative thimerosal, according to a report in 2004 by the Institute of Medicine's (IOM) Immunization Safety Review Committee.

Five large studies in the United States, the United Kingdom, Denmark, and Sweden done since 2001 found no evidence of a link between autism and vaccines containing thimerosal. In addition, 14 large studies consistently showed no link between the MMR vaccine and autism. The IOM committee also reviewed several studies that had reported associations between vaccines and autism, and found that these studies had limitations and lacked supporting evidence.

Limiting Thimerosal use

Since the 1930s, small amounts of thimerosal have been used as a preservative in multi-dose vials of vaccines to prevent bacterial contamination. The active ingredient in thimerosal is ethylmercury.

Even though the risk of thimerosal is hypothetical, thimerosal began to be removed from childhood vaccines in 1999. The US government agreed that thimerosal should be reduced and eliminated in vaccines as a precautionary measure. The HSA encouraged companies to comply with this recommendation. Currently, all routinely recommended vaccines manufactured for infants in the United States are either thimerosal-free or contain only trace amounts.

In its latest report, the IOM's immunisation committee reported that it does not dispute that mercury-containing compounds, including thimerosal, can be damaging to the nervous system. However, the committee did not find that these damaging effects are related to the development of autism.

Late vaccinations and interrupted schedules

If the childhood vaccination schedule is started late or interrupted by more than one month, the accelerated (catch-up) vaccination schedule should be used. Use of the minimal intervals between planned doses ensures catch-up as quickly as possible. All prior doses of vaccine count toward fulfilling requirements regardless of elapsed time. Required vaccines and number of doses vary by age. The careful clinician should consider vaccination status for each patient regardless of the reason for medical care and provide appropriate catch-up vaccination. When children have missed many vaccine doses, it is important to bring them up to date as quickly as possible.

This may require more than two injections at some visits. The following is a guide in deciding what immunisation needs to be given and the timing:

- When more than one vaccine is overdue, it is preferable to give the maximum possibly at the first visit.
- For children above 12 months old, MMR should be the priority because these diseases pose the greatest immediate risk.
- Determine the total number of vaccines required and subtract the number of previous documented doses. Complete the primary programme using the minimum intervals of one month between doses. When a fourth dose is required, give it not less than six months after the third dose (for the booster response to occur).
- At primary 1 or seventh birthday, adult Td or Tdap (Boostrix) should be used.

Minimal intervals and interference

Doses of a specific vaccine given too close together or prior to the minimum age may be less immunogenic than appropriately spaced or timed doses. A dose given five or more days earlier than the minimum interval or prior to the minimum age is not valid. A repeat dose should be given at or after the proper age and follow the invalid dose by at least the minimum dosage interval for that particular vaccine.

Simultaneous vaccination

Simultaneous administration of routine vaccines at different anatomic sites is immunogenic, safe, and recommended in order to increase vaccination rates and avoid missed opportunities to vaccinate. Simultaneous vaccination is preferred whenever possible because compliance with vaccination schedules increases as the number of visits required to complete immunisations decreases.

Simultaneous administration of different inactivated vaccines and/or live viral vaccines does not interfere with the immune response. Different live viral vaccines administered on different dates within 28 days of each other pose a theoretical concern of interference. Whenever possible, live viral vaccines, e.g. MMR and varicella (not oral polio vaccine), should be administered on the same day, or four weeks and above apart. If live-virus vaccines are administered on different days but less than four weeks apart, the vaccine administered second should be considered invalid and repeated at least four weeks after the invalid dose.

Interchangeability of vaccines from different manufacturers

Different manufacturers produce vaccines to prevent the same disease that vary in their contents. These vaccines may be interchanged when a particular antibody titer is known to protect against disease (called the serologic correlate of immunity) and when each of the different vaccines induces protective antibody titers. Hepatitis B, hepatitis A, or Hib vaccines from different manufacturers, given appropriately, confer protective titers. Although all three brands of the Hib vaccine are interchangeable, PRP-OMP requires only two doses (as opposed to three) during the first year of life. However, if PRP-OMP and Hib vaccine from another manufacturer are interchanged during the first year of life, then three doses (at two, four, and six months of age) are recommended for the primary series. All Hib products require a booster dose, preferably at 12 to 15 months of age, when any Hib vaccine may be given.

For diseases such as pertussis, in which the serologic correlate of immunity is unknown, use of a vaccine from a single manufacturer for at least the first three doses is preferred. If the manufacturer of a child's previous dose is unknown or that manufacturer's product is not available in the office, then any product is satisfactory, rather than missing the opportunity to vaccinate.

International adoptions and children from another country

For a child who has arrived from another country and will be staying in Singapore for six months or more, a change to the local recommended schedule may have to be considered with due account being taken of prior vaccine administration. The vaccine records that accompany many international children are unreliable. Evaluation of antibody concentrations against vaccine antigens may be an alternative method to determine that effective vaccines were given and thus to avoid reimmunisation with the full number of required vaccines due at the child's current age. To confirm immunity, IgG antibody levels can be assessed for measles, mumps, rubella, varicella, hepatitis B, and hepatitis A. However, IgG antibody testing is not available locally for diptheria, tetanus, or pertussis. When in doubt about which immunisations have been given, full catch-up vaccination should be given.

If the child has not had any immunisations and is aged 12 months or older, the priority is to give MMR first. Polio and DPT/ DTaP can be given at the same time as MMR at separate injection sites. However, the total number of doses of diptheria, and tetanus toxoid vaccines should not exceed six doses before the fourth birthday, otherwise, there is a risk of large local reactions.

CONTRAINDICATIONS

Two permanent contraindications to administering a dose of vaccine are:

1. Severe allergy to a vaccine component or history of anaphylactic reaction to a previous dose of the vaccine.
2. For pertussis vaccine, encephalopathy without a known cause in seven or fewer days after administration.

If the pertussis component is withheld because of a contraindication (e.g. uncontrolled convulsions, worsening focal neurologic deficit, or other unstable neurologic condition) or precaution, paediatric DT should be administered instead. For the case of true anaphylaxis, both the diphtheria and

pertussis components are permanently contraindicated. In such instances, referral may be made to an allergist for an assessment of whether tetanus toxoid can be given or for possible desensitisation to tetanus toxoid.

Some allergies, including contact dermatitis from neomycin, are not contraindications. Previous anaphylactic reactions after MMR vaccination may be due to gelatin allergy. Other contraindications to specific vaccines include allergy to baker's yeast for hepatitis B vaccine; anaphylactic reaction to neomycin for MMR or varicella, and inactivated poliovirus vaccines; and anaphylactic reaction to streptomycin for inactivated poliovirus vaccine. No currently recommended vaccines contain penicillin or its derivatives.

Egg allergy

Egg allergy is not a contraindication to MMR or MMRV vaccine because the vaccine does not contain egg albumin, but is derived from chicken embryo fibroblast tissue cultures. Studies show that children with egg allergy, even those with severe hypersensitivity, are at low risk of anaphylactic reaction to these vaccines. Therefore, children with egg allergy may be given MMR, MMRV, measles, and mumps vaccines without prior skin testing.

However, influenza vaccine is prepared in eggs containing egg protein and rarely, may induce immediate allergic reactions including anaphylaxis. Skin testing has been used in children with severe anaphylactic reactions to eggs who are to receive inactivated or live-attenuated influenza vaccines. History of severe egg allergy in a family member is not a contraindication to influenza vaccines. Less severe or local manifestations of allergy to egg or feathers are not contraindications to influenza vaccine and do not warrant vaccine skin testing. Influenza vaccine is contraindicated for a patient who has previously experienced a severe allergic reaction to eggs.

Conditions that are mistakenly labeled as contraindications to vaccination include local reactions, low-to-moderate fevers after previous doses, a family history of severe adverse events related to DTP vaccine, mental retardation, stable neurologic disorders, breast-feeding, or seasonal allergies. None of these conditions are contraindications.

Four conditions considered temporary contraindications to vaccination are severe acute illness, immunosuppression (all live vaccines), pregnancy (all live vaccines), and recent receipt of blood products, including RhoGAM , MMR, MMRV, rotavirus, and varicella vaccines.

Severe acute illness

Severe illness, such as pneumonia with high fever requiring antibiotics and bronchodilators, usually warrants postponement of vaccination until the patient has recovered from the acute phase of illness. Low-grade fever and minor respiratory disease are not contraindications to vaccination.

Prematurity

Premature infants should be vaccinated at the correct chronological age for all vaccines. Even the most extremely premature infants (<29 weeks gestation and weighing <1000 g at birth) vaccinated at the recommended chronological ages usually maintain antibody titers in the protective range.

Immunosuppression

Generally, suppressed immune function as a result of an immune deficiency disease, malignancy, or therapy with high-dose corticosteroid drugs (prednisone equivalency of $\geq$2 mg/kg per day for $\geq$14 days), alkylating agents, antimetabolites, or radiation is a contraindication to administration of live vaccines but not killed vaccines. Rotavirus, MMR, and varicella vaccines should be avoided. Although inactivated vaccines may be given to immunosuppressed persons, immunosuppression may decrease the antibody response.

Recent administration of blood products

Blood products, including RhoGAM, can interfere with development of an immune response to a live but not an inactivated vaccine or toxoid. MMR or varicella vaccine should not be given within six months after receipt of whole blood or within 11 months of a large dose of IV immunoglobulin, e.g. in Kawasaki disease. If MMR or varicella vaccine is given first, blood product administration should preferably be delayed at least two weeks. To ensure rubella immunity, susceptible women of childbearing age should be given MMR/MMRV vaccination immediately after delivery despite the use of RhoGAM and tested for rubella antibody eight weeks later. Reimmunisation may be necessary.

Tuberculin testing

A tuberculin skin test (TST) can be applied at the same visit during which a live vaccine is administered. Measles vaccine can temporarily suppress tuberculin reactivity for at least four to six weeks. If tuberculin testing is indicated, measles immunisation should be deferred until testing is completed or the TST should be deferred for four to six weeks. Data for varicella immunisation is not available but it is reasonable to assume that TST should be deferred for the same period of time as for measles vaccine.

PRECAUTIONS

Some conditions may increase the risk for a serious adverse event or may compromise vaccine-produced immunity. The decision to vaccinate is made by weighing an individual's risk of acquiring the disease in question against his or her risk for a vaccine-related adverse event, and the possibility that the disease itself will not produce lasting immunity. Precautions with respect to vaccination in general include moderate-to-severe vomiting or diarrhea or localised infection, such as otitis media. Unless given to treat specific underlying illness, such as Kawasaki disease, aspirin should be avoided during childhood. Caution is advised when considering administration of rotavirus vaccine to infants with chronic gastrointestinal disorders.

For patients with bleeding diathesis, the risk of bleeding after IM injections can be minimised by giving vaccine immediately after the patient's receipt of replacement factor, the use of a 23G or smaller needle, and immediate application of direct pressure to the immunisation site for at least two minutes. Some vaccines, e.g. PedvaxHIB recommended for IM injection, may be given subcutaneously to people with bleeding disorders.

Precautions and warnings for pertussis vaccination

After pertussis vaccination, precautions (no longer contraindications) to further doses are (1) temperature of 40.5°C or higher (≥105°F), not due to another identifiable cause, within 48 hours of a dose, (2) collapse or shock-like state (hypotonic-hyporesponsive episode) within 48 hours of a dose, (3) persistent, inconsolable crying lasting three or more hours, occurring within 48 hours of a dose, or (4) convulsions (possibly accompanied by fever) within three days of a dose. DTaP vaccination should be postponed for infants with evolving neurologic disorders, unevaluated seizures, or neurologic events that have occurred between doses of pertussis vaccine. Vaccination should be resumed after the condition is treated and stabilises.

Adverse reaction and vaccine reporting

All childhood vaccinations should be notified to the Central Immunisation Registry, Ministry of Health (www.hpp.moh.gov.sg, go to Health Professionals, log in and go to National Immunization registry). For post-vaccination adverse reactions, report to Health Sciences Authority at www.hsa.gov.sg or download the file from www.hsa.gov.sg/docs/ADR_form.pdf.

PAIN CONTROL MEASURES

Fear of the pain from a shot is nearly universal. Techniques to reduce anxiety for both patients and parents include psychological preparation, proper injection technique, and topical and oral analgesics (both of which require time to work).

Psychological preparation

Providers should counsel parents that multiple injections are generally well tolerated. Parents should not use shots as threats to improve their children's behaviour. Parents should offer support and comfort, calm the child, or provide distraction while vaccines are administered. During the injection, parental attitudes clearly affect the child's pain behaviours. Excessive parental reassurance, criticism, or apology appears to increase distress, whereas humor and distraction may reduce distress.

Children may be held either on a parent's lap or chest-to-chest to reduce fear, but the limb to be injected must be held firmly, preferably against an immobile surface, to limit recoil from the injection and the need to repeat a partially injected vaccine dose. For older children, truth about impending immunisation helps to establish trust for the future.

For infants, various nonpharmacologic techniques said to be of value. These include using a pacifier, breast-feeding, sugar on the tongue or pacifier, rocking or stroking, music, and gentle words of reassurance. For older children, deep breathing exercises, blowing on a pinwheel or to make soap bubbles, reading, storytelling, a magical switch that transforms pain into love (close to the truth!), and singing are all reported to reduce pain.

Topical anaesthesia

Physical methods and medication can induce topical anaesthesia. Because ice and vapocoolant spray provide only brief anaesthesia and can be frightening or initially bothersome, some sources do not recommend either. However, others sing their praises. Pressure on or pinching of the skin for 10 seconds prior to injection can reduce injection pain. EMLA® Cream (2.5% lidocaine and 2.5% prilocaine) effectively provides pain prophylaxis to a depth of 5 mm. The cream must be applied 30-60 minutes prior to the injection under an occlusive dressing. EMLA cream does not seem to reduce the immune response. Lidocaine under iontophoresis for 10 minutes provides anesthesia to a depth of about 10 mm, but the electrical current may cause discomfort.

Oral analgesics

Oral administration of acetaminophen, 10 to 15 mg/kg, 30 to 60 minutes prior to vaccination may lessen pain. Acetaminophen is commonly prescribed after vaccination to reduce side effects. Some favor ibuprofen, 5 to 10 mg/kg, especially if EMLA cream is used, to avoid the unlikely possibility that simultaneous administration of EMLA cream and acetaminophen will produce methemoglobinemia.

Longer, and not shorter needles, are more likely to penetrate muscle than shorter ones, cause less pain, fewer adverse effects, and less local reaction.

VACCINE STORAGE

Proper storage is imperative for vaccine efficacy. Vaccine storage requires a continuous electrical feed outlet with a plug safety lock to the refrigerator/freezer, a thermometer used to maintain a daily temperature log, and cold-chain monitor cards. Vaccines must be on a tray in the central storage area of the unit, not on the door. Cold sinks such as water bottles or ice trays can fill empty refrigerator/freezer space. Food or radioactive materials must not be in the same refrigerator. Providers should regularly inspect the refrigerator/freezer for outdated vaccines and discard old products. All shipped vaccine should be received within 48 hours and the enclosed cold-chain monitor card reviewed prior to storage.

COMBINATION VACCINES

To reduce the number of injections needed for the child, combination vaccines have become important solutions to the number of infectious diseases that children need to be protected from.

The advantages of combination vaccines are:

- Overcome the constraints of multiple injections, especially for catch-up vaccines
- Improve timely vaccination coverage
- Overcome parents' objection to more than two or three injections during a single visit due to fear of needles and pain
- Reduce the cost of stocking and administering separate vaccines, facilitating the addition of new vaccines into the immunisation programme. The combination vaccine might be a better economic value considering the direct and indirect costs of extra injections, delayed or missed vaccinations, and additional handling and storage.

Some of the disadvantages are:

- Chemical incompatibility or immunologic interference may result when different antigens are combined into one vaccine and this has to be excluded for each specific combination.
- Vaccine combinations that require different schedule might cause confusion and uncertainty when children are treated by multiple vaccine providers who use different products.

Combination vaccines currently available include: DTwP (whole cell pertussis), DTaP (acellular pertussis), DTaP and Hib (4 in 1), DTaP and Hib and IPV (Infanrix-IPV with Hib, or 5 in 1 vaccine, including *Haemophilus influenzae* type b), DTaP and Hib and IPV and hepatitis B (Infanrix Hexa). MMR.

A combination vaccine that protects against both hepatitis A and hepatitis B (Twinrix®) is now licensed for children aged one year and above and is administered IM (but not in the buttocks) as a 1mL dose and given as two doses 6-12 months apart.

A combination of MMR and varicella vaccines forms MMRV (ProQuad), which can be given from 12 months to 12 years of age. It can also be used if a second dose of measles, mumps and rubella vaccine is to be administered.

Combined hepatitis A and B vaccine (Twinrix) can now be used for children above one year old. For children 1-15 years old: two doses of 1 ml are given with the second dose 6- 12 months later. For children 16 years and above, three doses of 1 ml at 0, 1, 6 months. The protection against hepatitis B may not be obtained until after the second dose, therefore Twinrix should only be used when the risk of hepatitis B is low.

THE SINGAPORE CHILDHOOD IMMUNISATION PROGRAMME

The childhood immunisation programme in Singapore offers vaccination against tuberculosis, hepatitis B, diptheria, pertussis, tetanus, poliomyelitis, measles, mumps, rubella (MMR). Only diptheria and measles immunisation are compulsory by law.

Since 1 Jan 1990, the monovalent measles vaccine given to one year old children was replaced by MMR. As of 1 Jan 1998, the monovalent rubella vaccine given to primary school leavers was replaced by the second dose of MMR vaccine.

Hepatitis B vaccination for infants born to carrier mothers was incorporated into the national childhood immunisation programme

Hepatitis B

HBsAg-negative mothers. If the mother is HBsAg-negative, the first vaccine dose should be given at birth, prior to hospital discharge or at any time before two months of age. Hepatitis B immunoglobulin (HBIG) is given to all babies born to carrier

Table 2. Singapore childhood immunisation

Disease	Primary course Infants < 1 year	Booster doses Pre- school children (1-5 years)	Booster doses Primary school students(6-11+ years)
Tuberculosis	Birth – BCG	Nil	Nil
Diptheria Pertussis Tetanus	3 mths DPT (1st dose) 4 mths DPT (2nd dose) 5 mths DPT (3rd dose)	18 mths – DPT (1st booster)	6+ years (Primary school entrants) – Td (2nd booster) 11+ years (Primary school leavers) – Td (3rd booster)
Poliomyelitis	3 mths 4 mths 5 mths	18 mths – 1st booster	6+ years (Primary school entrants – 2nd booster 11+ years (Primary school leavers) – 3rd booster
Measles/ Mumps/ Rubella (MMR)		12-15 mths: 1st dose	11+ years (Primary school leavers) – 1st booster
Hepatitis B	Birth, 1, 5 or 6 mths	*	

* For babies born to carrier mothers, screen the HBs antigen and anti-HBs antibody at 9-12 months old. If both are negative, give a booster dose of hepatitis B vaccine at 12 months of age.

mothers regardless of Hbe Ag status. For infants weighing less than 2 kg, the first dose may be delayed until 30 days of age. Consistent weight gain in preterm infants is a predictor of good immune response. Combination vaccines may be used for all subsequent doses.

HBsAg-positive mothers. Infants born to HBsAg-positive mothers should be given both hepatitis B vaccine and HBIG within 12 hours of birth, regardless of the HBe Ag status of the mother, gestational age or birth weight. Ideally, infants weighing 2 kg or more should receive the second dose of vaccine between the ages of one and two months and the third dose at six months of age. If the infant weighs less than 2 kg, the initial dose of hepatitis B vaccine should not be counted toward completion of the vaccine series; additional hepatitis B vaccine should also be given at one month, two to three months, and six to seven months of age. If a mother has chronic HBV infection, her infant should be tested between the ages of 9-12 months for both HBsAg to detect infection and anti-HBs to prove successful vaccination. If the HBs Ag and anti-HBs are both negative, a booster dose at 12 months of age is indicated. For an infant born to an HBsAg-positive mother, noncombination hepatitis B vaccine is utilised for the first injection and preferably for all follow-up injections.

Measles

Measles vaccination was first introduced into the childhood vaccination programme in October 1976 and made compulsory in August 1985. The monovalent measles vaccine was replaced by the trivalent measles, mumps, rubella (MMR) vaccine in January 1990. A resurgence of measles was noted in 1992-1993 but the highest incidence in the last decade was seen in 1997 in which 1,413 cases were notified. This resurgence was not due to vaccine failure but a build-up of susceptible among older children, youths and adults who were not vaccinated. A catch-up measles (MMR) vaccination campaign was conducted in July-November 1997 for all students aged 12-18 years. In January 1998, the two-dose MMR vaccination schedule was introduced with the second dose given to primary school leavers (11+ years old).

Mumps

In January 1990, vaccination against mumps was introduced in the national childhood immunisation program when the monovalent measles vaccine was replaced by the trivalent measles, mumps, rubella (MMR) vaccine. Since January 1990, three mumps-virus strains have been used in the MMR vaccine: Urabe strain, Jerryl-Lynn strain and Rubini strain. The Urabe strain was substituted by the Rubini strain during 1993-1995. Although the incidence of measles and rubella has declined, that of mumps increased significantly in 1999 and 2000 due to primary vaccine failure (lack of protection by the Rubini strain vaccine). In view of the low protection conferred by the Rubini strain vaccine, the Ministry of Health deregistered the MMR vaccine containing the Rubini strain in May 1999. The current vaccine contains the Jerryl-Lynn strain.

Rubella

Rubella immunisation was introduced in Nov 1976 for female primary school leavers 11+ years of age. However, as rubella outbreaks continued to occur in susceptible populations, especially national servicemen (NS men), the vaccination was extended to cover male primary school leavers in 1982. NS men were also routinely vaccinated to eliminate rubella in army camps. The programme was further expanded to include children one to two years of age using the trivalent measles, mumps, rubella (MMR) vaccine in Jan 1990. The second dose of MMR was introduced in 1997 for secondary and junior college students in a catch-up measles vaccination programme and to all primary school leavers in 1998. With the catch-up MMR vaccination program, the number of rubella cases has gradually declined.

Measles, Mumps, Rubella prevention and control

All pre-school children should be immunised against measles. Combined Measles/Mumps/Rubella (MMR) vaccine is given to all children between 12 and 15 months of age as part of the childhood immunisation programme in Singapore. Proof of vaccination is required for admissions to crèches, kindergartens and primary schools.

All primary school leavers should be given a second dose of MMR vaccine.* It is important to ensure that at least 95% of the children are immunised at one to two years of age. Congenital rubella can only be completely eliminated if every woman in the 15-44 year age group is immunised against the disease. They should be advised to be vaccinated before they are married and plan to have a child.

* The second dose of MMR may be brought forward to ≥6 yrs (Primary school entrants).

Pertussis

Pertussis cases have increased worldwide mostly due to waning immunity or inadequate immunisation. Other potential reasons for this include genetic changes in *Bordetella pertussis* (which make vaccines less effective), decreased potency of pertussis vaccines, greater awareness of pertussis, and improved diagnostic tests. Pertussis in children tend to occur in infants too young to be vaccinated or who had incomplete vaccination. These infected children were mostly contacts of adult index cases within their family. Tdap (Boostrix) instead of Td or child DT is now available for children above four years of age, adolescents, and adults, and can prevent resurgence of pertussis in older children, adult family members and therefore, in infants.

Bacillus Guérin Barre vaccine (BCG)

BCG vaccination was started in mid 1950s in Singapore. All newborns were vaccinated at birth and close to 100% have been vaccinated in the past decade. As of 1st July 2001, BCG revaccination in primary school was discontinued as no additional benefit was found with booster doses. BCG complications range from localized BCGitis or abscess, regional lymphadenopathy, suppurative lymphadenitis and rarely

disseminated BCG infection. Newborn BCG, despite its complications, still is important in protecting against the most serious forms of TB, i.e. TB meningitis and military TB in childhood.

OPTIONAL VACCINES

Influenza

Vaccination is associated with reductions in influenza-related respiratory illness and physician visits among all age groups, hospitalisation and death among persons at high risk, otitis media among children, and work absenteeism among adults.

The effectiveness of inactivated influenza vaccine depends primarily on the age and immunocompetence of the vaccine recipient, and the degree of similarity between the viruses in the vaccine and those in circulation. The majority of vaccinated children and young adults develop high postvaccination hemagglutination inhibition antibody titers. These antibody titers are protective against illness caused by strains that are antigenically similar to those strains of the same type or subtype included in the vaccine.

The vaccine is only indicated for children above six months of age. For children under nine years of age, who have not previously been vaccinated against influenza, they will need two doses of the vaccine given at least one month apart. No effectiveness was demonstrated among children who had received only one dose of influenza vaccine, illustrating the importance of administering two doses of vaccine to previously unvaccinated children aged more than nine years. Children nine years of age or older require only one dose, regardless of their influenza vaccination history. For children under three years old, the dose is 0.25 ml. For children above three years old, the dose is 0.5 ml.

Vaccination with inactivated influenza vaccine is recommended for the following persons who are at increased risk for complications from influenza:

- persons aged ≥50 years;
- residents of nursing homes and other chronic-care facilities that house persons of any age who have chronic medical conditions;
- anyone with chronic disorders of the pulmonary or cardiovascular systems, including asthma (hypertension is not considered a high-risk condition);
- anyone with chronic metabolic diseases (including diabetes mellitus), renal dysfunction, hemoglobinopathies, or immunosuppression (including immunosuppression caused by medications or by human immunodeficiency virus [HIV]);
- Anyone with a neuromuscular condition (e.g., cognitive dysfunction, spinal cord injuries, seizure disorders) that can compromise respiratory function or the handling of respiratory secretions or that can increase the risk for aspiration;
- children and adolescents (aged 6 months-18 years) who are receiving long-term aspirin therapy and, therefore, might be at risk for experiencing Reye syndrome after influenza infection;
- women who will be pregnant during the influenza season; and
- children aged 6-23 months.

Hepatitis A

Hepatitis A vaccine can be given to children aged above 12 months of age. A repeat dose is given 6-12 months later for lifelong immunity. Hepatitis A disease is usually asymptomatic in children below eight years of age, however, it can cause outbreaks especially at child-care centers. This vaccine is therefore indicated in children who attend child care centers, who travel to countries where hepatitis A is endemic and who have chronic liver disorders including hepatitis B carriers.

Twinrix is a combination vaccine that protects against both hepatitis A and hepatitis B and is now licensed for children aged one year and above. For children aged 1-15 years, two doses are given IM with the second dose given 6-12 months later. For persons above 16 years, it is discussed in the section on Adult Vaccination.

Varicella vaccine

Varicella is very contagious and up to 90% of household exposures result in chickenpox illness in family members. The varicella vaccine is given after 12 months of age, although some studies have shown that giving the vaccine after 15 months of age can reduce breakthrough chickenpox. This is a live attenuated vaccine given by the subcutaneous route. For children under 13 years of age, one dose is given; for those above 13 years of age, two doses separated 6-8 wks apart should be given. In the US, due to declining immunity to varicella, a second dose is given at ages four to six years for all children and a catch-up second vaccination for all older children, adolescents, and adults who received only one dose. MMRV (ProQuad®) may be used from 12 months of age.

Rotavirus vaccine

Rotavirus immunisation (Rotarix) is now available for all infants ages 6 to 24 weeks. This vaccine is a live attenuated vaccine containing the human monovalent G1 rotavirus strain. The vaccine is given orally. The current rotavirus vaccine available in Singapore is Rotarix which is given as two doses orally – first dose at 6-14 weeks and second dose at 14-24 weeks of age. The interval between doses should not be less than four weeks. This vaccine has not been shown to increase the risk of intussusception unlike Rotashield, which has been discontinued. The vaccine should not be given to patients with ongoing vomiting, diarrhea, or with known or suspected immune deficiency disease or chronic gastrointestinal disease, including any uncorrected congenital malformation of the gastrointestinal tract. The protective efficacy of the vaccine against any rotavirus gastroenteritis was 73% and 83-91% against severe gastroenteritis.

Human papillomavirus (HPV) vaccine

HPV vaccine (Gardasil) is a quadrivalent vaccine indicated in girls and women aged 9-26 years for the prevention of cervical cancer, cervical and vulvar precancerous or dysplatic lesions, genital warts and infection caused by the HPV types 6, 11, 16 and 18. Types 6 and 11 cause 90% or more of genital warts, and types 16 and 18 cause 70% of cervical cancer. The vaccine is given IM in a three-dose schedule at 0, 2, and 6 months, with a minimum dose interval of four weeks. This vaccine is best given before the patient becomes sexually active. This vaccine will be further mentioned under Adult Vaccination.

Pneumococcal conjugate vaccine

The vaccine currently available as Prevenar, which contains seven of the most common invasive serotypes (serotypes has a protective efficacy of more than 90% against invasive pneumococcal disease, 50-60% of pneumococcal pneumonia and 30% of otitis media). The vaccine is given as a four dose (3 primary plus 1 booster) schedule for children starting vaccination at six months or under, three doses (2 primary plus 1 booster) for children between 7-11 months, two doses for children 12-23 months and one dose for children above two years of age. This vaccine currently covers about 80% of all invasive pneumococcal strains in children below the age of five years old. It is the preferred vaccine to the pneumococcal polysaccharide vaccine (Pneumo 23) as it reduces nasopharyngeal carriage, thereby, decreases transmission and improves herd immunity, reduces antibiotic-resistant pneumococcal disease, and has the additional ability to reduce transmission to adults. Therefore, it reduces the invasive disease in adults and the elderly.

Meningococcal vaccine

This vaccine is not routinely recommended due to the low incidence of the disease. However, travelers to countries experiencing epidemics should be given the meningococcal vaccine. This is available locally as the quadrivalent polysaccharide vaccine for children above two years old. The conjugate meningococcal vaccine for children above two months of age is available only upon request from the drug manufacturer.

LEARNING POINTS

- **Vaccination not only protects children against infectious diseases, but potentially may eradicate the disease.**
- **Good understanding of injection techniques, site selection, minimum intervals, and simultaneous vaccinations ensures optimal immunologic response.**
- **When children have missed many vaccine doses, it is important to bring them up to date as quickly as possible.**
- **The myth of autism being caused by MMR vaccine should be forever dispelled.**