Immunisations – New Vaccines, Schedules, Catch-ups and Contra-indications

Ms L. Baker
Dip Pharm
❒ Managing Director, Amayeza Info Services cc

Vaccination has greatly reduced the burden of infectious diseases worldwide. According to the World Health Organization (WHO), only clean water has had a greater impact on the world's health.[1,2] To maximise this benefit, it is essential to ensure that the vaccines are available to all and are stored and administered correctly.

South Africa is in the fortunate position that many of the new vaccines are available, some new entities and some combination vaccines, both of which have improved the fight against infectious diseases.

COMBINATION VACCINES

Combination vaccines allow protection of more infections with fewer injections.

- **Six-in-one vaccines (DTaP-IPV-HBV-/Hib)**. These protect against diphtheria, tetanus, pertussis, *Haemophilus influenzae* type b (Hib), poliomyelitis and hepatitis B. This type of vaccine is registered for use for the primary immunisation schedule as well as for a booster in children under the age of two years.[3] A new, fully liquid product has recently been registered that can be used up to the age of 5 years.[4]
- **Diphtheria, tetanus, acellular pertussis and polio (TdaP-IPV) vaccines**. These vaccines are registered as a booster for adolescents and adults who have had their primary series. Studies have shown that immunity to these antigens, especially to pertussis, wanes with time and a booster is required to maintain immunity.[5,6]
- **Hepatitis A and typhoid vaccine**. These two infections have a common route of transmission and there is a considerable overlap in the distribution of the two diseases, resulting in many travellers requiring protection against both. For these reasons, a combination vaccine has been developed. It is registered from 16 years of age and should be given 14 days before travelling. A booster of hepatitis A is required for long-term protection of hepatitis A, given at least six months later. In subjects who remain at risk of typhoid fever, revaccination against typhoid fever should be carried out with a single dose of purified Vi polysaccharide typhoid vaccine with an interval of not more than three years.[7]

NEW VACCINE ENTITIES

- **Conjugated pneumococcal vaccines**. Although vaccines against pneumococcal infections have been available for many years, they are manufactured from the polysaccharide capsule of the bacteria and as such, are associated with poor or absent immunogenicity in children under two years of age and failure at any age to induce an anamnestic antibody response upon revaccination, as they induce a T cell-independent response. They also have no Impact on carriage rate.[8] These problems have been overcome by conjugating the polysaccharide capsule to a molecule that is immunogenic (such as a tetanus or diphtheria protein). These conjugated vaccines are now indicated for babies from the age of six weeks. One of the vaccines contains 10 serotypes, some of which are conjugated to a nontypeable *Haemophilus influenzae* (NTHI) protein and has some protection against NTHI infections.[8] The product that contains 13 serotypes has recently been registered for adults over the age of 50 years.[9]
- **Human papillomavirus (HPV) vaccines**. Cervical cancer, which is caused primarily by the human papillomavirus,

is the second most common cause of cancer amongst women aged 15-44 years. There is also growing evidence of HPV being a relevant factor in other anogenital cancers (anus, vulva, vagina and penis) and head and neck cancers.[10] Two prophylactic vaccines are available, one against types 16 and 18 (which are responsible for 70% of cervical cancer worldwide) and a quadrivalent one against types 6, 11 (which are responsible for genital warts) as well as 16 and 18. These vaccines are made using a recombinant technique to form virus-like particles (VLPs) which contain no DNA. These vaccines are most effective if given to persons prior to onset of sexual activity. Three doses are required (0, 1 and 6 months for the bivalent vaccine and 0, 2 and 6 months for the quadrivalent vaccine). Both vaccines are indicated for girls from nine years of age and the quadrivalent vaccine is also indicated for boys from nine years of age. In March 2014, an HPV vaccine was introduced into the school health programme. All girls in grade 4 in public schools will get two vaccines – six months apart. Studies have indicated that the immunogenicity of two doses given between the ages of nine and 14 years is as effective as three doses in older adolescents.[11]

- **Zoster vaccine**. Herpes zoster, a reactivation of chickenpox, is associated primarily with older age and immunosuppression. The most common complication is post-herpetic neuralgia and this adds significantly to the morbidity of this condition. A vaccine is now available which is indicated for adults aged 50 years and older. It is a live attenuated vaccine that contains the same varicella zoster virus as the varicella vaccines but in a much higher titre (14 times stronger). A single subcutaneous dose is recommended for adults over the age of 50 years, even if they have already had an attack of shingles.[12]

NEW INDICATIONS

- **Hepatitis A and B combined vaccine.** A combined hepatitis A and B vaccine for adults (16 years and older) has been available for a number of years. It contains a paediatric dose of hepatitis A (720 ELISA units) and an adult dose of hepatitis B (20 µg). The standard schedule is 0, 1 and 6 months. (There is also an accelerated schedule of 0, 7 and 21 days and a booster at 12 months). This product has now been registered for children from one to 15 years of age and the schedule is two doses – 0 and 6 months.[13]

IMMUNISATION SCHEDULES

The South African expanded programme on immunisation (EPI) is the most comprehensive one in developing countries and all children have the benefit of being protected from many life-threatening infections. There are also a number of additional vaccines or combinations available in the private sector and more than one schedule is therefore possible.

Refer to Table 1 for recommended immunisation schedules. Notes to Table 1:

General guidelines:
(0) Birth dose which does not count as part of primary series
(1) First dose in a series
(2) Second dose in a series
(3) Third dose in a series
(4) Fourth dose – a booster

Abbreviations
- **OPV:** Oral polio vaccine
- **BCG:** Bacille Calmette-Guerin vaccine
- **HBV:** Hepatitis B vaccine
- **RV:** Rotavirus vaccine
- **Td vaccine:** Tetanus and reduced amount of diphtheria vaccine
- **TdaP-IPV:** (Quadrivalent): Tetanus and reduced amount of diphtheria vaccine with acellular pertussis and inactivated polio vaccine
- **DTaP-IPV/Hib:** (Pentavalent): Diphtheria, tetanus, acellular pertussis/ inactivated polio vaccine and *Haemophilus influenzae* type b
- **DTaP-IPV-Hib-HBV:** (Hexavalent): Diphtheria, tetanus, acellular pertussis/ inactivated polio vaccine/*Haemophilus influenzae* type b and hepatitis B vaccine - already mixed
- **DTaP-IPV-HBV/Hib:** (Hexavalent): Diphtheria, tetanus, acellular pertussis/ inactivated polio vaccine/hepatitis B and *Haemophilus influenzae* type b vaccine
- **PCV:** Pneumococcal conjugated vaccine

Table 1. Recommended immunisation schedules

Age of child	EPI schedule	Age of child	Option 3 in Private
At birth	OPV(0)	**At birth**	OPV(0)
	BCG		BCG
6 weeks	OPV(1)	**2 months**	OPV(1)
	RV (1)		RV (1)
	DTaP-IPV/Hib[1] (1)		DTaP-IPV-Hib-HBV (1) **or** DTaP-IPV-HBV/Hib (1)
	HBV[1](1)		PCV (1)
	PCV(1)		
10 weeks	DTaP-IPV/Hib (2)	**3 months or 4 months**	DTaP-IPV-Hib-HBV(2) **or** DTaP-IPV-HBV/Hib (2)
	HBV(2)		PCV (2)
			RV[2](2)
14 weeks	RV (2)	**4 months or 6 months**	DTaP-IPV-Hib-HBV(3) or DTaP-IPV-HBV/Hib (3)
	DTaP-IPV/Hib (3)		
	HBV(3)		PCV (3)
	PCV(2)		RV[2] (2 or 3)
9 months	Measles vaccine(1)	**9 months**	Measles vaccine
	PCV(3)		
18 months	DTaP-IPV/Hib (4)	**12-15 months**	Chickenpox (varicella) vaccine[3] (1)
			MMR (1)
			Hepatitis A vaccine (repeat 6 months later)
			PCV (4)[4]
	Measles vaccine (2)	**18 months**	DTaP-IPV/Hib or DTaP-IPV-Hib-HBV (3) or DTaP-IPV-HBV/Hib (3)[5]
6 years	Td vaccine	**5-6 years**	DTaP **or** TdaP-IPV vaccine
			MMR (2)
			Chickenpox (varicella) vaccine[3] (2)
9 years	HPV[6]	**9 years**	HPV[7](from 9 years)
12 years	Td vaccine	**12 years**	TdaP-IPV vaccine [8]

- **MMR:** Measles, mumps and rubella
- **HPV:** Human papillomavirus vaccine

Referenced notes

1. The pentavelent vaccine + HBV will be replaced by the fully liquid hexavalent vaccine for all doses in the near future.
2. If pentavalent rotavirus vaccine is used, then three doses are required: 6, 10 and 14 weeks. If monovalent vaccine is used, only two doses are given: 6 and 14 weeks.
3. Chickenpox vaccine can be given any time from nine months of age, but is probably most effective if given over the age of 12 months. If not given on the same day as measles vaccine, must then be separated by at least one month.
4. When PCV10 is used, the fourth dose can be given from 9.5 months provided it has been six months since the last dose.
5. A booster of HBV is not routinely recommended in South Africa.
6. HPV – bivalent vaccine for girls only. Two doses six months apart. From February 2014.
7. HPV – quadrivalent vaccine – for boys and girls. Course consists of two doses six months apart for children 9-13 years of age, or three doses – 0, 2 and 6 months for older adolescents. Bivalent vaccine – for girls only. Course consists of two doses six months apart for children 9-13 years of age or three doses – 0, 1 and 6 months for older girls.
8. If not given at six years, as products are currently only licensed as a single dose.

CATCH-UP SCHEDULES

Ideally, children should have all their vaccinations on time, according to the recommended schedule, but unfortunately many children either miss a couple of doses or do not get any for a number of reasons. When the opportunity arises, the schedule should be completed. Each situation involving a catch-up is unique and needs to be evaluated on an individual basis. Decisions need to be made on how best to protect the child with what is available. A number of factors need to be considered and these include:

How many doses are required?

A single dose of a live vaccine is usually sufficient to prime the immune system. Additional doses are given to ensure that everyone seroconverts.

For inactivated vaccines, a series of doses is required to prime the immune system (usually three doses) and boosters are given to maintain immunity. The older a child gets, the fewer doses may be required. For example, if the fourth dose of tetanus and diphtheria is given after four years of age, a fifth dose is not required. Conjugated pneumococcal and *Haemophilus influenzae* type b vaccines also require fewer doses as the child gets older.[14]

If a dose is missed or the interval between doses is extended, it is not necessary to restart the schedule, the missed doses should be given following the correct intervals going forward – efficacy will not be diminished, but it will take longer before optimal immunity is achieved.[14]

Is the vaccine still required at this age?

The majority of pneumococcal and *Haemophilus influenzae* type b infections occur before the age of five years and the vaccines are therefore not necessary in healthy children over the age of five years.[14,9]

Is it still safe to give the vaccine at this age?

Rotavirus vaccines should only be given from the age of six weeks up until 24 weeks for monovalent vaccine and until 32 weeks for the pentavalent vaccine, due to concerns regarding intussusception.[15]

Vaccines containing paediatric diphtheria (higher dose) are usually confined to children aged seven years and younger in order to minimise the risk of severe adverse effects.

Is the vaccine registered for use at this age?

Most of the current paediatric vaccines containing diphtheria, tetanus, pertussis, Hib, polio (with or without hepatitis B) are only licenced for use up until the age of two years and this makes "catch-ups" in children over the age of two years a challenge.[3] A new combination vaccine was

Table 2. Private sector guide for unvaccinated child up to 5 years of age

Age	Product	Primary Series	Booster series
6 weeks to 6 months	DTaP-IPV-Hib-HBV OR DTaP-IPV-HBV/Hib (after 8 weeks)	3 doses – 4 weeks apart	1 dose – at 18 months of age (HBV not necessary). TdaP-IPV at 4-6 years of age
	Rotavirus vaccine	Monovalent vaccine – 2 doses – at least 4 weeks apart (last dose before 24 weeks) Pentavalent vaccine – 3 doses at least 4 weeks apart (last dose before 32 weeks)	none
	PCV	3 doses – 4 weeks apart	1 dose – 12-15 months
6 months to 12 months	DTaP-IPV-Hib-HBV OR DTaP-IPV-HBV/Hib	3 doses – 4 weeks apart	1 dose – at 18 months of age TdaP-IPV at 4-6 years of age
	Measles	1 dose	MMR at 15-18 months of age MMR at 5-6 years
	PCV	2 doses – 4 weeks apart	1 dose after 12 months of age and at least 2 months after second dose
12 months to 24 months	DTaP-IPV-Hib-HBV OR DTaP-IPV-HBV/Hib	3 doses – 4 weeks apart	1 dose of DTap-IPV/Hib 6 months later (if under 24 months) OR DTaP-IPV-Hib-HBV. TdaP-IPV at 4-6 years of age
	Hepatitis A	1 dose any time from 12 months of age	1 dose 6-12 months later
	MMR	1 dose	1 dose at 4-5 years of age
	Varicella vaccine	1 dose any time from 9-12 months of age	1 dose at least 4-6 weeks after first dose but usually at 5-6 years of age
	PCV	2 doses at least 2 months apart	
>24 months to 5 years	DTaP-IPV-Hib-HBV	3 doses – 4 weeks apart	1 dose – 6 months later. TdaP-IPV at 4-6 years of age. (not necessary if fourth dose given after 4 years of age)
	HBV	3 doses – 4 weeks apart	
	MMR	1 dose	1 dose at 5-6 years of age but at least 4 weeks later
	PCV	1 dose	
	Hepatitis A	1 dose	1 dose 6-12 months later.
	Varicella vaccine	1 dose	1 dose at least 4-6 weeks after first dose but usually at 5-6 years of age

recently registered, which can be used up to the age of five years.[4]

Products containing TdaP-IPV are only registered as a booster from the age of three or four years (depending on which product) and not for the primary series.[5, 6]

The "catch-up" guidelines for a child in the public sector will differ because of different schedules and available products (see Table 2).

The BCG (Bacille Calmette-Guerin) vaccine is usually given at birth. If missed, it can be given up until the age of one year. (Once a child has been living in South Africa for a year, it will have been in contact with tuberculosis and then the vaccine is of little value. The benefit of the vaccine is also primarily in young infants.)

It is, however, not harmful or contra-indicated and can be given with other routine vaccines.

Routine vaccination does not end in childhood. Adults may require booster doses of vaccines received during childhood, as well as other vaccines depending on their previous vaccination history, any underlying health conditions, lifestyle, occupation or travel plans (see Table 3). Travel vaccines will not be discussed here.

CONTRA-INDICATIONS

There are very few true contra-indications and precautions for vaccines.[14]
These include:

- A severe (anaphylactic) allergic reaction to a vaccine component or following a prior dose of a vaccine.
- Encephalopathy not due to another identifiable cause occurring within seven days of pertussis vaccination.

Table 3. Recommended adult vaccines

Vaccine	Recommendations
Hepatitis A	For those who are susceptible, two doses separated by at least six months.
Hepatitis B	No previous doses – three doses according to product schedule, especially high risk groups. A combination Hep A/Hep B vaccine can be used if protection against both viruses is needed.
Human papillomavirus	Three doses (see text above)
Influenza	Annually for all adults but especially for high-risk groups.
Measles, mumps, rubella	For those who are susceptible – two doses separated by at least one month. One dose is sufficient for rubella protection. Have at least one month prior to falling pregnant.
Meningococcal	One dose given to those at high risk – travellers to meningitis belt and anyone going to live in close quarters/dormitories.
Pneumococcal (PCV)	>50 years. One dose
Pneumococcal (PPSV)	>65 years and certain high-risk groups. Revaccination not normally recommended
Tetanus, diphtheria, pertussis, polio booster	One dose and thereafter a tetanus booster every 10 years
Varicella	For those who are susceptible – two doses given at least six weeks apart.
Zoster	>50 years. One dose.

Table 4. Intervals between doses of vaccines and immunoglobulins[20]

Antigen or immunoglobulin combination	Recommended minimal intervals between doses
Two or more inactivated vaccines	Can be administered simultaneously or at any interval between vaccines
Inactivated and live vaccine	Can be administered simultaneously or at any interval between vaccines
Two or more live, intranasal or injectable vaccines (not applicable to oral vaccines)	Four week minimal interval if not administered simultaneously
Inactivated vaccine and immunoglobulins	Can be administered simultaneously or at any interval between doses. Exception is rabies immunoglobulin that should not be given more than 7 days after the first vaccine dose.[21] Administer vaccine and immunoglobulin in opposite limbs.
Live vaccine and immunoglobulins	Must not be administered simultaneously. If vaccine first, wait 2 weeks before giving the immunoglobulin. If immunoglobulin first, wait 3 or more months (depending on type and dose of immunoglobulin) before giving the vaccine.

- Live vaccines should generally be avoided during pregnancy.
- Live vaccines are contra-indicated in severe immunosuppression.

For rare contra-indications to specific vaccines, please refer to the relevant package inserts.

Some conditions are considered permanent precautions to further doses of paediatric pertussis-containing vaccines. These include:

- A temperature of >40°C or higher within 48 hours of a dose.
- Collapse or shock-like state (hypotonic hypo-responsive episode) within 48 hours of a dose.
- Persistent inconsolable crying lasting three or more hours occurring within 48 hours of a dose.
- A seizure, with or without fever, occurring within three days of a dose.

SOME COMMON MYTHS

- **Children with egg allergy should not have a measles vaccine**
  Data suggest that anaphylactic reactions to measles- and mumps-containing vaccines are not associated with hypersensitivity to egg antigens but to other components of the vaccines (such as gelatin) and children with egg allergies should be vaccinated with a measles-containing vaccine.[16] A contra-indication to the vaccine is an anaphylactic reaction to a previous dose of the vaccine.
- **The combination MMR vaccine causes autism**
  This myth is based on a study on 12 children, which was found to be seriously flawed and several very large independent studies on collectively millions of children have subsequently found no association between MMR and autism.[16, 17, 18]
- **Thiomersal in the vaccines, specifically the MMR vaccine, causes autism**
  Live vaccines, of which MMR is one, do not contain preservatives as this would inactivate the vaccine. Thiomersal is a mercury-based preservative that is found in very few vaccines today. There is no evidence to support any link between thiomersal and autism.[17]
- **If a child is on an antibiotic, you must not administer a vaccine.**
  Antibiotics would only interfere with a live bacterial vaccine (and the only one in South Africa is BCG), as antibiotics have no effect on viruses or on

killed, inactivated vaccines. However, if the child is acutely ill, it is preferable to defer vaccination.[14]

- **Giving too many vaccines at one time will overload the system**
  Scientific evidence shows that giving several vaccines at the same time has no adverse effect on a child's immune system. Children are exposed to several hundred foreign substances that trigger an immune response every day. The simple act of eating food introduces new antigens into the body, and numerous bacteria live in the mouth and nose. A child is exposed to far more antigens from a common cold or sore throat than they are from vaccines.[19]
- **True immunity can only be obtained through natural immunity. Vaccines suppress the immune system.**
  A vaccine contains either the whole causative organism (either killed or weakened so that it can't cause disease), or noninfectious parts of the organism, and thus interacts with the immune system to produce an immune response similar to that produced by the natural infection.[18] Immunoglobulins on the other hand, do not stimulate the immune system and provide passive immunity which is only temporary.

QUICK NOTES

- Do not administer vaccines or rabies immunoglobulin in the buttocks.
- Separate live vaccines and immunoglobulins by three months or more (see Table 4).[14]
- There is no limit to which vaccines or how many can be administered at the same time.
- An interrupted schedule need not be restarted.
- If the immunisation status is unknown, assume that the patient is unvaccinated and administer the required vaccines.

CONCLUSION

In order to maintain and improve on the success of vaccination, efforts should be made to ensure that all those requiring protection receive the vaccines on time, and complete the schedules. When additional vaccines become available, health professionals should familiarise themselves with the products in order to use them appropriately.

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