What's new in childhood immunisation

This article provides an update on the issues facing our existing immunisation program, the reasons behind the new Australian Standard Vaccination Schedule, and the future of vaccines.

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Since the introduction of childhood vaccination for diphtheria in 1932 and the widespread use of vaccines to prevent tetanus, pertussis and poliomyelitis in the 1950s, Australia has witnessed a 99% decline in deaths from vaccine preventable diseases. In 2000, Australia had the lowest measles notification rate on record, and with dramatic reductions in rubella and *Haemophilus influenzae* type B (Hib) disease we are now close to their elimination. High vaccination rates in Australia have allowed this control of vaccine preventable diseases; however, pertussis continues to be responsible for significant morbidity and deaths in infants. Also, while the incidence of vaccine preventable diseases declines and new vaccines are marketed, adverse events following vaccination assume greater public and provider attention.

Some of the issues addressed in this article are in the 8th edition of *The Australian immunisation handbook*. The handbook, including the Australian Standard Vaccination Schedule (Table 1), was approved by the NHMRC in September 2003 and is now available in hard copy (telephone 1800 020 103 ext. 8654) or online (http://immunise.health.gov.au/handbook.htm).[1]

Issues for the existing program and the new vaccination schedule

Pertussis

Addressing the adolescent disease burden

Pertussis is now a problem in two broad age groups in Australia: those over the age of 10 years and those under the age of 5 months.[2] The former were born in an era of low vaccination coverage, exacerbated by waning immunity. Since the replacement in 1995 of the diphtheria–tetanus vaccination at age 4 to 5 years with one that also contains pertussis vaccine, the age peak of pertussis has moved progressively to older age groups, and now adolescents aged 13 to 18 years have the peak

IN SUMMARY

- **The new Australian Standard Vaccination Schedule includes pneumococcal and meningococcal conjugate vaccines and the varicella vaccine.**
- **The new schedule omits the DTPa booster dose at 18 months and replaces it with a low dose (dTpa) booster for adolescents (at 15 to 17 years).**
- **Inactivated poliomyelitis vaccine (IPV) will maintain polio immunity without vaccine-associated paralytic poliomyelitis, and a polio booster at 15 to 17 years of age is no longer recommended.**
- **A two-dose adult-strength hepatitis B vaccine can be used in adolescents.**
- **Pentavalent and hexavalent DTPa-containing vaccines will be available for use in the primary vaccination schedule.**
- **There is very good evidence that measles–mumps–rubella vaccine does not cause autism. Two doses of the vaccine provide lifelong immunity.**

incidence. School-based outbreaks of pertussis have occurred.[3]

Adolescents are less often diagnosed or hospitalised and are a potential pool capable of transmitting pertussis, most importantly to unvaccinated infants. The youngest infants, who are too young to have received two or more doses of the diphtheria–tetanus–acellular pertussis (DTPa) vaccine, are a particular concern because they are more likely to experience severe disease, resulting in hospitalisation or death. Therefore, a priority issue for Australia is to reduce the burden of pertussis among susceptible adolescents.

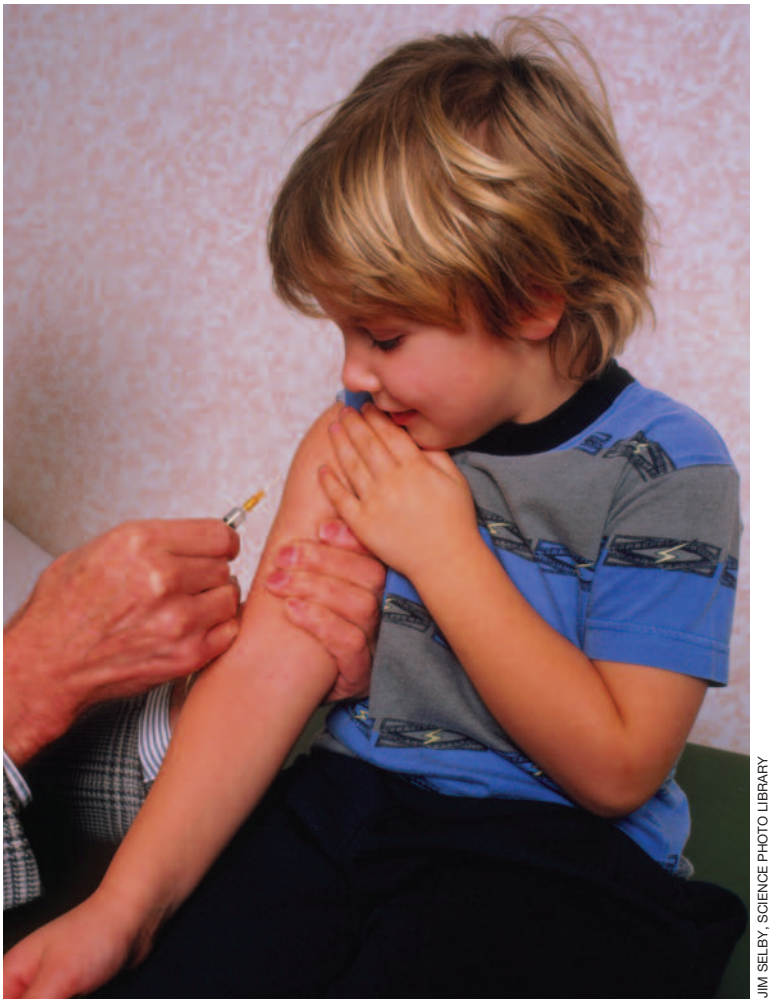
The DTPa vaccine licensed for use in children is not suitable for use as a booster in adolescents or adults because of a high rate of local reactions, and so a reduced antigen content vaccine (designated 'dTpa') has been developed. The current licensed vaccine in Australia is Boostrix. It is indicated for use as a booster vaccination against diphtheria, tetanus and pertussis in individuals aged 10 years and older. Boostrix was developed from the paediatric DTPa vaccine Infanrix and contains approximately one-third of the pertussis antigen concentrations and lower concentrations of diphtheria and tetanus toxoid than Infanrix.

In summary, to reduce the burden of disease in adolescents, a low dose dTpa vaccine (e.g. Boostrix) is recommended as a single dose at 15 to 17 years of age instead of the current ADT vaccine.

Minimising local reactions after booster doses

Systemic adverse reactions are uncommon after five doses of DTPa and are much less frequent than reactions seen following five doses of whole cell pertussis DTP (DTPw). However, DTPa is not completely free of side effects, and it is well established that the incidence of local reactions (redness, swelling and pain) increases with increasing number of doses of DTPa. Localised swelling greater than 5 cm occurs in 10 to 20% of children after a fourth or fifth dose of DTPa, and entire limb swelling in 1 to 2%.[4-6]

Recent evidence has indicated that three doses of acellular pertussis vaccine in the first year of life provide good protection until the age of 6 years,[7] and so a DTPa booster at age 18 months is not essential. Following the decision to remove this dose from the vaccination schedule, it will be important to reassure parents whose children have experienced a local reaction at the 18-month dose about the importance of the booster dose at age 4 years prior to school entry.



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In summary, in view of the prolonged immunity now known to result from a three-dose primary course of DTPa, the booster dose at age 18 months is omitted and the fourth dose is given at 4 years of age. It is anticipated that postponing the fourth dose of DTPa until 4 years of age will reduce the proportion of children experiencing extensive local reactions, with no reduction in protection against pertussis.

Poliomyelitis

Because of the success of the oral polio vaccine (OPV), there have been no reported cases of wild poliomyelitis in Australia since 1978, and the western Pacific region (including Australia), was

continued

Table 1. Australian Standard Vaccination Schedule[1]

Age	Vaccine							
Birth	Hep B							
2 mths	Hep B[a,b]	DTPa	Hib[d,e]	IPV		7vPCV[g]		
4 mths	Hep B[a,b]	DTPa	Hib[d,e]	IPV		7vPCV[g]		
6 mths	Hep B[a]	DTPa	Hib[d]	IPV		7vPCV[g]		
12 mths	Hep B[b]		Hib[d,e]		MMR		MenCCV	
18 mths					VZV	23vPPV[h]		
2 yrs								
4 yrs		DTPa		IPV	MMR			
10–13 yrs	Hep B[c]				VZV[f]			
15–17 yrs		dTpa						
≥50 yrs		dT				23vPPV		Influenza (annual)
≥65 yrs						23vPPV		Influenza (annual)

Note: Vaccines currently funded under the National Immunisation Program are shaded yellow. Vaccines shaded green are recommended but not funded. Vaccines shaded purple are recommended and funded only for Aboriginal and Torres Strait Islander persons.
Key: Hep B[a], B[b] – alternative schedules for hepatitis B vaccine according to combination formulation used. Hep B[c] – three-dose primary schedule for hepatitis B for adolescents not vaccinated in childhood. Hib[d], Hib[e] – alternative schedules for Hib vaccine depending on formulation used. VZV[f] – varicella vaccination only for children without a history of previous clinical varicella or vaccination. 7vPCV[g] – pneumococcal conjugate vaccine recommended for all infants, funded only for Aboriginal and Torres Strait Islander children and children with certain medical risk factors. 23vPPV[h] – pneumococcal polysaccharide vaccine recommended only for Aboriginal and Torres Strait Islander children residing in Western Australia, Northern Territory, South Australia and Queensland. For further explanation, see reference 1.

declared polio free in 2000. OPV's effectiveness has been due in part to its ability to induce intestinal immunity and to confer secondary community protection and its ease of administration, availability and low cost.

Vaccine-associated paralytic poliomyelitis

OPV is a live attenuated vaccine, and very rarely it causes vaccine-associated paralytic poliomyelitis. The risk of this is approximately one in 2.4 million doses administered. The risk is higher in a population with low vaccine coverage, and higher after the first dose than subsequent doses. Based on the incidence in the USA, Australia should see one case of vaccine-associated paralytic poliomyelitis every three years (one case per 750,000 first doses administered); however, the last reported Australian case was in an unvaccinated mother of a recently vaccinated infant, whose onset of illness was in December 1994.

There is no risk of vaccine-associated paralytic poliomyelitis with inactivated poliomyelitis vaccine (IPV) because inactivation of the poliovirus by formalin renders it noninfectious; however, this option is more costly. It has been estimated that the use of a monovalent IPV schedule in Australia would cost $50 million per case of vaccine-associated paralytic poliomyelitis prevented. However, the use of IPV in a combination vaccine is cheaper at $17 million per case prevented, so, subject to availability, use of an IPV combination vaccine has been recommended by the Australian Technical Advisory Group on Immunisation.

In summary, to maintain polio immunity without vaccine-associated paralytic poliomyelitis, IPV is recommended in a combination vaccine – such as the quadravalent, pentavalent or hexavalent vaccines (see later section) – to replace OPV for the three-dose primary series (2, 4 and 6 months of age) and for the booster dose at 4 years of age. The fifth dose of OPV, previously scheduled at 15 to 17 years of age, is no longer recommended because immunity from four doses is lifelong.

Meningococcal C disease

The incidence of meningococcal C disease varies by State and age group across Australia. In 2000, serogroup C was more common than B in people aged over 5 years. Serogroup B predominated in children under 5 years in all parts of Australia except Victoria and New South Wales. There are two types of meningococcal vaccines licensed for use in Australia: conjugate vaccines (serogroup C only) and polysaccharide vaccines (types A, C, W135, Y). There is currently no vaccine available for serogroup B disease in Australia. The national meningococcal C vaccination program commenced in 2003. At present, preschool children aged 1 to 5 years are eligible to receive a single dose of the meningococcal conjugate serogroup C vaccine at no cost, and schoolchildren up to 19 years of age are being vaccinated under a school-based program.

Meningococcal conjugate serogroup C vaccines

Currently three conjugate vaccines are available: Meningitec, Menjugate and NeisVac-C. Conjugation refers to the

process of chemically linking the meningococcal serogroup C antigen to a carrier protein, such as diphtheria (Menjugate and Meninigtec) or tetanus toxoid (Neis-Vac-C), to produce a T-cell dependent response and hence immune memory. It is expected that protection against serogroup C will be lifelong. Each of the vaccines is inactivated, considered safe and similarly effective.

At present the conjugate vaccine is on the schedule and funded as a single dose at 12 months of age. It can be administered at the same time, in a separate site, as other vaccines. If the meningococcal polysaccharide vaccine has been given, the conjugate vaccine can be administered after an interval of six months.

Meningococcal polysaccharide vaccines

The polysaccharide vaccines provide protection against serogroups A, C, W135 and Y. Two vaccines are available: Mencevax ACWY and Menomune. As there is currently no serogroup A disease in Australia, these vaccines are recommended for travellers to areas where these serogroups are more common. In contrast to the conjugate vaccines, the polysaccharide vaccines have several disadvantages:

- a diminished immune response in children under the age of 2 years
- no immune memory, so no lifelong protection and therefore repeated doses are required
- hyporesponsiveness following a second or third dose.

Measles elimination

Long term measles control necessitates continued high vaccination coverage with the routine two-dose schedule. In the United Kingdom, concern about a suggested link between measles–mumps–rubella vaccine and autism has caused a fall in vaccination rates, resulting in outbreaks of measles and mumps in some groups of children. Concern has also spread to Australia, especially following media coverage. However, a large number of high quality studies have all failed to demonstrate a link between the vaccine and autism. Fact sheets appropriate for parents can be found at the Immunise Australia website (http://immunise.health.gov.au/faq.htm).

Hepatitis B vaccination: alternative regimen for adolescents

Adolescents vaccinated with the 10 μg (adult) hepatitis B vaccine (H-B-Vax II) administered in a two-dose regimen at 0 and 4 to 6 months develop similar protective antibody levels compared with those having the three-dose regimen with the 5 μg (paediatric) preparation at 0, 1 and 6 months. Therefore a two-dose option using H-B-Vax II (adult) can be used as an alternative to the standard three-dose schedule for adolescents aged 11 to 15 years of age and is suggested in the 8th edition of the immunisation handbook.

New vaccines

Several vaccines have been licensed for use in Australia over the past 10 years, including the pneumococcal conjugate vaccine, varicella vaccine, DTPa combination vaccines and hepatitis A combination vaccines. The following sections discuss each of these vaccines. At present, the pneumococcal conjugate and varicella vaccines are recommended on the standard vaccination schedule but are not publicly funded, so the responsibility rests on doctors and parents to make risk-based decisions.

Pneumococcal conjugate vaccine

Infections caused by *Streptococcus pneumoniae* include otitis media, sinusitis, pneumonia, septicaemia and meningitis. About 200 cases of pneumococcal meningitis occur each year in Australia, making *Streptococcus pneumoniae* the leading cause of meningitis in children under 5 years of age. Children aged under 1 year have the highest risk of pneumococcal meningitis, which has a high case-fatality ranging from 10 to 30% (this may be as high as 80% in the very elderly). As the incidence is much higher in Aboriginal and Torres Strait Islander children and those with predisposing medical conditions, a publicly funded pneumococcal conjugate vaccine program for these groups was commenced urgently in 2001.

The pneumococcal conjugate vaccine (7vPCV; Prevenar) is composed of seven pneumococcal antigens that cause over 85% of invasive disease in nonindigenous children under 5 years old. 7vPCV is now licensed in Australia for infants and children aged 6 weeks to 9 years. Efficacy data from a pivotal trial found greater than 95% protective efficacy against invasive pneumococcal disease caused by the serotypes contained in the vaccine. Other types of pneumococcal infection (pneumonia and otitis media) not associated with a positive sterile site culture are also reduced by 7vPCV, but the evidence is either for lower efficacy (otitis media) or less well established (pneumonia).

At present, pneumococcal conjugate vaccines are free of charge for Aboriginal and Torres Strait Islander children and those with predisposing medical conditions. For other children, vaccination should be encouraged but each dose of the vaccine costs $130 to $150. Recommended dosing schedules are shown in Table 2.

Varicella vaccination

There are approximately 240,000 cases, 1500 hospitalisations and seven deaths each year from varicella in Australia. The highest rates of hospitalisation occur in children under 4 years of age. Two live attenuated varicella vaccines, Varilrix and Varivax Refrigerated, are registered for use in Australia. Vaccination against varicella would significantly decrease its morbidity and so it is included on the standard vaccination schedule, as a single dose at 18 months of age. At present the vaccine is not funded and costs over $40 per dose. Not only is cost effectiveness a consideration, the future impact of vaccination on

herpes zoster incidence is significant.

Herpes zoster, resulting from a reactivation of varicella, is uncommon before the age of 12 years (1% of cases), and most cases (81%) occur over the age of 40 years. Two epidemiological studies from the United Kingdom suggest that re-exposure to natural varicella may help prevent herpes zoster, presumably by boosting immunity. A study using mathematical modelling has predicted that following the introduction of varicella vaccination, naturally infected persons would have less opportunity to be exposed to wild varicella–zoster virus, and therefore less boosting effect may occur. This may result in an increase in the incidence of herpes zoster, especially in the younger age groups, and an increase in morbidity and cost. However, as the vaccine strain of varicella–zoster virus causes herpes zoster significantly less frequently than the wild virus, not only varicella but also herpes zoster could ultimately be eliminated.

It must also be emphasised that there is no direct proof that herpes zoster epidemiology will be altered by the introduction of varicella vaccination. Indeed, current surveillance in the USA shows no change in herpes zoster incidence after five years of routine vaccination. It is also likely that a higher dose formulation of varicella vaccine will prove useful in preventing zoster when given to older adults.

At present, varicella vaccination is recommended as a single dose for children aged 12 months to 13 years. Children 14 years and over require two doses, one to two months apart. People with a reliable history of varicella should be considered immune and do not require serological confirmation or vaccination. If in doubt, there is no harm in vaccinating those who have had natural varicella. Varicella vaccine can prevent or modify infection if given to exposed individuals within five days of a varicella contact.

Table 2. Recommended 7vPCV dosing schedule

Age at first dose	Number of doses*	Additional doses†
ATSI children† and children under 2 years with no specified medical risk factors		
2 to 6 months	3	None
7 to 17 months	2	None
18 to 23 months	1	None
Children with specified medical risk factors		
2 to 6 months	3	7vPCV booster dose at 12 months. Give 23vPPV at 4 to 5 years
7 to 11 months	2	7vPCV booster dose at 12 months or at least two months after last dose (whichever is the latest). Give 23vPPV at 4 to 5 years
12 to 59 months	2	No further 7vPCV doses. Give 23vPPV at 4 to 5 years

ATSI = Aboriginal and Torres Strait Islander. 7vPCV = pneumococcal conjugate vaccine (Prevenar). 23vPPV = pneumococcal polysaccharide vaccine (Pneumovax).
*Optimal interval ≥ two months. †Some areas of Australia have different specified vaccination schedules for ATSI children. Consult with your State and Territory Health department.

Combination vaccines

The ideal vaccine would be a single dose, encompassing all antigens, given orally at birth and providing lifelong protection. This now seems unlikely to be achieved, but the new combination vaccines are a step in this direction. Although multi-combination vaccines and reduced injections are appealing, the potential for interactions between components increases with higher valencies. The practical importance of this has recently been demonstrated in the United Kingdom, where use of a combination Hib– acellular pertussis vaccine resulted in a significant resurgence of Hib disease due to decreased antibody responses. This is unlikely to be an issue in Australia because a booster dose is included in the schedule, but it highlights the need for caution.

Combinations with diphtheria, tetanus and acellular pertussis vaccines

In addition to the DTPa–hepB (Infanrix HepB) and DTPa–IPV (Infanrix-IPV, Quadracel) vaccines already in use, two new vaccines have recently been registered. In April 2001, the Australian Drug Evaluation Committee approved the registration of a pentavalent combination vaccine, (diphtheria, tetanus, acellular pertussis, hepatitis B and inactivated poliovirus; DTPa–hepB–IPV; Infanrix Penta) and a hexavalent combination vaccine including the above with Hib (DTPa–hepB–IPV–Hib; Infanrix Hexa) for use in the primary vaccination schedule.

The immunogenicity of these new combination vaccines has been shown to be equivalent to the administration of separate vaccines (except for slightly lower Hib antibody titres), with the advantage of fewer injections and no increase in adverse effects. These vaccines are not suitable for booster doses; they are expected to be available in the near future for use in the primary schedule.

Hepatitis A combinations

In addition to the combined hepatitis A and B vaccines (Twinrix and Twinrix Junior), a combined hepatitis A–*Salmonella typhi* vaccine (Vivaxim) has been registered for at risk travellers aged 16 or over. A single dose of Vivaxim does not ensure long term protection against hepatitis A, and so a second dose of inactivated hepatitis A vaccine (Avaxim, Havrix 1440, VAQTA) is recommended six to 12 months after vaccination with Vivaxim.

The future of vaccines and immunisation

Vaccine development and new vaccines

Genetic engineering continues to play an important role in the design and production of vaccines. Techniques include using DNA plasmids, recombinant vectors and prime boost strategies and the development of new adjuvants. New routes of administration, including edible vaccines (vaccine antigens produced in antigenic plants), transcutaneous, rectal and aerosolised vaccines, lie ahead.

Some of the vaccines currently under investigation in clinical trials are those against respiratory syncytial virus, group B streptococcus, human papillomavirus, cytomegalovirus, rotavirus, herpesviruses, HIV, hepatitis C, malaria and tuberculosis. The target diseases for vaccination are also broadening to include chronic noncommunicable diseases such as cancer, insulin-dependent diabetes, multiple sclerosis, rheumatoid arthritis and Alzheimer's disease.

Surveillance of vaccine preventable diseases

Surveillance of vaccine preventable diseases via hospitalisations and notifications is currently supplemented by regular community-wide serosurveys (to assess immunity), and there are enhanced surveillance schemes for specified diseases (e.g. Hib and pneumococcal diseases).

In the future, linked electronic databases will enable vaccination histories to be matched with hospitalisations and GP consultations and provide better information on vaccine failures, adverse events associated with vaccines, and morbidity. Mathematical modelling will assume greater importance, as decisions about vaccine funding will rely more and more on morbidity and mortality impacts and cost–benefit analyses. Quantitative models, such as one developed by the US Institute of Medicine, will decide which diseases are considered significant threats to public health and require intervention. In an era where adverse events associated with a vaccine may outnumber occurrences of the disease it is preventing, newer vaccines that further minimise reactions will be sought. Communication with the public through media campaigns and GP consultations will be required to maintain public confidence and high vaccination coverage.

Conclusion

Vaccination has progressed considerably in the past decades, and there is a need to be kept informed of the latest developments in a constantly changing field. The 8th edition of *The Australian immunisation handbook* provides GPs with the NHMRC-endorsed vaccination schedule. GPs can be certain of one thing – that more changes lie ahead in immunisation. MT

A list of references is available on request to the editorial office.

DECLARATION OF INTEREST: None.

Medicine Today 2004; 5(5): 68-76

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