What's new in childhood immunisation?

Human papillomavirus and rotavirus vaccinations were added to the Australian National Immunisation Program (NIP) in 2007. Here is a discussion on the rationale behind these additions as well as several other changes to the schedule.

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Childhood immunisation is one of the greatest public health achievements of modern times. Australia can report a 99.75% decline in deaths due to vaccine preventable diseases since the prevaccination era, despite a threefold increase in the Australian population since that time.[1] Dramatic reductions in the incidence of diseases following the introduction of specific vaccines, such as *Haemophilus influenzae* type b (Hib) and pneumococcal conjugate vaccines, are recent examples of the ongoing success of our immunisation program. The maintenance of high vaccination rates is central to this success. However, this can be challenging when new vaccines are introduced into the immunisation schedule, and when concerns about vaccine safety and adverse events gain greater awareness than vaccine preventable diseases themselves.

In April 2008, the 9th edition of *The Australian Immunisation Handbook* was launched, updating the guidelines for immunisation providers on the use of vaccines in Australia. The Handbook is written by the Australian Technical Advisory Group on Immunisation (ATAGI) with technical support from the National Centre for Immunisation Research and Surveillance (NCIRS), and is endorsed by the National Health and Medical Research Council (NHMRC).[2] It also contains, as an insert, the National Immunisation Program (NIP) Schedule card, which was last updated in July 2007.

The NIP Schedule is amended periodically and is likely to change again soon. *The Australian Immunisation Handbook* and the NIP Schedule are available online at http://immunise.health.gov.au/. This site also has information about the

IN SUMMARY

- **In 2007, vaccination against human papillomavirus (HPV) infection and cervical cancer started under the National Immunisation Program (NIP) via school-based and GP delivery.**
- **In the same year, two oral vaccines for the prevention of rotavirus gastroenteritis were added to the NIP for infants.**
- **The meningococcal C vaccine campaign and ongoing immunisation with one dose of vaccine given to infants at the age of 12 months have led to a decline in the incidence of meningococcal C disease.**
- **Combination measles, mumps, rubella and varicella (MMRV) vaccines are being considered for incorporation on to the NIP, together with a possible move of administration of the second dose of MMR vaccine to the earlier age of 18 months.**
- **Strategies to prevent pertussis in vulnerable young infants include immunisation of their parents and carers with the adolescent/adult formulation of the dTpa vaccine, known as the 'cocoon strategy'.**
- **Children are often ill with influenza and spread the infection to adults. The potential impact of routine annual influenza immunisation of young children is under study.**

improved processes for more transparent and evidence-based evaluation and decision making on the use of vaccines in Australia, such as how cost-effectiveness is determined. Fact sheets for immunisation providers on vaccines and vaccine safety are available online from the NCIRS at http://www.ncirs.usyd.edu.au.

A version of the current NIP Schedule for children and adolescents is shown in the Table. Changes to the NIP Schedule are influenced by changes in the epidemiology of vaccine preventable diseases, the availability of new vaccines and vaccine safety, as discussed in some specific examples below.

New vaccines on the NIP Schedule

Human papillomavirus

Of the more than 40 distinct types of human papillomavirus (HPV) that can infect the genital tract, two 'high-risk' types (types 16 and 18) are responsible for the development of about 70 to 80% of all cases of cervical cancer. In April 2007, the national HPV vaccination program was launched with the aim of reducing the incidence of cervical cancer through the prevention of HPV 16 and 18 infections. Ongoing routine vaccination of 12- to 13-year-old girls, generally in the first year of high school, is occurring. There has also been an initial 'catch-up' program for both female adolescents aged 13 to 18 years (largely through school-based vaccination) and young adult women aged 19 to 26 years (mainly via general practice). The program for 19 to 26 year olds is due to finish by the end of 2009 (to complete the funded vaccine series, first doses need to be given before July).

The quadrivalent vaccine (Gardasil), which includes protection against HPV types 6 and 11 as well as types 16 and 18, has been used in the program, as it was the only vaccine approved when the program started. A bivalent vaccine (against types 16 and 18 only; Cervarix) is now also available for use under the NIP. (Note: the choice of vaccine is determined by each state and territory program and can vary between jurisdiction.)

The national HPV vaccine register has recently been launched and now accepts immunisation records from general practice and the school-based program (http://www.hpvregister.org.au/). It is valuable for providers to lodge immunisation records, particularly to aid long-term monitoring of vaccine effectiveness and the program impact.

PHOTOLIBRARY

Although there has been media attention given to reports of adverse events, including fainting and allergic reactions, following HPV vaccination, the HPV vaccines have been observed to have a good safety record, generally comparable to that of similar existing vaccines. The adolescent and young adult female population in which HPV vaccines have been used (often in a school-based setting) do seem to be more likely to experience adverse events, such as vasovagal episodes, after vaccination. They also have high 'background rates' of other conditions, such as autoimmune diseases, which need to be taken into account before considering a causal relationship with vaccination. Ongoing monitoring of adverse events via established systems at both a national and state and territory level is occurring.

It is important to continue cervical screening programs, as the HPV vaccines do not protect against all cancer-causing types of HPV.

The HPV vaccines are not currently recommended for use in males, but studies in this area are ongoing.

Rotavirus

In Australia, about 50% of all hospitalisations for acute gastroenteritis in children under 5 years of age are due to rotavirus. This equates to roughly

continued

Table. National Immunisation Program Schedule for children and adolescents*

Vaccine	Age								
	Birth	2 months	4 months	6 months	12 months	18–24 months	4–5 years	10–13† years	12–17† years
Hep B	✓	✓	✓	✓‡	(✓)‡				✓‡
DTPa (dTpa§)		✓	✓	✓			✓		✓§
IPV		✓	✓	✓			✓		
Hib‖		✓	✓	✓‖	✓‖				
7vPCV¶		✓	✓	✓	(✓)¶				
23vPPV						✓**	✓¶		✓**
Rotavirus		✓	✓	(✓)††					
MMR					✓		✓		
MenCCV					✓				
HPV									✓‡‡
VZV						✓		✓§§	
Hep A‖ ‖					✓‖ ‖	✓‖ ‖			
Influenza ¶ ¶				(✓)¶ ¶					✓¶ ¶

ABBREVIATIONS: Hep B = hepatitis B vaccine; DTPa = diphtheria, tetanus, acellular pertussis vaccine; IPV = inactivated poliomyelitis virus vaccine; Hib = *Haemophilus influenzae* type b vaccine; 7vPCV = pneumococcal conjugate (7-valent) vaccine; Rotavirus = rotavirus vaccine (oral only); MMR = measles, mumps, rubella vaccine; MenCCV = meningococcal C conjugate vaccine; HPV = human papillomavirus vaccine; VZV = varicella-zoster virus vaccine; Hep A = hepatitis A vaccine; Influenza = annual influenza vaccine; 23vPPV = pneumococcal polysaccharide (23-valent) vaccine.

* The NIP Schedule is updated periodically; this version became valid on 1 July 2007 and is available online at: www.immunise.health.gov.au. For additional information on vaccine schedules see *The Australian Immunisation Handbook*.

† NIP-funded vaccines for adolescents are provided by state and territory school-based immunisation programs. The age/school year at which vaccines are provided varies by jurisdiction.

‡ A total of three doses of hepatitis B vaccine is required following the birth dose, at either 2, 4 and 6 months of age or at 2, 4 and 12 months of age. 'Catch-up' hepatitis B vaccine (given as either a two or three dose course) is provided to adolescents with no prior history of disease or vaccination.

§ Given as dTpa (adolescent/adult formulation triple antigen).

‖ If using PRP-T Hib (purified *Haemophilus influenzae* capsular polysaccharide bound to tetanus toxoid), give four doses (at 2, 4, 6 and 12 months of age). If using PRP-OMP (purified *H. influenzae* capsular polysaccharide bound to *Neisseria meningitidis* outer membrane protein), give three doses (at 2, 4 and 12 months of age).

¶ Medically at-risk children require a fourth dose of 7vPCV at 12 months of age, and a dose of 23vPPV at 4 to 5 years of age.

** 23vPPV is recommended for Aboriginal and Torres Strait Islander children living in areas of higher risk (Queensland, the Northern Territory, Western Australia and South Australia) at 18 to 24 months of age, and Aboriginal and Torres Strait Islander adolescents (aged 15 years and above) who are medically at risk.

†† Third dose of rotavirus vaccine is dependent on vaccine brand used.

‡‡ A three-dose series of HPV vaccine is required.

§§ One dose of varicella vaccine is given as 'catch-up' if there is no prior history of disease or vaccination.

‖ ‖ Two doses of Hep A vaccine are required for Aboriginal and Torres Strait Islander children aged between 12 and 24 months living in areas of higher risk (Queensland, the Northern Territory, Western Australia and South Australia).

¶ ¶ Influenza vaccine is recommended annually for children over 6 months of age who are medically at risk of complications from influenza. Influenza vaccine for medically at-risk children is PBS subsidised, but is under consideration for availability under the NIP. It is on the NIP Schedule for Aboriginal and Torres Strait Islander adolescents over 15 years of age.

10,000 hospitalisations per year and a one in 27 chance that a child will be admitted with rotavirus before the age of 5 years.

Two oral, live attenuated, rotavirus vaccines are available. They have been on the NIP since July 2007 and are given at either 2 and 4 months of age (Rotarix) or 2, 4, and 6 months of age (RotaTeq). In clinical trials, the vaccines prevented about 88 to 100% of all hospitalisations due to rotavirus, and about 70% of rotavirus gastroenteritis of any severity.[3,4]

The vaccines are very well tolerated. Although infants can shed the vaccine viruses in their stools, particularly after the first dose, restrictions on contact with others, as was needed for the oral polio vaccine, are not required. This is because reversion of the vaccine viruses to a virulent form has not been documented, and would be unlikely to pose the risk that virulent polioviruses do. (Rarely, cases of vaccine-associated paralytic polio were seen following oral poliovirus vaccine [OPV] administration.) Rotavirus vaccines can be given in the hospital setting and to those with immunocompromised contacts, but they should not be given directly to immunocompromised infants because they have not been studied in this population.

Because a previous rotavirus vaccine formulation (used only briefly in the USA in the late 1990s) was associated with a rare form of intestinal obstruction called intussusception that occurred particularly in older infants, the new rotavirus vaccines are subject to upper age limits for both the first and final doses in the course (as specified in *The Australian Immunisation Handbook*). This is the first time that such strict upper age cut-offs for infant vaccines have applied; however, preliminary data suggest that most doses are being given on time. The current rotavirus vaccines have not been associated with an increased risk of intussusception, in either the large prelicensure studies or the postlicensure monitoring in Australia and the USA.

Issues relating to recently added or existing NIP vaccines

Meningococcal C disease

The two most common serogroups of *Neisseria meningitidis* that cause disease in Australia are serogroups B and C. There is currently no vaccine available against serogroup B meningococcal disease (other than highly strain-specific vaccines used in countries such as New Zealand and Cuba). In Australia, the national meningococcal C immunisation program started in 2003, with one dose of conjugate meningococcal C vaccine (MenCCV; Meningitec, Menjugate Syringe, NeisVac-C) offered to all children aged 1 to 19 years in a large 'catch-up' campaign. That vaccine is now provided as a single dose on the NIP Schedule at 12 months of age. However, funded catch-up vaccination is still available in some jurisdictions.

The number of cases and deaths from meningococcal C disease has fallen dramatically since 2003, with evidence suggesting a herd immunity effect, in addition to individual protection. During this time, the incidence of meningococcal disease due to other serogroups, including serogroup B, has remained steady.

Varicella and herpes zoster

Varicella-zoster virus (VZV) is so named because it causes two diseases: varicella (chickenpox) following primary infection and herpes zoster (shingles) following reactivation of virus that is dormant in sensory nerve ganglia. Approximately 1% of cases of varicella are complicated, leading to about 1500 hospitalisations and about eight deaths a year prior to vaccine introduction.

Varicella vaccine (Varilrix, Varivax Refrigerated), given in a one-dose schedule at 18 months of age, was added to the NIP in November 2005, together with a 'catch-up program' via school-based immunisation for older children who report no history of disease or immunisation (one dose is given between 10 to 13 years of age, depending on the state or territory program). In children, one dose of the vaccine is only about 85% protective, so some vaccinated children may still develop chickenpox; however, it is usually a milder disease, with patients having fewer skin lesions and systemic symptoms. The use of a second dose of the vaccine in children has been suggested but is not currently on the NIP Schedule.

Adolescents and adults require two doses of varicella vaccine, administered at least a month apart, to be adequately protected.

It is expected that as the population of children immunised with varicella vaccine age, they will have lower rates of herpes zoster, since their primary infection with wild-type VZV was prevented and because vaccine virus rarely reactivates to cause herpes zoster. Although modelling studies suggest that rates of herpes zoster in those who had natural chickenpox may increase once there is less varicella in the community (because of less immune boosting), this has not yet been observed in ongoing population-based studies.

Influenza

Annual influenza immunisation of older adults (65 years and over) and anyone aged 6 months or older who has an underlying medical condition that increases the risk of complications from influenza has been recommended for many years. However, the highest annual attack rates of influenza, up to 30 to 50% per season, are in children. Children are efficient spreaders of influenza because they:

- shed virus in greater quantities and for longer periods than do adults
- often have poor infection control practices
- often have many social contacts (e.g. at school and preschool)
- have less pre-existing immunity.

Previously healthy children can also experience complications from influenza, resulting in hospitalisations and, rarely, death.

Most influenza vaccines (Fluarix, Fluvax, Influvac, Vaxigrip) are licensed for use in children from 6 months of age, and *The Australian Immunisation Handbook* states that 'annual influenza vaccination in Australia is recommended for any person aged 6 months or older who wishes to reduce the likelihood of becoming ill with influenza'. Children aged 9 years or below who are receiving the vaccine for the first time need two doses, at least one month apart, and those aged under 3 years should receive a smaller dose than older children and adults.

In 2008, the Western Australian Department of Health began a pilot study that provides influenza vaccine free for all children under 5 years of age. The study is ongoing and will provide information on both the feasibility of vaccine delivery and vaccine effectiveness. Similarly, immunisation of young children has been recommended in the USA since 2004. Overall, both programs will inform ongoing review of recommendations for influenza vaccination of children Australia-wide.

Infants younger than 6 months of age can be offered protection against influenza both by vaccinating those around them and by immunising their mother in pregnancy. This also benefits pregnant women,

an often overlooked group who are at increased risk of complications from influenza.

Influenza vaccine is funded on the NIP for Aboriginal and Torres Strait Islander adolescents aged 15 years or above who are medically at risk. It is not currently on the NIP for other adolescents or children, but is PBS-subsidised for those medically at risk.

Pneumococcal disease

The main diseases caused by *Streptococcus pneumoniae* are meningitis, bacteraemia/sepsis, pneumonia, sinusitis and otitis media. The highest rates of invasive pneumococcal disease, defined as isolation of *S. pneumoniae* from a normally sterile site, are seen in children under 2 years of age, with the disease rate in Indigenous Australians being more than three times that in non-Indigenous Australians.

In 2001, the pneumococcal conjugate vaccine containing seven vaccine antigens (known as 7vPCV; Prevenar) was introduced on the NIP for Indigenous children and children with underlying medical conditions predisposing them to invasive pneumococcal disease. In January 2005, the vaccine became available on the NIP for all children, in a three-dose schedule at 2, 4 and 6 months of age. Booster doses of 7vPCV and/or the 23-valent pneumococcal polysaccharide vaccine (known as 23vPPV; Pneumovax 23) are recommended for those with underlying medical conditions and Indigenous children residing in some states and territories, depending on their age and immunisation history.

Since the introduction of the conjugate vaccine, rates of invasive pneumococcal disease have declined substantially in all children in Australia, and also in older children and adults due to the effect of herd immunity. The decline has been in disease caused by pneumococcal serotypes contained in the vaccine. The emergence of pneumococcal disease caused by nonvaccine serotypes, which has been observed in the USA, is being closely monitored.

Measles, mumps and rubella

Australia has recently declared elimination of endemic measles on the basis that, although an average of about 50 measles cases occur each year, almost all can be traced back to an imported case, such as in a returned traveller or visitor with measles. There has been no sustained spread of the virus because of our high immunisation rates. Most recent cases of measles in children have occurred in those who received only one or no doses of the measles, mumps, rubella (MMR) vaccine. A modelling study has demonstrated that if the second dose of MMR vaccine was provided at the earlier age of 18 months, rather than at 4 years of age when it is currently scheduled, the levels of vaccine coverage and

population immunity are likely to rise.[5]

Recommendations to administer the second dose of MMR vaccine at 18 months of age, and to use the newly registered 'four in one' combination measles, mumps, rubella and varicella (MMRV) vaccine as this second dose, are currently being considered for the NIP. The importance of administering two doses of MMR vaccine is also underpinned by the occurrence of a number of large mumps epidemics that have occurred in the last two years in places such as Canada, the USA and the UK, with cases particularly in underimmunised children and adolescents.

Pertussis

Pertussis (whooping cough) is an endemic disease that still occurs in epidemics approximately every three to four years. Pertussis outbreaks have been reported in late 2008 to early 2009 across Australia, predominantly in population age groups who have not been recently or fully immunised. Although epidemics are much smaller in immunised compared with nonimmunised populations, certain groups, such as young infants who have not yet been able to receive at least two doses of a pertussis-containing vaccine (Infanrix Hexa, Infanrix-IPV, Infanrix Penta), remain susceptible to severe disease.

Two adolescent/adult formulation, pertussis-containing vaccines are available (Boostrix and Adacel). They are both designated as dTpa vaccines because they contain a reduced antigen content of both diphtheria and pertussis compared with those in the childhood (DTPa) vaccines. The availability of these adolescent/adult formulations has enabled a booster dose of pertussis vaccine to be given via the school-based immunisation program to adolescents (the school year in which the vaccine is given depends on the state or territory program). Data from this program suggest that the disease incidence has been reduced in this age group.

dTpa vaccines should also be promoted for use in those who care for infants and young children, such as healthcare and childcare workers, and parents and grandparents (or those anticipating having a new infant in the home). This has been referred to as a 'cocoon strategy' to protect young infants who are most at risk of hospitalisation, pneumonia, neurological complications and death from pertussis.

Implementation and surveillance of the NIP

GPs, practice nurses, midwives, community nurses, public health staff, and school-based teams all have a vital role in enabling immunisation of children in Australia. For providers, new resources, such as *The National Vaccine Storage Guidelines: Strive for 5* available at http://immunise.health.gov.au/, have been developed to ensure

high standards for vaccine storage. Also available are resources for responding to parent queries about vaccination, such as the popular booklet *Myths and Realities: Responding to Arguments Against Immunisation* (4th edition, 2008; www.health.gov.au/internet/immunise/publishing.nsf/Content/uci-myths-guideprov). Providing 'catch-up' vaccination is often challenging, but many tables and worksheets in *The Australian Immunisation Handbook* and an online 'catch-up calculator' (www.health.sa.gov.au/immunisationcalculator) can provide assistance.

GPs also have a critical role at the front line of surveillance for both vaccine preventable diseases and adverse events following immunisation. Accurate diagnosis and timely reporting of vaccine preventable diseases, and of any serious or uncommon adverse event, is vital to monitoring immunisation programs. Reports of both vaccine preventable diseases and adverse events following immunisation are published regularly in the journal *Communicable Diseases Intelligence*, available online via the Australian Government's Department of Health and Ageing website (http://www.health.gov.au/). In addition, active surveillance for some specific diseases and adverse events following immunisation (such as meningococcal and pneumococcal disease, polio and intussusception) is being undertaken via specific mechanisms.

The ability to link (de-identified) data from major electronic databases also holds great promise to provide better information on many aspects of disease prevention by immunisation.

Future developments

Vaccines combining antigens for existing diseases, vaccines with extended serotype coverage, new vaccine formulations, and vaccines against newly preventable diseases are all on the horizon. Examples include the combination measles, mumps, rubella, varicella vaccines, a vaccine combining the conjugated meningococcal C antigen and a conjugated *H. influenzae* type b antigen (Hib-MenC), and pneumococcal conjugate vaccines that contain additional antigens. Both 10-valent and 13-valent pneumococcal conjugate vaccines are likely to be available soon. Each offers protection against additional pneumococcal antigens, and one uses the protein D of nontypable *H. influenzae* (which causes otitis media) as its conjugate protein. These extended-valency vaccines are also being tested in adults.

Another example is the cold-adapted, live attenuated, intranasal trivalent vaccine for seasonal influenza (CAIV-T), which is being used in the USA in children aged over 2 years but is not yet available in Australia. Influenza vaccines using new adjuvants and new delivery techniques, such as intradermal injection, are also likely to be available in the near future.

Conclusion

Australia is well recognised as having an excellent national immunisation program, often with early introduction of new and important vaccines such as HPV, rotavirus and pneumococcal conjugate vaccines. Immunisation providers, including GPs and practice nurses, have a key role in maintaining Australia's high immunisation coverage. This is achieved not only by delivery of vaccines, but also by maintaining public awareness of vaccine preventable diseases and consumer confidence in immunisation, responding to adverse events following immunisation, and contributing to disease surveillance.

To keep pace with changes to the NIP Schedule and to be well informed regarding issues related to control of vaccine preventable diseases, resources such as the recently published 9th edition of *The Australian Immunisation Handbook* are valuable.

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