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Abbreviations used in this review:
- ALT = alanine transaminase
- BCG = Bacillus Calmette-Guérin
- HBIG = hepatitis B immune globulin
- HBsAg = hepatitis B surface antigen
- HBV = hepatitis B virus
- HPV = human papillomavirus
- JCVI = Joint Committee on Vaccination and Immunisation
- MenB = meningococcal group B
- MenC = meningococcal group C
- MMR = measles, mumps, rubella
- OMV = outer membrane vesicles
- SSI = Serum Staten Institute
- TB = tuberculosis

IMMUNISATION IN NEW ZEALAND 2014
Associate Professor Nikki Turner (IMAC, University of Auckland)

New Zealand has historically had very poor paediatric immunisation coverage. However, particularly within the last decade, there has been a considerable improvement in coverage, timeliness of delivery and reduction of equity gaps. There still remain important areas of concern for the New Zealand programme which Dr Turner and colleagues discussed at this meeting: vaccine-preventable diseases that are still not well controlled such as pertussis and measles, and suboptimal immunisation coverage including in pregnancy, older children, adolescents and adults. The future of New Zealand’s immunisation programme will require attention both to improving immunisation coverage for all ages, increased focus on particular groups and consideration of important new international vaccines and their possible role in our immunisation schedule.

HEPATITIS B IN NEW ZEALAND – PREVENTION AND MANAGEMENT IN CHILDHOOD
Dr Chris Moyes (Bay of Plenty DHB)

Hepatitis B is endemic in New Zealand especially in Maori, Pacific and Asian communities and prevention is based primarily on effective vaccination. Immunisation can be passive – hepatitis B immune globulin (HBIG) within 48 hours of exposure for short term protection followed by active vaccination, or active – hepatitis B surface antigen (HBsAg) produced by recombinant gene technology with added adjuvant. Vaccination must be intramuscular and can be as short as 2 weeks between injections or as long as up to a year apart. As far as we know, vaccination on a three-dose schedule gives effective immunity long after the loss of anti-HBsAg.

Perinatal transmission of hepatitis B virus (HBV) is a special case. Infants of carrier mothers need to receive HBIG within 48 hours of birth followed by usual vaccination. Such an approach has efficacy of 91%–94% versus usual vaccination alone efficacy of 70%–85%. Most failures occur in very high titre mothers, i.e. HBV DNA >20 million IU/mL. This can be lessened by use of antiviral agents such as tenofovir or lamivudine in pregnancy.

When should hepatitis B carriers be treated? An HBsAg positive child with sustained raised alanine transaminase (ALT) should be considered for treatment – but one should be conservative and wait and see in the majority of cases. When Dr Moyes followed up such children prior to the introduction of modern treatments, two thirds had spontaneous resolution of raised ALT in <2 years and their histology normalised. HbsAg negative children with sustained raised ALT and high HBV DNA and cirrhosis should also be treated, however these are largely adult problems. The goal of treatment in HBsAg positive children is to achieve HBsAg seroconversion, normalise ALT and reduce HBV DNA to low levels. Treatment does not normally lead to HBsAg loss. Both pegylated interferon and entecavir are funded for treatment of chronic HBV infection in New Zealand. Compared with earlier drugs, modern drugs such as entecavir and tenofovir are more potent and are associated with less resistance to monotherapy.

IMMUNISATION OF SPECIAL GROUPS
Dr Elizabeth Wilson (Starship Children’s Hospital)

This publication summarised Chapter 4 in the Immunisation Handbook 2014, where tables and recommended schedules can be found for the following groups.

Infants with special immunisation considerations

There are immunisation issues to be aware of in a number of special groups including:

- Children with congenital heart disease; may have associated asplenia or immune deficiency syndromes such as DiGeorge. Children with complex single ventricle or shunt-dependent lesions (e.g., post-Norwood procedure) may have an increased risk of deterioration or collapse following immunisation. Infants with congenital biliary or renal conditions...
Issues in Vaccination of Preterm Infants

Premature and low birth weight infants are at greater risk of increased mortality and morbidity from vaccine preventable diseases. Vaccines should be given at the usual dosage at 6 weeks chronological age (i.e. do not adjust for preterm birth). BCG (live vaccine) can be given from 34 weeks gestation. Rotavirus vaccine is an exception to the above recommendation. It is best to vaccinate preterm infants as they leave hospital because of vaccine virus shedding in the stool. However, if discharge is not anticipated before age 15 weeks, which is the upper age limit for giving dose one, then giving rotavirus vaccine in hospital is acceptable. Preterm infants have an inferior response to some vaccines, although evidence suggests the response is still protective. Immunisation in these infants is safe and effective, however post-vaccination afebrile with or without associated bradycardia up to 48 hours post-immunisation may be increased in some groups. Reasons include: an increase in adverse events within the 24 hours before immunisation, more severe illness at birth, chronological age less than 67 days and/or earlier gestational age in infants with a birth weight of less than 1500g, or an afebrile episode following the first immunisation event. Afebrile monitoring should be considered after the first immunisation event and after subsequent immunisation events when an infant has experienced afebrile after their first immunisation event.

Why do preterm infants not respond as well to vaccines as full term infants? They do not produce antibodies as well as full term infants and those that are produced don’t last as long. In naïve B cells, preterm infants have decreased expression of cell surface receptors, such as CD21, CD40, CD80 and CD86. In plasma cells, preterm infants have limited IgG responses to protein and polysaccharide antigens and limited persistence of IgG antibodies. Additionally, they have impaired germinal centre responses, a limited functional follicular dendritic cell network and limited access to plasma cell niches in bone marrow. The one positive is that preterm infants do effectively produce memory B cells. Transplacental transfer of maternal IgG can protect against some vaccine preventable diseases but is affected by past exposure of the mother and the infant’s gestational age. Infants born at <34 weeks gestation have less IgG and it wanes more rapidly.

Immune-deficient individuals of all ages

Individuals with chronic conditions, an immune deficiency, or who are immunosuppressed for underlying disease control, are at increased risk of vaccine preventable disease. These individuals should be immunised as a matter of priority. Special care is required with some live vaccines. It is important to ensure that the household contacts of these individuals are immune to vaccine-preventable diseases wherever possible.

Asplenia/splenectomy

No vaccines are contraindicated in asplenic patients and it is essential that they receive maximal protection, particularly against pneumococcal disease which can cause overwhelming sepsis. Where possible, immunisation should be commenced at least 2 weeks preoperatively.

Solid organ transplant

An accelerated immunisation schedule is recommended for children likely to be listed for solid organ transplant. Individuals older than 12 months who have been scheduled for solid organ transplantation should receive measles, mumps, rubella (MMR) and varicella vaccines at least 4 weeks before the transplant. In patients undergoing organ transplantation, pneumococcal vaccine should be given at least 2 weeks before the transplant. Hepatitis A, hepatitis B, HPV, influenza, meningococcal conjugate and varicella vaccines are funded for transplant patients.

Oncology

In oncology patients, annual influenza vaccine is recommended. Post-chemotherapy, those who have received routine immunisations prior to cancer diagnosis do not need full re-immunisation. Booster doses of a diphtheria/tetanus/pertussis containing vaccine, hepatitis B, polio and pneumococcal vaccines should be given, starting not less than 3 months after chemotherapy has ended, when the lymphocyte count is >1.0 x 10^9 L^-1. Live viral vaccines should be delayed for at least 6 months after chemotherapy, but MMR and varicella vaccine should then be given to seronegative patients.

Complete re-immunisation is recommended following bone marrow transplant, starting with inactivated vaccines 12 months after transplant. Hexavalent DTaP-IPV-HeptoB/Hib can be given to children up to 10 years, but from the 10th birthday Tdap should be given. Pneumococcal vaccines, meningococcal, hepatitis B and a booster dose of Hib and IPV are all recommended. MMR and varicella vaccine can be given not less than 2 years after transplant. Second doses of MMR and varicella vaccine should be given 4 weeks or more after the first doses, unless serological response to measles and varicella is demonstrated after the first dose. The vaccines should not be given to individuals suffering from graft-versus-host disease because of a risk of a resulting chronic latent virus infection leading to central nervous system sequelae.

Ocultural and lifestyle risk

Certain occupations result in increased risk of contracting some vaccine preventable diseases. Health care workers and those working in early childhood education services, may transmit infections such as influenza, rubella, measles, mumps, varicella and pertussis to susceptible contacts, with the potential for serious outcomes. Health care workers have a duty to know their MMR and varicella status, should receive adult pertussis booster if working with young infants and receive annual influenza immunisation.

Pain Management for Immunisation

Immunisations are the most common recurring health care procedure in childhood, but associated pain causes distress for children and their parents and can lead to needle fears and health care avoidance. Use of distraction techniques to reduce pain and distress during immunisation is something done very well in New Zealand in Dr Russell’s opinion. The most common methods used are colourful or noisy toys, bubbles, and reward stamps and mascots. The use of or rubbing above the injection site or using a device like the BuzzyBee. Breast feeding and oral sucrose are often used in infants to reduce pain, but there is still room for improvement in this area. Dr Russell observed >150 vaccinations by 12 school nurses of Boostrix and the second or third HPV vaccination. Most nurses limited procedural talk and time before injection and all used a good variety of distractions. But three quarters of nurses used a slow injection technique, a long-standing practice that has never been subjected to scientific evaluation. The theory is that injecting slowly will minimize pressure and sudden distension of tissues. However, slow delivery adds to pain due to longer contact time between needle and tissue and through lateral movement of the needle. Inspiration is not necessary because vaccination sites are devoid of large blood vessels. A randomised controlled trial of injection technique in infants showed a rapid technique (1 second for 0.5 mL) resulted in less pain versus a slow technique with aspiration (up to 9 seconds). Dr Russell pointed out that a fast injection technique is indeed that – only about 2 seconds long.

What does the future hold? There may be more antigens introduced to each vaccination but this could come with increased risk of febrile seizures in 1–3 year olds with MMRV. Different delivery modes may hold promise such as a nasal spray or transdermal flu vaccine and a nanopatch HPV vaccine. Better pain management training for immunisers and parents would also be useful, as would the use of EMLA® patches in the 15 month age group where four immunisations are given and distraction techniques are limited.

What works

• Distraction
• Parent acting calm
• Rapid injection technique
• EMLA® – but dose concerns under 1 year
• Sucrose, breastfeeding, parent holding baby (Infants)
• Tactile input and non-procedural talk (>1 years)

Meningococcal Vaccination

In 2013, the rate of meningococcal disease in New Zealand was 1.5/100,000, half that seen in 2009 and a much more favourable situation than a decade ago. There were 61 confirmed cases in 2013, including 30 group B (53%) and 17 group C (30%). The fatality rate was 6%. Not surprisingly, most cases were in children aged <1 year (18.4/100,000) and these were predominantly meningococcal group B (MenB) disease. Rates declined throughout childhood but there was a peak in the 15–19 year old group (3.9/100,000) which was predominantly meningococcal group C (MenC) disease. Pacific and Maori had higher disease rates than European at 6.2 versus 1.3 and 2.6 versus 1.2 per 100,000, respectively. Regrettably, 2 of the 34 MenB cases were the epidemic strain, while almost all the MenC cases were from one subtype (P1.5-1,10-8).
Potential MenC vaccine strategies

The UK now uses a 1+1+1 MenC immunisation schedule and is contemplating dropping the infant dose. Catch ups are not recommended but there may be an adolescent programme in the future. The Netherlands and Australia only give an adolescent dose, with good disease control. However, all three countries have had to use significant catch up doses which may be critical to good disease control and expensive. A 2006 model suggests that a two-dose MenC immunisation strategy at 12 months and 12 years is close to ideal.11,12 New Zealand’s low MenC disease rate, Dr Reid proposes introducing a two-dose immunisation schedule with no catch up, with disease monitoring and catch ups considered if disease rates increase.

Potential MenB vaccine strategies

The MenB vaccine Bexsero is combined with outer membrane vesicles (OMV) from a New Zealand group B strain and has broader coverage and probably greater duration of protection than MenNZB. Bexsero is licensed in Australia with the recommendation from the Australian Technical Advisory Group on Immunisation (ATAGI) that it can be used from 6 weeks of age. However, the Australian and European product information only recommend its use in infants from age 2 months. Dr Reid understands there is no data supporting the use of Bexsero under 2 months of age which would need to be considered carefully if Bexsero was to become available in New Zealand. Dr Reid’s suggestion for Bexsero, assuming it will be licensed in New Zealand, is to use it short term for outbreak control and await effectiveness data from the UK before introducing it into the routine schedule.

The Joint Committee on Vaccination and Immunisation (JCVI) in the UK has made a very comprehensive statement on the use of Bexsero. In April 2013 they reported it was unlikely to be cost effective. After more information led to a modelling change, they recommended in March 2014 that it be included on the infant immunisation schedule with borderline cost effectiveness at a reduced cost per dose. If implemented in the UK, effectiveness data will become available for consideration of its introduction in New Zealand. In the UK, MenB disease is responsible for 80% of meningitis cases and is fatal in 5%. Data for Bexsero with the New Zealand OMV showed efficacy of 73%, but on the basis of immunogenicity assumed efficacy was 95% and assumed strain coverage for the UK was estimated at 88%. The estimated duration of protection was 18 months after the infant dose, 36 months after the toddler dose, and 10 years after the adolescent dose. The JCVI noted increased reactogenicity of the childhood schedule when Bexsero was given with other vaccines. A 2, 4, 12 month immunisation schedule is recommended considering peak age of disease is 5 months and most vaccines in the UK are given on time.

Suggestions for the NZ immunisation schedule include:

• Conjugate group C vaccine: consider introduction now with a two-dose schedule and no catch up
• Bexsero: when licensed in New Zealand consider use for short term outbreak control and
• await long-term effectiveness data from the UK before considering introduction to routine schedule

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VARICELLA VACCINATION – WHY, WHO AND WHY NOT

Dr Emma Best (Starship Children’s Hospital)

The burden of varicella hospitalisations in New Zealand is underestimated and complications are associated with significant morbidity in children. In a typical year in New Zealand, there are 50,000 varicella infections,1,2 200–300 result in hospitalisation and 1–2 result in long-term disability or death. Two-thirds of the disease burden is in otherwise healthy children. Dr Best and colleagues conducted a study of varicella and post-varicella complications requiring hospitalisation in New Zealand children <15 years between November 2011 and October 2013.13 Maori and Pacific Island children are over-represented – the incidence rate ratio of hospitalisation was 2.8 for Maori and 3.9 for Pacific compared with European children. Secondary bacterial infection was the most common complication of varicella. Preliminary results show high rates of secondary infective complications, particularly with Streptococcus pyogenes infection. S. aureus and Streptococcus pyogenes consistent with prior reports of New Zealand’s rates of S. aureus and S. Pyogenes as amongst the highest reported in the developed world.13

High-risk groups have recently been made eligible for funded varicella vaccination. Such groups include non-immune patients prior to immunosuppression or transplantation. Non-immune household contacts of such individuals are also eligible. But targeting varicella vaccination of susceptible family members has questionable effectiveness as it may be neglected or forgotten by the managing team. A survey of paediatric oncologists in the UK and Italy showed only 15% attempted to identify varicella-susceptible individuals in households of their immunocompromised patients, despite treatment guidelines.15

Why not introduce routine varicella vaccination? There are theories that inadequate vaccination coverage (<80% of the entire non immune cohort) would shift disease burden to the older population resulting in increased morbidity and mortality.14 In addition, it has been long hypothesised that immunity against herpes zoster virus is boosted by contact with wild type varicella-zoster virus.15 The resultant hypothesis is that varicella vaccination may actually increase the incidence of herpes zoster.17 But there is now much real world evidence that these theories are not the case. Australia has funded varicella vaccine from 2005 as a single dose at 18 months. A school vaccination programme also offered the vaccine to 12–13 year olds who were not immune. Data shows marked declines in varicella hospitalisations in both targeted and untargeted age groups in other age groups. There is no evidence for a shift in varicella hospitalisation to older age groups and no change in rates of herpes zoster hospitalisations. Prior to the vaccine being funded, indigenous Australians were hospitalised at twice the rate of non-indigenous population (incidence rate ratio 2.6). By including varicella vaccination on the routine immunisation schedule, the disparity between indigenous and non-indigenous hospitalisations rates for children has been eliminated. Similar data have been shown in the US where the vaccine has been publicly funded since 1995.

Take home messages

• Who? All from age 1 year and non-immune preteens
• Why? High burden of disease and secondary infections
• Well why not?
7 to 9 year olds. Pertussis is a major public health issue in Australia, with a continuous increase observed over a long period of time. First in adults related to availability of serologic tests, then in adolescents related to low historical vaccine coverage, and most recently in younger children consistent with waning immunity in the context of increased test availability and use. Cessation of the 18 month booster dose appears to be an important contributor to resurgence in 2 to 4 year olds, with early waning immunity following the last acellular vaccine dose at 6 months. Large increases in cases over 6 years of age have been observed, and there are data to support a shorter duration of immunity among children who have received acellular vaccines than in those who received the earlier whole cell vaccine. The resurgence was not associated with any increase in infant pertussis deaths, which have remained similar or lower to that of previous pertussis epidemics in the past two decades despite more sensitive diagnostic tests.

**PERTUSSIS IN NEW ZEALAND**

Associate Professor Nikki Turner (IMAC, University of Auckland)

New Zealand’s recent pertussis epidemic is finally declining. The highest risk group for hospitalisation is infants aged <1 year, with hospitalisation rates 45 times higher than other groups. Rates of pertussis hospitalisation are highest in Maori and Pacific Island children and those from areas of high deprivation. During 2012–2013, 63 children were admitted to Starship PICU with pertussis, with an average length of stay of 11.3 days. Twenty-eight patients required invasive ventilation and 4 patients died; 3 of these were too young for full vaccination and 1 was unvaccinated with underlying morbidity. Dr Turner thinks we are probably considerably underdiagnosing pertussis. In 2011, the COUSH study evaluated 226 patients aged 5–49 years presenting to Auckland GPs with cough >2 weeks. Ten percent of patients had evidence of recent pertussis infection, including more children than adults (17% vs 7%). Clinical differentiation of pertussis from other causes of persistent cough is difficult, with no distinctive clinical symptoms noted. Since 2000, New Zealand has used an acellular pertussis vaccine given at 6 weeks, 3 months and 5 months, and in 2006 introduced a booster at 4 and 11 years. Since January 2013, vaccination of pregnant women at 28 to 38 weeks gestation has been funded. Immunisation of new mothers, family and close contacts of newborns, health care and childcare workers is recommended but not funded (health care workers are variably funded). The pregnancy pertussis immunisation programme was introduced in response to the epidemic that started in 2011. Pharmac will maintain the pregnancy programme for the foreseeable future with annual review, even though the epidemic is waning. Nationwide, the uptake of pertussis pregnancy vaccination is incredibly low, for a number of reasons. Availability of the vaccine in pregnancy was not well publicised, there are many service delivery challenges of vaccination in the antenatal arena, primary care is not engaged with antenatal care, and pregnancy vaccination is not embedded as a concept. However, flav vaccination may be leading the way with a greater emphasis over the last few years on flu vaccination in pregnancy, which Dr Turner is hoping pertussis immunisation can ‘piggy back’ on.

**Outstanding questions**

- How can we improve uptake of the maternal pertussis vaccination programme?
- How long will we continue maternal pertussis vaccination after the current epidemic has waned?
- Can we get adult Tdap on the National Immunisation Register?
- Acellular pertussis versus whole cell pertussis schedules or mixed?
- Outbreak of Bacillus Calmette-Guérin-associated lymphadenitis and abscesses in patients requiring invasive ventilation and 4 patients died; 3 of these were too young for full vaccination and 1 was unvaccinated with underlying morbidity. Dr Turner thinks we are probably considerably underdiagnosing pertussis. In 2011, the COUSH study evaluated 226 patients aged 5–49 years presenting to Auckland GPs with cough >2 weeks. Ten percent of patients had evidence of recent pertussis infection, including more children than adults (17% vs 7%). Clinical differentiation of pertussis from other causes of persistent cough is difficult, with no distinctive clinical symptoms noted. Since 2000, New Zealand has used an acellular pertussis vaccine given at 6 weeks, 3 months and 5 months, and in 2006 introduced a booster at 4 and 11 years. Since January 2013, vaccination of pregnant women at 28 to 38 weeks gestation has been funded. Immunisation of new mothers, family and close contacts of newborns, health care and childcare workers is recommended but not funded (health care workers are variably funded). The pregnancy pertussis immunisation programme was introduced in response to the epidemic that started in 2011. Pharmac will maintain the pregnancy programme for the foreseeable future with annual review, even though the epidemic is waning. Nationwide, the uptake of pertussis pregnancy vaccination is incredibly low, for a number of reasons. Availability of the vaccine in pregnancy was not well publicised, there are many service delivery challenges of vaccination in the antenatal arena, primary care is not engaged with antenatal care, and pregnancy vaccination is not embedded as a concept. However, flav vaccination may be leading the way with a greater emphasis over the last few years on flu vaccination in pregnancy, which Dr Turner is hoping pertussis immunisation can ‘piggy back’ on.

**REFERENCES**