

Paediatric Vaccines Research Review™

Making Education Easy

Issue 18 – 2014

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Welcome to the latest issue of Paediatric Vaccines Research Review.

Highlights include Australian evidence of the “real world” effectiveness of the HPV vaccine, plus intriguing findings that our attempts to increase concerns about communicable diseases or correct false claims about vaccines may in fact be counterproductive. We have also included an analysis that confirms the cost-effectiveness of childhood immunisation programmes, and we have a report from Starship Children’s Hospital of the severity of varicella infection in children.

We hope you find these and the other selected studies interesting and look forward to any comments you may have. Kind regards,

Associate Professor Nikki Turner and Dr Helen Petousis-Harris
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Effectiveness of quadrivalent human papillomavirus vaccine for the prevention of cervical abnormalities

Authors: Crowe E et al.

Summary: This case-control study nested within a population-based screening programme in Australia investigated the effectiveness of quadrivalent HPV vaccines for the prevention of cervical abnormalities. Women who were eligible for free vaccination (aged 12–26 years in 2007) and were attending for their first cervical smear test between April 2007 and March 2011 were included. High grade cases (n=1062) were women with histologically confirmed high grade cervical abnormalities, “other cases” (n=10,887) were women with any other abnormality at cytology or histology, and controls (n=96,404) were women with normal cytology. The adjusted odds ratio for exposure to 3 doses of HPV vaccine compared with no vaccine was 0.54 for high grade cases and 0.66 for other cases compared with controls (vaccine effectiveness of 46% and 34%, respectively). The adjusted exposure odds ratios for 2 vaccine doses were 0.79 for high grade cases and 0.79 for other cases (vaccine effectiveness of 21%).

Comment (NT): This is an excellent study looking at the effectiveness of the vaccine after four years in usage in Australia. The results clearly demonstrate that this vaccine is acting in the real world as would be expected from the clinical trials. The authors calculate that the NNV (numbers needed to vaccinate) with three doses of HPV vaccine to prevent one cervical abnormality identified at the first screening event were 125 for a high grade abnormality and 22 for any other abnormality, and this also translates to a risk reduction of nearly 50% in all high grade cervical abnormalities. This translates to a very large reduction in cytological abnormalities. Of note was that a two dose course of the vaccine still does show some protection as well. The challenge as now described by the authors is that the resultant falling population prevalence of cervical abnormalities in Australia will reduce the sensitivity and positive predictive value of cytology testing, therefore “screening programmes will need to adapt to maintain their effectiveness”. We await the outcomes of the current Australian review of their cervical screening programme with interest.

Reference: *BMJ* 2014;348:g1458

[Abstract](#)



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Effective messages in vaccine promotion

Authors: Nyhan B et al.

Summary: This US study tested the effectiveness of messages designed to improve vaccination rates for measles-mumps-rubella (MMR). A web-based nationally representative survey was conducted with 1759 parents who had children aged ≤ 17 years in their household. Parents were randomly assigned to a control group or to receive 1 of 4 interventions: (1) information explaining the lack of evidence that MMR causes autism; (2) textual information about the dangers of the diseases prevented by MMR; (3) images of children with measles-, mumps- or rubella-related diseases; (4) a dramatic narrative about an infant who almost died of measles. None of the interventions increased parental intent to vaccinate a future child. In fact, the interventions increased some parents' misconceptions and reduced their vaccination intention. In conclusion, attempts to increase concerns about communicable diseases or correct false claims about vaccines may be counterproductive.

Comment (NT): While we are all well aware of the impact that the misinformation around MMR and autism has had on public confidence in the vaccine, we are less certain about how to undo the myth once it has become embedded. This unique study tackles the important question of which messages are most effective in vaccine promotion and myth dispelling. The authors hypothesised that people with anti-vaccination sentiments would be more likely to increase their beliefs in anti-vaccination claims when presented with scientific corrective information. This study confirmed their hypothesis: when 'corrective information' was presented not only did it make respondents more convinced of their position but also helped to bring to mind other anti-vaccination concerns. Apparently similar findings are seen with motivated reasoning in political views. Perhaps of greater concern was that the corrective information approach reduced misperceptions among parents who were not antivaccination in principle but ALSO reduced their intent to vaccinate presumably through raising general fears of side effects. Furthermore emphasising the diseases was not very effective, and presenting stories around the disease and sickness actually increased misperceptions. While there are limits to this study its results are important and sobering. How many of our well-intended public health messages may be backfiring.

Reference: *Pediatrics* 2014;133(4):e835-e842

[Abstract](#)

Economic evaluation of the routine childhood immunization program in the US, 2009

Authors: Zhou F et al.

Summary: This study investigated the economic impact of the 2009 routine US childhood immunisation schedule. Costs were estimated using the direct cost and societal (direct and indirect costs) perspectives. Program costs included vaccine, administration, vaccine-associated adverse events, and parent travel and work time lost. Analyses showed that routine childhood immunisation among members of the 2009 US birth cohort will prevent approximately 42,000 early deaths and 20 million cases of disease, with net savings of \$US13.5 billion in direct costs and \$US68.8 billion in total societal costs.

Comment (NT): WOW! For all those service providers out there who are feeling tired and jaded with vaccinating – this is another way of saying you are doing an incredible job! For the US in 2009 there were around 20,000,000 fewer cases of vaccine preventable disease and 42,000 fewer early deaths related to these diseases. The \$ savings are LARGE. While the benefit-cost ratios for the newer vaccines (hepatitis A and rotavirus are the most recent on the US schedule) are lower than the historical ones, they still come out very cost-effective from a societal point of view. So if you ever feel like giving up just remember how much you are achieving day in day out with our regular national vaccination programme.

Reference: *Pediatrics* 2014;133(4):577-585

[Abstract](#)

Are well-child visits a risk factor for subsequent influenza-like illness visits?

Authors: Simmering J et al.

Summary: This study determined whether well-child visits are a risk factor for subsequent influenza-like illness visits within a child's family. 84,595 families who participated in the Medical Expenditure Panel Survey 1996–2008 were reviewed. For each family, 23,776 well-child-visit weeks and 97,250 influenza-like illness visit were identified. Logistic regression analysis showed that an influenza-like illness visit by a family member was positively associated with a well-child visit in the same or one of the previous 2 weeks (odds ratio 1.54). The additional risk translated to potentially 778,974 excess cases of influenza-like illness per year in the US, with a cost of \$US500 million annually.

Comment (NT): This is a very well-designed study showing healthy children and their families can and do pick up respiratory infections from waiting rooms. While this is a US setting, there is no reason to believe the outcomes would be different in a NZ general practice setting. The overall risk of catching a flu-like illness following a well-child visit was relatively small but significant. This is an important reminder to think very hard about the environment of our waiting rooms in general practice and how we can improve upon infection control. I think this is a real challenge for many of us as we often have significant space constraints and a mix of healthy people coming for preventive issues alongside infectious patients. The authors list strategies to consider such as improving environmental cleaning, respiratory hygiene and cough etiquette. I would also add that social distancing approaches to separate those who are likely to be infectious where at all possible may be worth considering! Creative ideas are needed here I suspect.

Reference: *Infect Control Hosp Epidemiol* 2014;35(3):251-256

[Abstract](#)



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Quantification of risk factors for herpes zoster

Authors: Forbes H et al.

Summary: This case-control study determined risk factors for herpes zoster at different ages. 144,959 adults diagnosed with zoster in 2000–2011 (cases) and 549,336 age- and sex-matched healthy individuals (controls) were included. Factors associated with increased risk of zoster included rheumatoid arthritis (adjusted odds ratio 1.46), inflammatory bowel disease (1.36), chronic obstructive pulmonary disease (1.32), asthma (1.21), chronic kidney disease (1.14), and depression (1.15). Type 1 diabetes (but not type 2) also showed an association with zoster (adjusted odds ratio 1.27). The relative effects of many assessed risk factors were larger in younger patients.

Comment (NT): This is an important study to help us in decision-making. Now that we have the zoster vaccine available on the private market the challenge is in knowing who we should prioritise to offer this to, particularly as cost may be a significant barrier for many. Unsurprisingly the strongest risk factor was severe immunosuppression, although overall numbers in this group were low. As the vaccine is live attenuated its use is contraindicated in this group. The other groups shown to have higher rates were those with rheumatoid arthritis, COPD, asthma, chronic kidney disease, type 1 diabetes and depression. Depression is an interesting one I would not have initially thought of but I assume there is an effect of stress on cellular immunity making varicella virus reactivation more likely. All these risk factors had a greater than 10% increased risk of zoster. Interestingly the relative importance of these factors lessened with age i.e. zoster becomes a bigger issue for everyone the older we get. While there is no clear answer here as to how to prioritise offering the vaccine to our patients in a systematic way, I would suggest based on the study findings that all those over 70 years could be offered the vaccine in view of the higher prevalence of the disease and post-herpetic neuralgia, but I would suggest for those 60–70 years or even 50–70 we should be targeting the above risk groups specifically. But bring on the discussion here

Reference: *BMJ* 2014;**348**:g2911

[Abstract](#)

Varicella in a paediatric intensive care unit: 10-year review from Starship Children's Hospital, New Zealand

Authors: Wen S et al.

Summary: This study reviewed cases of varicella requiring paediatric intensive care in NZ over a 10-year period to examine the severity, morbidity and mortality associated with the disease. 34 cases admitted to the paediatric intensive care unit (PICU) at Starship Children's Hospital from 2001–2011 were identified and 26 cases were reviewed. Of the 26 cases, 84.6% were Maori or Pacific Island ethnicity, 54% had no preceding medical condition and 23% were immunocompromised. The main reasons for admission to the PICU were neurological (38.5%), secondary bacterial sepsis or shock (26.9%), respiratory (15.4%) and disseminated varicella (11.5%). 81% of the children required invasive ventilation. Four children died and eight children had ongoing disability at hospital discharge.

Comment (HPH): In a typical year, the New Zealand population experiences approximately 50,000 chicken pox infections (almost equal to the birth cohort). This is because varicella zoster virus is highly infectious with a basic reproduction number of around 8–10. The only way to control or eliminate the disease is through vaccination. Highly effective vaccines have been available for twenty years and countries who have gained and maintained high coverage have achieved good control with a single dose programme, although a two dose programme gives optimal protection. It is possible to eradicate varicella, and ultimately shingles should we eradicate varicella and dispense with the vaccine. This study highlights that varicella can lead to serious illness – the tip of a very large iceberg. It is also salient to remember that adults are 25 times more likely to develop severe disease than children. Hence offering vaccination is also very pertinent to adults with no history of chicken pox.

Reference: *J Paediatr Child Health* 2014;**50**(4):280-285

[Abstract](#)

Safety and immunogenicity of tetanus diphtheria and acellular pertussis (Tdap) immunization during pregnancy in mothers and infants

Authors: Munoz F et al.

Summary: This study investigated the safety and immunogenicity of tetanus diphtheria and acellular pertussis (Tdap) immunisation during pregnancy. 48 pregnant women aged 18–45 years were randomised to receive Tdap or placebo at 30–32 weeks' gestation in a double-blind design, with crossover immunisation given postpartum. Primary outcomes were maternal and infant adverse events, pertussis illness, and infant growth and development until age 13 months. No Tdap-associated serious adverse events were reported. Growth and development were similar in both infant groups during follow-up to 13 months. No cases of pertussis occurred. Higher levels of pertussis antibodies were measured at delivery in women who received Tdap during pregnancy vs postpartum ($p < 0.001$) and in their infants at birth and at age 2 months (both $p < 0.001$). Antibody responses in infants born to women given Tdap during pregnancy were not different after the fourth dose of diphtheria and tetanus toxoids and acellular pertussis (DTaP) vaccine.

Comment (HPH): Evidence suggests that maternal immunisation may be the single best strategy for preventing pertussis in young infants. The first rule of thumb is that subunit vaccines are expected to be safe for pregnant women and their unborn babies and there are decades of experience of routinely vaccinating during pregnancy. There is no biological mechanism by which such vaccines would be expected to pose a safety risk to mother or fetus. What we now need are robust studies demonstrating safety outcomes in pregnant women and their infants. As a randomised placebo controlled trial this study is the gold standard for assessing safety outcomes although with just 48 participants there are few conclusions to be drawn in terms of safety outcomes other than there was nothing unexpected. However of note was that the antibody responses in the infants born to mothers receiving the vaccine were not different to those who did not receive the vaccine. This is reassuring, although from New Zealand's perspective it still remains to be seen whether the same results are achieved when immunisation commences at 6 weeks of age rather than 8 weeks of age as it did in this study.

Reference: *JAMA* 2014;**311**(17):1760-1769

[Abstract](#)

Independent commentary provided by Associate Professor Nikki Turner.

Nikki is a NZ-trained GP with background experiences also in paediatrics and public health. She currently works as the Director of the Immunisation Advisory Centre, a national public health programme based at the University of Auckland.

For full bio [CLICK HERE](#).



Independent commentary provided by Dr Helen Petousis-Harris.

Helen is Senior Lecturer in the Department of General Practice and Primary Health Care at the University of Auckland and the Academic Lead for Immunisation Research and Vaccinology at the Immunisation Advisory Centre. She has a PhD in Vaccinology and is particularly interested in factors associated with vaccine safety and reactogenicity.

For full bio [CLICK HERE](#).





Decreased immune response to pneumococcal conjugate vaccine after 23-valent pneumococcal polysaccharide vaccine in children

Authors: Sigurdardottir S et al.

Summary: This study characterised immune responses to 13-valent pneumococcal CRM197 conjugate vaccine (PCV13) in children vaccinated in infancy with 9-valent pneumococcal-meningococcal C-CRM197 conjugate combination vaccine (PCV9-MnCC), followed by a toddler dose of PCV9-MnCC or 23-valent pneumococcal polysaccharide vaccine (PPV23). 89 children who received PCV9-MnCC in infancy and PPV23 or PCV9-MnCC at age 12 months were vaccinated at age 7.5 years with PCV13 (groups PPV23/PCV13 and PCV9/PCV13, respectively). Immunoglobulin (Ig)G antibodies were measured before and after vaccination. One week postvaccination, IgG levels increased significantly for all serotypes in both groups, and >97% of children achieved IgG ≥ 0.35 $\mu\text{g/ml}$ 4 weeks after PCV13 vaccination. The PCV9/PCV13 group had higher IgG responses than the PPV23/PCV13 group. In conclusion, PPV vaccination of toddlers may compromise subsequent responses to PCV.

Comment (HPH): This study is an important contribution to the question around polysaccharide vaccines and hyporesponsiveness. We already know that meningococcal polysaccharide vaccines result in hyporesponsiveness (a blunted response in a repeat dose). Can giving a conjugate first before a polysaccharide mitigate this effect? Children who received PPV prior to PCV had lower baseline antibody titres to key serotypes than those who had received only PCV vaccines. This was more pronounced at 1 week and 1 month after PCV vaccination. Of key relevance here is that there were significant differences in the immune response between children who received PPV after being primed with the PCV and those who had only ever received PCV. This was demonstrated even years after the PPV had been given. The take home message is that even after priming with a conjugate vaccine a polysaccharide has a detrimental effect on both serum IgG and functional antibody, although the clinical relevance of this is not known. This should not currently stop us using polysaccharide vaccines for those at high risk of pneumococcal disease in view of their wider serotype coverage, but where at all possible we should be using a conjugate first and remaining mindful that future doses of any pneumococcal vaccine may have a lower than optimal response. We await more data.

Reference: *Vaccine* 2014;32(3):417-24

[Abstract](#)

Maternal and neonatal vaccination protects newborn baboons from pertussis infection

Authors: Warfel J et al.

Summary: This study in a primate model evaluated the impact of maternal and neonatal vaccination on pertussis infection in newborns. Baboons were vaccinated with acellular pertussis (aP) vaccine at 2 days of age or at 2 and 28 days of age. To model maternal vaccination, adult female baboons primed with aP vaccine were boosted in the third trimester of pregnancy. Neonatally vaccinated infants, infants born to vaccinated mothers, and naïve infants born to unvaccinated mothers were infected with *Bordetella pertussis* at 5 weeks of age. Naïve infant baboons developed severe disease when challenged with *B. pertussis*, but those receiving aP vaccine and those born to mothers vaccinated in their third trimester were protected.

Reference: *J Infect Dis* 2014; published online Feb 12

[Abstract](#)

Acellular pertussis vaccines protect against disease but fail to prevent infection and transmission in a nonhuman primate model

Authors: Warfel J et al.

Summary: This study evaluated the hypothesis that current aP vaccines fail to prevent colonisation and transmission. Infant baboons were vaccinated at 2, 4, and 6 months of age with aP or whole-cell pertussis (wP) vaccines and challenged with *B. pertussis* at 7 months. The baboons vaccinated with aP were protected from severe pertussis-associated symptoms but not from colonisation, they did not clear the infection faster than naïve animals, and readily transmitted *B. pertussis* to unvaccinated contacts. In contrast, vaccination with wP induced a more rapid clearance compared with naïve and aP-vaccinated animals.

Reference: *Proc Natl Acad Sci USA* 2014;111(2):787-92

[Abstract](#)

Comment (HPH): The recent development of a baboon model for human pertussis has enabled some ground-breaking research to be conducted. These two studies provide extremely valuable insight into the growing global challenge of pertussis control. The first message is that maternal vaccination in the third trimester confers protection against pertussis in the newborn baboon. The second is that neonatal vaccination is also protective; however evidence from Australia does suggest that neonatal vaccination with pertussis vaccine can reduce the responses to later doses of vaccine. Perhaps the most surprising revelation and the one that may explain some of our problem is that while acellular pertussis vaccine is effective at preventing clinical pertussis, it does not appear to prevent colonisation and therefore transmission. In other words, acellular vaccines are unlikely to contribute much to herd immunity; they only provide personal protection against the illness. While both whole cell and acellular vaccines appear to slightly reduce colonisation compared with no vaccine the whole cell vaccine appears to result in more rapid clearance which probably contributes more to reducing transmission. In the absence of more effective vaccines against pertussis, and none on the immediate horizon, we are left with focusing on the best strategies to protect the youngest of our infants who are at highest risk of severe disease. Despite high vaccine coverage, pertussis remains in circulation. There is no clear evidence to show that vaccinating mothers postpartum is effective in preventing disease in their infant, or any other cocooning strategies thus far evaluated. Both the baboon studies and human data indicate that acellular vaccination prevents severe pertussis and that vaccination of pregnant women in the third trimester can prevent disease in their babies for the first weeks of life until they can receive their own vaccination. Pregnancy vaccination appears currently to be the best approach to protecting our youngest infants.

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