

Making Education Easy

10-12 September 2013, Auckland Waipuna Hotel and Conference Centre

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About Research Review

Research Review is an independent medical publishing organisation producing electronic publications in a wide variety of specialist areas.

Research Review publications are intended for New Zealand medical professionals.

About Expert Forums

Expert Forum publications are designed to encapsulate the essence of a local meeting of health professionals who have a keen interest in a condition or disease state. These meetings are typically a day in duration, and will include presentations of local research and discussion of guidelines and management strategies.

Even for local events it is not always possible for everyone with a similar therapeutic interest to attend. Expert Forum publications capture what was said and allows it to be made available to a wider audience through the Research Review membership or through physical distribution. This publication is a summary of the 8th New Zealand Immunisation Conference and Pre-Conference Workshop 2013, held at the Waipuna Hotel and Conference Centre in Auckland from Tuesday 10 September to Thursday 12 September.

TUESDAY 10 SEPTEMBER, PRE-CONFERENCE WORKSHOP

Vaccine Education: 'An evidence-based approach' Dr Nigel Crawford (Medical Head of Immunisation Services, Royal Children's Hospital, Melbourne)

A number of groups worldwide host immunisation Web sites, including the World Health Organization, Public Health England, Great Ormond Street Hospital for Children (London), the University College London, The Children's Hospital of Philadelphia, The British Columbia Centre for Disease Control, Centers for Disease Control and Prevention (CDC), the US-based Vaccine Adverse Event Reporting System (VAERS), the American Pediatrics Society, the Bill & Melinda Gates Foundation and the NZ Immunisation Advisory Centre (IMAC).

Other useful resources for parents and caregivers include "Vaccines and your child: separating fact from fiction", by Drs Paul Offit and Charlotte Moser and the US Web site PKIDs (Parents of Kids with Infectious Diseases, <u>http://www.pkids.org/</u>), founded in 1996, with a mission to educate the public about infectious diseases, the methods of prevention and transmission, the latest advances in medicine, and the elimination of social stigma borne by the infected. PKIDs Online provides videos of individual patient stories and of families struggling with infectious disease experiences.

Resources available in Australia include "Myths and Realities" (http://www.immunise.health.gov.au/), "The Science of Immunisation", the Australian Government's Department of Health and Ageing (DHA) website, and the Immunisation page hosted by the Department of Health in Victoria and the Better Health Channel and the National Centre for Immunisation Research and Surveillance (NCIRS) in Sydney. The evidence-based 90-minute Australian documentary "JABBED: Love, Fear and Vaccines" features well-known medical leaders in the vaccination field (http://www.sbs.com.au/shows/jabbed) exploring the reasons for complacency and concerns around immunisation. This film reminds viewers of the consequences of delaying or refusing immunisation.

Various email alert services exist and disseminate information on vaccine safety and media releases. These include the CDC's vaccine safety email list, the Brighton Collaboration in Europe and the NCIRS email list used by Australasian immunisation providers and interested members of the public. Vaccine-preventable disease-specific email lists exist, such as the Media Bulletin of the Asia-Pacific Alliance for the Control of Influenza, which publishes influenza-related items collected from a range of media sources throughout the Asia-Pacific region. Such lists are a useful way to learn about events as they unfold.

A number of anti-immunisation websites exist and these can be very interactive, easy to read and follow, such as the Australian Vaccination Network, an anti-vaccination lobby group that has been heavily criticised by immunisation experts for providing misleading, inaccurate and deceptive vaccination information. The US CDC has published advice on how to evaluate immunisation-related information on the Web (http://www.cdc.gov/vaccines/vac-gen/evalwebs.htm) and determine the accuracy of the resource.

GlaxoSmithKline is proud to support the 2013 New Zealand National Immunisation Conference and continuing medical education with this publication

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Vaccine-preventable disease outbreaks, such as the measles epidemic in Swansea, Wales during 2012–2013, offer an opportunity for publicity campaigns about immunisation.

Social media is the new era of discussion – encompassing Facebook, Twitter, SMS, Chat groups (discussion) and blogs. Healthcare professionals (HCPs) need to be aware of the various sites hosting discussions between parents interested in immunisation: know how to utilise these social media and potentially moderate any discussions voicing concerns. The Seattle Children's Hospital hosts the "Seattle Mama Doc" Web site, which is a Blog run by a paediatrician addressing queries around children's health including immunisation. "ImmunizeBC" is hosted by the British Colombia Centre for Disease control, providing immunisation information, materials and resources for parents and HCPs. The site employs a fulltime nurse to disseminate information on vaccines, participate in and moderate daily Chat room discussions, maintain a Blog on new vaccines as they appear, and address email queries.

Parent groups are important. A couple of examples include the US-based "Word of Mom", encouraging mothers and caregivers to advocate for childhood,

adolescent and adult vaccinations, as well as "Every child by Two", which is designed to raise parental awareness of the need for timely immunisations and helps to moderate parental discussions about vaccine safety as they emerge. A strength of these discussions is that they are generated by parents, rather than HCPs.

Immunisation providers must keep up-to-date with new vaccines, be aware of potential vaccine safety concerns (e.g. HPV and influenza vaccines), and identify local expert resources (i.e. Web site(s), email lists, clinical services) for advice on how to treat any vaccine-related adverse reactions.

COI statement

- Dr Crawford has acted as an independent chief investigator for epidemiological studies sponsored by vaccine manufacturers (CSL) and serological testing (Merck)
- All payments, including for sitting on advisory boards and lecturing at scientific meetings, are paid directly to an administrative fund held by Murdoch Childrens Research Institute

CONFERENCE PLENARY SESSION: GLOBAL AFFAIRS

Peeping over the Horizon – increasing timely immunisations: a Rapid Cycle Improvement Strategy Dr Pat Tuohy (Chief Advisor Child and Youth Health, The Ministry of Health, Wellington), Rayoni Keith (Acting National Programme Manager, Immunisation, The Ministry of Health, Wellington)

New Zealand's Ministry of Health has announced a health target of increased immunisation, aiming for 90% of 8-month-olds completing their primary course of immunisation (6 weeks, 3 months and 5 months immunisation events) on time by July 2014 and 95% by December 2014 (see other talks in this publication for further details on immunisation coverage and timeliness in New Zealand). Increasing coverage for 8-month-olds requires on-going engagement with primary care and well child services. This interactive session explored what is happening in New Zealand's General Practices and sought to determine what might make a difference. Attendees participated in an exercise that applied the PDSA (Plan, Do, Study, Act) cycle. This approach characterises an issue:

Plan – identify factors to be addressed, make predictions, develop plan

Do – document problems

Study – compare data to predictions

Act – what changes are to be made?

Immunisation: Clinical Myths, a Healthcare Professional's Guide

Theo Brandt (Communications Manager, Immunisation Advisory Centre WellHealth, School of Population Health, University of Auckland)

The University of Auckland's 'Immunisation Myths and Facts' (http://www. immune.org.nz/immunisation-myths-and-facts) covers some of the common misconceptions that persevere among primary care health professionals, many of whom lack the time to keep up-to-date with current developments in immunisation. The video features prominent immunisation spokespeople, paediatricians and doctors, including Drs Teuila Percival, Nikki Turner and Jennifer Njenga. It is aimed at helping clinicians to best communicate immunisation information to parents. The video was funded by Waitemata, Auckland and Counties Manukau District Health Boards (DHBs) and is freely accessible.

Pain Management for Immunisations Dr Kathryn Russell (Clinical Psychologist, Kidz First Paediatric Consult Liaison Team, Auckland)

This presentation discussed the ways in which procedural pain can lead to procedural anxiety, needle fears and health care avoidance and, in particular, noncompliance with immunisation.¹⁻⁵ It described pharmacological and nonpharmacological techniques that can help to reduce children's acute pain and distress and subsequent behaviours and anxieties during vaccination. Oral sweet-tasting solutions such as sucrose are analgesic for infants up to 12 months.^{1.6} Good evidence supports the use of topical anaesthetic for reducing vaccination pain in infants and children (up to 15 years).⁷ Breastfeeding has an

analgesic effect.⁸ Infants lying supine experience more pain than those who sit upright or who are held by a parent.⁸ For infants aged <6 months, the 5-S rule (swaddling, side/stomach position, shushing, swinging, sucking) can effectively soothe a non-breastfeeding baby after vaccination (with no pain relief provided during immunisation with this method).⁹ Breathing techniques effectively reduce pain in >3-year-olds, while parent coaching during immunisation (distraction and appropriate parent behaviours) reduces child distress.⁸

Methods found to be ineffective include vapocoolants in children <3 years and ice packs in young children. Simultaneous injections are not associated with less pain than sequential injections and there is no evidence to suggest that subcutaneous/IM methods differ in pain. No evidence exists for or against oral analgesics for immunisation pain AND these drugs may interfere with the immunogenicity of the vaccines.

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Vaccine Safety: HPV vaccine as a case study Dr Nigel Crawford (Medical Head of Immunisation Services, Royal Children's Hospital, Melbourne)

During the early implementation phase of the human papillomavirus (HPV) vaccination programme in Australia, mass psychogenic reactions occurred among adolescent girls being offered the vaccine.¹ This phenomenon may in part be due to the short timeline between notification in February 2007 of the vaccine's inclusion in the vaccine program and its first delivery in May 2007, allowing little time for education around background concerns relating to HPV vaccination (e.g. some believe that the HPV vaccine will condone or promote sexual promiscuity). The stigma of this link to sexually transmitted disease is not seen with the MMR and varicella vaccines and is possibly a contributing factor to the mass psychogenic response.

The HPV vaccine currently covers four serotypes (HPV 6 and 11 for anogenital warts, HPV 16 and 18 for cervical cancer); new vaccines containing more serotypes are in the pipeline. The Victorian Cervical Cytology Registry has reported a decrease in incidence of high-grade cervical abnormalities within

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3 years after the implementation of the HPV vaccination programme² and national surveillance data show significant declines in the proportion of voung women with genital warts during the vaccination period 2007 to 2011.3

HPV vaccine and males: The national school-based HPV Vaccination Program has been extended to include males. From February 2013. males and females aged 12-13 years receive the HPV vaccine at school.⁴ Males aged 14-15 years will also receive the vaccine as part of a catchup programme until the end of the 2014 school year. Immunogenicity evidence demonstrates robust and equivalent anti-HPV type-specific virusneutralising antibody responses in both male and female 10- to 15-yearolds after HPV vaccination⁵ and a review of HPV vaccination in the Australian setting suggests that a degree of population protection has been achieved in adolescent males and females.6

AEFI reporting: Australian passive surveillance data for adverse events following immunisation (AEFI) show spikes in recording trends following the commencement of vaccine programmes, probably due to hypervigilance around the detection of AEFI.7 Background information from clinical trials and immunisation providers prior to the introduction of the HPV vaccine identified the most commonly reported AEFI as fever and local reaction; syncope was uncommon, while syncopal seizure, allergy and anaphylaxis were rarely reported. The evidence base for immunisation-related AEFI ⁸ and US data demonstrate that most of the AEFI rates for HPV vaccine did not exceed the background rates compared with other vaccines.9 True hypersensitivity to the HPV vaccine in Australian schoolgirls is uncommon and most vaccinees tolerate subsequent doses.¹⁰ In addition, there have been few reports in Victoria of syncope and seizure post-HPV vaccination.¹¹ Nevertheless, in June 2013, the Japanese Government withdrew its recommendation to use HPV vaccine in girls, citing concerns from the public about AEs.¹² Complex regional pain syndrome following HPV vaccination (4 cases) has been reported in Victoria.¹³ Recognising that this syndrome can occur is important for the prompt and effective management of potential complications. It can also be helpful to know background rates of target conditions that might be perceived as AEFI.

Dr Crawford and colleagues are running a 12-month pilot aimed at formalising their AEFI-Clinical Assessment Network, through which they discuss interesting cases of serious immunisation reactions following HPV vaccination by teleconference with colleagues in all Australian States. The funding will enable the case series to be formally collated at a national level. Telecommunication techniques enable physicians to consult with Australians who have difficulty in getting to a specialist or live in rural and remote areas; TeleHealth could be used to determine whether patients need to undergo more formal assessment such as allergy testing in Melbourne, or whether they can be immunised by their local physician. Improved communication around adverse events following immunisation can help

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PHARMAC's Role in Vaccines

Dr Peter Moodie (PHARMAC Medical Director and a practising GP in Wellington)

PHARMAC has assumed responsibility for evaluation and assessment of all new vaccines. MOH will continue to manage vaccine registration (Medsafe), while funding and payment of the immunisation benefits will remain with the DHBs and MOH. Vaccine targets will be determined by the DHBs and MOH. Promotional and educational work will also be conducted by the MOH.

PHARMAC actions to date

- Changed the name and reporting line for the expert advisory group: the Immunisation Technical Forum is now the Immunisation sub-committee of PTAC
- Widened access to Boostrix (Tdap vaccine) to include pregnant women
- Widened access to influenza vaccine to include high-risk children
- Released an RFP for all the existing vaccines on the Pharmaceutical Schedule and Opened the door for proposals on other vaccines.

The Gains and the Challenges

Associate Professor Nikki Turner (Director of the Immunisation Advisory Centre, a practising GP and an Associate Professor in the Division of General Practice and Primary Health Care, University of Auckland)

As of September 2013, the estimated 93% of fully immunised New Zealand children aged 2 years is a dramatic improvement over 55% in 1992. Nevertheless, important challenges remain:

- National Immunisation Register (NIR) data for the 3-month reporting period ending June 2013 reveal that timeliness of immunisations has improved to 90% for 8-month-olds, but the struggle remains to achieve 95% by the age of 2 years.
- NIR data reveal timeliness gaps for immunisation delivery among children at ages of 6 and 8 months living in the most-deprived deciles compared with those in the least-deprived deciles.
- The same phenomenon is seen among Maori children and Pasifika children, although coverage for Pasifika children aged 8 months shows that they have caught up to New Zealand European children (>90% as at 30 June 2013).
- Regional inequities remain; ~20% fewer 6- and 8-month-olds in the leastresourced DHBs complete age-appropriate immunisations compared to their counterparts in the highest-resourced DHBs.
- Immunisation also needs to focus on national coverage of 5-year-olds and adults, particularly in relation to administration of ADT Vaccine in adults.

Pertussis remains a perennial challenge in New Zealand. The acellular vaccines that have been used in New Zealand since 2000 have less efficacy overall than the traditional whole-cell pertussis vaccines, providing ~80% protection against typical disease with 71-78% protection against mild disease. Better/long-lasting vaccines are required.

Pneumococcal vaccines. The conjugate vaccines are very effective in infants. The role of conjugate vaccines in adults remains unclear. Duration of immunity remains a challenge.

Influenza vaccine. SHIVERS data reveal a substantial burden of influenza in young children (aged <1 years) presenting to Auckland and Counties Manukau hospitals (30 April through 30 September 2012). Scant data are available to assess the efficacy of influenza vaccines in children aged <2 years. Vaccine efficacy against influenzalike illness for the trivalent inactivated influenza vaccine (TIV) varies markedly between studies (30–78% VE). TIV are the only current vaccines in New Zealand. Future options include the use of live attenuated vaccines (LAIVs) for children, quadrivalent vaccine (additional B strain), and the use of adjuvanted vaccines and higher antigenic doses in the elderly/immunosuppressed.

Rotavirus vaccine. Rotarix (RV1) 2-course and RotaTeq (RV5) 3-course are available in New Zealand. Safety issues include possible prolonged shedding, particularly with RV1 in HIV-positive and other immunocompromised individuals, although there are no clear safety issues. The risk of intussusception is increased (1.9-2.6 times) at 1-7 days after the first dose, but it remains unclear as to whether there is an overall increase of intussusception.

Meningococcal vaccine. Meningococcal disease rates are highest in young children (1-4 years), with a secondary peak in late adolescence (15-19 years) (ESR, 2012). Pasifika children, followed by Māori, carry a particularly heavy burden of disease (as with influenza); the adolescent peak affects mostly European ethnicity. Most meningococcal disease cases in 2007-2011 in New Zealand were Group B strains (>60%) and Group C (~33%). Conjugate vaccines (Meningococcal Group A, C,

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W135 and Y conjugate vaccine) have been used since the 1990s and all have excellent herd immunity. Waning immunity is age-dependent (faster in infants). Booster doses are required to maintain individual protection if herd immunity has waned.

Varicella vaccine. Breakthrough disease is usually mild. Cases of zoster postvaccination are rare. Quadrivalent MMRV appears to be effective, but increases risk of febrile seizures 7–10 days post-dose one. The advice is to use MMR + V for the first dose, then MMRV for the second dose; there is approximately 80% effectiveness with a single dose, which is lower than with 2 doses. The vaccine should be used in healthy family contacts of high-risk individuals.

- There is a theoretical risk of increasing zoster if no wild boosting
- Use Zostavax in >50 years or >60 years (but may have a short immunity)

Issues for changing immunisation schedules

1. Pertussis control

- Some other scheduling options may help
- 2. Flu vaccination
 - Individual protection versus community protection

- 3. New infant/childhood vaccines
 - Which ones could be usefully added in (e.g. rotavirus vaccine)
- Where possibly on the schedule
- 4. Adult/adolescent vaccination (e.g. HPV)
- 5. High-risk groups vaccination

Communication/education challenges

- Sector tiredness how to maintain energies?
- Loss of focus
- Community confidence how to keep it high?
- The impact of new vaccine introduction often adds new impetus (but sometimes works the other way)

Communicating causality – a huge challenge for HCPs – vital to build effective, trusting relationships

Ever increasing complexities

- international schedules and translating them into New Zealand's environment
- multiple options/combination
- polysaccharide versus conjugate vaccines

WEDNESDAY 11 SEPTEMBER, CONFERENCE DAY 1

New Zealand immunisation – current status, challenges and achievements

Associate Professor Nikki Turner (Director of the Immunisation Advisory Centre, a practising GP and an Associate Professor in the Division of General Practice and Primary Health Care, University of Auckland)

The proportion of children fully immunised at 2 years of age has increased from \sim 50% in 1991 to >90% in 2012 and coverage of Māori and Pasifika children has caught up to New Zealand European children. From 2007 to 2012, immunisation rates have improved dramatically for children in areas of poverty.

The impetus driving this improvement in immunisation status began with the Public Health Commission report in 1993, calling for national immunisation coverage rates of 95% by 2000. NIR data reveal impressive gains in national immunisation coverage of 2-year-old children in response to the release of the national health targets in July 2007, and then again in response to timeliness targets released in July 2012 (calling for 90% of 8-month-olds to have their primary course of immunisation on time by July 2014 and 95% by December 2014), but there has been a levelling off since then. The targets are important drivers, but other aspects of the immunisation programme need to be considered.

Equity gaps remain. NIR data from 1 April 2013 to 30 June 2013 reveal that at the ages of 6 months and 8 months, fewer children are immunised from areas of poverty versus those in the least-deprived areas, that Māori children (particularly at 6 months) have lower rates of immunisation compared to other ethnicities, and timeliness remains a challenge in Pasifika children. Moreover, fully immunised percentage rates for 6-month and 8-month-olds vary by ~20% between the highest and lowest performing DHBs.

Vaccine preventable disease. Measles outbreaks will continue to happen for a long time yet, because of a historical lack of full immunisation coverage. The now-waning pertussis epidemic has been an enormous challenge. While existing vaccines are effective they lack long-lasting immunity. Gaps remain in coverage rates, and challenges remain in regard to how to deal with pertussis. New Zealand continues to have outbreaks of a range of diseases, such as the meningococcal C outbreak in Northland in 2011. Among all hospitalised influenza cases among Auckland and Counties Manukau DHB residents between April and September 2012, a large burden of disease was seen among the <1-year-olds; most were Pasifika or Māori and from the most-deprived socioeconomic backgrounds.

Current immunisation coverage has to improve for 4- and 5-year-olds in New Zealand, data are lacking as to adult uptake of ADT vaccination and more awareness is needed as to the role of pertussis and the adult burden of disease.

SUBSCRIBE TO RESEARCH REVIEW www.researchreview.co.nz The high-risk programmes need more attention; these are very complex and many adult patients are living in the community with multiple illnesses. Confusion surrounds the use of pneumococcal vaccines in adults. Consideration must be given to the role of future vaccines such as shingles and whether the right strategy is being employed such as the influenza programme.

The current ethical challenge in the New Zealand environment. A number of good vaccines are available on the private market (e.g., varicella, rotavirus), some of which are provided for free in other countries. The IMAC helpline 0800 IMMUNE is fielding an ever-increasing number of queries from immunisation providers and the public asking increasingly complex questions about aspects of immunisation. The centre is tasked with translating international immunisation schedules and advising on catch-up programmes for people moving into the New Zealand environment. Immunisation providers are seeking advice on vaccine errors, split-vaccine challenges and consumer choice issues.

Public health impact after introduction of a new Group A meningococcal vaccine in Africa Dr F Marc LaForce (Albert B. Sabin Gold Medal Award recipient in 2012, and former Director of the Meningitis Vaccine Project)

Over 90% of global meningococcal disease occurs in the 21 countries of the Sub-Saharan meningitis belt and a single strain, Group A, has accounted for an estimated 80% of all cases. Focal epidemics occur yearly and major epidemics occur every 7–14 years. Group A meningococcal disease has a case fatality rate of about 10% and about one-quarter of survivors have serious sequelae.

Following a huge meningitis epidemic in 1996, African public health officials approached WHO for help to address this problem. The Meningitis Vaccine Project was created in June 2001 with Gates Foundation support as a 10-year partnership between WHO and PATH. The project's single goal was to eliminate epidemic meningitis in Africa as a public health problem through the development, testing, licensure, and widespread use of conjugate meningcoccal vaccines. Through an innovative public/private partnership, a new and affordable Group A meningcoccal conjugate vaccine, MenAfriVac[™], was developed and manufactured at the Serum Institute of India in Pune, India.

In clinical trials conducted in four African countries involving 10,000 1–29-yearolds, MenAfriVac[™] (PsA 10 µg) was well tolerated and showed superior immunogenicity over the licensed polysaccharide vaccine. The Men A vaccine induced immune memory, sustained bactericidal antibodies and boosted antitetanus immunity. MenAfriVac[™] was licensed in December 2009, prequalified by WHO in June 2010 and was first introduced in mass vaccination campaigns in Burkina Faso on 6 December 2010. In a 10-day campaign, 10.8 million Bukinabes (coverage of 95.9% of Burkinabes 1–29 years of age) were vaccinated. Cases of Group A meningococcus in Burkina Faso have fallen dramatically from more than 45,000 cases occurring during 2006–2009 to none since 2010. Bacteriological data have shown a disappearance of serogroup A Nm meningitis (see Fig. 1).

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			Nº	Percent
Reporte	d meningitis cases		3875	
Number	of CSF specimens		3412	88.1
Number	of CSF sent for lab o	onfirmation	3318	97.2 22% in
				2007
Bacteriologic results (PCR, latex or culture)				
	Contaminated		609	18.3
	Negative		1552	46.8
	Positive		1157	34.9 9% in
	Total		3318	100 2007
Distribution of pathogens (% based on positive samples)				
86% 2007-	NmA	1 (0.1%)	Pneumococcus	837 (72.3%)
10	NmX	161 (13.9%)	Hib	43 (3.7%)
	NmW135	110 (9.5%)	Other	3 (0.3%)
	Nm indeterminant	2 (0.2%)		

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Figure 1. 2011 meningococcal bacteriological data – Burkina Faso.

Carriage studies in two rural and one urban area before and after the MenAfriVac[™] campaign showed a disappearance of Group A meningococcal carriage after vaccination. Similarly, Niger observed the disappearance of Group A meningococcal disease after the introduction of MenAfriVac[™] over a 2-year span. To date, over 100 million Africans in the meningitis belt have been immunised and the 2013 meningitis data from meningitis belt countries show the lowest number of cases reported over the last 20 years.

The vaccine owes its success to the combined input from many individuals and organisations worldwide working in collaboration with Health Authorities of 26 countries in Sub-Saharan Africa and of India. As the benefits of this vaccine continue to accrue meningitis belt countries have pushed for the introduction of other products like pneumococcal and pentavalent vaccines in an effort to fully control bacterial meningitis in this heretofore hyperendemic area.

Ghosts and Miasmas: Vaccination for the 1918 pandemic of influenza in Polynesia Dr Ryan McLane (Senior Advisor Nursing, Office of the Chief Nurse, The Ministry of Health, Wellington)

In 1918, vaccines and anti-toxins were being utilised against smallpox, rabies, typhoid fever, and diphtheria. However, viral diseases such as influenza were not well understood. Influenza was commonly attributed to a miasma, an invisible gas or condition of the air, causing infection. The 1918 flu pandemic (January 1918 to December 1920) infected 500 million people worldwide. Influenza arrived in Polynesia from New Zealand via infected passengers on the USS Talune, which docked in Fiji, Tonga, and Western Samoa, killing 7%, 9% and 26% of the populations, respectively. Lethality was greatest among 18–45-year-olds. No effective vaccines existed. In New Zealand, vaccination was seen as useless once the pandemic had swept the country. Public health systems in Polynesia largely developed as a direct result of these mass vaccination efforts and almost all of them lack records prior to 1914. The controversy over vaccine use and the pandemic in 1918 helped to drive the establishment of global criteria for vaccine trials.

GLOBAL EXPERIENCE, PROGRAMMES AND POLICIES

Use of varicella vaccine in the United States: overview of 15 years of follow-up Dr Barbara Kuter (Executive Director of Medical Affairs, Pediatric, Merck, USA)

The varicella vaccine was licensed in the US in 1995, and was routinely recommended in early 1996 by the Advisory Committee on Immunization Practices (ACIP). The one-dose recommendation (given at 12–15 months of age) lasted for ~10 years. In the face of ongoing outbreaks of varicella, the CDC added a second dose of varicella vaccine in 2006 to the routine immunisation schedule for children aged 4–6 years. The vaccine has been licensed in New Zealand since 1996 for use in children aged between 12 months and 12 years. It is available in the private sector only. No significant safety signals have been reported.

Impact of the 1-dose vaccine. Between 1998 and 2006, varicella-related hospitalisations in the US decreased dramatically during the 1-dose vaccination era and by ≥65% in all age groups (by >70% in persons aged <20 years) compared with those in the prevaccination era.¹ The 1-dose vaccination programme is also credited with an impressive decline (88%) in varicella deaths between 1990 and 2007.² Comparisons of reported incidence and case-specific data for 2005 and 2008 show a further overall reduction of ~50% in varicella incidence among 1–14-year-olds in Connecticut after implementation of routine 2-dose varicella vaccination.³ A 2008 US review of postlicensure data reported that one dose of varicella vaccine was 84.5% effective in preventing all varicella, 97% effective in preventing moderate-to-severe disease and 100% effective in preventing severe varicella.⁴

Effectiveness of 2 doses of varicella vaccine. Case-control evidence shows vaccine effectiveness (VE) of ~86% with 1 dose and 98.3% with 2 doses.⁵ The second dose of vaccine may be important not only for preventing breakthrough varicella and continuing transmission of the virus, but also for lowering the subsequent risk of developing zoster by decreasing latent infection with wild-type varicella-zoster virus.

Two long-term VE studies have been conducted by the Kaiser Permanente Vaccine Study $\text{Center:}^{6,7}$

In the first study, 7585 children aged 2 years were vaccinated with varicella vaccine in 1995 and followed for breakthrough varicella and herpes zoster (HZ) through 2009.⁶ Rates of varicella were 9- to 10-fold lower in the vaccinees versus the prevaccine era. Most cases were mild. VE was stable over the 14-year period, ranging from between 73% and 90% per year; the lowest effectiveness

was in the first couple of years. Over time, VE stabilised and averaged at ~80–90%. None of the 2826 children who received a second dose in 2006–2009 developed varicella. Forty-six cases of HZ occurred over the 14-year period. All cases were mild, and the incidence of HZ was lower by ~40% in vaccinated children than in unvaccinated children during the prevaccine era.

Why is zoster less common after vaccination than after natural disease? Two theories:

- The attenuated virus may not be able to reactivate as much as the wild-type virus.
 The vaccine strain is associated with less rash and therefore less frequent access to sensory neurons to establish any latency.
- The second study assessed changes in varicella incidence over the 15 years following vaccine licensure in children and adolescents aged 5–19 years and also hospitalisation rates for varicella and HZ in people of all ages.⁷ Five cross-sectional surveys (1995, 2000, 2003, 2006 and 2009) each randomly sampled ~10,000 members aged 5–19 years in the Kaiser Permanente Northern California databases. Varicella incidence fell in all age groups (5–9 years, 10–14 years, 15–19 years) from 1995 to 2009; the reduction was 94% in the 10–19-year-olds (from 13.354 per 1000 person-years in 1995 to 0.842 per 1000 person-years in 2009). In all ages, varicella hospitalisations were reduced overall by 88% from 1994 to 2009.

Overall zoster hospitalisation rates appeared to increase over time. However, these findings are consistent with prior studies and not clearly related to varicella vaccination. Moreover, it is uncertain as to how real this increase is, since many changes in coding practices occurred over the 15 years in the Kaiser Permanente databases. There may also be confounding by age: the size of the older age category (\geq 75 years) more than doubled over time, likely resulting in more immunocompromised and higher reinfection rates.

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Introduction of Pneumococcal, Rotavirus and Human Papillomavirus Vaccines in Fiji Kylie Jenkins (Technical Facilitator Infant & Child Health, Fiji Health Sector Support Program)

In July 2012, Australian Aid announced funding of over \$5 million to support the introduction of three new vaccines to Fiji's immunisation schedule: the pneumococcal, rotavirus and HPV vaccines. Immunisation with the pneumococcal and rotavirus vaccines commenced with babies born from 17 September 2012; HPV vaccination began in 2013 among Year 8 schoolgirls.

Fiji has a high burden of pneumococcal disease, with an annual incidence rate for hospitalised all-cause pneumonia of 1817 per 100,000 children aged <5 years and an annual *Streptococcus pneumoniae* incidence of 9.9 per 100,000 children aged <5 years and a case fatality rate of 36%.^{1,2} Similarly, of 1610 stool samples analysed over a 5-year period (2007–2011), 39.8% proved positive for rotavirus (RV) antigen.³ Two-thirds of RV occurred in children aged 6–24 months. Cervical cancer accounts for 19% of all cancers in Fiji,⁴ with an incidence rate of 49.7 per 100,000 and a high mortality rate (70% die within 5 years of diagnosis).⁵ PAP smear coverage for eligible women is only 8%; high-grade abnormalities have been detected in 10% of PAP smears.⁵

A Partnership between the Government of Fiji and Australian Aid has provided significant technical support at all stages of the introduction. The support has also established surveillance systems. An Effective Vaccine Store Management

Assessment enabled the MOH to assess cold chain resources to accommodate the new vaccines. Fiji's Public Health Information System was revised to a computerised system and a new Child Health Record accommodates the new vaccines.

The launch of Child Health Week on 17 September 2012 signified the first cohort of babies to receive the new immunisations and Child Health Record. The first doses of vaccine were administered on 29 October 2012. The national rollout of the HPV vaccine for class 8 girls began in February 2013.

At the time of this report, coverage was as follows:

- 6 weeks Pneumococcal 1 and Rotavirus 1 was 98%
- 14 weeks Pneumococcal 3 and Rotavirus 2 was 80%
- Class 8 girls HPV HPV1 coverage in schools visited was 92%

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VACCINE SAFETY

Postmarketing Surveillance: Influenza vaccine – Fluvax science Dr Jim Buttery (Director of Monash Immunisation and Director of Research at Monash Children's Hospital, Melbourne)

Irrespective of vaccination status, febrile seizures are common in young children (affecting 2–3%), triggered usually by a minor infection (e.g. upper respiratory tract infection, influenza). The classic age group is between 6 months and 5 years. The seizures are generally brief (lasting <5 minutes) and overwhelmingly benign with no neurological sequelae in the vast majority. An increased risk has been described following some vaccines, including the MMR, MMRV and influenza vaccines. Febrile convulsions following influenza vaccines classically occur 7–11 hours post-vaccination. The US CDC has described a febrile convulsion rate of 0.03 (0.16 over 7 days) per 1000 influenza vaccine doses.¹

In Australia, TIV is funded for special risk groups only in children. The estimated coverage in children is ~5%; influenza vaccine is not required on the ACIR Immunisation Register, so coverage is hard to determine and the majority of data are held in primary care practice software. The local manufacturer, CSL Biotherapies, provides inactivated TIV as Fluvax/ Fluvax Jnr/ Panvax (H1N109). Other international manufacturers also provide vaccines within the funded National Immunisation Programme for special risk children. This situation exists throughout Australia, except for Western Australia. There, the deaths in 2007 of three young children were attributed to influenza. This triggered State funding for annual routine influenza vaccination of all children aged 6 months to 5 years, commencing in 2008. TIV uptake in 2008 and 2009 was high (30–35%). The vaccine was well publicised and combined with high-quality VE studies.

Australia TIV 2010 experience. No RCT data were available in children for this batch. This seasonal vaccine had well-established components including the monovalent H1N109, which had been used in the monovalent Panvax H1N109 trials in 2009 with a 15 μ g dose. The paediatric data described severe fever in 1.2% of children given the 15 μ g dose (same dose as in TIV) and in 5.1% given the 30 μ g dose. After the introduction of TIV in March 2010, a problem arose initially in primary care followed approximately a month later by reports of febrile convulsions in children presenting to the Emergency Department (ED). The Therapeutic Goods Administration (TGA) was notified on 13 April. On 22 April, against the advice of the Federal Government, Western Australia suspended the preschool influenza vaccination programme; on 23 April, the TGA suspended the national TIV vaccination programme.

Febrile convulsion data from Princess Margaret Hospital in Perth, revealed that in 2008 and 2009, the vast majority of children presenting with febrile

convulsions had not been vaccinated with TIV. In 2010, approximately half of all cases were TIV temporally-associated. Further investigations in WA examined the State ED Information System (EDIS) database combining 9 Perth EDs for all presentations coding for febrile seizure in children aged <5 years, 1 January to 2 May 2010.³ As with the Princess Margaret Hospital data, the WA data showed febrile convulsions occurring that were not associated with TIV vaccination, leading up to the commencement of the immunisation programme. An estimated maximum of 18,816 doses of TIV were administered in 2010 and 63 febrile convulsions were recorded, giving an estimated rate of 3.3 per 1000 doses of TIV administered (>100-fold increase in febrile convulsions). The estimated risk of febrile convulsions was >200-fold for Fluvax and Fluvax Junior formulations (CSL Biotherapies) compared to the major alternate brand Influvac.

Most cases of convulsion were in the 6 month to 2 year age group; the risk was much lower amongst children aged up to 5 years, consistently across all States.⁴ An analysis of the risk of febrile seizure post-influenza vaccine (CSL seasonal Fluvax, CSL monovalent 'Panvax', and other influenza vaccine brands, from 1 March to 30 April 2010) in children aged 6 months to 5 years revealed an incidence rate ratio (IRR) of 15.2 for Fluvax-associated febrile seizures within 48 hours compared to the unexposed periods.⁵ In age-adjusted analyses, IRRs for Fluvax and febrile seizures within 48 hours were 15.2 for <2 years and 0.7 for >2 years of age.

Incomplete splitting appears to be responsible for the increased reactogenicity with TIV 2010. Australia now requires all TIV formulations new to the Australian market to provide a data package including comprehensive reactogenicity in children and active surveillance at least in the first season of vaccine use in children. Ongoing ED surveillance is measuring febrile convulsions in children, to detect any adverse association as early as possible. The TIV published data show a significant season to season variation within the same brand for rates of fever for all TIV formulations, with higher rates of fever for the CSL TIV. Adjuvanted vaccines also have a higher rate of fever.

It is unclear as to whether it is possible to predict an unacceptable febrile convulsion rate before introducing a TIV formulation to the public – either from preclinical correlates or by using existing data to determine a fever rate threshold in clinical trials for application to children. Questions remain as to whether adults can be used as surrogates, or whether the target age group is examined directly.

Fluvax is not licensed for the <5-year-olds, but it continues to be given to a small number of children. In April 2012, a 22-month-old was admitted to intensive care after suffering a prolonged febrile convulsion following Fluvax



administration and has sustained significant brain damage. The family are now strong advocates for improving vaccine safety and have maintained concerns around the safety of the surveillance system in Australia.

In response to the 2012 episode, TGA and WA Parliamentary inquiries recommended that States retain adverse event reporting and that AEFI reporting for States be harmonised (i.e. forms, methods), user-friendly and timely internet reporting with built-in flags for rate changes. The inquiries also called for increased consumer and health professional awareness, defining of surveillance objectives, a priority for e-health, a national vaccine safety committee, agreed protocols for action and making de-identified AEFI reports available for open review.

Many of these recommendations have already been implemented. Internet reporting is on the way. No fault compensation schemes are available in 19 countries worldwide, including New Zealand, the USA, Taiwan and around 13 European countries.⁶ Vaccine injury compensation has been advocated by the Public Health Association of Australia; the position of the new Federal Government is awaited.

Where to from here?

For signal detection the following are needed:

- denominator (administration) data
- automated statistical methods reports
- transmit data from States to central government instantly and uniformly
- other datasets; nonspecific flags
- incorporation of geocoding and visual data

For signal investigation:

- Datasets; primary care and hospital
- Linkage with immunisation datasets
- All of life immunisation registry
- Risk plans being prospectively developed by the National Regulatory Authority

Other data sources that will become available include the National Prescribing Service (a network of 500 linked general practices) that is designed to examine the links between general medicine and vaccines, and all vaccine-related outcomes. Medicare locals are conglomerating records and providing group data in the millions. Potentially rich data sources for surveillance are available from better use of health advice telephone lines and also Google searches, which may serve as an early warning that a problem exists. PREDICT (Paediatric Research in Emergency Departments International Collaborative) pools ED data to provide an early warning system and serves as a model for improving vaccine-related warnings. Frontline SMS offers a source-free text management platform for examining adverse events 48 hours post-vaccination.

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Global Initiatives in Vaccine Safety and New Zealand's Capacity

Presented by Associate Professor Nikki Turner (Director of the Immunisation Advisory Centre, a practising GP and an Associate Professor in the Division of General Practice and Primary Health Care, University of Auckland) on behalf of Dr Helen Petousis-Harris

Modern approaches to vaccine safety include passive safety surveillance, post-licensure clinical trials and Phase IV surveillance studies, large linked databases, and clinical centres. Passive safety surveillance systems are in place in \sim 35% of all countries worldwide:

- The Advantages: sensitive to serious events, can detect programme errors, applies to whole population
- The Disadvantages: no unexposed, under-reporting of less serious events, reliance upon voluntary reports

Global examples of passive surveillance systems include the VAERS established in 1990, sponsored by the CDC and FDA and disseminated to the public. Health professionals are required to report. VAERS has proven effectiveness (e.g. Rotashield and intussusception reports in 1999 led to CDC investigations). Around 30,000 reports are generated annually.

Europe has established the Vaccine Adverse Events Surveillance & Communication (VAESCO) Project and the Pharmacovigilance in European Economic Area (EURDAVIGILANCE; est. 2001), sponsored by the European Medicines Association and National Competent Authorities. EURDAVIGILANCE requires mandatory reporting, is disseminated to the public with proven effectiveness (e.g. narcolepsy and H1N1 vaccine). The WHO Uppsala Monitoring Centre (UMC) was set up in 1978 after the thalidomide tragedy in the early 1960s.

In Australia, the TGA processes voluntary reporting of AEFIs by health professionals and consumers, and mandatory reporting from sponsors. It involves a coordinated approach from States and territories, and routine reporting via the National Centre for Immunisation Research and Surveillance (NCIRS) and the Australian Technical Group on Immunisation (ATAGI).

New Zealand examples:

• The Centre for Adverse Reaction Monitoring (CARM; est. 1965), Dunedin, University of Otago, collects data with the Uppsala Monitoring Centre. CARM involves a very small population but has the third highest reporting rate in the world.

1. The postmarketing safety monitoring of the meningococcal B vaccine (MeNZB) through 2004–2006 used two key platforms – the NIR and NHI. This ensured that this was a very effective integrative passive and active surveillance system and is yet to be matched anywhere else in the world.

2. A method for rapid signal verification via primary care 2011: Participating general practices identified flu vaccinees aged 6 months to 5 years via the Practice Management System (PMS). Practice nurses contacted the family and documented vaccine, batch number, then surveyed parents. The data revealed an increased risk of febrile convulsions and other febrile-associated events within 24 hours following administration of Fluvax compared with Vaxigrip, Influvac and Fluarix, respectively. Febrile events also differed between the vaccine brands.

An advantage of global collaboration in vaccine safety is illustrated by Western Australia's signal detection uncovering febrile convulsions in infants and children following the 2010 influenza vaccine. This was not detected in New Zealand (probably due to its low population rates of febrile convulsions and also, passive surveillance systems do not detect more minor reactions such as high fever). Signal verification was an initial collaboration between NCIRS, sanofi pasteur and IMAC – the data suggested an increased risk for fever with Fluvax compared with Vaxigrip (RR 4.33). The resulting risk assessment was a collaboration between IMAC and sanofi pasteur, CSL and GSK.

3. **Evaluating the safety of pertussis vaccine in pregnancy.** The New Zealand Pertussis in Pregnancy Safety (PIPS) Study will evaluate health outcomes in infants of mothers vaccinated with the tetanus, diphtheria, and pertussis (Tdap) vaccine during pregnancy and describe any adverse events in pregnant women who received the Tdap vaccine. One substudy will actively follow mothers who received Tdap during pregnancy; another will follow their infants for up to 1 year after birth.

An advantage of New Zealand data is the presence of 4 important datasets – Healthpac claims for maternal immunisation status, Maternity Collection for pregnancy/birth outcomes, National Minimum Dataset for infant outcomes, and ESR notification data. These can be encrypted and merged into a single line level dataset including ~320,000 individuals, yielding both exposure and outcomes results. New Zealand can now combine with international colleagues and conduct local safety vaccine monitoring. Exposures data consist of the NIR and the pharmaceutical data collection for vaccines not on the NIR, while outcomes data



are comprised of primary (PMS) and national collections (hospitalisations on the National Minimum Dataset, maternity collection, and disease notifications from the ESR). The newly evolved New Zealand Vaccine Safety Experts Advisory Group (EAG) will pool immunisation expertise for effective collaboration and action.

The Way Forward

Global vaccine safety initiative (GVSI)

WHO global vaccine safety blueprint 2011

Vision: to establish effective vaccine pharmacovigilance systems in all countries

• Brighton Collaboration

- Setting vaccine safety research standards
- Conducting collaborative studies
- Linking large databases
- Building research capacity
- Communicating timely and accurate findings

• GRIP: Global Research in Paediatrics

- EC-funded
- Globally identifying population-based data sources capturing immunisation and health information of children

Safety Monitoring and Adverse Reactions to Tdap Vaccine in Pregnancy – the SMART VIP Study

Dr Tony Walls (Infectious Diseases Specialist and General Paediatrician, Christchurch)

Infants with pertussis have the highest rate of hospitalisations amongst all age groups. In the most recent New Zealand pertussis epidemic, 40–50% of notifications and hospital admissions were for infants aged <12 months. High rates of pertussis exist with no means of protecting infants directly. Moreover, severe disease is most likely to occur prior to the first dose of pertussis vaccine in infants. Transplacentally-acquired antibodies against pertussis are minimal at birth in infants born to women who have not been recently vaccinated. Good data attest to the safety of tetanus, diphtheria and influenza vaccines in pregnant women. The following recommendations have been issued:

- ACIP (USA) Oct 2011 recommended Tdap (1 dose) for pregnant women
- ACIP (USA) 2012 recommended Tdap for every pregnancy
- JVCI (UK) 2012 recommended Tdap for pregnant women

Canterbury introduced Tdap in April 2012, funded by Canterbury DHB, which agreed to fund safety monitoring. The vaccine has been nationally funded since January 2013.

SMART VIP Study:

This ongoing study funded by Canterbury DHB is assessing the safety and tolerability of Tdap vaccine in pregnant women and safety in infants. Within 2 weeks of vaccination, the women are asked to participate in a structured telephone questionnaire, followed by a written questionnaire on adverse events emailed at 4 weeks after vaccination. Following delivery, outcomes data are collected on gestation, birth weight, complications. Infants are followed up for 12 months for growth, congenital anomalies, vaccination (status and timeliness), and exposure to pertussis or pertussis-like disease.

By the end of August 2013, the study had received 429 eligible claims and enrolled 300 mothers. So far, 284 babies have been born (including 4 sets of twins) and are undergoing follow-up. The mean age at vaccination was 32 years and the mean gestational age at vaccination was 33 weeks. MOH funds the vaccine from 28–38 weeks' gestation. Canterbury DHB funds vaccination between gestation weeks 30–38 and also post-delivery. Thirty-three (11%) had received influenza vaccine during pregnancy. Ethnicity is predominantly European or other European, ~3% Māori and 6% Asian.

- Most adverse events immediately post-vaccination occurred at a rate of <10%. A total of 242 women (>80%) reported pain at the site of injection, defined as mild by 111 women (mild = having normal movement of the arm), moderate by 129 (moderate pain = some limitation in the movement of the arm), and severe in 2 (severe pain = unable to move the arm). Redness/ swelling was reported by 20 women (<1 cm in 15 women, >1–2.5 cm in 4, and >2.5 cm in 1).
- 84% of respondents completed the adverse events questionnaire at 4 weeks post-vaccination. Events were mostly infection (>60%) and any sort of medically attended event (>90%); most infections were urinary tract infections or superficial skin infections for unrelated reasons. The majority of the other adverse events were events in addition to those caused by vaccination and included pregnancy-related outcomes such as premature labour, or vaginal bleeding. There was one ED presentation (probably due to inflammatory bowel disease-related labour complications); the majority of cases presented to their GP or medical clinic.
- The 284 babies had a mean gestational age of 39 weeks and mean birth weight of 3849 g. Sixteen (6.7%) were preterm deliveries; 2 infants <33 weeks, 3 infants 33–35 weeks, 14 infants 35–37 weeks. Congenital anomalies were reported in 4 infants (1.4%). The rates for both preterm births and congenital anomalies fit within the background rates for Canterbury.
- Similar rates were reported by a recent study from the UK, also using Brighton collaboration methods and involving women vaccinated with a pandemic influenza vaccine during pregnancy; the medically attended event rate was 22.1%, spontaneous abortion 3.3%, congenital anomaly 1.9%, and preterm delivery 5.4% (Tavares F, et al. Vaccine. 2011;29(37):6358-65).

MEDIA AND COMMUNICATION

Keeping It Short and Sweet: Animation as a Communication Tool Dr Siouxsie Wiles (Microbiologist, The University of Auckland)

Animation is a more effective communication tool than scientific publications for interacting with the general public and for highlighting the message of immunisation and disease. Wide-reaching media tools allow easy dissemination of messages such as Twitter (200 million users), Facebook (1.1 billion), and YouTube (1 billion unique visits per month). In 2011, the Australian scientist Daniel Keogh (aka Professor Funk) uploaded a YouTube video entitled "The strange powers of the placebo effect" (http://www.youtube.com/watch?v=yfRVCaA5o18&feature=youtu.be), which has been viewed >1 million times. Dr Wiles has created a video about her research, featuring the *Lampyridae* firefly, which has been viewed >5000 times (Meet the Lampyridae http://www.youtube.com/watch?v=kP_RaHo1Pmw) and is a very useful teaching tool that explains the focus of her work within around 2 minutes. Using this tool to convey key messages gave Dr Wiles the opportunity to transform the very long and important publication "*Solutions to Child Poverty in New Zealand: Evidence for Action*" into a series of 1.5-minute YouTube videos (for example, http://www.youtube.com/watch?v=5SsfGmHBiYk&feature=youtu.be

>2000 views to date). The videos explain the issue of child poverty in New Zealand and promote solutions. Their intention is to give child poverty a communitywide focus that can be shared on Facebook and Twitter, helping to drive action for change amongst a much wider audience beyond the readers of the published document.

Are Māori hard to reach or is General Practice hard to use? Engaging Māori parents on immunising their children

Tim Corbett (Managing Director, ThinkSpace, Auckland)

This presentation discussed findings from an investigation into the barriers that General Practice creates for Māori (a 'customer' view) as opposed to the conventional approach that seeks to explore what barriers Māori have (victim blame approach). The bottom line is:

⁶ The degree of **comfort** individuals feel with seeking health services impacts on their use of services and, in turn, health outcomes' (Durie MH. Mauri Ora: the dynamics of Māori health. 2001). The entire General Practice patient



management system should be in line with this concept. A significant aspect of access to care involves the way in which General Practice reaches out to Māori patients and their whanau and welcomes them into the General Practice environment. Other key areas for action involve pronunciation, professional development, customer service, and the waiting and consultation rooms. Follow-up is vital: supporting the mother in a culturally positive way will help her feel positive about the experience and be more willing to return for later vaccinations. Focus on 'comfort' to improve access: decrease practice barriers – adjust the tone and look of the place – increase access.

Filling the Information Void: Not the Tooth Peter Griffin (Manager, Science Media Centre, Wellington), Dr Siouxsie Wiles (Microbiologist, The University of Auckland), Tim Corbett (Managing Director, ThinkSpace, Auckland)

Hamilton City Council's decision in June 2013 to stop adding fluoride to Hamilton's drinking water overturned a 2006 public referendum in support of continued fluoridation. Three vocal dentists and the Fluoride Action Network fronted a misinformation campaign of science underpinning fluoridation. The scientific community had to quickly find experts to present the case for adding fluoride to the water supply. Dentist Dr Jonathan Broadbent became a national spokesman and helped to mobilise other scientists to speak up and enter into the media. Hamilton subsequently announced another referendum, to enable a public vote on the issue. The MOH Fluoride Information Network unit is charged with presenting evidence for fluoride use in New Zealand. Clearly, simply presenting information is not enough – advocacy is essential. Amongst other reactions to the Council's decision, science bloggers published material that fed into media coverage. The Waikato DHB recognised the importance of playing an active role in backing the science behind fluoridation, and a new, fast-growing Facebook group called "Pro-evidence on Public Health" has enlisted members with high profiles in public health.

Options for science communication have proliferated in the last decade and the fragmentation of media consumption continues. Scientists must become media savvy and match the tactics of the other side of information.

THURSDAY 12 SEPTEMBER, CONFERENCE DAY 2

Vaccinations in Special Risk: rheumatological diseases

Dr Jim Buttery (Director of Monash Immunisation and Director of Research at Monash Children's Hospital, Melbourne)

Special risk categories include patients at increased risk of vaccine preventable diseases (VPDs) due to underlying medical conditions or their therapy, children and adults at increased risk of VPD due to epidemiological exposure, and children and adults at increased risk of AEFI. The risk of infectious diseases, including VPDs, is increased with rheumatological diseases.¹ Therapy for the condition also increases the risk of infectious diseases (i.e. corticosteroids, disease-modifying antirheumatic drugs [DMARDs], biological DMARDs) as well as increased attendance in clinics and hospitals. Infectious disease mortality is significant in patients with rheumatic diseases, e.g. 5.2% in patients with connective tissue diseases.²

DMARDs increase the risk of serious infections in patients with rheumatoid arthritis (RA)³ and tumour necrosis factor (TNF) antagonists in rheumatic diseases increase the risk of hospitalisation due to varicella zoster virus infections.⁴ A differential risk appears to exist among TNF- α inhibitors for a single condition such as herpes zoster in RA.⁵ RA patients are at increased risk of confirmed influenza, a ~3-fold risk of complications and ~2-fold risk of community-acquired pneumonia.^{6,7} In US immunisation coverage data, ~50% of patients with chronic rheumatic or autoimmune diseases are immunised (50–80% annual influenza vaccine, ~50% pneumococcal vaccination).⁸ UK primary care providers were less likely to offer influenza vaccine to patients on immunosuppressive therapy and more likely to offer it to patients with an end-organ disease as a complication from the rheumatic condition.⁹ Among Canadian children with juvenile idiopathic arthritis (JIA), only 52% had a complete vaccination status at 2.5 years, 68% at 10.5 years and 61% at their last clinic visit.¹⁰

<u>Safety, immunogenicity and efficacy</u>. Multiple case reports describe flares occurring post-vaccination, but low patient numbers preclude definitive conclusions. In a study involving 137 children with JIA that examined whether MMR booster vaccination affects disease activity, flare rates did not differ between those given the MMR booster dose and those who were not (0.44 vs 0.34).¹¹

No evidence currently suggests that rheumatological diseases are precipitated by vaccination. An increased risk for Guillain-Barré syndrome exists following influenza vaccine (1976 H1N1 RR 7.6; 2009 H1N1 RR 2.1).¹² No evidence exists for HepB and no data suggest an increased risk of ANCA vasculitis post-influenza vaccine.¹³

The Public Health Agency of Canada advises that corticosteroid therapy is not a contraindication to administering a live vaccine when steroid therapy is short-term (<14 days), low-to-moderate dose (<20 mg of prednisone or equivalent per day in adults, <2 mg/kg/day up to 20 mg total in children) or long-term, alternate-day treatment with short-acting preparations, maintenance physiological replacement therapy, has been ceased for >4 weeks.

Most empiric data on the safety of live vaccines in patients on immunosuppressive

therapy involve booster doses. Paediatric studies involving >300 children reveal no vaccine-related systemic disease.¹³ Varicella vaccine has an excellent safety profile in oncology and solid organ transplant. More data are needed for the higher-dose zoster vaccine; it is not recommended with immunosuppressive therapy.¹⁴ In general, most vaccines elicit similar magnitude of immune response in rheumatological conditions. However, the trials are inconsistent. ^{8,13} Findings vary with bDMARDs.^{14,15}

Advice for special risk groups, including rheumatological conditions:

- Influenza vaccine: there is a lower response to new strains (vs same strain of previous year) therefore 2 doses are recommended in years of strain change
- Pneumococcal vaccine:
 - more variable results have been observed with PPV23
 - questions exist around immune tolerance with repeat dosing
 - questions on its efficacy in various patient populations
 - PCV13 now licensed by the EMA for adults
 - more immunogenic (including those with rheumatological disease)
 induces immune memory in normal hosts
 - Consider PCV13 prime then PPV23 or PCV alone

Varicella/zoster vaccination in adults

- Demonstrate seropositivity
- Varicella vaccine has a good safety profile in oncology and rheumatological disease
- Zoster vaccine has fewer data
 - If seropositive and minimal immune suppression
 - delay immune suppression for 4 weeks post-immunisation if possible

bDMARDs, pregnancy and infant risks.^{16,17}

At least two of the most commonly used biologics, infliximab and adalimumab, are humanised antibodies that are actively transported across the placenta. Foetal/newborn drug levels are often higher than those in the mother receving bDMARD therapy. Infliximab has been measured in a baby up to 7 months of age – it remains unclear as to how this affects their immune responses to routine vaccines and no safety data exist clarifying what this means for live vaccines. An infant exposed to infliximab *in utero* died of disseminated Bacillus Calmette-Guérin (BCG) infection after vaccination at age 3 months.¹⁸ Most guidelines do not recommend live vaccines in the first 6 months of life. It is highly unlikely that rotavirus vaccine poses a risk to any children except those with a severe combined immunodeficiency, but safety data are awaited. BCG is contraindicated.

New vaccines

- Zoster vaccine: efficacy against herpes zoster 50%, postherpetic neuralgia 60–70%. Efficacy declines with increased age at immunisation ?surrogate for rheumatological disease
- PCV13
- Asplenics: MenACWY conjugate; MenB

Expert Forum NZ Immunisation Conference and Pre-Conference National Workshop for Health Professionals

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DISEASE AND VACCINE EPIDEMIOLOGY

Pneumococcal immunisation and hospitalisations for invasive pneumococcal diseases, all-cause pneumonia and otitis media in New Zealand between 2006 and 2014

Presented by Dr Sarah Radke (Immunisation Advisory Centre, University of Auckland and Environmental Science and Research, National Centre for Biosecurity and Infectious Disease, Wallaceville) on behalf of Dr Helen Petousis-Harris

This study examined the impact of the introduction of PCV vaccines (PCV7 in 2006 for high-risk children; PCV7 on schedule for children born beginning Jan 2008; PCV10 distributed from Sept/Oct 2011) against hospitalisations for invasive pneumococcal disease (IPD), all-cause pneumonia, and otitis media. Data were obtained from the NHI database, the NIR and the National Minimum Dataset (NMDS) then linked by NHI number. The study population included 446,076 children born 2006–2012 (observation ends 31 Dec 2012).

Provisional Results

PCV immunisation 2008–2012. The proportion of children who received all 4 doses has improved over time; ~7% of children born in 2008 received no PCV vaccination versus 3.5% of children born in 2012. By ethnicity, Pacific children had the highest coverage for all 4 doses and European children had the highest proportion of children who were not fully immunised. Vaccination status varied little by NZDep status; 68% of least-deprived children had received all 4 doses vs 64% of the most-deprived.

IPD hospitalisations 2006–2012. The rate of initial IPD hospitalisations decreased between the 2008 and 2010 birth cohorts (data are incomplete for children born in 2011/12, who had not been observed in the data long enough to detect IPD in the highest risk age group). Māori and Pacific children had the highest rates of IPD hospitalisations. Rates increased slightly with increasing NZDep.

All-cause pneumonia hospitalisations 2006–2012. For children born between 2006 and 2010, rates steadily increased over time. Māori and Pacific children had the highest rates of all-cause pneumonia and rates that increased substantially faster over time compared to other ethnic groups. Rates increase with increasing deprivation.

Otitis media hospitalisations 2006–2012. Rates increased over time (to a lesser extent than with all-cause pneumonia) and rates were higher in Māori and Pacific children compared to European and Asian children. Rates increased with increasing deprivation.

Impact of PCV7 on hospitalisations 2008–2010. The rates of hospitalisations for IPD and all-cause pneumonia prior to introduction of PCV7 (June 2008) were higher than the rates after introduction of PCV7 (before PCV10 was introduced in 2011). More data are needed to clarify the impact of PCV on otitis media.

The epidemiology of pertussis and timeliness of pertussis immunisation in New Zealand Georgia Deane (Masters Research, Wellington)

This research aims to describe patterns of pertussis immunisation timeliness and factors affecting timeliness (e.g., DHB, demographic characteristics) amongst all children on the NIR 2007–2011 (n=310,369; 52% European, 23% Māori, 11% Pasifika, 11% Asian, 2% Other/Unknown); children in the Wellington region made up ~11% of the total population and were of a similar ethnic distribution.

Preliminary results

- As dose number increases the proportion of children receiving vaccination on time decreases: ~88% on time for dose 1; ~75% for dose 2; ~60% for dose 3
- Asian children had the highest proportion with on time vaccination for all 3 doses, followed by European, Others, Pasifika Peoples and Māori
- Children living in the least deprived areas had the highest proportion receive their doses on time
- Proportion of children vaccinated on time dropped after 2007 and remained consistent between 2008–2011
- The Southern region had highest proportion of children with on time vaccination for all 3 doses, followed by Central, Northern, Midland

Impact of immunisation timeliness on pertussis vaccine effectiveness

Dr Sarah Radke (Immunisation Advisory Centre, University of Auckland and Environmental Science and Research, National Centre for Biosecurity and Infectious Disease, Wallaceville)

This investigation into the pertussis immunisation experience of New Zealand children hospitalised with pertussis during 2006–2012 examined whether and to what extent delays between doses impacted upon the incidence of hospitalisation. 'Delay' was defined as any interval between doses of >30 days longer than the scheduled interval (regardless of age at receipt).

NHI, NIR and NMDS data included 441,896 children, 674 of whom were hospitalised for pertussis. After narrowing the study population down to children born between 2006–2011 (allowing for children born at the end of 2011 to be followed in the data for one year), almost 500 cases of pertussis hospitalisation were observed among ~390,000 children. Most hospitalised children were very young (median age <2.3 months) with Māori children making up nearly half of all pertussis hospitalisations, followed by European and Pacific. Hospitalisation for pertussis was associated with increasing deprivation.

In a comparison of pertussis incidence (adjusting for gender, ethnicity, DHB, deprivation and year of birth) comparing children who had delays between immunisation doses to those who did not:

- a delay in immunisation interval between birth and dose 1 meant twice the risk of pertussis hospitalisation compared to no delay in immunisation
- children who had at least 2 doses of pertussis vaccine and were delayed for the interval between doses 1 and 2 had a ~50% increased risk for hospitalisation compared to no delay for immunisation



 having immunisation delayed between doses 2 and 3 or between doses 3 and 4 did not significantly increase the risk of pertussis hospitalisation compared to having vaccination on time. Timeliness may be more important when doses are scheduled closer together than when they are scheduled further apart (particularly in consideration of the 3.5-year interval between doses 3 and 4).

Southern Hemisphere Influenza and Vaccine Effectiveness Research and Surveillance (SHIVERS) Associate Professor Nikki Turner (Director of the Immunisation Advisory Centre, a practising GP and an Associate Professor in the Division of General Practice and Primary Health Care, University of Auckland)

Early results were presented from this US CDC 5-year funded project, which has 9 objectives:

- 1. Understand severe respiratory diseases caused by influenza & other pathogens
- 2. Assess influenza vaccine effectiveness
- 3. Investigate interaction between influenza & other pathogens
- 4. Understand causes of respiratory mortality
- 5. Understand non-severe respiratory diseases caused by influenza & other pathogens
- 6. Estimate influenza infection by conducting serosurvey
- 7. Identify & quantify risk factors (age, ethnicity, SES etc.) for getting influenza
- 8. Assess immune response among individuals with varying disease spectrum
- 9. Estimate healthcare, societal economic burden caused by influenza and vaccine cost-effectiveness

The Auckland study site covers the ADHB and CMDHB population (n=837,696). Two surveillance systems are involved:

- Hospital-based: enhanced, active, longitudinal (5 yrs from 2012), populationbased surveillance for hospital Severe Acute Respiratory Infection (SARI) cases, ICU admissions and deaths caused by influenza and other respiratory pathogens in Auckland
- Community-based: enhanced, active, longitudinal (4 yrs from 2013), population-based surveillance for community ILI cases caused by influenza and other respiratory pathogens in Auckland

The SARI surveillance is using the WHO case definition – for all age groups: An acute respiratory illness with a history of fever or measured fever of ≥38°C, AND cough, AND onset within the past 10 days, AND requiring inpatient hospitalisation

Community-based surveillance includes all acute respiratory illnesses presenting to general practice with cough and fever within 10 days

- Swab for flu and other viruses
- PMS-based questionnaire (advanced form)
- PMS data extraction
- A subgroup is planned for more in-depth analysis, using this case definition:

an acute onset of at least one of the following 4 respiratory symptoms: cough, sore throat, shortness of breath, coryza; and a clinician's judgment that the illness is due to an infection

Results. Hospital database: SARI & influenza incidence May 2012 - April 2013 data show that of all influenza-positive cases, most were Influenza A (not subtyped) and among the subtyped cases most were Influenza A(N1N1) pdm09 and Influenza A(H3). The highest burden of disease was in the <1-yearolds and the >80-year-olds. The burden for the <1-year-olds was higher than expected and particularly high in Pacific children. SARI and influenza incidence is highest in areas with greatest socioeconomic deprivation. A comparison of NMDS and SHIVERS influenza hospitalisations by age groups shows that the SHIVERS coding approach is detecting many more influenza cases and showing that the disease burden in children and >80-year olds is even higher than previously thought. To date, the highest number and proportion of influenza viruses from ILI specimens involve Influenza B, Influenza A (not subtyped) and Influenza A(H3). Analyses also reveal that other respiratory illnesses do not follow the influenza epidemic pattern - instead, they wax and wane over time; rhinovirus has persisted throughout the season and a considerable burden exists for respiratory syncytial virus, cases of parainfluenza virus and adenovirus.

Early analyses of VE case-control data against hospitalised confirmed influenza in the New Zealand setting (data from 2012; controls being the influenza-negative cases) reveal an overall propensity-adjusted (i.e. adjusted for the timing of admission relative to the influenza season) VE of 37, which is low, but data are not yet analysed by subgroup. Subtype analyses indicate that the vaccine used in 2012 was more effective against the pandemic A(H3N1)pdm09 virus, less effective against influenza A(H3N2) and reasonably effective against influenza B.

POTENTIAL AND EMERGING VACCINES

The search for a vaccine against group A Streptococcus Associate Professor Thomas Proft (Microbiology and Infectious Diseases, The University of Auckland)

Joint Australian and New Zealand government funding for a rheumatic fever vaccine was announced in February 2013. While most group A *Streptococcus* (GAS) infections are relatively mild illnesses such as pharyngitis/tonsillitis, or impetigo, serious autoimmune sequelae of GAS infection include acute rheumatic fever and rheumatic heart disease.

Two GAS virulence factors M protein and pili are well exposed on the bacterial surface. The N-terminal region of the M protein is highly immunogenic, but also highly variable. The first investigation to use an M protein vaccine reported a reduction in the number of GAS infections, but 3 vaccinees developed rheumatic fever (JAMA. 1969;207(6):1115-9), leading the FDA to prohibit group A *Streptococcus* organisms and derivatives from bacterial vaccines (FDA 21 CFR 610.19) in 1979. When this was revoked in 2006 research resumed and three potential GAS vaccines are currently under investigation:

<u>Candidate 1 = 30-valent M protein-based vaccine</u>. Current status: ongoing phase I trials.

An initial 26-valent vaccine was well tolerated with good immune responses in phase I/II clinical trials (McNeil SA, et al. Clin Infect Dis. 2005;41(8):1114-22). A new 30-valent M protein-based vaccine subsequently developed for wider coverage evokes cross-opsonic antibodies against non-vaccine serotypes of group A streptococci (Dale JB, et al. Vaccine. 2011;29(46):8175-8). The vaccine was immunogenic in animals and evoked bactericidal antibodies against all 30 vaccine serotypes of GAS. It also contained significant levels of

bactericidal antibodies against 24/40 non-vaccine serotypes of GAS, indicating good cross-protection.

In an analysis of 2,138 invasive GAS isolates in New Zealand 2002–2012, the vaccine covered 17/30 (57%) of the 30 commonest invasive *emm* types; adding the cross-opsonic antibodies increased the coverage to 23/30 (77%) (Williamson D. MS in press). Similarly, if the effect of cross-opsonic antibodies were included, the vaccine covered 24/30 (80%) most common *emm* types among 278 pharyngeal isolates. This vaccine would have to be modified to include New Zealand serotypes, if it is taken into clinical trials.

<u>Candidate 2 = M protein conserved region-based vaccine</u>. Current status: ongoing phase I trials.

Preclinical evidence indicates that immunity to GAS infection can be evoked by intranasal immunisation with a GAS M protein C-region peptide vaccine that contains a protective B cell epitope and lacks a T cell autoepitope (Olive C, et al. Vaccine. 2002;20(21-22):2816-25). However, immunisation with J8 peptide requires coupling to carrier molecules. J8 also protects against non-group A streptococci in animals. An advantage of this vaccine is its broad coverage, but it lacks good immunogenicity.

<u>Candidate 3 = non-M protein-based Combo vaccine (Novartis)</u>. Current status: ready for phase I trials.

Using a reverse vaccinology approach, 40 GAS proteins were identified, 6 of which were protective in animal models (Bensi G, et al. Mol Cell Proteomics. 2012;11(6): M111.015693). This vaccine showed protection against a range of GAS strains.

<u>Auckland candidate = Pilus-based vaccine</u>. Current status: preclinical research. Each GAS strain produces 1 of 9 pilus structures (FCT-1 to 9) on the cell surface. Mice were intranasally immunised with *Lactococcus lactis* (1x10⁸ CFU in 50 μ L) that were genetically modified to express GAS pili. IgG and IgA responses were strong for all pilus components, particularly the pilus backbone protein. Phylogenetic analysis reveals a correlation between pilus type and M serotype. Most M types carry the FCT-3 and FCT-4 type pilus. When mice were immunised with *L. lactis* carrying the GAS M18 pilus (FCT-3 type), good cross-reactivity was observed with other FCT-3/4 type pili.

The next step is to assess the diversity of the backbone pilus in New Zealand isolates, then elicit the structure of the backbone proteins from each FCT and map the epitopes onto these structures. The long-term goal is to design chimeric backbone antigens comprising several different pili that elicit cross-protective immunity.

Developing vaccines to fight cancer Dr Lindsay Ancelet (Malaghan Institute, Wellington)

Glioblastoma Multiforme is an aggressive and incurable brain cancer that has limited treatment options, with a median survival of 15 months. An autologous tumour cell-based vaccine has been developed that incorporates the adjuvant α -galactosylceramide (α -GalCer), which boosts T cell responses by targeting natural killer T cells. The vaccine provides significant protection against intracranial brain tumours in preclinical models (Hunn MK, et al. Clin Cancer Res. 2012;18(23):6446-59). However, the vaccine is not protective in the therapeutic setting; the VE is inhibited by tumour-induced immune suppression. The vaccine is effective therapeutically in animals when tumour-induced immune suppression is removed. Anti-tumour responses are dramatically boosted by ipilimumab (FDA approved, 15% objective response rates with >80% tumour reduction in patients), lambrolizumab (>35% for melanoma in clinical trials), nivolumab + ipilumumab (>40% clinical responses). These drugs are nonspecific, so can potentially be used in many different cancers. However, they can trigger undesirable immune responses, especially against selfantigens. Combining immunosuppressive drugs with an anti-cancer vaccine has resulted in >80% protection against intracranial brain tumours in preclinical models (ipilimumab + autologous tumour vaccine), with 80-100% survival in intracranial models. The Malaghan Institute is hoping to progress this research into clinical trials with GBM patients.

Looking back to move forward: What are the lessons? Dr F Marc LaForce (Albert B. Sabin Gold Medal Award recipient in 2012, and former Director of the Meningitis Vaccine Project)

This presentation described the progress made in global childhood immunisation programmes over the last 50 years. Vaccinology began with Edward Jenner's discovery of smallpox vaccination in 1798. The vaccine was used in the global public health effort against smallpox, which was declared eradicated in 1979. In 1974, as smallpox activities were looking very promising, the WHO Director General created the Expanded Programme on Immunisation (EPI), which has had huge global impact and continues to evolve. Global immunisation coverage has increased significantly from 1980 to the present day; e.g. DTP3 global coverage has expanded from \sim 17% in 1980 to 83% in 2012.

Lessons learned

<u>1. Invest in disease epidemiology</u>. Define the public health problem. When community surveys in the 1980s established rates of neonatal tetanus to be 30–60 per 1000 live births in some countries, this information encouraged WHO and UNICEF to lead a major global campaign that has subsequently dramatically reduced the global incidence of NNT, through tetanus toxoid vaccination of pregnant mothers. Another example is the lameness survey tool developed by WHO in the 1970s used in children as a surrogate for poliomyelitis, which effectively highlighted the disease as a major problem in many countries.

2. Measure operational results. Assessing performance in a rigorous or even semi-rigorous way requires money, planning, implementation and analysis. WHO's 30 cluster sampling method to determine coverage (1978) was a key tool that facilitated comprehensive country reviews by outside groups.

<u>3. Financing is key</u>. The Gates Foundation's investment of 750 million dollars in 1999 to establish the Global Alliance on Vaccines and Immunization (GAVI) has been a "game changer", providing an "acceptable home" for funds donated to support global vaccination programmes. GAVI has a strong secretariat in Geneva, well-structured country-specific application protocols and sound evaluations.

<u>4. Invest in infrastructure</u>. The infrastructure of country-based immunisation programmes requires a functioning regulatory system, an EPI with its cold chain, supplies, surveillance, and vaccination activities.

5. Continue to develop better vaccines. Access to affordable and needed vaccines is the key to public health success, e.g. Heb B and Hib, pneumococcal conjugate vaccines, the Group A meningococcal conjugate vaccine, HPV and rubella vaccines. Challenges remain – an effective vaccine is needed for malaria, the existing typhoid vaccine is problematic for developing countries, work is proceeding on cholera vaccines and polyvalent meningococcal conjugate vaccines.

<u>6. Foster international collaboration</u>. WHO, UNICEF, GAVI, Gates Foundation, etc... are large, cumbersome bureaucracies that compete for agendas, prominence and funding. Personalities and patience matter.

Paying attention to these lessons has accomplished much: of the 133.2 million infants surviving globally each year, 110.6 million children are vaccinated (83% DTP3 coverage).

Summary and conclusions of the 2013 Immunisation Conference

Dr Lynn Taylor (Immunisation Advisory Centre, Auckland)

Many stakeholder groups enjoyed the opportunity to share information about their activities – MOH, PHARMAC, DHB and PHO representatives, service delivery providers, pharmacy brands, vaccine manufacturers and also cold chain refrigerator manufacturers.

The 3-day programme covered more than 70 presentations from prominent international and local speakers on a wide range of topics. A highlight was Marc LaForce's description of 10.8 million people vaccinated within just 10 days.

New Zealand's vaccination coverage has improved over the last decade, but timeliness needs to improve. The cocoon strategy seems to have been adopted and people appear to be becoming more mindful of protecting others around them from influenza virus. Pharmacy vaccination has been a positive move for increasing numbers of people being vaccinated in 2013. Canterbury has appointed champion vaccinators.

Presentations emphasised the importance of communication – of combining the scientific knowledge and skills in a way that the target audience understands and absorbs. We need to use the technologies that our clients use every day: social media and animation, SMS, texts, E-mails, Smart phone apps. We need to consider vaccines that are recommended but not publicly funded

(available on the private market) and give parents the option to make their own judgement.

Finally, vaccines have a good future. Presentations described new and improved vaccines, as well as vaccines for cancer. Updates are anticipated at the 2014 Immunisation Conference.

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