Current developments in varicella-zoster virus disease prevention

A report on the varicella-zoster virus workshop convened by the National Centre for Immunisation Research and Surveillance of Vaccine Preventable Diseases on 16–17 November 2006

Anita E Heywood, Kristine K Macartney, C Raina MacIntyre, Peter B McIntyre

Introduction

On 16 and 17 November 2006, the National Centre for Immunisation Research and Surveillance of Vaccine Preventable Diseases (NCIRS) hosted a workshop on varicella-zoster virus (VZV) disease. The workshop was aimed at presenting the latest information on the clinical, epidemiological, and diagnostic aspects of both primary varicella ('chickenpox') and herpes zoster (HZ or 'shingles') both in Australia and internationally, and to highlight important developments in the prevention of these diseases by vaccination. This workshop was held at a significant stage in the control of VZV disease in Australia with the recent addition of the varicella vaccine to the National Immunisation Program (NIP) schedule, the anticipated availability of combination measles-mumps-rubella-varicella (MMRV) vaccines for use in children, and the availability of a zoster vaccine for use in older adults to prevent reactivation of VZV causing HZ.

The workshop was attended by prominent international researchers and leading Australian experts. All state and territory jurisdictions were represented and participated in panel discussions, particularly with the regard to disease surveillance. The first day of the workshop was devoted to varicella disease with presentations on the clinical features, current epidemiology, the Australian varicella vaccination program, and the impact of varicella vaccination in the United States of America (USA). An overview of the development of the MMRV vaccines was provided, and the day closed with a panel discussion of the issues surrounding varicella vaccine scheduling.

The second day focused on HZ with presentations on the burden of disease in Australia, the pathologic mechanisms and diagnostics. An overview and update on data from the zoster vaccine clinical trials was presented. The day concluded with state and territory representatives presenting plans for disease surveillance, and a panel discussion focusing on the best approach for the control of VZV disease in Australia.

Day one – varicella

Clinical overview

Professor Margaret Burgess, NCIRS, began proceedings with a presentation on clinical features of primary VZV disease including varicella (chickenpox), and neonatal and congenital varicella. As she highlighted, varicella is usually a relatively mild disease of childhood, however, complications (such as pneumonia, secondary bacterial infections and neurologic conditions) occur in approximately 1% of cases, especially those most at risk such as neonates, the immunosuppressed, pregnant women, adolescents, adults and those with pre-existing co-morbidities.[1,2] Professor Burgess presented the results of community-based surveys and seroprevalence studies in Australia that indicate that the majority of the burden of varicella is in childhood and adolescence with almost 90% of cases occurring before the age of 20 years and the most common age of acquisition between 5–9 years of age.[3]

Congenital and neonatal varicella are rare in Australia with the Australian Paediatric Surveillance Unit (APSU) reporting 44 cases of neonatal varicella

and seven cases of congenital varicella syndrome (CVS) between 1995 and 1997.[5] Of the cases of CVS, maternal varicella infection occurred between 8 and 26 weeks gestation with sequelae including skin scarring, severe limb, heart and nervous system defects resulting in death, and zoster in infancy.[5] Studies of varicella immunity in women of childbearing age show that 8% of women over the age of 14 are susceptible to varicella.[4,5] Overall, since primary varicella infection still occurs in Australia, the risk of CVS remains.

Epidemiology and the varicella vaccination program in Australia

Epidemiological data on the burden of varicella in Australia prior to the inclusion of varicella vaccine on the NIP was presented by Dr Kristine Macartney, NCIRS. It was estimated that prior to the availability of varicella vaccine, the annual number of cases of varicella in Australia approximated the birth cohort with approximately 240,000 cases each year.[6] Approximately 1,500 cases were hospitalised each year (with a principal diagnosis of varicella), of which 10% were infants under 12 months of age, 30% children aged 1–4 years and 43% aged over 15 years.[7] On average 7–8 varicella-related deaths are recorded in Australia each year.[6]

Varicella vaccines have been available in Australia since 2000 and were recommended, but not publicly funded, for use in all children at 18 months, in September 2003.[8] In November 2005, varicella vaccine was included on the NIP with funding provided for a single dose for all children aged 18 months and for 'catch-up' immunisation at 10–13 years, administered through the school-based programs nationally, for those with no prior history of varicella or vaccination. Reliable rates of vaccine coverage prior to the inclusion of varicella vaccine on the NIP are not available, with reported estimates from national serosurveys, the Australian Childhood Immunisation Register (ACIR) and from a household survey ranging from 13.4%–48%.[6,9,10] Dr Macartney presented preliminary data from the ACIR which, as of September 2006, indicated that less than a year into the program, vaccine uptake is climbing nationally with approximately 45.3% of two-year-olds reported as having been vaccinated. Data on varicella hospitalisations since the vaccine has been on the NIP were not available, however, a decline in varicella hospitalisations from 2003–2005 has been observed especially in the 1–4 year age group where rates (assessed using a principal diagnosis of varicella) declined from 48.9 cases per 100,000 (95% CI 46.8–51.1%) during July 1999–June 2003 to 38.2 per 100,000 (95% Cl 35.6–41.1%) during July 2003–June 2005.[11]

Modelling the impact of a varicella vaccination program in Australia

Evaluation of the impact of childhood varicella vaccination on the incidence of VZV disease has been the focus of numerous studies internationally. Ms Heather Gidding, Centre for Infectious Diseases and Microbiology, presented information from a study that modelled the impact of an immunisation program in Australia, using similar assumptions to studies performed in Canada and the United Kingdom. Australian-based data, including that from national serological surveys, were used in the model to determine changes in the incidence and morbidity of varicella and HZ following universal varicella vaccination in the second year of life.[12] The model suggested that varicella vaccination resulted in a significant decrease in varicella associated-morbidity, especially once infant vaccination coverage is greater than 60%, albeit with a shift in morbidity to older age groups. However, total morbidity, including morbidity resulting from HZ reactivation (assuming that exposure to varicella boosts immunity to HZ for 20 years) increases in the first 8–52 years of the program (at 90% coverage in early childhood), after which there is a rapid decline in morbidity. Vaccination of adults may be required in such a scenario.

Varicella vaccination program in the United States of America

Professor Anne Gershon, Department of Pediatrics at Columbia University Medical Center, USA, has played a pivotal role in varicella vaccine research and development. In her first presentation at this workshop, Dr Gershon summarised the available data on the impact of the 10-year one-dose varicella vaccination program in the USA where over 50 million doses have been distributed since 1995. Overall vaccine safety has been excellent, with vaccine-virus transmission and cases of post-vaccination HZ being rare occurrences in healthy vaccinees. Disease surveillance has been undertaken at sentinel sites in the USA, which have reported a decline in the incidence of varicella of at least 84% from 1995 to 2000.[13] Hospitalisations and ambulatory visits have declined by 88%[14] and deaths from varicella declined by 66% across the USA between 1990 and 2001.[15] Vaccine effectiveness studies in the USA estimate that one dose of varicella vaccine in children is approximately 80%–85% protective against disease.

In the USA, investigation into factors associated with outbreaks in highly vaccinated populations have found that the waning of immunity may only partially explain this. In early studies of the Oka/Merck varicella vaccine, the presence of any detectable antibody by gpELISA test was used to determine seroconversion resulting in a high seroconversion

rate and a 4% primary vaccine failure rate. Evidence suggests that the gpELISA cut-off of 5 units is a better correlate with protection from varicella than any detectable antibody (reported as seroconversion). However, a more accurate surrogate marker of protection may be found with the fluorescent-antibody-to-membrane-antigen test (FAMA), with less than 2% of persons with a FAMA greater than 1:4 developing modified illness, known as 'breakthrough varicella', in a household study. Using FAMA, seroconversion after one dose of varicella vaccine may be as low as 76%–88%.[16] Additionally, some studies suggest that cases of breakthrough varicella are increasing over time, suggesting secondary vaccine failure (waning immunity). Both primary and secondary vaccine failure are likely to be overcome with the use of two doses of vaccine. A 10 year study comparing children who received one versus two doses of vaccine found that breakthrough varicella was 3.3-fold lower in children after two doses than after one dose of varicella vaccine (2.2% vs. 7.3%) ($P < 0.001$).[17] The results of these studies has led to the adoption of a recommendation for two doses of varicella vaccine in children the USA.[18]

In her presentation, Dr Gershon also summarised advances in understanding the role of the skin in the basic mechanisms of VZV infection, latency and immunity and how this may underpin changes in the approach to disease control. She demonstrated that VZV transmission to a susceptible host is dependent on the presence of enveloped cell-free virions in skin vesicles where mannose-6-phosphate receptors are absent and that VZV latency is established by these cell-free virions infecting sensory nerve endings in the epidermis. Studies have shown that vaccine virus transmission is associated with the appearance of skin lesions post-vaccination[19] and that HZ in leukaemic vaccinees is associated with post-vaccination rash.[20]

Measles-mumps-rubella-varicella vaccine development

Dr Barbara Kuter, Merck & Co. Inc, outlined the clinical development of Varivax® (varicella vaccine) and the subsequent development of the combination measles-mumps-rubella-varicella vaccine, ProQuad®. The development of ProQuad® has taken over 20 years with initial formulations limited by suboptimal immunogenicity to the varicella component compared with the monovalent varicella vaccine. Re-formulation of the vaccine, with increased VZV titre, has overcome this issue. In a total of five clinical trials of MMRV, 5,833 healthy children aged 12–23 months and 399 healthy children aged 4–6 years received one or two doses of ProQuad® with concomitant administration of MMR and monovalent varicella vaccine used as controls for most studies.[21] Both one and two doses of the MMRV formulation were found to be as immunogenic and well tolerated by 12–23-month-olds and 4–6-year-olds as the separate vaccines.

Dr Gershon then presented a comparison of the safety and immunogenicity of both MMRV vaccines; Pro-Quad® (Merck & Co. Inc. West Point, Pennsylvania, USA) and Priorix-Tetra® (GlaxoSmithKline Biologicals, Rixensart, Belgium). Both vaccines have an excellent safety profile and are highly immunogenic when compared to the MMR and varicella vaccines given at separate injections sites. As a result of suboptimal response rates to the varicella component, both products have higher titres of vaccine-strain VZV and both products result in similar rates of seroconversion, but higher geometric mean titres to varicella than the monovalent varicella vaccines. Vaccine efficacy has not been studied in clinical trials and licensure of both products is based on non-inferiority compared with existing component vaccines. Both MMRV vaccines are under consideration for licensure in Australia, and it is expected that application for funding of MMRV vaccine/s under the NIP will proceed.

Varicella vaccine scheduling

The first day of the workshop concluded with a presentation by Professor Terry Nolan, chair of the Australian Technical Advisory Group on Immunisation on issues around the funding and scheduling of vaccines in Australia. He presented a framework outlining the newly adopted immunisation policy advisory structures and discussed the role of the Pharmaceutical Benefits Advisory Committee in assessing the cost-effectiveness of vaccines. His talk highlighted that future considerations around a two-dose varicella schedule and the use of MMRV on the NIP would be considered under this structure. A discussion panel of various speakers from the day answered questions from audience, chaired by Professor Terry Nolan.

Day two – herpes zoster and varicella-zoster virus disease surveillance

Clinical overview

The opening presentation of Day 2 provided an overview of the burden of disease from HZ, particularly focusing on post-herpetic neuralgia (PHN). Dr David Gronow, Sydney Pain Management Centre and the Westmead Hospital Pain Services, highlighted the difficulties faced in the management of HZ and PHN, using a particularly detailed case study of zoster in a previously independent elderly woman who became bedridden and institutionalised as a result of post-herpetic neuralgia. Dr Gronow discussed that PHN is most commonly defined as pain lasting longer than three months

post-HZ rash and can affect 25%–50% of HZ cases in persons aged over >50 years, depending on use of antiviral therapies.[22] Risk factors for PHN include older age, severity of acute pain, severe prodromal pain, and severity of rash, being female and lack of timely antiviral therapy. Other HZ complications are many, including ophthalmic disease, Ramsay-Hunt syndrome and encephalitis.

Management of HZ and PHN may be very difficult and a variety of drugs of different classes are used, often in a multimodal approach. Evidence from randomised control trials of tricyclic antidepressants, anticonvulsants, antidepressants and topical applications, such as lidocaine patches, indicate varying degrees of effectiveness. There is limited evidence for other treatment options including botulinum toxin, nerve blockers and cognitive behavioural therapy.

Epidemiology

Professor Raina MacIntyre, National Centre for Immunisation Research and Surveillance, presented available data on the epidemiology of HZ in Australia in the context of an evolving surveillance system and a universal varicella program. Results from a 1999 serosurvey, prior to the availability of varicella vaccine, found that by 30 years of age more than 97% of the Australian population had primary varicella, and as such, are at risk of developing HZ.[3] Currently, the best available data on HZ in Australia is from the Australian Institute of Health and Welfare hospital morbidity database. However, this is subject to various limitations. Analysis shows that HZ is implicated in approximately 2.5 times more hospitalisations than varicella with longer length of stay and greater case-fatality rates.[23]

Data on clinical presentations to general practitioners have been analysed to determine the burden of HZ not requiring hospitalisation. Extrapolating to the Australian population suggest similar rates from two separate sources: 477 per 100,000 per year (calculated from the Bettering the Evaluation and Care of Health (BEACH) longitudinal data collection); and 491 per 100,000 per year (from the General Practice Research Network (GPRN) cross-sectional data collection). These results are not dissimilar to international studies[24] and indicate that approximately 100,000 cases of HZ occur in Australia each year. The community burden as assessed by prescriptions for antivirals on the Restricted Pharmaceutical Benefits Scheme (RPBS) is also considerable, with 59,200 prescriptions for anti-viral medication dispensed under the RPBS in 1999, rising to 76,000 prescriptions in 2005.[23] Approximately 60% of cases of HZ in both the BEACH and GPRN databases were treated with antivirals.

Varicella-zoster virus immunopathogenesis, diagnostics in Australia, and molecular studies

Three presentations discussed the immunopathogenesis of the VZV, the current approach to diagnosis, and the molecular tools available for both clinical diagnostics and VZV surveillance. Dr Allison Abendroth, Centre for Virus Research, Westmead Millennium Institute and the Department of Infectious Diseases and Immunology, University of Sydney, presented results from her laboratory's research, which aims to better determine how the VZV interacts with the immune system, particularly dendritic cells (DC), a specialised immune cell. This cell type appears critical in the immunopathogenesis of VZV disease. VZV interferes with the maturation of DC, prevents migration and antigen presentation to CD3+ T-cells and VZV infection alters the subsets of dendritic cells found in the skin. Productive VZV infection in primary human neurons has also been shown to be resistant to apoptosis. In addition, Dr Abendroth's laboratory has also explored the immune response to human ganglion cells following reactivation causing HZ and found that a predominantly non-cytolytic immune infiltrate. These findings make a contribution to understanding the pathogenesis of this complex virus and the best directions toward improvements in prevention and treatment.

Associate Professor Alison Kesson, medical virologist and infectious disease physician at the Children's Hospital at Westmead discussed laboratory diagnosis of VZV disease. She emphasised that the various methods of laboratory diagnosis, using either antigen or antibody detection, are primarily utilised when a patient is immunosuppressed; a neonate; in those presumed immune; or for unusual clinical cases. Differential diagnoses of varicella in children include Stevens Johnson Syndrome, enterovirus infection, herpes simplex, and a number of other conditions. The traditional diagnostic test for varicella has been the Tzank smear which detects intranuclear inclusions in multinucleated cells. However this test is not sufficiently sensitive or specific. The detection of the virus from culture of vesicle fluid takes 5–14 days and also has a low sensitivity (50%). Antigen detection using immunofluorescence is a more rapid and sensitive test, and nucleic acid detection (VZV PCR) is both sensitive and specific. Detection of IgM and IgA antibody can be utilised within 1–2 days of infection. However, absence does not exclude infection; IgM is also detected in HZ, and cross-reaction with HSV can occur.

Professor Judy Breuer, Centre for Infectious Disease, Barts and London School of Medicine and Dentistry discussed her work in VZV molecular diagnostics.

Molecular studies are useful for determining if vaccine virus or wild-type virus are responsible for rashes occurring after vaccination, for virus identification in the rare cases of possible disseminated disease from vaccine-virus and for identifying vaccine virus transmission. Professor Breuer presented the results of a genetic analysis comparing the Oka parent wild-type VZV (the virus originally isolated in Japan) with the attenuated Oka vaccine virus (now used in varicella vaccines), which identified 42 differences in the gene sequence. The vaccine virus is actually a mixture of viruses with only one of the vaccine viruses usually predominating in each vesicle of a vaccine-associated rash. Professor Breuer emphasised that the vaccine viruses from both the Merck and Co. and GSK varicella vaccines are indistinguishable. It was discussed that genomic analysis of VZV will become increasingly important in countries with established varicella vaccination programs as disease incidence declines. This was highlighted by an interesting case presentation in which samples from two separate episodes of HZ in the same individual were analysed and found to be caused by two genetically distinct wild-type varicella-zoster viruses.[25] Interestingly, this finding indicates that the individual had two separate primary varicella infections, a phenomenon not previously demonstrated by molecular methods.

The Shingles Prevention Study – the Veterans Zoster trial

Dr Myron Levin, University of Colorado and The Children's Hospital, USA, presented the results of the Shingles Prevention Study (SPS), a large clinical trial of the use of high titre live attenuated (Oka/Merck strain) VZV vaccine to prevent HZ in older adults (Zostavax®, Merck and Co. Inc.). The SPS involved 22 sites across the USA and included 38,500 subjects with a median age of 69 years. The occurrence of HZ or PHN in subjects was validated through a diagnostic algorithm, in which more than 93% of all cases of suspected HZ were confirmed using PCR. In addition to HZ and PHN (significant pain ≥90 days post-rash), the endpoints for the study also included a burden of illness (BOI) score, which is a sum of individual severity of illness scores of HZ cases. Vaccine efficacy was calculated as 61.1% (95% CI 51.1–69.1%) against HZ BOI, 66.5% (95% CI 47.5–79%) for PHN and 51.3% (95% CI 44.2–57.6%) for HZ incidence.[26]

Study of the persistence of zoster vaccine efficacy is still underway, however, preliminary data to 4 years post-vaccination indicate that the vaccine is most effective in the first year, with a slight but stabile decline in efficacy in the 2–4 years post-vaccination. Professor Levin also presented the results of the SPS sub-studies. The adverse events sub-study found no clinically meaningful differences in systemic adverse events between the two groups. In the vaccine group the most frequent adverse events at the injection site were erythema, pain or tenderness, swelling, and pruritus. In the USA, where the vaccine is now in use, post-marketing surveillance will be conducted to monitor adverse events. The immunology sub-study, assessing both antibody and various measures of cell mediated immunity (CMI), conducted assays at baseline and annually. The results indicate that immune response to the vaccine decreases with age, with the CMI response being 1%–2% lower for each additional year of life. This study was unable to determine a surrogate marker of protection, but further investigation is underway.

Following the morning's presentations, a panel discussion of the potential use and benefits of zoster vaccination occurred, with audience questions addressed by the speakers.

Economic modelling of zoster vaccine

Dr James Pellissier, Merck Research Laboratories described the complex economic modelling required to determine the cost-effectiveness of a zoster vaccine in the elderly. The model developed by the manufacturer included many considerations, such as rates of HZ, and PHN, complications avoided, healthcare costs and healthcare utilisation avoided, and the Quality Adjusted Life Years (QALYs) gained by use of this vaccine. Using this model, applied to the USA healthcare system (payer perspective), the cost of the zoster vaccine is $19,831 per QALY for all persons aged 60 years or older. This was compared to other preventative measures such as the influenza vaccine for the 50–64 year age group ($16,500 per QALY gained) and colon-cancer screening ($10,000–25,000 per QALY gained). The model was the most sensitive to vaccine price, age of vaccine recipient, the costs associated with PHN, duration of vaccine efficacy, QALY measurements associated with pain states, and the costs of complications. The model needs to be applied to an Australian perspective.

Varicella-zoster virus surveillance

The afternoon of Day 2 of the conference was dedicated to a discussion of surveillance mechanisms for varicella and HZ, both locally and internationally.

British Paediatric Surveillance Unit study

Professor Breuer presented data on the British Paediatric Surveillance Unit (BPSU) study of neonatal and congenital varicella and severe varicella requiring hospitalisation in children. Surveillance over 12 months in 2002–2003 identified 112 confirmed cases of hospitalised varicella in children aged less than 16 years at a rate of 0.82 per 100,000 per year, similar to the German Paediatric Surveillance Unit

figures. Most varicella cases hospitalised had complications of bacteraemia, pneumonia, encephalitis and ataxia with no clear high risk categories. The surveillance method has been modelled in a new VZV study adopted by the APSU, commencing in 2006.

Surveillance of zoster in the United States of America

Surveillance of both varicella and HZ in the USA was described by Professor Gershon. Active surveillance of varicella in the USA has been conducted by the Centers for Disease Control and Prevention in sentinel sites in the USA. Surveillance of HZ has been more challenging, but is important to determine if an increase in cases is occurring as VZV circulation declines. The results of studies of HZ incidence vary depending on the population and study methods with estimates ranging from 1 case per 1,000 person-years in adult varicella vaccinees and 2–4 in unvaccinated adults[27] to 14 per 1,000 person-years in adults aged greater than 75 years[28] and as high as 163 cases per 1,000 person-years in children with HIV.[29] Studies in the USA, including those in active surveillance sites, report conflicting rates of zoster prior to and since the commencement of the varicella vaccination program.[30]

Surveillance plans for Australia

The surveillance to be undertaken in Australia was described by Dr Paul Roche, Surveillance Branch, Office of Health Protection, Australian Government Department of Health and Ageing. The potential goals of VZV surveillance are to assess the impact of the varicella vaccination program, monitor changes in epidemiology, measure vaccine effectiveness, monitor trends in neonatal and congenital varicella and trends in hospitalisations and to measure population immunity. The proposed Australian surveillance methods include notification of cases of varicella and HZ to the National Notifiable Disease Surveillance System (NNDSS), surveillance of severe complications in children via APSU, national serosurveys undertaken by NCIRS, and continued assessment of hospitalisations. The APSU recommenced surveillance of CVS, neonatal varicella and varicella complications requiring hospitalisation in children aged 1 month to 15 years in May 2006.[31] Disease surveillance data would be complemented by information on adverse events following immunisation as reported to the Therapeutic Goods Administration, and vaccine coverage data.

The proposed NNDSS system will have three disease categories: chickenpox, zoster and varicella infection (unspecified). Confirmed cases are to require laboratory confirmation and clinical evidence, or an epidemiological link to a laboratory confirmed case, whereas probable cases will require clinical evidence only. Varicella (unspecified) will be reported for laboratory evidence of VZV without clinical correlation. Funding from the Commonwealth has been allocated to states and territories to establish VZV surveillance systems and approaches by each State and Territory differ. Five jurisdictions will be notifying VZV using passive notification from General Practitioners and laboratories (Australian Capital Territory, Northern Territory, Queensland, South Australia and Tasmania), and two jurisdictions will collect sentinel surveillance data in addition to passive notification data (Victoria and Western Australia). New South Wales will report VZV through use of Emergency Department syndromic surveillance data.

Data quality and the usefulness of data collections is affected by issues such as the delay in the implementation of surveillance well into the universal vaccination program and the diversity of populations in Australia. The under-estimation of vaccine effect due to incomplete reporting, and a variety of data sources across the states and territories may make the development of a national picture challenging.

Surveillance in South Australia

In anticipation of the widespread use of varicella vaccine, the state of South Australia implemented a notification system for both varicella and HZ in 2002.[32] Dr Rod Givney, South Australian Department of Health, presented data on the program indicating that a centralised collection of dual notifications from both medical practitioners and laboratories should provide the ability to track changes in childhood varicella, varicella cases in adolescents and adults, and any change in the age distribution of HZ since the implementation of a universal program in Australia. Data collection is proceeding, with notifications representing an estimated 4% of actual cases occurring for both varicella and HZ.[33]

Discussion panel 3 – jurisdictional surveillance and recommendations

The workshop concluded with representatives from all Australian jurisdictions participating in a discussion panel of the benefits of the proposed surveillance mechanisms, and future directions.

Presentations from both days of the workshop are available on the NCIRS website: http://www.ncirs.usyd.edu.au/newsevents/vzv_workshop_presentations_nov_06.doc

Acknowledgements

NCIRS would like to thank all the speakers and attendees of the two day workshop for contributing to the success of this event. Including international speakers: Dr Anne Gershon, Professor of Pediatrics

and Director of the Division of Pediatric Infectious Disease within the Department of Pediatrics at the University of Colorado Medical Center; Dr Barbara Kuter, Executive Director, Pediatric Vaccine Medical Affairs, Merck & CO; Dr Myron Levin, Professor of Paediatrics and Medicine and Director of the Paediatric Infectious Diseases Fellowship Program at the University of Colorado and The Children's Hospital; Dr James Pellissier, Director of Heath Economic Statistics at Merck Research Laboratories; and Professor Judy Breuer, Professor of Virology at the Centre for lnfectious Disease and the Barts and London School of Medicine and Dentistry and national speakers: Ms Heather Gidding, formerly from the Centre for Infectious Diseases and Microbiology, Westmead Hospital; Dr David Gronow, Sydney Pain Management Centre and the Westmead Hospital Pain Services; Dr Allison Abendroth from the Centre for Virus Research at the Westmead Millennium Institute and the Department of Infectious Diseases and Immunology, University of Sydney; Associate Professor Alison Kesson, medical virologist and infectious disease physician at the Children's Hospital at Westmead; Dr Rod Givney, formerly of the South Australian Department of Health; Dr Paul Roche from the Surveillance Branch of the Office of Health Protection of the Australian Government Department of Health and Ageing; Professor Terry Nolan, chair of the Australian Technical Advisory Group on lmmunisation; and Professor Margaret Burgess, Founding Director of NCIRS.

Author details

Ms Anita E Heywood, Research Assistant

Dr Kristine K Macartney, Deputy Director, Policy Support

Professor C Raina MacIntyre, Senior Principal Research Fellow

Professor Peter B McIntyre, Co-Director

National Centre for Immunisation Research and Surveillance of Vaccine Preventable Diseases, The Children's Hospital at Westmead, University of Sydney

Corresponding author: Ms AE Heywood, National Centre for Immunisation Research and Surveillance of Vaccine Preventable Diseases, The Research Building, The Children's Hospital at Westmead, Locked Bag 4001, Westmead NSW 2145. Telephone: +61 2 9845 1232. Facsimile: +61 2 9845 1418. Email: anitah2@chw.edu.au

References

1. Choo PW, Donahue JG, Manson JE, Platt R. The epidemiology of varicella and its complications. *J Infect Dis* 1995;172:706–712.
2. Heininger U, Seward JF. Varicella. *Lancet* 2006;368:1365–1376.
3. Gidding HF, MacIntyre CR, Burgess MA, Gilbert GL. The seroepidemiology and transmission dynamics of varicella in Australia. *Epidemiol Infect* 2003;131:1085–1089.
4. Forrest J, Mego S, Burgess M. Congenital and neonatal varicella in Australia. *J Paediatr Child Health* 2000;36:108–113.
5. Australian Paediatric Surveillance Unit. Factsheet. Burgess M, Chant K, Forrest J. Congenital and neonatal varicella. Completed study factsheet. 2006. Available from: http://www.apsu.org.au/download.cfm?DownloadFile=69C3ACFF-E352-0E4B-956EC61F8788803A Accessed July 2006.
6. Macartney KK, Beutels P, McIntyre P, Burgess MA. Varicella vaccination in Australia. *J Paediatr Child Health* 2005;41:544–552.
7. Australian Institute of Health and Welfare. Interactive national hospital morbidity data. Principal diagnosis data cubes. National Hospital Morbidity Database. 2006. Available from: http://www.aihw.gov.au/cognos/cgi-bin/ppdscgi.exe?DC=Q&E=/AHS/principaldiagnosis0304
8. National Health and Medical Research Council. *The Australian Immunisation Handbook,* 9th edition. Canberra: 2007. In Press.
9. Gilbert GL, Gidding HF, Backhouse J, McIntyre PB. Varicella seroprevalence and vaccine uptake in preschool children. [Letter]. *Med J Aust* 2005;182:42.
10. Marshall H, Ryan P, Roberton D. Uptake of varicella vaccine-a cross sectional survey of parental attitudes to nationally recommended but unfunded varicella immunisation. *Vaccine* 2005;23:5389–5397.
11. Heywood AE, Macartney KK, Hull B, Wang H, McIntyre P. Age-specific trends in varicella hospitalisations in Australia prior to a universally funded program. [Poster #24]. Communicable Diseases Control Conference. 14–1 5 March 2007; Canberra, Australia.
12. Gidding HF, Brisson M, MacIntyre CR, Burgess MA. Modelling the impact of vaccination on the epidemiology of varicella zoster virus in Australia. *Aust N Z J Public Health* 2005;29:544–551.
13. Seward JF, Watson BM, Peterson CL, Mascola L, Pelosi JW, Zhang JX, et al. Varicella disease after introduction of varicella vaccine in the United States, 1995–2000. *JAMA* 2002;287:606–611.
14. Zhou F, Harpaz R, Jumaan AO, Winston CA, Shefer A. Impact of varicella vaccination on health care utilization. *JAMA* 2005;294:797–802.
15. Nguyen HQ, Jumaan AO, Seward JF. Decline in mortality due to varicella after implementation of varicella vaccination in the United States. *N Engl J Med* 2005;352:450–458.
16. Gershon AA. Immune responses to 1 and 2 doses of varicella vaccine. Advisory Committee on Immunization Practices. Record of Proceedings, 29–30 June 2006. Atlanta Georgia. 2006. Available from: http://www.cdc.gov/vaccines/recs/acip/downloads/min-jun06.pdf Accessed July 2006.
17. Kuter B, Matthews H, Shinefield H, Black S, Dennehy P, Watson B, et al. Ten year follow-up of healthy children who received one or two injections of varicella vaccine. *Pediatr Infect Dis J* 2004;23:132–137.
18. Centers for Disease Control and Prevention. Prevention of Varicella. Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep* 2007;56 RR-4:1–38.
19. LaRussa P, Steinberg S, Meurice F, Gershon A. Transmission of vaccine strain varicella-zoster virus from a healthy adult with vaccine-associated rash to susceptible household contacts. *J Infect Dis* 1997;176:1072–1075.

20. Hardy I, Gershon AA, Steinberg SP, LaRussa P. The incidence of zoster after immunization with live attenuated varicella vaccine. A study in children with leukemia. Varicella Vaccine Collaborative Study Group.[see comment]. *N Engl J Med* 1991;325:1545–1550.

21. Kuter BJ, Hoffman Brown ML, Hartzel J. Safety and immunogenicity of a combination MMRV vaccine (ProQuad®). *Human Vaccines* 2006;2:205–214.

22. Schmader K. Herpes zoster in older adults. *Clin Infect Dis* 2001;32:1481–1486.

23. MacIntyre CR, Chu CP, Burgess MA. Use of hospitalization and pharmaceutical prescribing data to compare the prevaccination burden of varicella and herpes zoster in Australia. *Epidemiol Infect* 2003;131:675–682.

24. Conway L, Lenkic C, MacIntyre CR. Herpes zoster and associated health care use in general practice in Australia. Successes in Immunisation. 10th National Immunisation/2nd PHAA Asia Pacific Vaccine Preventable Diseases Conference; July 2006; Sydney.

25. Taha Y, Scott FT, Parker SP, Syndercombe Court D, Quinlivan ML, Breuer J, et al. Reactivation of 2 genetically distinct varicella-zoster viruses in the same individual. *Clin Infect Dis* 2006;43:1301–1303.

26. Oxman MN, Levin MJ, Johnson GR, Schmader KE, Straus SE, Gelb LD, et al. A vaccine to prevent herpes zoster and postherpetic neuralgia in older adults. *N Engl J Med* 2005;352:2271–2284.

27. Hope-Simpson RE. The nature of herpes zoster: a long-term study and a new hypothesis. Proceedings of the Royal Society of Medicine 1965;58:9–20.

28. Donahue JG, Choo PW, Manson JE, Platt R. The incidence of herpes zoster. *Arch intern Med* 1995;155:1605–1609.

29. Gershon AA, Mervish N, LaRussa P, Steinberg S, Lo SH, Hodes D, et al. Varicella-zoster virus infection in children with underlying human immunodeficiency virus infection. *J Infect Dis* 1997;176:1496–1500.

30. Jumaan AO, Yu O, Jackson LA, Bohlke K, Galil K, Seward JF. Incidence of herpes zoster, before and after varicella-vaccination-associated decreases in the incidence of varicella, 1992–2002. *J Infect Dis* 2005:191:2002–2007.

31. Australian Paediatric Surveillance Unit. Current studies. 2006. Available from: http://www.apsu.org.au/download.cfm?DownloadFile=F189AF8B-EFA7-C0F5-8E5DABB0794BBDB5 Accessed July 2006.

32. Brotherton J, McIntyre P, Puech M, Wang H, Gidding H, Hull B, et al. Vaccine preventable diseases and vaccination coverage in Australia 2001 to 2002. *Commun Dis Intell* 2004;28 Suppl 2:SI–S116.

33. Givney R. Varicella surveillance: simpler than you think? [published erratum in *Commun Dis Intell* 2003;27:284]. *Commun Dis Intell* 2003;27:100–101.