

## \*\*\*SPECIAL EDITION\*\*\*

### A Decisive Decade in Immunisation NCIRS 10<sup>th</sup> Anniversary Conference 18 July 2007

#### "A Decisive Decade in Immunisation" NCIRS is 10!

The National Centre for Immunisation Research and Surveillance of Vaccine Preventable Diseases (NCIRS) celebrated its first 10 years with an Anniversary Conference at The University of Sydney on Wednesday 18<sup>th</sup> July 2007 entitled **A Decisive Decade in Immunisation**.

The Conference preceded the 2<sup>nd</sup> National Immunisation Workshop which was held on Thursday 19<sup>th</sup> July 2007.



Happy Birthday!

A number of renowned international and national guest speakers took part in the Conference. Speakers included the Hon Dr Michael Wooldridge, Professors Scott Halperin (Canada), Heinz-Josef (Joe) Schmitt (Germany), Terry Nolan, Margaret Burgess, Lyn Gilbert and Sir Gustav Nossal.

Both the Conference and Workshop were very well attended by representatives from State and Federal Governments, academia and vaccine manufacturers.

#### NCIRS 10<sup>th</sup> Anniversary Conference Presentation Summaries

##### Opening Address: The Honourable Dr Michael Wooldridge

Dr Wooldridge opened the conference with a high level overview of Australia's recent immunisation history. He noted that "success has a thousand fathers but failure is always an orphan. We celebrate a success in public health today but it wasn't always this way". Dr Wooldridge noted that as a medical student, a single case of measles was unusual but by 1993 Australia was having measles epidemics and the total number of cases was higher than in China.

Immunisation was an obvious area to tackle when Dr Wooldridge took over the health portfolio in 1996. The 7 point plan was developed as a sweeping approach consisting of the following:

1. Better use of GPs;
2. Making it more difficult not to immunise by links to welfare payments without compulsion;
3. Putting evaluation strategies in place;
4. Immunisation days;
5. A program to eradicate measles (October 1998 was the first month with not a single case reported since 1988);
6. Education and research initiatives to ensure education was underpinned by quality evidence-based research;
7. School entry requirements in cooperation with the States and Territories.

Dr Wooldridge stressed the need to remain vigilant. He noted that the public generally supports immunisation strongly but that the support can be eroded - citing the recent experience with HPV as an example of the controversy that can be escalated via the media - but ended his presentation by saying "With our current successes in control of diseases like polio, diphtheria and tetanus, this is an enormous celebration".

## Session 1: Resources underpinning immunisation programs: comparisons, contrasts & conquests

### Australia – History – Professor Margaret Burgess (foundation Director of NCIRS)

In the early 1990s, large outbreaks of measles, rubella and pertussis occurred and several children were born with congenital rubella. In 1993, the NHMRC drew up a national immunisation strategy to address the problem which proposed a fully-funded vaccine schedule, incentives, a register and coverage goals. In 1997, this was more fully realised under the 7 point plan which included a register, incentives, and a measles elimination program. Research and education were emphasised.

The National Centre for Immunisation Research and Surveillance of Vaccine Preventable Diseases was established in August 1997. Its primary focus was to perform research aimed at reducing the incidence of vaccine preventable diseases and improving vaccine uptake.



A few of the original NCIRS team

The NCIRS research plan covered the broad areas of: VPDs epidemiology, including disease burden and serosurveys; coverage and the ACIR; sociodemography, including special populations; adverse events associated with immunisation; risk communication; program and economic evaluation; vaccine preventable disease surveillance; and support for developing the Australian Immunisation Handbook.

Growth over the past 10 years is reflected in the rise of staff numbers from 11 FTE to 37 FTE; over 300 publications in peer reviewed journals and books and a large number of national reports. During this decade Australia has seen the introduction to the schedule of new vaccines, including hepatitis B, varicella, rotavirus, pneumococcal, meningococcal and HPV, which now target 14 diseases.

Australia now has arguably one of the most comprehensive publicly funded vaccination programs in the world. Measles, Hib and rubella are at the lowest rates ever recorded. We need to maintain vigilance with excellent surveillance and reporting to know where and when to modify programs.

In summary, the decade has seen unprecedented focus on vaccine preventable diseases and vaccines; significantly improved surveillance and program evaluation; and an increase in industry investment in production capacity and new vaccine development.

NCIRS has been involved in and has anticipated much of this progress.

### Australia – Surveillance and policy support – Professor Peter McIntyre

What issues face programs worldwide? All industrialised countries now have more vaccines for more age groups, but also more public concern. Australia needs to maintain its program and evaluate program impact, evaluate evidence for new vaccines, have high quality surveillance and good communication. Research efforts must pay attention to special groups such as Indigenous people and be collaborative to maximise benefit.



Peter McIntyre, Tony Adams,  
Joe Schmitt, Michael Wooldridge

NCIRS and other organisations around Australia have made important contributions to this. In terms of vaccine preventable diseases and coverage, before 1997 there was patchy reporting and we relied on ad hoc reviews to estimate vaccine coverage. We now have the ACIR which provides the big picture. NCIRS adds value to that through coverage reports, program evaluation, parental surveys and mapping.

For example, parental surveys have shown that less than 3% object to vaccination but mapping shows pockets of much lower vaccination rates. The register can also tell us about timeliness which, now that we have high vaccination rates, is the next important goal.

Data and reporting of Adverse Events Following Immunisation have improved. Before 1997, there were periodic bulletins from TGA and separate databases between jurisdictions. Now there is a regular national reporting mechanism. With respect to new vaccines, a series of national workshops have drawn together experts from Australia and overseas to look at the vaccines, epidemiology of the relevant diseases and the effectiveness of programs overseas. The serosurveillance program has been an important addition to overall integration of data sources for

looking at one disease from a range of aspects. For Indigenous people we have gone from having only 50% to close to 100% on the register and we have been involved in national initiatives to measure HPV prevalence in Indigenous women. NCIRS now provides all technical support for ATAGI and its working parties. The area of communication is also important and includes development of the website and a large series of fact sheets. We now have a large staff with close interaction within NCIRS and with other groups, which allows maximal research output.

### **Australia – Clinical and Epidemiological Research – Professor Robert Booy**

Worldwide there has been a massive increase in funding for vaccines. Australia has eclipsed Europe and the USA in terms of fully funded programs.

NCIRS has made a contribution to what we know about vaccine preventable diseases. For example, a 10 year review of death data shows the significant morbidity and mortality from rotavirus disease. NCIRS work looked at the burden of varicella disease to support vaccine policy.



Robert Booy

But vaccines don't act in isolation. For example, antivirals have the potential to minimise the morbidity from influenza. NCIRS is involved in an ARC study of antivirals in aged care. The effectiveness of masks in preventing respiratory disease is also under-studied and NCIRS has undertaken a cluster randomised trial of them in preventing seasonal flu in families.

Our modelling research has increased dramatically and we are supported by grant funding to increase capacity in disease modelling. This has seen us engaged in modelling studies of pandemic influenza.

NCIRS also undertakes social research, ACIR-related research and research on high-risk groups. Overseas we have collaborations in many countries including Canada, Kenya and China to name a few.

### **Support for immunisation programs in Canada – a personal view – Professor Scott Halperin**

Canada has 13 jurisdictions and shared responsibility between federal government and provinces/territories and a total population of 30 million. This creates a patchwork of systems in which there is potential for redundancy, gaps and overlap.

Communicable disease surveillance is reported by province or territory based on statute. Vaccine preventable disease surveillance is a subset of that and has many flaws including passive surveillance with under-reporting; filtered reporting from local to provincial government which produces loss of information; and resulting in data that are 2-3 years out of date.

Supplemental surveillance of vaccine preventable diseases (VPD) occurs in the form of the Flu Watch network and an immunisation monitoring program or IMPACT. IMPACT is a network of 12 paediatric hospitals. Nurse monitors actively seek certain targeted hospitalised VPDs and report to a central data centre. Along with certain hospitalised VPDs, IMPACT also assesses adverse events using an active system, particularly looking at neurological events, injection site reactions and thrombocytopenia. The national adverse events reporting system encompasses passive surveillance which again follows a local - provincial - federal reporting pathway with intermittent summaries.

There is no national approach to other facets of vaccine programs, including assessing disease burden, where research is often done by academic investigators or local/regional public health organisations. Measuring vaccine coverage is currently determined using intermittent surveys. There is, however, a current federal priority to establish a register. There is no ongoing evaluation of vaccine program effectiveness and insufficient resources to assess function and impact. Many programs are implemented without any evaluation component. Health economic studies are more often undertaken by or for industry, which can result in perceived bias, or through stand alone studies by academics. Similarly, disease modelling tends to be based in academic institutions with some capacity in provinces.

In summary, Canada has a patchwork of resources that support its immunisation programs. This includes a division of responsibilities between federal government, provinces and territories leading to significant gaps. Attempts to fill the gaps lead to a further patchwork of programs and intergovernmental structures that are slow and unwieldy. Despite these inherent difficulties, support for vaccine programs is still achieved through the combined efforts of the public health community.

### Support for immunisation programs in Germany - Professor Joe Schmitt

Germany is a federal republic of 85 million people. Sixteen states regulate health and health insurance is mandatory.

Germany does not have a vaccination program, rather vaccination recommendations resulting in low coverage. Recommendations are given by a scientific advisory committee called "Ständige Impf-Kommission" (STIKO). To date, all recommended vaccines have been voluntarily paid for by insurance companies. However, as of 1 July 2007, payment for STIKO-recommended vaccines by insurance companies is compulsory.

The resources underpinning vaccine recommendations are limited, but include large vaccine producing multinational companies who are located in Germany but produce vaccines for the world market. European Medicines Evaluation Agency (EMA) and the Robert Koch Institute do research, surveillance, and receive mandatory AEFI reports. Additional resources come from STIKO, insurance companies and physicians.

Ninety percent coverage at school entry fails to reflect the poor coverage attained by age two which has resulted in measles outbreaks. This year there have been 184 cases and 2 deaths from measles. Since 1988, there have been 138 SSPE cases. Measles does not get sufficient consideration as a public health threat in Germany.

In summary, there are a number of factors contributing to poor coverage by due date and disease outbreaks, including the voluntary nature of vaccination and many organisations and players with no meetings to bring them all together. Currently, paediatricians in private practice are the key to the existing success of vaccine programs.



Back: Joe Schmitt, Kristine Macartney, Peter McIntyre, Scott Halperin  
Front: Robert Booy, Gus Nossal, Shelley Deeks, Margaret Burgess, Raina MacIntyre, Terry Nolan

### Session 2: Sources of Evidence: Measuring VPDs

The second session of the presentations consisted of some more detailed insight on the sources of evidence for measuring and tracking vaccine preventable diseases and current mechanisms for policy-relevant vaccine trials in Australia and Canada.

#### Disease databases - valid measures or dredging - Professor Peter McIntyre

The routinely collected datasets is often questioned. While ecological analyses of such datasets provide a weaker level of evidence than specific research studies, there are advantages and disadvantages to both. Routinely collected data have the advantage of being readily available, low cost and including the whole population, none of which applies to specific research studies. Studies such as the impact of the preschool pertussis booster are relatively easy to conduct using routine data and extremely difficult with other approaches. A study showing a correlation between delayed vaccination and higher pertussis hospitalisation rates in Indigenous infants is an example of preliminary hypothesis testing using hospitalisation and ACIR data. Studies validating the specificity of routine data are particularly useful, as specificity is one of the main attributes of studies. Examples include the low specificity of epiglottitis hospitalisation data post-Hib vaccination, versus the high specificity of pertussis hospitalisation data in children. Combined analyses of different independently collected datasets also add weight to the evidence, such as with tetanus, where notifications, hospitalisations and deaths all show higher rates in the elderly, suggesting the need for vaccination policies targeting this age group.

#### Serosurveillance - snapshots of national immunity - Professor Lyn Gilbert

The national serosurvey program conducted by NCIRS and the Centre for Infectious Diseases and Microbiology uses residual sera submitted for diagnostic testing from more than 40 laboratories. Three surveys have been conducted - in 1996-99, 2002 and 2007. Samples are tested for identified diseases that are currently, or potentially in future, vaccine preventable. The data complement other sources and are used to evaluate vaccination programs, identify at-risk groups, and model the future impact of different schedules. Particular examples include demonstrating the impact of the Measles Control Campaign in decreasing susceptibility in primary school children, identifying young adults at risk of measles, and demonstrating the disappointing impact of the adult measles control campaign. The varicella results were used to model the impact of different vaccination schedule options and coverage levels. While the surveys are conducted on convenience rather than random samples, the specimens have similar age and sex distributions to the Australian population, and the seroprevalence results are similar to those obtained from other sources and overseas. The surveys are also highly cost-effective at less than \$1 per test.

### Modelling – science or crystal ball gazing – Professor Raina MacIntyre

Modelling is a useful tool for predicting the behaviour of infectious diseases prior to their occurrence and to assist in rational decision making on funding and policy. Randomised controlled trials, while the gold standard of evidence-based medicine, are not always available or ethical when answering public health problems. Modelling is appropriate for predicting future events, giving a dynamic picture based on information from current sources of data such as serosurveillance, enhanced surveillance, vaccine coverage data, vaccine/drug efficacy, disease transmission data and economic data. A simple compartmental model will classify persons as susceptible, infected or immune (recovered) with susceptible persons added to the model through birth, immigration and waning immunity.



Raina MacIntyre

Mathematical modelling at NCIRS includes the modelling of measles to calculate the R value before and after the Measles Control Campaign and the modelling of the impact of infant varicella vaccination on the incidence of varicella and zoster in Australia. A model looking into the effect of domestic travel restrictions on the influenza pandemic has also recently been developed. NCIRS was instrumental in the establishment of the Network of Infectious Disease Modellers of Australia, which provides capacity for training in infectious disease modelling in Australia for the first time. Recent examples of economic modelling at NCIRS have been used to provide a rational basis for decision making on funding for influenza and rotavirus vaccination and requires a multidisciplinary approach that is transparent, reproducible and uses sound assumptions.

### Clinical trials – tribulations – in Australia – Professor Robert Booy

Phase I clinical trials allow centres to be closer to the cutting-edge and influence product development. NCIRS and other Australian centres have recently been engaged in Phase I trials of influenza and meningococcal vaccines. Regarding vaccine safety, phase III trials can detect outcomes that occur 1 in 10,000, but other approaches are needed, such as database review, time-series analysis, enhanced surveillance, cohort, case-control, genetic studies and social research, to detect rarer events.

A trial example undertaken by NCIRS is that of the Sanofi 2005 southern hemisphere influenza vaccine formulation which was produced with a reduced dose of the A/Wellington strain. The trial was to determine if the reduced dosing affected the immunogenicity in adults 18-59 and adults >60 years. 120 subjects were recruited in 3 days with >90% of each group having satisfactory serum antibody responses post-vaccination. This trial allowed the release of 30 million doses of Vaxigrip within time for the southern hemisphere influenza season.

In addition to this trial, NCIRS is undertaking a number of studies into influenza control including a study into the use of masks to prevent transmission of respiratory viruses, and another on antiviral prophylaxis versus treatment. Other trials being conducted by NCIRS, the Centre for Clinical Research Excellence in Child and Adolescent Immunisation and others in Australia include an influenza vaccine trial to prevent ischaemic heart disease and trials of influenza vaccination in young children, the vaccination of geriatric and bone marrow transplant patients with pneumococcal conjugate vaccine, and the HPV and HZ vaccines for use in the immunosuppressed.

### Clinical trials – tribulations – in Canada – Professor Scott Halperin

Vaccine manufacturers have been the main sources of funding clinical trials on vaccines in Canada, with little government funding available. The Public Health Agency of Canada was established concurrently with the National Immunization Strategy, which includes a role for vaccine research. However, no strategic plan has yet been developed, and funding for research is unclear. In the absence of public funding for clinical trial infrastructure, the Canadian Association for Immunization Research and Evaluation (CAIRE) was established as a network for clinical trial academics and public health vaccinologists which interacts with industry on issues of importance to vaccine research. To remain competitive in a global marketplace, Canada needs to establish a competitive environment with efficient mechanisms and establish partnerships between industry, government and academic institutes. Professor Halperin discussed the issues surrounding clinical trials in a country with a small share of the global vaccine market (<1%) in an environment of globalised vaccine trials. These issues are likely to be similar to a number of countries with a small market and limited trial infrastructure such as Australia.



Scott Halperin, Joe Schmitt

### Session 3: Would you like evidence with that?

This session consisted of presentations from Australia, Canada and Germany on how evidence for new vaccines is assessed.

#### The role of NCIRS - Dr Kristine Macartney

High quality evidence is essential to underpin decision making, especially for additions to the funded National Immunisation Program (NIP). These changes are not only confined to new vaccines but also to new indications for existing vaccines.

Vaccine expenditure has increased enormously from a modest \$13 million spent on vaccine purchase in 1995 to over \$290 million in May 2005. This will have increased substantially with the recent addition of HPV and rotavirus vaccines to the NIP.

The funding structure for vaccines has substantially changed over the past 2 years with both increased support to the Australian Technical Advisory Group on Immunisation (ATAGI) and the new central role of the Pharmaceutical Benefits Advisory Committee (PBAC). As part of this funding agreement, NCIRS was allocated monies to support ATAGI working parties and to oversee the production of the 9<sup>th</sup> edition of *The Australian Immunisation Handbook*. NCIRS also produces fact sheets, brochures, receives phone enquiries, and coordinates an email professional group (Australian Immunisation Professionals). As an example of the public interest vaccination can generate, the NCIRS HPV fact sheet received 1200 internet hits in the last month.



Joe Schmitt, Kristine Macartney,  
Margaret Burgess

The NCIRS evidence-based project group provides support to the ATAGI working parties through a variety of mechanisms not limited to analysis of data, providing review documents pre and post-PBAC submission, and Handbook chapters, as well

as convening workshops. Typical working party reports are 150 pages in length and mechanisms to have these available for public information are being discussed.

#### How are vaccine policy options developed? - in Australia - Professor Terry Nolan

The elements required for good policy include funding, intelligence capability, disease surveillance, regulatory framework and organisational structures. The National Immunisation Program (NIP) is a joint State and Federal initiative with vaccine delivery via GPs, local government doctors and nurses, public health nurses, school-based vaccination programs and public health units. NIP vaccines are free to consumers. The NIP has resulted in excellent outcomes with strong disease control.

ATAGI was formed 10 years ago and was preceded by a NHMRC Expert Committee. ATAGI terms of reference include acting as an advisory body to the Federal Health Minister through technical advice, in which NCIRS plays a key role. The membership of ATAGI is for a fixed term and consists of 12 voting members including 1 ATAGI member who also sits on PBAC and a further 5 non-voting ex-officio members, including the Director of NCIRS, Professor Peter McIntyre.



Terry Nolan

In 2005, the PBAC pathway for funding vaccines either via the NIP or the Pharmaceutical Benefits Scheme (PBS) was introduced. This change also resulted in new resources for NCIRS to provide support to ATAGI. Another step was the formation of Medicines Australia Vaccines Industry Group (MAVIG), which provided an important voice for formulating vaccines. Requests for a NIP vaccine listing may come via MAVIG or advocacy groups, such as the Influenza Specialist Groups, or ATAGI. The decision on recommending vaccine funding via the NIP occurs at the PBAC.

There is an initial scoping phase with technical advice provided pre-submission to the PBAC. A request for either PBS or NIP listing must be responded to swiftly via the PBAC economic subcommittee. PBAC then makes a recommendation to the Minister or may request further information from either ATAGI or the company submitting the request. Where funding of a vaccine results in an annual expenditure in excess of \$10 million, the Federal Minister must then go to cabinet with the proposal for approval. The post-PBAC phase involves evaluation from the Pharmaceutical Benefits Pricing Authority (PBPA) for the funding of the vaccine.

Vaccine programs require decisions about the impact on herd immunity, delivery aspects, infrastructure needs, surveillance requirements, reliability of supply, and recommendations for use. In addition, factors such as broad population usage, whether an individual risk is required, and how to achieve maximum uptake are also considered.

### How are vaccine policy options developed? - in Germany - Professor Joe Schmitt

In Germany, there is a 20 page handbook and a side effects handbook. STIKO is the German immunisation advisory committee of which Professor Schmitt is chairman. Appointment is on a personal basis supported by statute, giving a high degree of independence. STIKO consists of an independent scientific committee for the 16 federal German states and only the states can make a public recommendation regarding vaccinations. STIKO also makes recommendations regarding other interventions, such as pertussis prophylaxis, and also defines adverse events following immunisation.



Joe Schmitt, Tony Penna, Alyson Kakakios

STIKO meets twice yearly and only makes recommendations for vaccines licensed for use in Germany. STIKO suggests recommendations and forwards the recommendations to paediatricians and other health professionals for a 4-week commentary period. STIKO then reviews the comments and recommendations are published.

A new process known as the Gemeinsame Bundesausschuss or G-BA (The Federal Joint Committee) will fund vaccines from 1 July 2007. The criteria used for recommending a vaccine includes public interest, the use of the vaccine in special groups, the occurrence of disease, transmission of the disease, and individual requirements.

For each vaccine, a working party considers the goal of introducing the vaccine, the morbidity and mortality of the target disease, including mathematic modelling, vaccine safety, epidemiological consequences after introduction, coverage requirements, and risk/benefit analysis. If there is found to be more benefit than risk, then legally the vaccine must be recommended.

Limitations of the German system are that there is no universal vaccination program; there is a perception that vaccination is industry driven with very little direct political support. There is no uniform or comprehensive system for disease management or implementation.

### How are vaccine policy options developed? - in Canada - Dr Shelley Deeks

Canada has a funded vaccination program and Health Canada approves vaccines, with recommendations made at the national level. There are 2 committees concerned with immunisation which are part of the Public Health Agency of Canada (PHAC). These committees are the Canadian Immunisation Committee (CIC) and the National Advisory Committee on Immunisation (NACI).

The CIC considers implementation issues and the prevention and control of vaccine preventable diseases. The CIC strives for harmonisation of immunisation issues and aims to meet the goals of the National Immunisation Strategy.

NACI was established in 1964 and, since 2004, reports to the Chief Public Health Officer (CPHO). There are 12 members who sit for 4 years and are then renewable once. NACI sits 3 times a year for 2 days and provides timely scientific and public health advice on the optimal vaccines for use in Canada. NACI considers the disease characteristics and vaccine characteristics and all NACI recommendations are approved by the PHAC. Appointment to the NACI is CV-based which may potentially not be representative but ensures expertise. There is no public consultation regarding NACI recommendations and all committee members sign confidentiality agreements. Conflicts of interest are declared but this is a challenging area and there are limited pools of experts available.

The vaccination recommendation process is led by NACI, with specific working groups. NACI reviews and approves the recommendation which is then published. Systematic reviews of the literature are contracted to outside bodies and are available at [www.naci.gc.ca](http://www.naci.gc.ca). Statements are reviewed at the NACI meeting and are then approved by CPHO and published on the CCDR (Canada Communicable Disease Report). Authorship is given to all members and a listing of the main authors is included. These statements are considered publications.

Recommendations are based on methodologies that are not explicit, and unlike the US, may be off-label (eg. age groups or route of administration). Expert opinion, burden of disease and what constitutes public health significance and the availability of data, in particular for vaccine use in high-risk groups and long-term effectiveness, are all considered. Final recommendations are graded according to the available evidence.