Vaccine Safety Seminar
Summaries prepared by Dr Aditi Dey, Dr Frank Beard, Dr Kevin Yin & Dr Helen Quinn

THIS ONE-DAY SEMINAR WAS ORGANISED BY NCIRS AND CONVENED BY A/PROF KRISTINE MACARTNEY. THE SEMINAR BROUGHT TOGETHER NATIONAL AND INTERNATIONAL RESEARCHERS, IMMUNISATION PROVIDERS AND PUBLIC HEALTH PROFESSIONALS TO SHARE CURRENT METHODS OF ACTIVE AND ENHANCED SURVEILLANCE OF ADVERSE EVENTS FOLLOWING IMMUNISATION (AEFI). TO STRENGTHEN COLLABORATIVE EFFORTS ACROSS JURISDICTIONS AND NATIONAL SYSTEMS TO IMPROVE VACCINE SAFETY SURVEILLANCE IN AUSTRALIA.

Following a Welcome to Country by Allen Madden and address by Prof Peter McIntyre, the seminar was officially opened by the Chief Medical Officer for the Australian Government, Prof Chris Baggoley, who also gave an overview of recent efforts in ensuring vaccines are safely delivered in Australia and the implementation status of recommendations made in the Horvath review.

Session 1: Active post-marketing surveillance of vaccine safety – why do we need it?
A/Prof Kristine Macartney, deputy director of NCIRS, presented an introduction of active surveillance of AEFI and explained how it complements passive surveillance. Her talk started with an overview of vaccine safety activities as well as advances since the 2005 vaccine safety workshop and the importance of the Horvath review and National Immunisation Strategy in this regard. The main future direction of signal detection and investigation highlighted by A/Prof Macartney was to ensure the passive surveillance system is functioning appropriately and also to work towards effective active surveillance mechanisms to complement the passive surveillance.

The importance of active surveillance at post-licensure phase was further echoed by A/Prof Jennifer Nelson, the Director of Biostatisticians in the Biostatistics Unit at Group Health Research Institute, USA. A/Prof Nelson introduced American experiences and systems for active surveillance of vaccine safety and, in particular, she discussed the strengths and challenges of the Vaccine Safety Datalink (VSD) project (started in 1990) and the recently established national electronic system, the Sentinel Initiative (from 2008).

Session 1 ended with a joint presentation by A/Prof Chris Blyth from Princess Margaret Hospital in Western Australia and Ms Alison Marcus, the consumer representative of the National Immunisation Committee. This presentation highlighted the reason for, and importance of, engaging patients and communities in vaccine pharmacovigilance from the perspectives of clinicians, researchers and consumers.
Ms Annette Regan, from the WA Department of Health, presented on a number of active surveillance initiatives conducted, in collaboration with the Telethon Institute, under the FAST (Follow-up and Active Surveillance) banner, following up children, pregnant women and healthcare workers who have received influenza vaccine. Initially conducted via telephone only, automated SMS alerts are now also used, allowing individuals who identify an adverse event the option to complete a survey either via their smart phone or a telephone call. A randomised trial in WA of follow-up via SMS versus telephone call found SMS to be associated with better completion rate and timeliness for around half the cost.

Alan Leeb, a GP in WA, presented on SmartVax, a GP-based vaccine safety surveillance system which utilises a fully automated application to extract all vaccination data from practice software. Automated SMSs are sent to individuals who have received any vaccine, with individuals reporting an adverse event prompted to complete a survey via their smart phone. Experience to date shows a high response rate for children (>85%) and people aged ≥65 years (74%), with 80% of responses received within 2 hours. Data are collated in a central database with algorithms used for signal detection of unexpected adverse event patterns. Medically attended adverse events are reported back to the treating GP, with identified data forwarded to the state health department meeting legislative notification requirements. Expansion is currently underway with the aim of creating a national GP network.

A/Prof Mike Gold, paediatric allergist and immunologist from South Australia, presented on Stimulated Telephone Assisted Rapid Safety Surveillance (STARSS) – a randomised controlled trial of SMS to vaccine recipients (with follow-up of adverse events via either computer-assisted telephone interview or web-based reporting) versus usual practice (passive surveillance). A follow-up survey will be conducted 4–6 weeks later on 20% of participants to assess process issues (understanding, acceptance, concerns and attitudes). This trial, funded under an NHMRC Partnerships Grant, is currently in the provider enrolment phase.

Mr Patrick Cashman, Immunisation Coordinator at Hunter New England LHD in NSW, presented on Vaxtracker, a web-based survey tool used for vaccine safety surveillance. Patients enrolled by clinics are sent email +/- SMS message at 3 and 42 days (to assess for late adverse events), requesting completion of a web-based survey. Patients who refuse are included in the data to enable calculation of denominators.

Dr Gulam Khandaker, from NCIRS, presented on AusVaxSafety an enhanced real-time surveillance system to monitor adverse events following immunisation with influenza vaccine in children under 5 years of age. This NCIRS coordinated system brings together information collected through the Vaxtracker system in NSW and Victoria and the FAST system in WA, and uses a novel safety signal detection system. AusVaxSafety surveillance in 2014 showed a good safety profile for seasonal influenza vaccine in children under 5 years of age. Expansion to other states is currently being considered.

In a panel discussion at the end of Session 2 it was emphasised that active surveillance data are complementary to (but don’t replace) passive vaccine safety surveillance data. It was noted that SMS-based follow-up systems will likely become cheaper over time while telephone-based systems become more expensive.

The importance of feedback loops to both the public and providers regarding vaccine safety was also emphasised, with communication particularly important given that these new systems are generating a lot of data that wasn’t previously in the public domain.
**Session 3: Surveillance for adverse events of special interest**

Dr Tony Hobbs, Therapeutic Goods Administration (on behalf of Dr Bronwen Harvey), opened the session with a presentation on the enhanced surveillance conducted as part of the HPV for boys school-based vaccination program which commenced in 2013. The background of the talk highlighted the AEFI experience with the commencement of the girls’ HPV school-based program, which included a mass psychogenic event and reports of anaphylaxis and allergic reactions, both of which caused media attention. He then went on to describe the establishment in 2012 of an ATAGI working group for the boys’ HPV program and the collaborative effort required from the states and territories to collect AEFI data, with a focus on anaphylaxis and allergic reactions, loss of consciousness and any AEFI that required emergency department or hospital attendance. A feature of the enhanced surveillance was daily reporting and review of selected AEFI, and weekly feedback of results to state and territory health departments. AEFI rates in the program were largely as expected, and similar to previously published rates.

The second speaker of the session was Dr Nick Wood from NCIRS who provided an overview of the Paediatric Active Enhanced Disease Surveillance (PAEDS) conducted at five tertiary paediatric hospitals around Australia. This system involves nurse-based surveillance, with cases of specified diseases identified from patient management and laboratory diagnostic systems, with detailed clinical forms being completed and vaccination status reviewed on the ACIR.

Nick presented some results of two studies: intussusception in children with recent receipt of rotavirus vaccine, and febrile seizure risk following MMR-containing vaccines. Strengths of the PAEDS system that were highlighted were the detailed clinical records obtained and the ability to collect biological samples. The need for accurate case definitions and the time and labour associated with the system were also highlighted.

Dr Nigel Crawford, from SAEFVIC, was the next presenter. He described the use of sentinel site surveillance for Guillain-Barrésyndrome (GBS) following the introduction of pandemic H1N1 vaccine. He described the difficulty in detecting a rare event such as this, and the need to include many sites to obtain as many cases as possible.

In total, 10 Victorian sites participated in the 1-year study and although an increased risk was observed, it was not significant. The data from Australia then provided a large contribution to an international study, where a slightly increased significant risk of GBS following pandemic H1N1 vaccine was detected.

The final speaker of the session was Dr Jim Buttery, from SAEFVIC, who presented on the use of emergency department (ED) data for assessing vaccine safety. Jim started by providing examples of syndromic surveillance systems that have been used for communicable diseases in the past and highlighted some of the issues with these. He then described SYNTRACK, a pilot study with real-time postcode mapping of symptoms using data from EDs at five paediatric hospitals. The pilot showed that this concept was technically and ethically feasible; however, there are currently some software issues with real-time extraction and use of free text fields for symptoms is required due to limited entering of ICD codes in EDs.
Session 4: Using large healthcare databases to assess vaccine safety

Dr Jennifer Nelson from Group Health Research Institute in the USA presented on use of large healthcare databases in the USA to assess vaccine safety.

She talked about the Vaccine Safety Datalink’s (VSD’s) general approach to proactive vaccine safety monitoring using Pentacel combination vaccine as an example.

She then talked about the methodological challenges and comparison of methods in vaccine safety studies. This was a nice follow-up session to her morning session where she had provided an overview of the role of the VSD and Mini-Sentinel projects. She elaborated on the sequential testing approaches used for rapid detection of adverse events.

The next speaker was Dr Rob Menzies from NCIRS. Rob presented findings from a project that investigated the use of GP encounters from the General Practice Research Network (GPRN) database for assessing vaccine safety. The primary aim of this project was to investigate the association between the administration of Pneumovax and AEFI presentations to general practice, using rates of reaction to seasonal trivalent inactivated influenza vaccines (excluding the 2009 pandemic influenza vaccine) as a control comparator. The secondary aim was to explore the potential strengths and limitations of the GPRN and similar datasets for future AEFI surveillance and investigations.

An important finding was that the GPRN data detected an approximately 10-fold higher rate of reactions per 100,000 vaccine doses compared to TGA data. The GPRN data quality was generally consistent with a small number of duplicates identified (6%). There were missing data for some variables for which data entry was not compulsory. As predicted, the number of Pneumovax vaccinations reduced sharply from April 2011 when the TGA’s interim advice to health professionals advising against administering a second/revaccination or subsequent doses of Pneumovax. The seasonality, age distributions of vaccinations, dose numbers and revaccination intervals were predominantly consistent with recommendations as specified in The Australian Immunisation Handbook for the respective vaccines, and immunisation data were consistent with reason for visit.

A/Prof Mike Gold, from University of Adelaide, followed the theme by exploring the concept of the use of data linkage of the Australian Childhood Immunisation Register (ACIR) for vaccine safety surveillance. In 2007, the Vaccine Assessment using Linked Data (VALID) Safety Study was initiated to examine whether Australian administrative data could be applied for vaccine safety evaluation. This study was funded by the Australian Research Council’s Linkage Projects funding scheme. The objective of this study was to determine the feasibility and acceptability of data linkage for vaccine safety assessment. A randomised controlled trial was undertaken to examine parental participation in an opt-in versus opt-out consent mechanism for vaccine safety surveillance. A follow-up computer-assisted telephone interview of a randomly selected population sample examined community views on vaccine safety, preferred consent mechanisms and research priority over privacy. In-depth qualitative interviews were also undertaken to examine values and belief regarding data linkage. Furthermore, a Citizen’s Jury debated the requirements for establishing a national vaccine safety system using data linkage.

This project also involved data linkage of the ACIR with the National Death Index (NDI) for the period 1999–2010. Also, linking of cross-jurisdictional morbidity datasets i.e. ACIR with hospital admissions/ED presentations (for five states – SA, WA, NSW, QLD, Vic) for the period, 2003–2013 were undertaken. Several complexities (e.g. governance, procedural and access requirements, policy constraints, resources, cost, technical/methodological limitations) were identified in linking datasets. At the start of the VALID study, individual jurisdictions and the Commonwealth were developing data linkage infrastructure and capability which resulted in hesitancy to commit to data linkage projects before the policy had been finalised. The recommendations were to streamline approvals and processes to ensure research and other activities occur in a more timely fashion to enable vaccine safety assessment.

The last session was presented by Dr Paul Effler from the Department of Health, Western Australia. He stressed the importance of communicating vaccine safety to the public in a timely fashion and the recommendation of a more coordinated approach in vaccine safety surveillance, particularly due to the recent developments, since 2010, of use of GP systems and involvement of several stakeholders across jurisdictions.
Photos captured from the seminar

Attendees at the seminar

A/Prof Chris Blyth presenting

Session 2 panel

Staff from NCIRS

Attendees with NCIRS Immunisation CNC, Kath CANNINGS (centre)

Session 1 panel

Ms Annette Regan participating in the Session 2 panel
L-R: A/Prof Mike Gold, Dr Gulam Khandaker, Dr Alan Leeb and Mr Ian Peters

Dr Jennifer Nelson

Dr Nicole Gilroy

Dr Tom Snelling

Dr Rob Merzies

A/Prof Kristine Macartney
From package to protection: how do we close global coverage gaps to optimise the impact of vaccination?

22–24 September 2014, Annecy, France

Summary by Dr Kerrie Wiley

There is rising global concern about gaps between target and actual vaccination rates. The strategies to address these gaps rely on evidence regarding what causes them and how they can best be addressed. NCIRS has been making a contribution to this evidence base since 2001.

In September, Kerrie Wiley, Hal Willaby and Julie Leask from the NCIRS social science unit had the opportunity to attend the Fondation Merieux meeting, “From package to protection: how do we close global coverage gaps to optimise the impact of vaccination?” held in Annecy, France. They were joined by Katie Attwell from Murdoch University and Sonya Ella from Melbourne’s Royal Children’s Hospital. This meeting brought together experts in a number of disciplines from around the world, including paediatricians, social scientists, health policy experts from governments and the WHO, science communicators, consumer advocates and industry leaders.

There were a broad range of topics covered, including the social and psychological barriers and facilitators to vaccination, risk perception and vaccine decision-making; interventions which could help address uptake issues in certain population groups; and evidence-based communication strategies for hesitant parents. Hal Willaby presented a proposed measure of vaccine acceptance – the Vaccine Attitudes, Beliefs and Concerns measure (V–ABC) – and Julie Leask presented on strategies to close the vaccination coverage gap. Kerrie Wiley led a workshop session group looking at improving uptake of maternal influenza vaccination and Katie Attwell shared her experience with the I Immunise Campaign.

After reviewing the current situation, the meeting delegates agreed that the main lessons learned from the meeting are:

• Facilitators and barriers to vaccination tend to be vaccine and population dependent, and therefore responses should be tailored to specific vaccines and populations.
• Healthcare professionals are a key part of the vaccination ‘journey’, and should therefore be trained to have the needed skill to communicate risk and benefit.
• Effective vaccine communication is multi-faceted: People are not moved by numbers alone, although how those numbers are presented can be influential.

The main challenges identified for closing coverage gaps moving forward are:

• Fostering a dynamic, multidisciplinary and better connected community of practice
• Establishing vaccination acceptance as a legitimate discipline for theoretical and applied research
• Ensuring the adoption of standardised and validated tools to measure barriers and drivers of vaccine acceptance and the impact of interventions
• Growing rigorous qualitative, quantitative, culturally and geographically balanced evidence-base on i) drivers and barriers to coverage and acceptance; ii) intervention options and iii) measuring impact of interventions
• Developing better communication strategies and improving communication frames
Advanced Course of Vaccinology (ADVAC)

This year marked the 15th anniversary of the Advanced Course of Vaccinology (ADVAC) held during 12 to 23 May 2014 at Les Pensières, France. This Advanced Course provides a comprehensive overview in the area of vaccinology including immunology, clinical trials, vaccination strategies, policy decisions related to the introduction of new vaccines and also the social, economic, political and ethical issues of vaccination.

Participants are selected by an international scientific committee based on their educational background, involvement/decision-making responsibility and expected impact of the course at a personal, institutional and national level. This course also provides a great opportunity for development of international collaborations. In 2014, there were 22 participants from Europe; 17 from Asia; 13 from North America; 8 from Africa; 3 from Latin America and Caribbean; and 3 from Australia. NCIRS staff members who have previously attended this prestigious course are Drs Nicholas Wood, Clayton Chiu and Kevin Yin. This year, Dr Aditi Dey from NCIRS was selected to attend this course.

ADVAC is co-sponsored by the European Commission, Fondation Mérieux, University of Geneva, World Health Organization, Centers for Disease Control (CDC) USA, European Society for Pediatric Infectious Diseases (ESPID), European Centre for Disease Prevention and Control (ECDC), Johns Hopkins Bloomberg School of Public Health, National Institutes of Health (NIH/NIAID-USA) and Fogarty International Center, National Vaccine Programme Office (NVPO). For more information on ADVAC, visit www.advac.org/
Age-specific strategies for immunization reminders and recalls: a registry-based randomized trial


Reminder and recall strategies are known to be effective in increasing immunisation rates but there is little information available on what is the optimal age to send reminder/recall notices.

This study in Detroit, USA, assessed the relative effectiveness of centralised reminder/recall strategies targeting age-specific vaccination milestones: a 7-month recall strategy, a 12-month reminder strategy, and a 19-month recall strategy. Eligible children were randomised to notification (intervention) or no notification groups (control).

Results indicated that although recall notifications can positively affect immunisation activity, the effect may vary by targeted age group. Immunisation activity was similar between notification versus no notification groups at both 7 and 12 months, suggesting that these groups were likely to receive medical care or immunisation services without prompting. Significantly more 19-month-old children in the recall group (26%) had immunisation activity following notification compared to those who did not receive a recall notification (19%).

This study has some useful lessons for Australians. The main one is that, although reminder/recall has been frequently shown to improve coverage and timeliness, it won’t necessarily work in all situations. There are a large number of well-care visits that are recommended by state authorities in Australia which include all vaccination schedule points, but they are not always followed. The most followed visits are probably those at 6–8 weeks of age and the Healthy Kids Check at 3 years. However, the general decline in primary care contact after 1 year of age which occurs in the USA is probably also applicable in Australia. Also important is the starting point for coverage and timeliness and other infrastructure supporting immunisation, before reminders/recalls are introduced. The authors did not talk about general coverage and timeliness in Detroit before the study commenced, but the pre-existence of a system of reminders/recalls may suggest there was limited room for improvement.

Presented by Dr Rob Menzies, Deputy Director - Surveillance, NCIRS

Efficacy, safety, and immunogenicity of an enterovirus 71 vaccine in China


Enterovirus 71 (EV71) is a Picornavirus which is one of several viruses which frequently cause hand, foot and mouth disease (HFM) or herpangina, a usually self-limiting childhood infection. However, in rare cases it can cause more serious infections with severe neurologic complications (including aseptic meningitis, brainstem encephalitis or acute flaccid paralysis) and can lead to permanent disability or death. Large outbreaks frequently occur across Asia, including China, where the C4 subgenotype has been predominant. This paper outlined a phase 3 trial to assess the safety and efficacy of a vero-cell derived, inactivated EV71 vaccine developed in China.

This was a large double blind randomised controlled trial involving 10,007 children 6–35 months of age, randomised to receive an inactivated EV71 vaccine against the C4 subgenotype or placebo. Children received a 2-dose schedule, 1 month apart, and had 12 months of follow-up for laboratory confirmed EV71 infection. The authors found that the vaccine efficacy against EV71 HFM or herpangina was 94.8% and against hospitalisation and severe neurologic complications was 100%. Almost all (98.8%) participants were seropositive 28 days after the second vaccination. A titre of 1:16 was calculated as the best ‘correlate of protection’. There were no safety concerns in the vaccinated cohort compared to the placebo group. There was a drop in neutralising antibodies from the beginning through to 6 months into the observation period but levels were then stable to 12 months.

This C4 subgenotype EV71 vaccine demonstrated safety and high efficacy against EV71 HFM/herpangina, including hospitalisation and neurologic complications, with protection lasting at least 12 months. However, its cross-protection against other subgenotypes of EV71 is unknown. Multivalent vaccines may be required to be effective in more than one region of the world.

Presented by Dr Jean Li-Kim-Moy, Clinical Research Fellow, NCIRS
The World Health Organization has just released
**Global Manual on Surveillance of Adverse Events Following Immunization**

This new manual from WHO provides guidance on setting up AEFI surveillance systems with standardised methodologies and tools.

Includes information on:
- most common vaccine reactions
- investigating AEFI
- analysing surveillance data
- causality assessment
- responding to serious AEFI, including communication
- most recent references in vaccine pharmacovigilance

The manual can be accessed at


1. WHAT DOES YOUR ROLE AT NCIRS ENTAIL?
Broadly, I am a member of NCIRS’s EB team and our core business is to provide evidence-based technical support to the Australian Technical Advisory Group on Immunisation (ATAGI). I also do a bit of most other things the centre does like analysis of vaccine preventable disease surveillance data, preparing immunisation resources, bit of teaching etc. and amidst this I also juggle a part-time PhD.

2. WHAT ISSUES IN IMMUNISATION CONCERN YOU THE MOST?
Well, I think......the barriers that exist that get in the way of making full use of disease and vaccine uptake data that’s already there to robustly monitor in real time how vaccines perform in our ‘real world’ which is a key to optimise vaccine gains and build public trust and confidence.....this can be quite frustrating.

3. WHAT IS THE MOST ENJOYABLE PART OF YOUR ROLE AT NCIRS?
I love the challenges my work brings and I must say it indeed is a pleasure to work with the nice bunch of smart and highly motivated people we have at NCIRS.

4. DESCRIBE YOURSELF IN THREE WORDS...
Calm, patient (most of the time) and flexible and a few more words, if I may, I like to think I am thoughtful and creative!!

5. WHAT WOULD YOU SPEND YOUR LAST $5 ON...
A goat.....for a deserving family in Africa, or Lotto.

6. YOUR IDEA OF HAPPINESS IS...
Being able to accomplish something I am passionate about, that sense of achievement would give me immense joy and to have my loved ones there to witness would multiply my joy.

7. IF YOU COULD INVITE THREE PEOPLE OVER FOR DINNER, WHO WOULD THEY BE?
Barry Humphreys, Dame Edna Everage and Sir Les Patterson (counted as one person, of course), Peter Kuruvita (actually I would get him to prepare the dinner), and Sir Viv Richards.

8. IF YOU COULD HAVE ANY SUPERPOWER, WHAT WOULD IT BE AND WHY?
Time travel, why not! Won’t that be awesome?

9. DO YOU HAVE ANY HIDDEN TALENTS?
Almost all of my talents are well known!! One that is less known I’d say in my work circle perhaps is that I blow my own trumpet....literally, I mean!!

10. IF YOU WEREN’T WORKING AT NCIRS YOU WOULD BE...
Involved in providing healthcare to a remote community somewhere far away or travelling as a doctor or statistician (or both) in a cricket team!!

STAFF SPOTLIGHT

Congratulations to Dr Gulam Khandaker who was the winner of the Young Investigators Award at the 7th Asian Congress of Pediatric Infectious Diseases (ACPID) held in China.

Gulam presented on two studies at the meeting:
1. Infectious causes of childhood disability: results from a pilot study in rural Bangladesh
2. Statins for influenza and pneumonia (Cochrane review).

Gulam was selected from a panel of 8 finalists from a range of different countries to win the award.