Vaccine Safety Seminar:
Active surveillance for adverse events following immunisation – new methods in vaccine pharmacovigilance

What is active surveillance and how does this complement passive surveillance?

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Harbour view Hotel, North Sydney

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Conflict of Interest Disclosure

• No conflicts
• Conduct studies funded by
  • Australian Government Department of Health
  • State/Territory Health Departments
Vaccine Benefits and risk

Vaccine impacts
Vaccine effectiveness
Prevention of morbidity and mortality
Better health

Minimise harms
Ensure individual and public health
Overview

• Reflections
• Surveillance aims and methods
• Active surveillance
• Meeting aims
National Vaccine Safety Workshop: summary and draft recommendations

Glenda Lawrence, on behalf of the National Immunisation Committee

November 2005
<table>
<thead>
<tr>
<th>Surveillance</th>
<th>Achieved?</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Implement a simple national system for passive AEFI surveillance</td>
<td>✓</td>
</tr>
<tr>
<td>2. Clarify the objectives of AEFI surveillance at local, jurisdictional and national levels.</td>
<td>✓</td>
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<tr>
<td>3. Conduct surveillance for vaccine failures through disease surveillance processes rather than AEFI surveillance processes</td>
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<tr>
<td>4. Review the AEFI surveillance case definitions for inclusion in the next (9th) edition of the <em>Australian Immunisation Handbook</em>.</td>
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<tr>
<td>5. Improve the timeliness and completeness of data submission</td>
<td>✓</td>
</tr>
<tr>
<td>6. Amend the current ADRAC (blue) notification form to collect data relevant to AEFI</td>
<td>✓</td>
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<tr>
<td>7. Improve feedback between ADRAC and providers and consumers with aggregate reports or at the individual level.</td>
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<tr>
<td>8. Ensure that the passive surveillance system is functioning appropriately before considering ongoing active surveillance at a national level while recognising that there is the occasional need to conduct active surveillance to investigate specific issues.</td>
<td>✓</td>
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### RECOMMENDATIONS cont..

<table>
<thead>
<tr>
<th>Clinical management and research</th>
<th>Achieved?</th>
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<tbody>
<tr>
<td>9. Ensure that providers and consumers have access to expert opinion on the clinical management of AEFI.</td>
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<tr>
<td>10. Standardise and collate data for the individual special AEFI clinics and report annually using Brighton Collaboration case definitions</td>
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<td>11. Develop uniform national guidelines on AEFI clinical management</td>
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<td>12. (Review resources)</td>
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<table>
<thead>
<tr>
<th>Communication</th>
<th>Achieved?</th>
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<tr>
<td>14. Produce information for providers and consumers about AEFI reporting procedures and the availability of special AEFI clinics.</td>
<td>√</td>
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<tr>
<td>15. Convene meeting to assess ways to obtain input from consumers.</td>
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<tr>
<td>16. Develop mechanisms to enhance communication between states and territories regarding vaccine safety issues.</td>
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What has happened since then?

2007

- HPV vaccine
  Multiple safety issues
  Expert panel formed by TGA
- Rotavirus vaccines
  Active sentinel surveillance for intussusception
Horvath review of vaccine adverse events 2011

7 recommendations including:
• Evaluate benefits of additional surveillance mechanisms to ensure vaccine safety
• Collection of vaccine usage and safety monitoring data key priority

National Immunisation Strategy 2013-2018

Strategic Priority 4: Continue to enhance vaccine safety monitoring systems
• Improve AEFI surveillance
• Vaccine safety plans for NIP
• Raise awareness of safety systems
• Data linkage for vaccine safety
Vaccine Safety in Australian
Recent improvements

- Improved governance and expert input
  - Advisory Committee on the Safety of Vaccines (ACSOV)
  - Reports to TGA and the NIP branch of Health
- Protocols for communication and action
- National AEFI-specific reporting form
- Increased collaboration between states, territories, TGA and Health
  - Monthly teleconferences, surveillance initiatives
  - Increased communication regarding vaccine safety
- Strengthening of reporting and data analysis within jurisdictions
  - e.g. SAEFVIC, WAVSS
  - Reporter feedback, clinical assessment integrated, causality assessment
- National network of specialist immunisation clinics - strengthened
  - clinical follow-up, management, causality assessment
- Vaccine safety plans and active surveillance occurring
- Increase in original research/publications having global impact
  - e.g. HPV and rotavirus safety investigations
Aims of this meeting:

- Bring together researchers, immunisation providers and public health staff interested in surveillance for adverse events following immunisation (AEFI)
- Share, and aim to improve upon, current methods of active and enhanced surveillance
- Strengthen collaborative efforts across state, territory and national systems to improve vaccine safety surveillance
Pharmacovigilance is the practice of detecting, assessing, understanding, responding to and preventing adverse drug reactions, including reactions to vaccines.

AEFI surveillance often relies on different systems and procedures.

Major goal: early detection and analysis of adverse events and appropriate and quick response to decrease negative impact on of individual health and immunisation program.
Specific objectives of immunisation safety surveillance

- detect problems due to the inherent properties of a vaccine or to defects in quality and/or immunisation error-related reactions;

- determine the observed vaccine reaction rate and relate to expected rates in the population by country, by region and globally;

- ensure that coincidental events are not mistaken for vaccine reactions and thus negatively affect the immunisation program;

- to ensure and facilitate causality assessment of individual AEFI reports (cases);

- to identify clustering or unusually high rates of AEFI, even if considered mild;
Specific objectives of immunisation safety surveillance cont..

- to identify events which may indicate a previously unknown and potential vaccine reaction (i.e. a signal)

- to generate new hypotheses about the causal relationship between the event and the vaccine (will require further investigations to support or refute hypothesis);

- to maintain the confidence of the community and health staff in the immunisation program by appropriate and timely responses

- to create awareness on immunisation safety among parents, community, the media and other stakeholders without jeopardizing the immunisation program;

- to collaborate and share information with the national regulatory authorities, program authorities, WHO, international community
**Administrative level**

**Responsibilities/Activities**
- Health workers/Immunization service-provider level:
  - AEFI detection and recording
  - Triage and reporting of serious AEIs to intermediate level
  - Routine reporting and line listing
  - Investigation
  - Corrective action
  - Public education / Communication

**AEFI classification status**
- Preliminary classification:
  - Non-serious
  - Serious

**Peripheral level**

**Surveillance units at sub-national level**
- Support peripheral level
  - Investigation of serious AEFI
  - Clinical and laboratory assessment
  - Causality Assessment of AEFI (preliminary)
  - Report to national expert committee
  - Data analysis and search for additional cases
  - Corrective action
  - Monitoring and supervision/training
  - Public education / Communication

**Intermediate level**

**National program (EFI/ NRA/ Supporting institutes including National Pharmacovigilance centre)**
- Provide expert support for field investigation
- Monitor information collection and assess serious AEFI
- Causality Assessment of AEFI (Final - National AEFI committee)
- Data analysis and search for signals
- Recommend decisions for policy
- Provide guidance on feedback to all levels
- Conduct research studies
- Provide guidance on Monitoring/supervision & training
- Define contents for Public education / Communication
- At global level share/obtain expertise and assistance

**National level**

**Provisional classification of serious AEFI**
- For referral to national level
  - Vaccine reaction
  - Coincidental
  - Unknown
- For local action
  - Immunization error related
  - Immunization anxiety related

**Final classification of all serious AEFI**

Maintain repository of all cases; serious and non-serious
Definitions..

Passive surveillance:
- encompasses all spontaneous AEFI reporting
- from immunisation service providers / hospitals / patients
- up to next levels: state/territory then national (TGA) and then global

Enhanced spontaneous surveillance
  - introduced during special immunisation campaigns to encourage reporting

Active surveillance:
- primarily used for characterization of the AEFI profile, rates and risk factors
- logistical and resource constraints limit wide application
- only for selected AEFI at selected institutions (sentinel) sites
- can also be carried out in the community setting (e.g. cohort event monitoring)

Ad hoc studies:
- epidemiological studies (e.g. cohort study, case-control study, case series studies)
- focus on selected vaccine safety concerns (e.g. testing causality hypotheses)
- retrospective or prospective
Observed rates (X+Y+Z)
Total number of cases reported from both vaccinated and unvaccinated groups

Known, expected vaccine reaction rates (Y)
detected in pre & post licensure studies, surveillance

Excess vaccine reaction rates (Z)

Vaccine reactions (Y+Z)
related to vaccine
Observed rate – Background rates

Background rates (X)
not related to vaccine
Occur among unvaccinated, recorded prior to or simultaneously to vaccination

*Rates can be expressed per 1000, 10000 or 100,000

Note: Vaccine reaction rate = observed (reported) rates – background rates (not related to vaccine).
Passive Surveillance Systems

**Strengths**
- Large population cover
- Simple to operate/inexpensive
- Signal detection
- Hypothesis generation
- Triggers further investigation

**Weaknesses**
- Reporting biases
  - Under-reporting
  - Stimulated reporting
  - Inconsistent data quality/completeness
- Can’t determine AEFI incidence
- Not designed to assess causality
Intussusception (IS) following Rotavirus vaccines

Evaluation of Australian surveillance

• Low but significant risk of IS following rotavirus vaccine
• Detected first in Australia: global recognition
• Surveillance was highly effective despite no formal plan

Weighing up the strengths and weaknesses of the 4 contributing surveillance mechanisms

<table>
<thead>
<tr>
<th>System</th>
<th>Number of IS cases</th>
<th>ADRS (TGA)</th>
<th>APSU #*</th>
<th>PAEDS #*</th>
<th>National inpatient databases*</th>
</tr>
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<tbody>
<tr>
<td>TGA</td>
<td>44</td>
<td>✓</td>
<td>✓</td>
<td>X</td>
<td>✓</td>
</tr>
<tr>
<td>APSU#</td>
<td>79</td>
<td>X</td>
<td>X</td>
<td>✓</td>
<td>X ✓</td>
</tr>
<tr>
<td>PAEDS#*</td>
<td>251</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>National inpatient databases*</td>
<td>1393*</td>
<td>X</td>
<td>X</td>
<td>✓</td>
<td>X</td>
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# Buttery at al, Vaccine 2011; * Carlin et al Clin Inf Dis 2013
When to consider active surveillance and/or epidemiologic studies?

• Informed decision based on vaccine characteristics, pre-licensure data, safety profile of similar vaccine/s, safety signal, other....

• An adverse event of special interest (AESI) and related vaccine/s
  – Fever/febrile convulsions and live viral vaccines (MMR, MMRV)
  – IS and rotavirus vaccines
  – viscerotropic/neurotropic disease and YF vaccines

• Limited pre-registration data
  – pandemic influenza vaccines, Ebola virus vaccines

• Variation in vaccine characteristics
  – annual changes to seasonal influenza vaccine

• To address vaccine safety ‘concerns’ that may/have damaged confidence
  – MMR and autism
  – SIDS and infant vaccines,
  – Neurologic/autoimmune diseases and HPV/inf vaccines
Overview:
Active surveillance and epidemiologic studies in vaccine pharmacovigilance

- essential to consider when forming a vaccine safety plan
- especially for serious events, new vaccines, large programs
- vaccine and/or condition specific and informed by a priori hypothesis
- need vaccine utilization data and to fully utilise data (-bases) that we have
- new methods abound.....
- Australia can continue to conduct ground-breaking surveillance and research in vaccine safety - especially if we pool our efforts!
NCIRS
National Centre for Immunisation Research & Surveillance