Adverse Event Information to be released to the Health Select Committee

Question
The Health Select Committee has asked about adverse events in association with vaccines, their classification in terms of severity and limitations on the data.

Response – Executive Summary

This document provides information on adverse events following immunisation reported to the Centre for Adverse Reactions Monitoring (CARM) for scheduled vaccines over the past five years (spontaneous reports). It also provides a summary of the reporting process and sets out how vaccine safety is monitored in New Zealand.

Information from spontaneous reports needs to be interpreted with caution. An adverse event reported after someone has an immunisation does not automatically mean the vaccine is responsible.

Between 1 January 2005 and 31 December 2009, 4,757 reports of adverse events following immunisation were submitted to the Centre for Adverse Reactions Monitoring. Data published by the World Health Organization shows that New Zealand has the highest spontaneous reporting rate per capita in the world.

The vast majority of reports describe known and expected reactions such as injection site pain, swelling, redness and itching or raised temperature, headache and general malaise. Expected reactions such as these are estimated from clinical trial information to occur at a rate of between 2 to 10 percent of people immunised.

A small number of reports describe rare or unexpected events. A number of reports describe events considered serious according to internationally defined criteria. Of the 4,757 reports, 174 (3.6%) meet the criteria of a serious report. Included in the 174 reports are four reports of death: one of these deaths is before the Coroner; the second has been before the Coroner although the Centre of Adverse Reactions Monitoring has not received a copy of the findings or any correspondence from the Coroner; the third was attributed by the Coroner to sudden infant death syndrome; the fourth occurred in an elderly patient with a history of heart disease.

There are limitations on what can be interpreted from this data. Further clinical details, investigation and research may be required before events can be considered as having been caused by the vaccine.

The purpose of having a catch-all system where health professionals, parents and anyone who has been immunised can report any adverse event following immunisation is to ensure that any potential warning signals are picked up, assessed and acted on if necessary. The nature of the system means that false signals will be detected.

In most cases, adverse events resolve or are subsequently found to be unrelated to the vaccine Continued analysis of spontaneous reports by Medsafe and the Centre for Adverse Reactions Monitoring does not show any new potential safety signals that are not already outlined in the vaccine data sheets. The balance of benefits and risks for each vaccine remains positive.

Introduction

All medicines and vaccines have risks and benefits.

Before a medicine or vaccine is approved for use it must be tested in clinical trials to determine its effectiveness. Information about potential risks is known from the clinical trial data and assessed before the medicine or vaccine is approved for use.

Known information about each medicine and vaccine is published for health professionals in a data sheet, available on the Medsafe website. Consumer Medicine Information is usually also published.

As the use of a medicine or vaccine increases, more information becomes available on its safety profile. Some adverse reactions are rare and may not be seen until a very large number of people have received the medicine or vaccine. This is one of the reasons why it is important to monitor all medicines and vaccines after they have been approved.

Most countries have a safety monitoring system which includes a voluntary spontaneous reporting scheme to help identify any possible safety concerns. In New Zealand, Medsafe is the medicines regulator responsible for monitoring available information to ensure that approved vaccines remain acceptably safe for use in New Zealand. Vaccine safety is never reviewed in isolation from the expected benefits of the vaccine, but in terms of the benefit risk balance.

In addition, the World Health Organization plays an important role in terms of vaccine safety through its Strategic Advisory Group of Experts on Immunisation and Global Advisory Committee on Vaccine Safety.

Spontaneous reporting

Two terms are used to describe spontaneous reports. Adverse events are undesirable events experienced by a person which may or may not be causally associated with the vaccine. Adverse reactions are undesirable effects from medicines or vaccines, i.e. they are causally associated.

Spontaneous reports are case reports of adverse events that people have experienced while or after taking a medicine or having a vaccine. Medsafe contracts the collection, review and analysis of this information to the New Zealand Pharmacovigilance Centre at the University of Otago in Dunedin.

Healthcare professionals and consumers are encouraged to report adverse events following immunisation to the Centre for Adverse Reactions Monitoring (CARM), which is part of the New Zealand Pharmacovigilance Centre. Pharmaceutical companies also submit adverse event reports.

Data published by the World Health Organization shows that New Zealand has the highest spontaneous reporting rate per capita in the world. It has been estimated that in general only around ten percent of all adverse reactions are reported. However, it is not necessary for all adverse reactions to be reported for a potential safety signal to be spotted.

What does Medsafe do with this information?

Medsafe and the Centre for Adverse Reactions Monitoring analyse spontaneous reports in conjunction with other information to determine if there are any new potential safety signals. Medsafe seeks the advice of independent experts, through the Medicines Adverse Reactions Committee, or may form working groups of experts to provide advice. Medsafe works closely with other regulatory authorities from around the world.

Medsafe undertakes a risk-benefit assessment on safety signals to decide if action is required. Further information on risk-benefit assessment is provided on the Medsafe website http://www.medsafe.govt.nz/Consumers/Safety-of-Medicines/Medsafe-Evaluation-Process.asp

Most safety signals are not supported by any additional information and no action is taken, although Medsafe may continue to closely monitor the issue. A small number of possible safety signals are confirmed as real. In these cases Medsafe has a number of regulatory actions it can take, including withdrawing the product.

Advantages and limitations of spontaneous reports

Spontaneous reports have been shown to be a very simple way of finding potential or possible safety signals with medicines and over 90 countries have a spontaneous reporting system. They can be used to monitor the safety of medicines in real life use over the lifetime of the medicine and for all types of people.

The limitations of using spontaneous reports include under-reporting, a lack of reliable information on the extent of use of the medicine and wide variations in the clinical details provided about the event and the history of the patient. Spontaneous reports are heavily subject to reporting bias such as media or other attention on an issue. They are also not very effective at detecting adverse reactions that occur a long time after starting the medicine. For this reason these reports are only used to identify safety signals. These signals require further formal epidemiological study before they can be validated or discounted.

Information obtained from spontaneous reports needs to be interpreted with caution.

Understanding vaccine safety and spontaneous reporting

Spontaneous report patterns can be variable and depend on many factors. Summaries of reported events following immunisation are not lists of known or proven adverse reactions to vaccines, cannot be used to determine the frequency of adverse reactions to vaccines in the whole population, and cannot be used to directly compare the relative safety of vaccines. They must not be interpreted and used as such.

Healthcare professionals and consumers are encouraged to report any *suspicions* that an event they have experienced may have been caused by vaccination. Therefore reports sent to CARM may be:

- real adverse reactions to the vaccine
- anxiety or nervousness about needles or the process of vaccination
- coincidental events that would have occurred anyway

With any vaccine various types of adverse events are expected to be reported.

- Injection site reactions.
- Well recognised reactions such as headaches, dizziness, muscle aches, mild fever and tiredness.
- Mild allergic reactions such as mild rashes and itching.
- Rare but serious allergic reactions called anaphylaxis. This can occur in response to any medicine or vaccine and some foods. Healthcare professionals giving vaccines are trained to spot the symptoms of serious allergic reactions and promptly treat them.
- Events due to anxiety such as fear or anticipation of the needle injection, such as fainting.
- Coincidental medical conditions.
- New adverse reactions i.e. those not already listed in the prescribing information (data sheet).

In New Zealand it is less likely that any new rare side effects to vaccines will be detected as the number of people immunised is usually small compared to the numbers immunised in other countries. Therefore Medsafe uses international data available from the World Health Organization, other regulators and pharmaceutical companies to help assess any reports of rare events following immunisation and to determine if they may be new events linked to immunisation.

There will always be a number of coincidental events reported because vaccines are given to large sections of the population. In some cases vaccines are specifically targeted to people with underlying medical conditions, such as the influenza vaccine. The challenge is to be able to distinguish these coincidental "background" events from those that may have been caused by the vaccine.

The time between immunisation and an event can be important in determining whether the event was coincidental; most reactions to vaccines occur within a very short time frame of immunisation, usually within days. In some circumstances a longer timeframe between immunisation and reaction onset has been considered where there is a scientific basis to support it.[1]

Another method is to compare the number of reports for a specific event with the expected background rate for that event. When doing this it is important to ensure that definite diagnoses of the events reported were made and to adjust the background rate for any differences in population groups and seasonal variations.[2] Table 1 shows the number of coincident events that might be expected as background rate events within one day, one week and six weeks after receipt of a hypothetical vaccine[3].

Table 1 – Predicted numbers of coincident, temporally associated events after a single dose of a hypothetical vaccine, based upon background incidence rates[3]

	Number of coincident events since a vaccine dose per 10 million people			Baseline rate used for estimate
	Within 1 day	Within 7 days	Within 6 weeks	
Guillian-Barré syndrome (per 10 million people)	0.51	3.58	21.50	1.87 per 100,000 person-years (all ages; UK Health Protection Agency data)
Optic neuritis (per 10 million females)	2.05	14.40	86.30	7.5 per 100,000 person-years in US females
Spontaneous abortions (per 1 million pregnant women)	397	2780	16684	Based on data from the UK (12% of pregnancies)
Sudden death within 1h of onset of any symptoms (per 10 million people)	0.14	0.98	5.75	Based upon UK background rate of 0.5 per 100,000 person-years

[1] Systemic reactions usually occur within 2 weeks – the longer time frame is to include any possible autoimmune reactions – onset time for these is around 6 weeks. Studies looking at the link between influenza vaccines and Guillain-Barré syndrome used a time period of 8 weeks based on the following ref: Stratton K, Alamario DA, Wizemann T McCormick MCl eds: Immunization safety review committee board on health promotion and disease prevention. Immunization safety review: Influenza vaccines and neurological complications. Washington DC: National Acadamies Press 2004.

[2] An example of the application of this approach in NZ vaccine monitoring was utilised at the time of the monitoring of the MeNZB vaccine and a condition known as Henoch-Schönlein Purpura - Sexton, K., et al., *Henoch-Schonlein purpura and meningococcal B vaccination.* Arch Dis Child, 2009. **94**(3): p. 224-6.

[3] Black S, Eskala J et al., *Importance of background rates of disease in assessment of vaccine safety during mass immunisation with pandemic H1N1 influenza vaccines.* The Lancet 2009; 374:2115-22

Summary of spontaneous reports in New Zealand

A summary of spontaneous reports associated with vaccines in the National Immunisation Schedule for the past five years follows (table 2).

This five-year time period was chosen to reflect the current safety status since the safety of vaccines has improved over time and the scheduled vaccines change regularly. Data for vaccines which are no longer used is not included.

Overall, between 1 January 2005 and 31 December 2009 more than 1.9 million doses of scheduled vaccines are recorded on the National Immunisation Register. The doses administered are undercounted because not all vaccines given are recorded on the register. For example, seasonal influenza immunisation is not recorded on the National Immunisation Register and in the 2010 season over 1 million doses have been distributed. For childhood immunisations, the register only captures information on the children who were born after the register was started. People can also choose not to have their immunisations recorded on the register.

Between 1 January 2005 and 31 December 2009, the Centre for Adverse Reactions Monitoring received 4,757 reports of adverse events following immunisation of which 174 (3.6%) were considered to be serious, as set out in table 2.

More than one vaccine may be given at the same time. Therefore some reports appear more than once in table 2.

The numbers of reports and the number of events described within those reports may change over time due ongoing quality control by the Centre for Adverse Reactions Monitoring such as the identification of duplicate reports or the provision of follow up information resulting in the addition, removal or change to the events reported.

Table 2 Overview of reports of events following immunisation reported to the Centre for Adverse Reactions Monitoring between 2005 and 2009 for scheduled vaccines

Vaccine	Trade name(s)	Reports – not serious	Reports – serious[1]	Total Number of reports
Adult tetanus-diphtheria vaccine	ADT booster	284	5	289
Diphtheria-tetanus-pertussis vaccine	Boostrix	33	2	35
Diphtheria-tetanus-pertusssis-polio-hepatitis B-*Haemophilus influenzae* type b vaccine	Infanrix hexa	215	25	240
Diphtheria-tetanus-pertussis-polio vaccine	Infanrix IPV	2114	73	2187
Haemophilus influenzae type b vaccine	Hiberix	195	10	205
Human papillomavirus vaccine	Gardasil	226	10	236
Measles-mumps-rubella vaccine	MMR II	663	25	688
Pneumococcal conjugate vaccine	Prevenar	228	26	254
Influenza vaccines	Influvac, Vaxigrip, Fluvax	589	34	623
TOTAL[1]		**4547**	**174**[1]	**4757**

[1] The total number of reports classified as serious is not the sum of the numbers in the table because in some reports more than one vaccine was given.

Non-Serious Reports

The most commonly reported reactions associated with vaccines given to infants and children were*:*

- injection site inflammation, pain, redness and itching
- vomiting
- headache
- fever
- irritability

The vast majority of reports were non-serious.

The most commonly reported reactions associated with vaccines given to adolescents and adults (ADT, Gardasil and Influenza) were:

- injection site inflammation, pain, redness and itching
- arm pain
- fever
- vomiting
- dizziness, fainting

With Gardasil, due to the age group being immunised, a small number of pregnancies have occurred either before immunisation or shortly afterwards. These cases are recorded as drug exposure during pregnancy to enable the pregnancy to be followed up but this does not mean that any ill effects are expected. To date, there has been no evidence here or overseas that there are any adverse effects on either mother or baby as a result of immunisation.

Seriousness of adverse events following immunisation

International convention defines the seriousness of reports based on the outcome or nature of the reported event as documented in the report irrespective of whether there is any association to the medicine or vaccine.

CARM consider a report to be serious based on the international criteria:

- hospitalisation (or prolonged hospitalisation) of the patient
- life threatening event
- persisting disability of the patient
- intervention required to prevent permanent impairment
- congenital anomaly
- death of the patient.

Since a report is defined as serious based on what is reported about a patient, it is possible to have both serious and non-serious reports describing the same event term.

Table 2 Overview of reports classified as serious irrespective of association to the vaccine.

Vaccine trade name(s)	Hospitalisation	Life threatening event	Persisting disability	Intervention Required	Congenital anomaly	Death
ADT booster	1	1	3			
Boostrix	2					
Infanrix hexa	22	1				2
Infanrix IPV	67	1	1	4		
Hiberix	7		2	1		
Gardasil	3	1	4	1		1
MMR II	16	3	2	3	1	
Prevenar	22	1	1			2
Influvac, Vaxigrip, Fluvax	18	4	8	3		1
Total[1]	**132**	**10**	**18**	**9**	**1**	**4**

[1] The total number of reports classified as serious is not a summation of the numbers in the table as some reports relate to more than one vaccine i.e more than one vaccine was given.

Hospitalisations

In 132 reports the patient was admitted to hospital for observation or treatment for the following categories of events:

- fever (32.5%)
- hypotonic hypotensive episodes (12.9%)
- allergic reactions (10.6%)
- neurological symptoms (8.3%)
- injection site reactions (7.6%)
- convulsions (7.6%)
- febrile convulsions (6.1%)
- gastrointestinal symptoms (3.8%)
- vasovagal (fainting) (3.0%)
- other (8.3%).

Hypotonic hypotensive episodes (HHE) – 12.9% of hospitalisation reports describe an infant experiencing an HHE episode, which is a collapse or shock-like state which occurs within 48 hours of immunisation. No long term effects have been found in infants who have had one of these events. Information on this possible adverse reaction was published by Medsafe in Prescriber Update in July 1998 and is attached as an appendix.

Convulsion – the number of reports of convulsions (fits) is well below the expected background rate for convulsions which is estimated at 70 cases per 100,000 people per year.[4] These reports did not raise any safety concerns.

Fever or febrile convulsions are expected in a small proportion of children experiencing fever following immunisation or due to infection. No long term effects are expected in infants who have experienced febrile convulsions.

Life threatening event

The 10 life threatening reports all describe acute onset allergic-type events including three of anaphylaxis and two of cardiac events. The latter two reports were in elderly patients following influenza vaccination.

[4] Black et al 2009 'Importance of background rates of disease in assessment of vaccine safety during mass immunisation with pandemic H1N1 influenza vacines' the Lancet 374: 5115-2122

There is a risk of serious allergic reactions with all medicines, vaccines and some foods. With vaccines, the risk of anaphylaxis is estimated to be around 1 – 3 reactions per one million doses administered. All vaccinators are trained and equipped to treat anaphylaxis if it does occur – this is the main reason people are asked to wait for 15 – 20 minutes following any immunisation and why there are at least two health professionals on site.

Persisting Disability

The 18 reports of persisting disability refer to clinical events that had been present for variable periods of time and were still persisting at the time of reporting. In most cases as further information becomes available other causes of the events are discovered, the patient recovers or is lost to follow-up and the report is never resolved.

- Two reports of injection site pain and one of brachial neuritis, which is inflammation of the nerves in the arm.
- Three reports of diverse generalised symptoms such as headaches, muscle and joint pains, fever symptoms and fatigue.
- One report of alopecia (hair loss) three months after immunisation in a patient taking other medicines.
- One report of persisting constipation and diarrhoea.
- One report of deafness, rash and a fever – the infant had also received cotrimoxazole antibiotic therapy.
- Three reports of transverse myelitis, which is a neurological disorder caused by an inflammation of the nerves. In two of the cases follow-up information reported that other causes had been identified.
- One report describes an ophthalmologic disorder. Follow-up information reported that the event was likely to be due to another cause.
- One report was of persisting injection site reaction.
- One report of persistence of symptoms including a hearing disorder.
- One report of Bells Palsy, which is a paralysis of the face, occurring within one day of immunisation. Bells Palsy is usually considered to be due to a viral infection and the onset of symptoms takes longer than 24 hours.
- One report of Motor Neurone Disorder – this report was still under active investigation by the reporter at the time of reporting.
- Subsequent information showed that two reports were miscoded. One related to a case of hives and the other was a report of fatigue in a patient with a history of chronic fatigue syndrome.

Intervention Required

There are 9 reports of a medical intervention being required.

- Two reports describe injection site abscesses that required draining.
- Five reports were for allergic reactions that required medical management or intervention.
- One report was for a febrile convulsion in which the parents administered supportive intervention.
- One report of a lung abscess of unknown origin that required draining.

Congenital anomaly

There is one report of an early (first trimester) termination of pregnancy in a woman who had received the MMR vaccine as an adult before her pregnancy status was established. This case does not describe an actual congenital anomaly but rather an event which placed the foetus at increased risk of injury due to the administration of a live vaccine during a crucial period of foetal development.

Deaths

There are four reports of death occurring some time following immunisation. This does not mean the vaccine caused the death.

Two deaths of infants were reported; in both cases the infants had been immunised with Infanrix-IPV and Prevenar vaccines. In the first case the Coroner determined that the cause of death was Sudden Infant Death Syndrome (SIDS). The second case has been before the Coroner although the Centre of Adverse Reactions Monitoring has not received a copy of the findings or any correspondence from the Coroner. The peak age for SIDS lies within the 6 week to 5 month range of the first series of childhood immunisations and it is expected that coincidental events will be reported with immunisation. Published evidence suggests that vaccination reduces the risk of SIDS[5,6]. Based on current information neither of these cases have raised any safety concerns with the Infanrix-Hexa and Prevenar vaccines.

There was one report of sudden death six months after immunisation with Gardasil vaccine. The cause of death has not been determined and this case is being reviewed by the Coroner.

There was also a death of an elderly patient following seasonal flu vaccination. The patient had a history of heart disease. It was unclear from the report if the patient experienced a serious allergic reaction or a cardiac arrest. There is no evidence in medical literature supporting an association between immunisation and death in the elderly.

Please note that this information has been updated. There were **three** reported deaths occurring some time following immunisation for the period 1 January 2005 and 31 December 2009, not four as listed above.

There was one infant death, not two. The Centre for Adverse Reactions Monitoring received a duplicate entry for the same child. Although CARM has a system to identify potential double-ups, incomplete reports or variations, discrepancies in identification data can lead to duplicate reports.

The rest of the information is correct. There was one report of sudden death six months after immunisation with Gardasil vaccine. The cause of death has not been determined and this case is being reviewed by the Coroner. There was also a death of an elderly patient following seasonal flu vaccination.

[5] Venneman MMT, Butterfass-Bahloul T, Jorch G et al 2007 'Sudden Infant Death Syndrome: No increased risk after immunisation' Vaccine 25: 336-340.
[6] Venneman MMT, Hoeffgen M, Bajanowski T et al 2007 'Do immunisations reduce the risk for SIDS? A meta-analysis' Vaccine 25: 4875-4879.

Prescriber Update Articles

Hypotonic-Hyporesponsive Episodes to Immunisation

Web site: July 1998
Prescriber Update No.16:34-36

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Hypotonic-hyporesponsive episodes (HHE) are recognised serious reactions to immunisation, especially pertussis-containing vaccine. Management involves checking the airway, breathing and circulation, then hospitalisation as a precaution. In reported cases, full recovery has occurred and there has been no long term sequelae. The paediatrician who assesses the child should also advise on the completion of the immunisation programme.

Since 1992, CARM has received 32 reports of children experiencing hypotonic-hyporesponsive episodes (HHE) following immunisation, all from pertussis-containing vaccines. The WHO database has over 600 reports of HHE, the majority following immunisation of pertussis-containing vaccines.

Serious effects but no long term sequelae reported

HHE is defined as an acute diminution in sensory awareness or loss of consciousness accompanied by pallor and muscle hypotonicity.[1] Variously described as shock, collapse or HHE, onset is within 12 hours after immunisation. Most children are initially irritable and febrile, then become pale, limp and unresponsive or hyporesponsive. Respiration is shallow and cyanosis frequently occurs. The duration of an episode varies from a few minutes to 36 hours.

The initial response should be as in any case of shock (airway, breathing, circulation). Careful clinical observation and documentation of the event are vital for differential diagnosis. Urgent hospital referral is advised for paediatric assessment and to exclude other causes.

A return to normal after the reaction has been reported in all published cases.[1] No long term sequelae have been identified in the small number of children who have had long term follow-up.[2]

HHE not a contraindication for further doses of pertussis vaccine

The *Immunisation Handbook* (pages 67 and 70) advises that HHE is no longer a contraindication to further doses of pertussis vaccine. The benefit/risk ratio should, however, be carefully considered for each child.

Paediatrician to advise on future immunisation options

The paediatrician who sees the child should also advise about future doses of pertussis and other vaccines. The options include:

- continue with normal immunisations, but give the next dose under supervision (e.g. in a day hospital);.
- omit pertussis in future (i.e. use DT plus Hib instead of DTPH). Note that although pertussis is most associated with this reaction, it has been reported with other vaccines including DT[3] and DTaP[4]; or
- use acellular pertussis vaccine (DTaP is available but not funded; DTaPH is not yet available in New Zealand) - limited data suggest a lower rate of HHE with acellular vaccine.[5]

A recently published Dutch study described 101 children who experienced HHE following immunisation, of whom 84 subsequently received further doses of pertussis vaccine.[6] None experienced a recurrence or other adverse event. One of the 17 children who did not continue with normal immunisation experienced severe pertussis.

Wide variation in incidence

Different studies have found an incidence of HHE following immunisation with DTP or its pertussis component varying between 3.5 and 291 per 100,000 injections.[1] This wide variation probably reflects the lack of an ideal case definition and difficult case recognition, as well as different vaccine formulations. The highest rate of 291 per 100,000 was found with plain DTP vaccine as opposed to a rate of 99 per 100,000 for adsorbed vaccines (the type used in New Zealand since 1971).[1] The largest study found a rate of 57 per 100,000,[7] and this is the rate quoted in the *Immunisation Choices* booklet and the *Immunisation Handbook.*

References

1. Howson CP, Howe CJ, Fineberg HV, eds. Adverse effects of pertussis and rubella vaccines. Washington DC: Institute of Medicine, National Academy Press, 1991.
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