MEDSAFE
NEW ZEALAND MEDICINES AND MEDICAL DEVICES SAFETY AUTHORITY
A BUSINESS UNIT OF THE MINISTRY OF HEALTH

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Radio New Zealand

Ref: H201502731

Dear

Response to your request for official information

Thank you for your request of 13 July 2015 under the Official Information Act 1982 (the Act) for

"How many New Zealanders reported suspected adberse reactions to the HPV Vaccine?
If you're providing a number of years please provide a breakdown for 2014, 2013, 2013, 2011.
How many of those reports were considered serious?
Did any of those reporters leave a patient disabled?
Did any of those reports leave a person dead?
What are the descriptions of the suspected reactions?
How many were reported by medical staff and how many by members of the public?"

The information relating to this request is itemised below, with copies of documents attached. Some of the information you request is already in the public domain. This information is available at.

- Suspected Medicine Adverse Reactions Search (SMARS): www.medsafe.govt.nz/projects/B1/ADRDisclaimer.asp.
- Adverse event information on vaccines provided to the Health Select Committee: www.medsafe.govt.nz/Consumers/Safety-of-Medicines/Health%20Select%20Committee%20Vaccines.pdf.
- OIA release: www.medsafe.govt.nz/Consumers/Safety-of-Medicines/Gardasil%20OIA%20Request.pdf.

Please note that information from spontaneous reports needs to be interpreted with caution. Further information on interpreting spontaneous reports can be found on the Medsafe website (see website addresses above).

Spontaneous reports are case reports of suspected adverse reactions that people have experienced after exposure to a medicine. They are a simple method of identifying possible safety signals with medicines. Other sources of information are used to confirm or refute a safety signal.

There are a number of limitations of spontaneous reporting systems including:

- under-reporting
- lack of information on number of people exposed to the medicine
- wide differences in the amount of information provided
- subject to stimulated reporting due to media scare stories
- poor at detecting reactions that occur a long time after exposure to a medicine.

In New Zealand, the collection of reports of adverse reactions is contracted to the Centre for Adverse Reactions Monitoring (CARM) by the Ministry of Health, Medsafe. CARM enter these reports into their database, determine whether these reports are serious and analyse the association between the medicine and reported event(s).

CARM consider a report to be serious based on the following internationally agreed 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. For example, a report where a patient was hospitalised with nausea and vomiting would be defined as serious and a report where a patient experienced nausea and vomiting but was not hospitalised would be defined as not serious. The report is categorised for seriousness whether or not CARM believe that there is a relationship between the medicine and event.

CARM analyse the association between the medicine and reported events using the World Health Organization causality assessment criteria. A copy is attached for your information.

If CARM identify a safety signal from these spontaneous reports they notify Medsafe and the Medicines Adverse Reactions Committee (MARC). Further review and investigation is then undertaken to determine whether the signal is real and if any action is required to manage the safety of the medicine. Safety signals, including one of photophobia (sensitivity to light), with or without headache, and one of hypoaesthesia (reduced sensation to touch) were identified from reports made to CARM. At the time of the review there was no evidence of an association with the HPV vaccine.

Medsafe is the medicines regulator for New Zealand. Medsafe monitors the safety of all approved medicines in use in New Zealand. The collection of spontaneous reports by CARM is only one of these monitoring methods. Other sources of information include other regulators, the scientific literature and the pharmaceutical companies.

When Medsafe determines that there is a new safety concern with a medicine action is taken to manage the risk of harm to patients. These actions can include:

- updating the product information (data sheet)
- changing the classification of a medicine
- suspending the use of a medicine
- withdrawing the consent to distribute the medicine
- communicating to healthcare professionals and consumers.

Medsafe communicates medicine safety concerns to healthcare professionals through *Prescriber Update*. This drug safety bulletin is sent to healthcare professionals four times a year and is published on the Medsafe website (www.medsafe.govt.nz/publications/prescriber-update.asp). In addition Medsafe communicates with healthcare professionals and consumers through the Early Warning System. These communications are sent to email subscribers and published on the Medsafe website (www.medsafe.govt.nz/safety/EWS/EWS.asp).

Request	**Response**
How many New Zealanders reported suspected adverse reactions to the HPV Vaccine? *If you're providing a number of years please provide a breakdown for 2014, 2013, 2013, 2011*	Attached is: A table '*Frequency of HPV reports per year to June 2015*' showing the number of reports received per year. CARM receives approximately 4,000 total reports per year. More than one report may be submitted by an individual therefore the number of New Zealanders who reported suspected adverse reactions to HPV vaccines may be less.
How many of those reports were considered serious?	Of the 568 reports received between 1 Jan 2007 and 30 June 2015, CARM considered 41 of the reports to be serious.
Did any of those reporters leave a patient disabled?	CARM state that there are no cases where the report indicates that a patient has been left disabled. There were 174 cases where the patient had *not yet* recovered at the *time* the report was made.
Did any of those reports leave a person dead?	CARM state that there are four cases where a death was reported. CARM considered that it was unlikely that the deaths were caused by HPV vaccination in these cases. Case 1 was a sudden death 6 months after the third vaccination investigated by the coroner. CARM is awaiting the coroner's decision on the cause of death. Case 2 was a report of suicide. Case 3 was a sudden death. The pathologist was investigating the

	possibility of a hereditary cardiac conduction problem. Case 4 was a medication error. Gardasil was administered to a baby. The baby died two years after the error.
What are the descriptions of the suspected reactions?	Attached is: A table '*Frequency of HPV reports to 30 June 2015*'.The first column on the left displays the System Organ Class, the second column displays the reaction/event term reported, the next five columns displays the number of reports for each reaction term in the different causality categories. The causality categories relate to the WHO causality assessment system. Category 1 is certain, 2 is probable/likely, 3 is possible, 4 is unlikely and 5 is unclassified/ unclassifiable. This information is also published on the Medsafe website (see website addresses provided above).
How many were reported by medical staff and how many by members of the public?	CARM state that 277 reports were made by medical staff and 8 reports by the public. Other reports are sent for example by pharmaceutical companies. For some reports CARM has been unable to clearly identify the reporter type.

I trust this information fulfils your request.

Yours sincerely

Acting Group Manager
Medsafe

the UPPSALA MONITORING CENTRE

The use of the WHO-UMC system for standardised case causality assessment

Why causality assessment?

An inherent problem in pharmacovigilance is that most case reports concern *suspected* adverse drug reactions. Adverse reactions are rarely specific for the drug, diagnostic tests are usually absent and a rechallenge is rarely ethically justified. In practice few adverse reactions are 'certain' or 'unlikely'; most are somewhere in between these extremes, i.e. 'possible' or 'probable'. In an attempt to solve this problem many systems have been developed for a structured and harmonised assessment of causality (1). None of these systems, however, have been shown to produce a precise and reliable quantitative estimation of relationship likelihood. Nevertheless, causality assessment has become a common routine procedure in pharmacovigilance. The advances and limitations of causality assessment are reviewed in *Table 1*[(2)].

Table 1. Advances and limitations of standardised case causality assessment

What causality assessment can do	What causality assessment cannot do
Decrease disagreement between assessors	Give accurate quantitative measurement of relationship likelihood
Classify relationship likelihood	Distinguish valid from invalid cases
Mark individual case reports	Prove the connection between drug and event
Improvement of scientific evaluation; educational	Quantify the contribution of a drug to the development of an adverse event
	Change uncertainty into certainty

The WHO-UMC causality assessment system

The WHO-UMC system has been developed in consultation with the National Centres participating in the Programme for International Drug Monitoring and is meant as a practical tool for the assessment of case reports. It is basically a combined assessment taking into account the clinical-pharmacological aspects of the case history and the quality of the documentation of the observation. Since pharmacovigilance is particularly concerned with the detection of unknown and unexpected adverse reactions, other criteria such as previous knowledge and statistical chance play a less prominent role in the system. It is recognised that the semantics of the definitions are critical and that individual judgements may therefore differ. There are other algorithms that are either very complex or too specific for general use. This method gives guidance to the general arguments which should be used to select one category over another.

The various causality categories are listed in Table 2. The assessment criteria of the various categories are shown in a point-wise way, as has been developed for practical training during the UMC Training courses.

and later on resumed), unless the evidence in the report is already convincing without a re-exposure.

For 'Probable', on the other hand, a rechallenge is not required. To qualify as 'Certain' the interval between the start of the drug and the onset of the event must be 'plausible'; this means that there is in sufficient detail a positive argument in support of the view that the drug is causally involved, pharmacologically or pathologically. For 'Probable' the time relationship should be 'reasonable'; this is a more neutral term covering everything that is not unreasonable. Also, with regard to the second criterion, 'alternative causes', the wording is different in 'Probable'. For 'Certain' the occurrence of the event cannot be explained by any disease the patient is known to have or any other drug taken. For 'Probable', on the other hand, the event is 'unlikely' to be attributable to another cause. Also the dechallenge situations (i.e. what happened after stopping) are different. In a 'Certain' case report, the course of events constitutes a positive argument in favour of holding the suspected drug responsible, in pharmacological or pathological respects, whereas in a 'Probable' case it is sufficient if it is 'clinically reasonable' (i.e. not unreasonable).

The essential distinctions between 'Probable' and 'Possible' are that in the latter case there may be another equally likely explanation for the event and/or there is no information or uncertainty with regard to what has happened after stopping.

The criteria that may render the connection 'Unlikely' are firstly the time relationship is improbable (with the knowledge at the time), and/or another explanation is more likely. The term 'Unclassified/Conditional' is of a preliminary nature and is appropriate when, for a proper assessment, there is more data needed and such data are being sought, or are already under examination. Finally when the information in a report is incomplete or contradictory and cannot be complemented or verified, the verdict is 'Unclassifiable'.

Since by far the most frequent categories in case reports are 'Possible' and 'Probable', the usual approach to using the system is to choose one of these categories (depending on the impression of the assessor) and to test if the various criteria fit with the content of the case report. If the report seems stronger one can go one step 'higher' (e.g. from 'Possible' to 'Probable'), if the evidence seems weaker one should try a 'lower' category. To see if that category is the right one or if it does again not seem to fit, the next adjacent term is tried.

For drug-drug interactions the WHO-UMC system can be used by assessing the actor drug, which influences the kinetics or dynamics of the other drug (which has usually been taken over a longer period), in the medical context of the patient.

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Summary description of Causality Assessment

Term	Description	Comment
Certian	A clinical event, including laboratory test abnormality, occurring in a plausible time relationship to drug administration, and which cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (dechallenge) should be clinically plausible. The event must be definitive pharmacologically or phenomenologically, using a satisfactory rechallenge procedure if necessary.	It is recognized that this stringent definition will lead to very few reports meeting the criteria, but this is useful because of the special value of such reports. It is considered that time relationships between drug administration and the onset and course of the adverse event are important in causality analysis. So also is the consideration of confounding features, but due weight must placed on the known pharmacological and other characteristics of the drug product being considered. Sometimes the clinical phenomena described will also be sufficiently specific to allow a confident causality assessment in the absence of confounding features and with appropriate time relationships, e.g. penicillin anaphylaxis.
Probable/ Likely	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfil this definition.	This definition has less stringent wording than for "certain" and does not necessitate prior knowledge of drug characteristics or clinical adverse reaction phenomena. As stated no rechallenge information is needed, but confounding drug administration underlying disease must be absent.
Possible	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.	This is the definition to be used when drug causality is one of other possible causes for the described clinical event.
Unlikely	A clinical event, including laboratory test abnormality, with a temporal relationship to drug administration which makes a causal relationship improbable, and in which other drugs, chemicals or	This definition is intended to be used when the exclusion of drug causality of a clinical event seems most plausible.

The FREQ Procedure

years	Frequency	Percent	Cumulative Frequency	Cumulative Percent
2007	5	0.88	5	0.88
2008	20	3.52	25	4.40
2009	211	37.15	236	41.55
2010	118	20.77	354	62.32
2011	50	8.80	404	71.13
2012	37	6.51	441	77.64
2013	43	7.57	484	85.21
2014	51	8.98	535	94.19
2015	33	5.81	568	100.00

		causal				
		1	2	3	4	5
		N	N	N	N	N
group	reaction					
Alimentary	ABDOMINAL DISCOMFORT			1		
	ABDOMINAL PAIN		15	8	4	1
	BLOATING			1		
	CRAMP ABDOMINAL		1	1		
	DIARRHOEA		5	3		
	NAUSEA	4	59	13		2
	TONGUE DISORDER		1	1		
	VOMITING	2	43	12	1	
	*** Total for Group ***	6	124	40	5	3
Application Site	reaction					
	INJECTION SITE ABSCESS		1			
	INJECTION SITE BRUISING		3	1		
	INJECTION SITE ERYTHEMA	1	7			
	INJECTION SITE INFLAMMATION	5	30			
	INJECTION SITE MASS		5		1	
	INJECTION SITE PAIN	2	29	1		
	INJECTION SITE PRURITUS		9	1		
	INJECTION SITE RASH		1			
	INJECTION SITE SWELLING		2			
	INJECTION SITE URTICARIA		1			
	*** Total for Group ***	8	88	3	1	
Cardiovascular	reaction					
	BRADYCARDIA	1				
	CHEST PAIN		4	2		1
	CHEST TIGHTNESS		2			
	CIRCULATORY FAILURE				1	
	CYANOSIS					1
	CYANOSIS PERIPHERAL		2			

(Continued)

		causal				
		1	2	3	4	5
		N	N	N	N	N
group	reaction					
Cardiovascular	DIZZINESS	1	46	12	2	1
	FAINTNESS	1	13	2		1
	FLUSHING	1	13	2		
	HYPERTENSION		3	1		1
	HYPOTENSION		1	1	1	
	PALPITATION		2			
	PERIPHERAL COLDNESS		1			
	SKIN COLD CLAMMY		2			
	SYNCOPE		4	1		2
	TACHYCARDIA		4	2	2	
	VASOVAGAL REACTION	1	61	7		
	*** Total for Group ***	5	158	30	6	7
Endocrine/Metabolic	reaction					
	AMENORRHOEA					1
	DEHYDRATION			1		
	DIABETES MELLITUS AGGRAVATED					1
	DYSMENORRHOEA					1
	HIRSUTISM					1
	HYPERGLYCAEMIA		1			
	HYPOGLYCAEMIA			1		
	MENORRHAGIA			1		1
	SERUM IRON DECREASED				1	1
	*** Total for Group ***		1	3	1	6
Haematological	reaction					
	C-REACTIVE PROTEIN POSITIVE			1		
	EPISTAXIS			1		
	HENOCH-SCHONLEIN PURPURA			1		
	LEUKAEMIA				1	

(Continued)

		causal				
		1	2	3	4	5
		N	N	N	N	N
group	reaction					
Haematological	LEUKAEMIA MYELOID				1	
	LYMPHADENOPATHY		2	3		
	LYMPHADENOPATHY CERVICAL				1	
	LYMPHOPENIA			1		
	PETECHIAE					1
	THROMBOCYTOPENIA			1		
	*** Total for Group ***		2	8	3	1
Musculoskeletal	reaction					
	ARM PAIN		37	13		
	ARTHRALGIA	1	5	4	1	
	ARTHROPATHY					1
	BACK PAIN		1	1		
	BURSITIS		1			
	CRAMPS		2			
	FIBROMYALGIA					1
	JOINT PAIN					1
	LEG PAIN		1	1		2
	MOVEMENTS REDUCED		2	1		
	MUSCLE SPASTICITY	1				
	MUSCLE WEAKNESS		10	4		2
	MYALGIA	2	16	7		1
	NECK STIFFNESS			1		
	PAIN NECK/SHOULDER		5			
	SKELETAL PAIN		1			
	*** Total for Group ***	4	81	32	1	8
Nervous System	reaction					
	ABSENCES		1			
	ATAXIA		1	1		1

(Continued)

		causal				
		1	2	3	4	5
group	reaction	N	N	N	N	N
Nervous System	BELLS PALSY		1			1
	COGNITIVE FUNCTION ABNORMAL					1
	CONSCIOUSNESS DECREASED		5	1		2
	CONVULSIONS		5	2	2	
	CONVULSIONS AGGRAVATED				1	
	CONVULSIONS GRAND MAL		1		1	
	DYSAESTHESIA		2	2		1
	DYSARTHRIA		1			
	ENCEPHALITIS					1
	EXHAUSTION		1			
	EYES ROLLING		1			
	GAIT ABNORMAL		2			
	GUILLAIN-BARRE SYNDROME				1	
	HEADACHE	6	65	32	5	3
	HYPERAESTHESIA		1	1		
	HYPERTONIA			1		
	HYPOAESTHESIA		1	1		
	HYPOTONIA			1		
	MIGRAINE		1	5		1
	MUSCLE CONTRACTIONS INVOLUNTARY		5			
	MYOCLONIC JERKS			1		
	NEUROPATHY		1			2
	NUMBNESS LOCALISED		13	7		
	PAIN		1			1
	PARAESTHESIA		8	6	1	2
	PARAESTHESIA DISTAL			1		1
	PARAESTHESIA TONGUE			1		
	SHAKING	1	7			

(Continued)

		causal				
		1	2	3	4	5
		N	N	N	N	N
group	reaction					
Nervous System	SLURRED SPEECH		1			
	TREMOR		1			
	TWITCHING			1		1
	VERTIGO		1	1		
	*** Total for Group ***	7	127	65	11	18
Others	reaction					
	ANAPHYLACTIC REACTION		1			
	BLADDER MALFORMATION					1
	CHILLS		1	1		
	ELECTIVE ABORTION	1				
	FACE OEDEMA		2	3		
	FEELING COLD		1			
	FEELING HOT AND COLD		2	2		
	FEELING OF WARMTH		3			
	FEVER	3	45	16	1	2
	HEAVINESS IN LIMBS		1			
	INFLUENZA-LIKE SYMPTOMS		3	3	1	
	LACERATION		1			
	LIPS SWELLING NON-SPECIFIC		2	1		
	LOCALISED OEDEMA			1		
	NECK OEDEMA		1	1		
	NIGHT SWEATS		1			1
	OEDEMA PERIORBITAL		4			
	OEDEMA PERIPHERAL		1	1		
	PALLOR		11	3		
	RIGORS		1	1		
	SERUM SICKNESS-LIKE DISORDER			1		
	SHIVERING		3			

(Continued)

		causal				
		1	2	3	4	5
		N	N	N	N	N
group	reaction					
Others	SUDDEN DEATH					2
	SWEATING INCREASED		1			
	TEMPERATURE CHANGED SENSATION			1		
	THROAT SWELLING NON-SPECIFIC		1			
	TONGUE SWELLING NON-SPECIFIC		3			
	UPPER LIMB OEDEMA		1			
	*** Total for Group ***	4	90	35	2	6
Procedure Related	reaction					
	DRUG ADMINISTRATION ERROR	3	1			
	MEDICATION ERROR	23	2			
	*** Total for Group ***	26	3			
Product Related	reaction					
	PRODUCT EXPIRED	9	1			
	VACCINE FAILURE					1
	*** Total for Group ***	9	1			1
Psychiatric Changes	reaction					
	ANXIETY		4	2		
	ASTHENIA		1			
	BEHAVIOUR ABNORMAL		1			2
	CONCENTRATION IMPAIRED		1			1
	CONFUSION		2			
	DEPERSONALIZATION			1		
	DEPRESSION		1			
	EMOTIONAL LABILITY		2			
	FATIGUE		1	3		
	HALLUCINATION		1			
	INSOMNIA			1		
	IRRITABILITY		1	1		

(Continued)

		causal				
		1	2	3	4	5
		N	N	N	N	N
group	reaction					
Psychiatric Changes	LETHARGY		8	5	3	1
	MALAISE		2	1		
	MEMORY IMPAIRMENT		1			
	MEMORY LOSS					2
	MOOD DISORDER				1	1
	NERVOUSNESS		1			
	PANIC REACTION		1			
	PARONIRIA					1
	PSYCHOSIS					1
	SLEEP DISTURBED		1			
	SOMNOLENCE		9	3	1	
	SUICIDE				1	
	TIREDNESS		10	5		
	*** Total for Group ***		48	22	6	9
Reproductive Disorders	reaction					
	DRUG EXPOSURE IN PREGNANCY	19				
	MENSTRUAL DISORDER			1		
	OVARIAN CYST				1	
	PELVIC INFLAMMATION				1	
	*** Total for Group ***	19		1	2	
Resistance Mechanism Disorders	reaction					
	GENITAL WART				1	1
	*** Total for Group ***				1	1
Respiratory	reaction					
	ANOXIA		1			
	APNOEA			1		
	BRONCHOSPASM		2			
	BRONCHOSPASM AGGRAVATED		1			

(Continued)

		causal				
		1	2	3	4	5
		N	N	N	N	N
group	reaction					
Respiratory	COUGHING		2	1		
	DYSPNOEA		11			
	HOARSENESS			1		
	HYPERVENTILATION		2			
	RESPIRATORY DISORDER			1		
	RHINORRHOEA		1			
	STRIDOR		1			
	TACHYPNOEA		1			
	THROAT IRRITATION		2	1		
	THROAT PAIN			3		
	THROAT SORE		1		1	
	THROAT TIGHTNESS		6			
	*** Total for Group ***		31	8	1	
Skin and Appendages	reaction					
	ALOPECIA				1	
	ANGIOEDEMA		3	1	1	
	BULLOUS ERUPTION		1			
	ECZEMA AGGRAVATED			2		
	ERYTHEMA MULTIFORME			1		
	HAIR DISCOLOURATION					1
	HAIR LOSS				1	
	HERPES ZOSTER				2	
	MACULAR RASH		7		1	
	MORBILLIFORM RASH		1			
	NAIL DISORDER					1
	PAPULAR RASH		2			1
	PITYRIASIS ROSEA					1
	PRURITUS	1	12	2		

(Continued)

		causal				
		1	2	3	4	5
		N	N	N	N	N
group	reaction					
Skin and Appendages	PURPURA			1	1	1
	RASH		28	4	1	
	RASH ERYTHEMATOUS		4	2		
	RASH MACULO-PAPULAR	1	3			
	RASH PRURITIC		7	4	1	
	RASH PURPURIC		1			
	SKIN DISCOLOURATION		1			
	SKIN EXFOLIATION		1			
	SKIN NODULE			1		
	URTICARIA	1	16	6		
	VERRUCA				2	1
	VESICULAR RASH			1	1	
	*** Total for Group ***	3	87	25	12	6
Special Senses	reaction					
	CONJUNCTIVAL HAEMORRHAGE			1		
	CONJUNCTIVITIS		2			
	DIPLOPIA		1			1
	EAR ACHE		1			
	LACRIMATION INCREASED		1			
	MYDRIASIS		3	1		
	OTITIS MEDIA				1	
	PHOTOPHOBIA		1	2		1
	PUPILLARY REFLEX IMPAIRED		1			
	TASTE METALLIC		1			
	TINNITUS		1		1	
	UVEITIS					1
	VISION BLURRED		4	4		
	VISUAL DISTURBANCE		2	1		

(Continued)

		causal				
		1	2	3	4	5
		N	N	N	N	N
group	*** Total for Group ***					
Special Senses			18	9	2	3
Urinary	reaction					
	URINARY TRACT INFECTION				1	
	*** Total for Group ***				1	
Total Reactions		91	859	281	55	69

(Continued)