Adverse Events Following Immunisation associated with the 1998 Australian Measles Control Campaign

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Abstract

The Measles Control Campaign (MCC) conducted in Australia from August to November 1998 resulted in a total of 1.7 million school children being vaccinated. This article reports on the Adverse Events Following Immunisation (AEFI) associated with measles-mumps-rubella vaccine (MMR) administered as part of the MCC. Reports of adverse events that occurred within 30 days of administration of the MMR vaccine were assessed by an expert panel that assigned a causality rating to each AEFI. Reports with missing onset dates or uncertain causality were excluded. Eighty-nine AEFI were classified as associated with MMR vaccine and the overall rate of adverse events was 5.24 per 100,000 doses of vaccine administered. Of these 46 were thought to be *certainly* caused by MMR vaccine, 23 were *probably* and 20 were *possibly* associated with the vaccine. Although 46 reactions were categorised to be *certainly* caused by the MMR vaccine, the majority of these were syncopal fits, syncope, local reactions, and allergic reactions that were short-lived, and all of these children recovered. The most commonly occurring adverse reaction was syncopal fit with a rate of 1.24 per 100,000. There was only one anaphylactic reaction, giving a rate of 0.06 per 100,000. The combined rate for anaphylaxis, anaphylactoid and allergic reactions was 1.06 per 100,000 administered doses. The rate of seizures (febrile and afebrile) was 0.30 and encephalopathy was 0.06 per 100,000 doses administered. Of the 89 children who had an AEFI, 43 did not require hospitalisation or medical attention while 13 were seen in an emergency room, 14 were hospitalised and 19 were seen by a doctor. There were no deaths reported resulting from the administration of the MMR vaccine during the period of the campaign. All children who had an AEFI have recovered although 9 children could not be followed up for reasons of confidentiality. The overall rate of adverse events was lower than that observed in the 1994 measles campaign conducted in the United Kingdom. On comparing the risks and benefits of MMR vaccine, the benefits of this MCC far outweigh the incidence of serious adverse events associated with immunisation. *Commun Dis Intell* 2000;24:27-33.

Introduction

In Australia, there have been frequent measles epidemics and measles remains the leading cause of vaccine preventable death.[1-3] Recent seroepidemiologic data from New South Wales, Victoria and South Australia have shown a high proportion of susceptibles,[4] making it likely that there would be a major epidemic in 1998-99 similar to that which occurred in New Zealand.[5] This prompted the formation of the Measles Elimination Advisory Committee (MEAC) in July 1997 by the National Centre for Disease Control, Canberra. MEAC subsequently recommended a national school-based measles vaccination campaign to coincide with the National Health and Medical Research Council (NHMRC) recommendation to bring forward the second dose of the measles-mumps-rubella (MMR) vaccine from 10-16 years to 4-5 years of age. The MMR vaccine used was the M-M-R II – Merck, Sharp and Dohme lyophilised product which contained live attenuated measles virus (Edmonston strain), mumps virus (Jeryl Lynn strain), and rubella virus (Wistar RA 27/3 strain), and 25mcg neomycin per 0.5ml dose.

The Measles Control Campaign (MCC) was conducted in Australia from August to November 1998 and offered all primary school children a one-off free dose of MMR vaccine.[6] A total of 1.7 million children were vaccinated. The aim of this article is to report on the adverse events associated with MMR vaccine administered as part of the MCC.

Methods

Reports were included only if the adverse event occurred within 30 days following administration of MMR vaccine to a primary school aged child and only if the report was received before 1 September 1999. There were three sources of reports.

The first source was the MCC vaccine providers, parents and general practitioners who were asked to report all significant adverse events following immunisation (AEFIs) possibly related to administration of the MMR vaccine to the State and Territory Measles Campaign Coordinators. A protocol was provided to the State and Territory Measles

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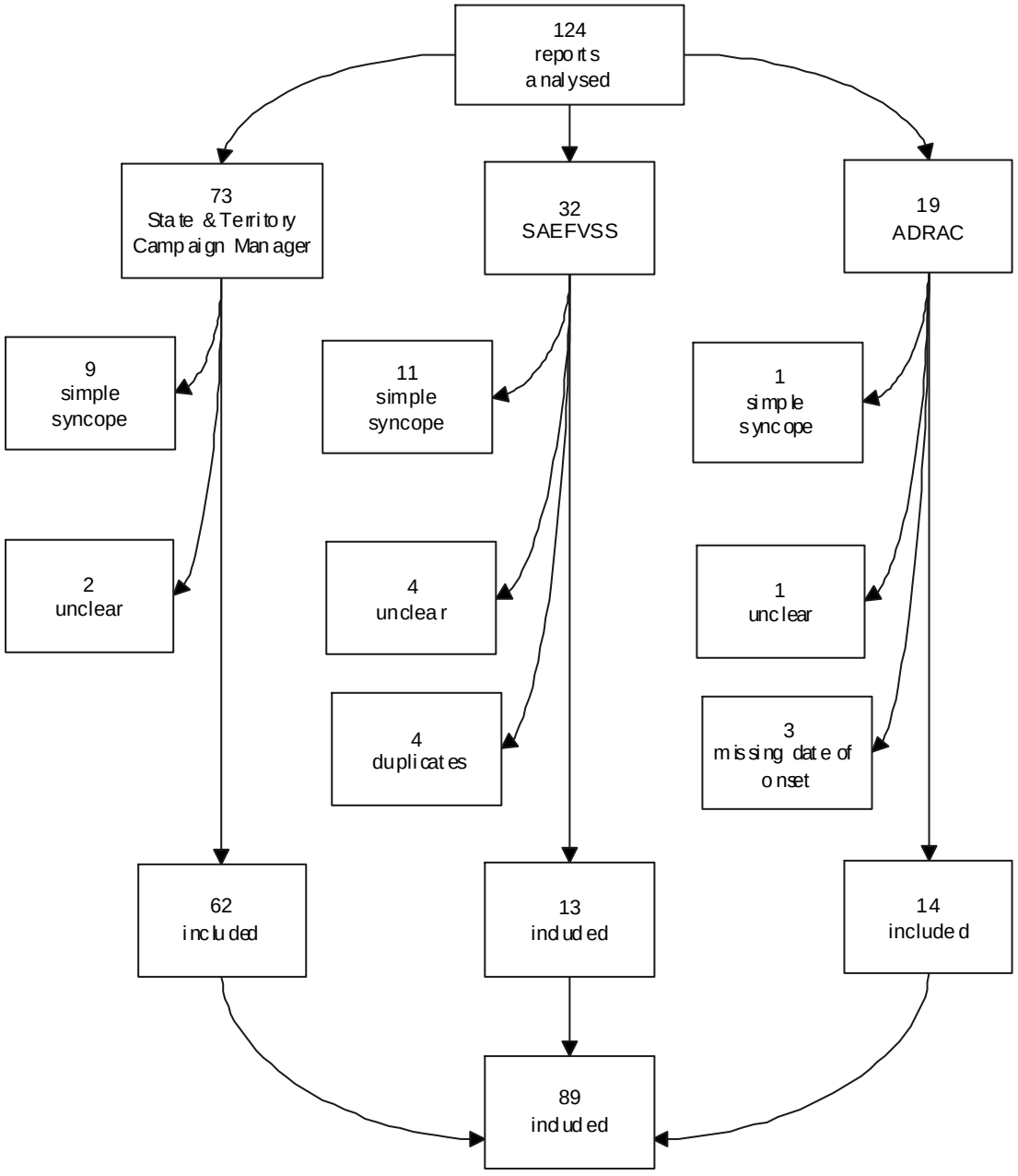
Coordinators to forward reports of anaphylaxis, shock, hypotonic/hyporesponsive episodes, encephalopathy, convulsions, aseptic meningitis, thrombocytopenia, acute flaccid paralysis, death and any other serious adverse events thought to be associated with the vaccination, including hospitalisation. Simple syncope was not required to be reported, unless it resulted in seizure(s) and/or hospitalisation.

Reports were screened by the State and Territory Measles Campaign Coordinators and only serious AEFIs were then notified to the National Campaign Manager by phone and this was followed by a written report. Follow-up of AEFIs was undertaken by States and Territories according to standard procedures.

The second source of adverse event reports was the Serious Adverse Events Following Vaccination Surveillance Scheme (SAEFVSS), a national surveillance scheme initiated through the National Childhood Immunisation Program. The SAEFVSS scheme has been operating since 1995 and has the advantage that local immunisation program directors are able to monitor reports and offer expert advice. Reports are initially reviewed by State and Territory Immunisation Coordinators and forwarded to the National Centre for Disease Control where they are collated and reported in *Communicable Diseases Intelligence*. Adverse event reports related to the MCC were also received by SAEFVSS from all States and Territories.

The third source was the Adverse Drug Reactions Advisory Committee (ADRAC) which has the responsibility of post-marketing surveillance of all drugs including vaccines. ADRAC receives reports from private practitioners, public health providers, hospitals, vaccine manufacturers, and vaccine recipients (or their parents).

Figure 1. Origin of reports of Adverse Events Following Immunisation in the Measles Control Campaign



Reports were collated from these three sources. Duplicate reports were picked up by using identifiers including date of birth, postcode, date of vaccination, adverse event and initials of first and last name. It was not possible to identify duplicate reports in the ADRAC reports as all person identifiers are confidential except for date of birth. All reports were followed up except those originating from ADRAC, because confidential identifying data could not be obtained. Hence, the recovery status of some of the individuals reported to ADRAC was classified as 'unknown'.

A panel comprising three paediatricians with a special interest in immunisation, two medical epidemiologists, and the National Measles Campaign Manager reviewed all reports. The panel classified each AEFI according to modified definitions recommended by the Pan-American Health Organization (Appendix 1).[7] A causality rating was assigned to each AEFI according to a classification developed by ADRAC (Appendix 2). Overall and individual adverse event rates for each AEFI were calculated by dividing the number of events by the number of doses of MMR administered during the MCC.

Results

There was a total of 124 adverse events reported in children aged 4-13 years. Of these, 19 were reported to ADRAC, 32 to SAEFVSS and 73 to the State and Territory Measles Campaign Coordinators (see Figure 1). There were 4 duplicate reports identified in the SAEFVSS that were also reported by the State and Territory Measles coordinators. There were 21 syncopal reactions that did not require any medical attention and were excluded. Following review of the AEFIs by the panel, 10 reports were excluded from further analysis because 3 adverse events had onset dates missing (1 parotitis and 2 rashes) and 7 had an *unclear* causality assigned (Table 1). These were injection site pain, local reaction, hysteria, a child who cried for a prolonged period, a child who claimed temporary loss of eyesight and hearing five minutes after being vaccinated and another child who developed a fever 4 hours after administration of the MMR vaccine. Lastly, there was a 12 year old girl who presented with a temporary myopathy and arthralgia 90 days after MMR vaccination. She complained of weakness in the thigh and truncal muscles and had a high ESR. Investigations including a Magnetic Resonance Imaging (MRI) spine and lumbar puncture were normal and an EMG of her thigh muscle was not diagnostic of a myopathy.

In addition to the 124 AEFIs, 1 case of idiopathic thrombocytopenic purpura in an 11 year old girl, with onset 4 months after MMR vaccine, came to the panel's attention. This case was not notified through any of the three sources, because it occurred late. The panel did not include it in the report because the onset was after the 30 day limit post-vaccine defined before the campaign started.

Thus there were 89 AEFIs for which causality could be assigned, of which 46 were thought to be *certainly* caused by MMR vaccine, 23 were *probably* and 20 were *possibly* associated with the vaccine (Table 1). Sex was recorded on 71 of the reports, with 32 males and 39 females.

Table 1. Assessment of causality of Adverse Events Following Immunisation associated with the Measles Control Campaign

Adverse event	Certain	Probable	Possible	Unclear	Total analysed (excluding unclear)
Allergic reaction	7	2	2		11
Anaphylaxis	1				1
Anaphylactoid reaction	6				6
Arthritis			1		1
Arthralgia		1	1	1	2
Fever			5	1	5
Encephalopathy			1		1
Hyperventilation	2	3			5
Local reaction	3				3
Lymphadeniti'		1			1
'Other reaction' *		6	4	2	10
Parotitis		4		1†	4
Pain				1	0
Rash	1	1	1	4†	3
Seizure			4		4
Seizure (febrile)			1		1
Severe local reaction	2				2
Syncope	5	3			8
Syncopal fit	19	2			21
Total	46	23	20	10	89

* for details see text

† 2 rashes and 1 parotitis had missing onset dates

The overall rate of adverse events based on 89 reports was 5.24 per 100,000 doses of MMR vaccine administered. The most common reaction reported was syncopal fit (23.6%) giving a rate of 1.24 per 100,000 doses administered, followed by allergic reaction with a rate of 0.65 per 100,000 doses administered (Table 2).

Table 2. Rates of Adverse Events Following Immunisation associated with the Measles Control Campaign

Adverse event	Number	Rate per 100,000 doses
Allergic reaction	11	0.65
Anaphylaxis	1	0.06
Anaphylactoid reaction	6	0.35
Arthritis	1	0.06
Arthralgia	2	0.12
Encephalopathy	1	0.06
Fever	5	0.29
Hyperventilation	5	0.29
Local reaction	3	0.18
Lymphadenitis	1	0.06
'Other reaction' *	10	0.59
Parotitis	4	0.24
Rash	3	0.18
Seizure	4	0.24
Seizure (febrile)	1	0.06
Severe local reaction	2	0.12
Syncope	8	0.47
Syncopal fit	21	1.24
Total	89	5.24

* for details see text

Fifty-seven per cent of reactions occurred within 1 hour of administration of the vaccine. These were syncope, syncopal fit, hyperventilation, allergic, anaphylactoid, anaphylactic and local reactions.

Forty-three children did not require hospitalisation or to be seen by a doctor, while 19 children were seen by a doctor, 13 were seen in an emergency room, and another 14 were hospitalised (3 following syncope, 1 following a seizure, 4 following hyperventilation, 2 with fever, 2 with anaphylactoid reactions, 1 with a local reaction and 1 with an 'other' reaction). Seventy-nine children are known to have recovered and the outcome was unknown for the remaining 9 because of ADRAC's confidential data. There were no deaths.

Allergic type reactions/ anaphylactoid/ anaphylaxis reactions

Twelve allergic, 6 anaphylactoid and 1 anaphylactic reaction were reported. Except for 4 allergic reactions, all of these reactions occurred within 1 hour of administration of the vaccine and were classified as *certainly* due to the vaccine. The anaphylactic reaction occurred 3 minutes after the child was vaccinated. Of the 6 anaphylactoid reactions, 4 children developed symptoms within 5 minutes of administration of MMR vaccine, 1 child developed them after 15 minutes and another after 60 minutes.

Adrenaline was administered to a total of 13 children, 7 for immediate allergic reactions (6 anaphylactoid and one anaphylaxis) and for 6 children without immediate allergic reactions (4 syncopes and 2 hyperventilation). There were no adverse effects of adrenaline in these children. Two children with anaphylactoid reactions were admitted to hospital whilst the remaining children with anaphylactoid reactions and the one with an anaphylactic reaction were treated in the hospital emergency department and then discharged. All the children recovered. The rate for anaphylactic, anaphylactoid and allergic reactions was 0.06, 0.35 and 0.65 per 100,000 administered doses (respectively) with an overall rate for any immediate allergic-type reaction of 1.06 per 100,000 administered doses.

Neurological reactions

There were 4 children reported with afebrile seizures, 1 with a febrile seizure and 1 with encephalopathy. All these children have recovered and the reactions were considered to be *possibly* related to the MMR vaccine. The rate of febrile seizures was 0.06, afebrile seizures 0.24 and any seizure 0.30 per 100,000 doses of MMR administered. The rate of encephalopathy was 0.06 per 100,000 doses administered.

The onset was less than 24 hours after vaccination for the child with a febrile seizure and for 1 of the 4 with an afebrile seizure. The latter was a 7 year old child who had a seizure lasting 20 minutes the day after receiving MMR vaccine. The child had no previous history of epilepsy and was taken to hospital. The afebrile seizures in the other 3 children occurred at 12, 15 and 28 days respectively after administration of the MMR vaccine. The recovery status of the 7 year old girl whose seizure occurred 12 days after vaccination is not known as the event was reported to ADRAC.

A 10 year old boy with a history of a viral infection 2 weeks prior to MMR vaccination had a focal seizure 15 days after vaccination. Three days later the child developed puffiness of the face, possibly related to the mumps component of the MMR vaccine. The history and an electroencephalogram (EEG) were considered diagnostic of benign Rolandic epilepsy. The child was treated with anti-convulsants and has recovered.

A 6 year old girl who had a seizure 28 days after receiving her second MMR vaccine was later diagnosed as having juvenile absence seizures by her paediatrician. The EEG findings were abnormal and diagnostic of absence seizures. The child is being treated with anti-convulsants and her symptoms are under control.

There was only one reported case of encephalopathy; an 8 year old boy who developed stomach pain, anorexia, headache, ear infection and demonstrated aggressive behaviour commencing 4 days after being vaccinated with MMR vaccine. He recovered in a week and did not require hospitalisation. This was considered to be a transient encephalopathy *possibly* related to the MMR vaccine.

Twenty-one children had syncopal fits that occurred within 1 hour of receiving the MMR vaccine. The rate of syncopal fits was 1.24 per 100,000 administered doses. This was

the most commonly reported adverse event and occurred equally in boys and girls. Five of the children who experienced a syncopal fit were seen by a doctor and 2 children were observed in hospital. None of the children with syncopal fits received adrenaline and all 29 recovered.

Syncope

There were 8 children reported with syncope who received medical attention (3 were hospitalised, 3 were seen in an emergency department and 2 were seen by a doctor). There were many more reports of simple syncope in children, which were reviewed by the State and Territory Campaign Managers and not forwarded to the National Campaign Manager.

Arthritis and arthropathies

Two cases of arthralgia and 1 case of arthritis were reported giving a rate of 0.12 and 0.06 per 100,000 administered doses (respectively). The arthritis developed in a 6 year old girl 1 day after MMR vaccine. The reaction was considered to be *possibly* related to the MMR vaccine. The onset of arthralgia in 2 children occurred 5 and 14 days respectively after MMR vaccination. All have recovered.

Parotitis

There were 4 parotitis reactions reported, occurring at 2 hours, 24 hours, 8 days and 10 days after receiving the MMR vaccine. All of the parotitis reactions were considered to be *probably* related to MMR vaccine. The rate of parotitis was 0.24 per 100,000 administered doses.

Local reaction/ severe local reaction

There were 3 local reactions and another 2 severe local reactions reported. All of these reactions were considered to be *certainly* caused by the MMR vaccine and all of the children have recovered. The rate of this reaction was 0.3 per 100,000 administered doses.

Lymphadenitis

There was only 1 case of lymphadenitis reported, which occurred 21 days after receipt of the vaccine and the child has recovered.

Other reactions

Ten children had reactions that were categorised as 'other reactions'. Of these, 2 children presented with a measles-like illness, 4 with a rubella-like illness, 1 had hallucinations and 1 was diagnosed as having hemiplegic migraine. In addition there was 1 child who had a late onset fever with headache and another child with fever and a stiff neck. The 4 rubella-like reactions occurred on 1, 3 , 8, and 12 days after receiving the MMR vaccine while the 2 measles-like reactions occurred 11 and 21 days after MMR vaccination. The fevers occurred 10 and 13 days after receiving the vaccine.

An 8 year old boy who presented with symptoms of encephalopathy 7 days after receiving MMR vaccine was initially diagnosed as having viral encephalitis. Although this child recovered from the acute episode with no neurological deficit, he had another attack 3 months later and has subsequently been diagnosed as having familial hemiplegic migraine. This child had received a previous dose of MMR. It is possible that the MMR viraemia triggered the episode, so the adverse event in this child was considered to be *possibly* related to the MMR vaccine. The child has recovered.

A 7 year old boy started hallucinating 2 days after receiving MMR vaccination and has made a complete recovery according to his parents. The child had a normal computerised tomography (CT) scan 3 weeks after onset of the reaction. This reaction was considered to be *possibly* related to MMR vaccine.

All of the reactions categorised as 'other reactions' were considered to be *possibly* related to the MMR vaccine. All children have recovered.

Discussion

Among the 1.7 million children vaccinated during the period of the MCC there were 89 AEFIs reported in association with MMR vaccine. This gave an overall rate of AEFIs of 5.24 per 100,000 administered doses. This is lower than the rate of 14.9 per 100,000 administered doses reported during the United Kingdom (UK) campaign in 1994 when 8 million children were vaccinated with measles-rubella vaccine and 1,202 experienced adverse reactions.[8] The rates of almost all of the individual adverse events reported were lower than those reported from the UK, except for the rate of seizures which was a little higher than the rate seen in the UK.[8]

There were no deaths reported resulting from the administration of MMR vaccine during the period of the campaign and all the children have recovered although 9 children could not be followed up for reasons of confidentiality (2 with fever, 3 with parotitis, 2 with rashes, 1 with an afebrile seizure and 1 with a measles-like illness).

Although 46 reactions were categorised to be *certainly* caused by the MMR vaccine, the majority of these were syncopal fits, syncope, local reactions, and allergic reactions that were short-lived, and all these children recovered.

The combined rate for anaphylaxis, anaphylactoid and allergic reactions was 1.06 per 100,000 administered doses which is also lower than the UK rate of 1.6 per 100,000 administered doses.[9] There was only 1 anaphylactic reaction, giving a rate of 0.06 per 100,000 as compared to 1 per 100,000 in the UK.[8] It is possible that the prompt use of adrenaline by the campaign nurses for children with anaphylactoid reactions averted more cases of anaphylaxis. This is a credit to the nurses who recognised the seriousness of these reactions.

Simple febrile seizures occur occasionally after measles or MMR vaccination and generally have no sequelae. An increased risk of febrile seizures may occur in children with a personal history or first degree family history of seizures.[10] A study in the United States of America linking vaccination records with computerised hospital admissions in five districts suggested that 67% of admissions with febrile convulsions 6 to 11 days after the first dose of MMR vaccination were attributable to the measles component of the vaccine (risk 1 in 3,000 doses) in children aged 12-24 months.[11] The overall rate of seizures (febrile and afebrile) in the MCC was 0.30 per 100,000 doses (1.76 per 600,000) which is slightly higher than the 1 in 600,000 reported in the UK.[8] The rate in the UK was based both on

reactions which were suspected to be vaccine-related and events thought to be causally unrelated so may be an overestimate.

One case of encephalopathy was notified, and this was considered only *possibly* related to the vaccination. The incidence of encephalitis after measles vaccination is approximately 1 in a million doses of vaccine,[12] whereas natural measles virus infection causes post-infectious encephalomyelitis in approximately 1 per 1,000 infected persons.[13] The rate of thrombocytopenic purpura in children receiving their first dose of MMR vaccine in Finland was 1 in 30,000[14] which was similar to the Swedish rate of 1 per 37,000.[15] There were no known cases of thrombocytopenic purpura considered to be causally related to the MMR vaccine in the MCC. Two cases (1 in 4 million doses) were reported in the United Kingdom's campaign. In comparison, thrombocytopenia caused by rubella disease varies in severity and incidence and has been reported as frequently as 1 in 3,000 cases.[16]

The overall reported rate of adverse events was low. It is not considered that this was due to under-reporting, but due to the fact that the campaign was targeted at school children. Most school children were receiving their second dose of MMR, so the incidence of adverse reactions would be expected to be lower than in infants receiving their first dose of MMR. The reactions reported in older children probably affect mainly those susceptible to the vaccine virus. As most of the data on adverse events relate to primary vaccination of infants, it may be inappropriate to compare the rates in school children receiving their second dose, except to other school-aged children receiving second doses of vaccine in measles campaigns in other countries.

The aim of the MCC was to avert an anticipated measles epidemic similar to the one which occurred in New Zealand in 1997.[5] Therefore the incidence of serious adverse events should be evaluated against the number of measles cases prevented through the campaign. On comparing the risks and benefits of MMR vaccine, the benefits of this MCC far outweigh the incidence of serious adverse events associated with immunisation.

Appendix 1

Definitions of adverse events

Allergic reaction

Characterised by one or more of the following:

- skin manifestations (for example; hives, eczema, pruritus);
- wheezing or shortness of breath due to bronchospasm; and/or
- facial or generalised oedema.

Anaphylactoid reaction (acute hypersensitivity reaction)

Exaggerated allergic reaction, occurring within 2 hours of immunisation, characterised by one or more of the following:

- wheezing and shortness of breath due to bronchospasm;
- laryngospasm/laryngeal oedema; and/or
- one or more skin manifestations, for example, hives, facial oedema, generalised oedema.

Anaphylaxis

Circulatory failure (for example; alteration of the level of consciousness, low arterial blood pressure, weakness or absence of peripheral pulses, cold extremities secondary to reduced peripheral circulation, flushed face and increased perspiration) occurring within minutes of immunisation with or without bronchospasm and/or laryngospasm/laryngeal oedema.

Arthralgia

Joint pain without redness or swelling.

Arthritis

Joint pain together with redness and/or swelling.

Encephalopathy

Diagnosis must be made by a physician.

Encephalopathy is an acute onset of major neurological illness temporally linked with immunisation and characterised by any two or more of the following three conditions:

- seizures;
- severe alteration in level of consciousness or mental status (behaviour and/or personality) lasting for one day or more; and/or
- focal neurological signs which persist for one day or more.

Encephalitis

Diagnosis must be made by a physician.

Encephalitis is characterised by the above mentioned symptoms and signs of cerebral inflammation and, in many cases, CSF pleocytosis and/or virus isolation.

Fever

Only very high fever should be reported, for example, over 40.5^{o} C.

Local reaction (severe)

Redness and/or swelling centred at the site of injection and one or more of the following:

- swelling beyond the nearest joint;
- pain, redness and swelling of more than 3 days duration; and/or
- requires hospitalisation.

Lymphadenitis (includes suppurative lymphadenitis)

Occurrence of either:

- at least one lymph node, 1.5cm in diameter or larger; or
- a draining sinus over a lymph node.

Almost exclusively caused by BCG on the same side as inoculation (mostly axillary).

Parotitis

Swelling and/or tenderness of parotid gland or glands.

Rash

Severe or unusual rash.

Seizure

- seizure lasting from several minutes to more than 15 minutes and not accompanied by focal neurological signs or symptoms;
- febrile seizure: with fever >37.5^{o} C;
- afebrile seizure: without fever.

Syncope

Transient loss of consciousness.

Syncopal fit

Tonic/clonic seizure or incontinence occurring in association with syncope.

Thrombocytopenia

Platelet count <150 x 10/L. Diagnosis must be made by a physician.

Other severe or unusual events

Any unusual event that does not fit into any of the categories listed above, but were of medical or epidemiologic interest should be reported with a detailed description of the clinical features.

Appendix 2

Assessment of causality

The panel used the basic ADRAC criteria in determining causality ratings, which are consistent with international criteria (WHO), as follows:

Certain

- confirmed by rechallenge; and/or
- confirmed by laboratory data; and/or
- reaction onset is immediately following drug/vaccine administration (within 60 minutes if injections was the method of administration); and/or
- precise spatial correlation with administration (for example, at the exact site of injection).

Probable

- temporal or spatial (for example, skin) correlation with administration; and/or
- recovery on withdrawal of the drug if no other drug is withdrawn and no therapy given; and/or
- an uncommon clinical phenomenon associated with the administration of the drug/vaccine in the absence of other factors.

Possible

- a possible alternative explanation exists; and/or
- more than one drug/vaccine is suspected; and/or
- data are incomplete; and/or
- recovery follows withdrawal of more than one drug/vaccine; and/or
- time relationship is not clear; and/or
- outcome of the reaction is not recorded and/or
- recovery follows therapy in addition to withdrawal of the drug/vaccine.

Unclear

This classification is accorded where a clinical event may well be explained as arising from factors related to underlying disease, or other non-vaccine aetiology. Reports given this classification are not used in further evaluation or statistical studies. However, they are held in case future developments alter their significance.

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