Health Council of the Netherlands

Adverse reactions to vaccinations in the national immunization programme 2002-2003

Gezondheidsraad
Health Council of the Netherlands

To the Minister of Health, Welfare and Sport
PO Box 20350
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Subject : presentation of advisory report *Adverse reactions to vaccinations in the national immunization programme 2002-2003*
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Dear Minister,

I hereby present you with the report on *Adverse reactions to vaccinations in the national immunization programme 2002-2003* by the Health Council's Committee on Adverse reactions to vaccinations in the national immunization programme. Until recently it was part of the committee's remit to review the recording and assessment of individual notifications of adverse reactions by the National Institute for Public Health and the Environment (RIVM). With the creation of a focus group of experts at the RIVM this function of the Committee has come to an end, so the present report is the last in the series. The document has been reviewed by the Standing Committee on Medicine and the Standing Committee on Infection and immunity.

The committee's main conclusion is that during this reporting period there have again been no significant shifts in the nature and severity of notified adverse reactions to vaccinations carried out under the National Immunization Programme. I concur with the committee.

In the closing Chapter the Committee draws attention to various topics that it considers important, for example the absence of adequate post-mortems in a substantial proportion of the fatalities it assessed. The Committee mentions these topics in particular because in its view they touch upon the work of the RIVM's newly created focus group.

Yours sincerely,
(signed)
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to:

the Minister of Health, Welfare and Sport

No. 2006/14E, The Hague, June 29, 2006

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Executive summary

The function of this advisory report

Hundreds of thousands of children are vaccinated every year against such diseases as whooping cough and measles as part of the National Immunization Programme (NIP). Although in most cases no adverse events occur, vaccination does sometimes give rise to health problems. In order to determine precisely which problems are a result of vaccination, we have in the Netherlands a comprehensive, graduated system for recording and evaluating the reports that are submitted about these problems.

This Health Council advisory report has a specific function within that system insofar as it contains a re-evaluation of some of the reports received in 2002 and 2003 with regard to possible adverse vaccine reactions. These vaccinations mostly took place in 2001 and 2002. Child health clinics and general practitioners pass on reports of possible adverse reactions to the National Institute of Public Health and the Environment (RIVM), that assesses which of the reported adverse events may be a result of vaccination and which are not. The RIVM's assessment of reports on serious or complicated adverse reactions is then reviewed by the Health Council's Committee on adverse reactions following vaccinations under the National Immunization Programme.

It should be noted that this procedure has been modified as of 2004 and consequently this advisory report is the last of its kind.

Review procedure

For each report that is selected, the Committee gives its opinion on the diagnosis that has been made and on the likelihood of there being a causal relationship between morbidity or mortality and the preceding vaccination. This procedure is known as the causality assessment. The Committee classifies causality into the following categories: very likely, probable, possible, unlikely or unrelated. If insufficient data is available, the Committee declares that it is unable to make a causality assessment.

Evaluation of the reports

This advisory report covers the reports from 2002 and 2003. The Committee discusses the 74 selected reports that it has reviewed.

Sixty-two of the reports concern morbidity. In 42 of these 62 reports, the Committee either believes that the inferred causal relationship with the preceding vaccination is unlikely or classifies the adverse events as unrelated to vaccination. It regards the existence of such a connection as possible in the case of 15 reports and probable in five.

Twelve reports relate to fatalities. In five of these cases, the Committee finds a causal relationship between vaccination and death unlikely, while six of the fatalities are adjudged to be unrelated to vaccination. The Committee is unable to fully evaluate the one remaining fatality owing to a lack of data. However, it notes that the data which it was able to examine do not suggest that death was causally related to preceding vaccination(s).

The Committee also discusses two reports of fatalities following vaccinations administered outside the NIP in this advisory report. In both cases a causal relationship between vaccination and death is considered unlikely.

According to the Committee, it is therefore conceivable that a connection exists between vaccinations performed under the NIP and the occurrence of (severe) morbidity in a total of 20 of the 74 reports selected, which were assembled over a two-year period. The adverse events identified in one of these reports were the first indication – but not the cause – of a prolonged, serious illness. In the remaining reports, the Committee has found no evidence to suggest serious residual effects.

The Committee believes that these 20 reports in no way detract from the benefits of the NIP – i.e. the large-scale prevention of serious disease and complications. During the period discussed in this advisory report more than 2.8

million vaccinations protected an estimated 1.6 million children against serious childhood diseases.

Conclusion

Based on the RIVM's thorough and readily comprehensible reports and its own findings, the Committee concludes that there have been no significant shifts in the nature and severity of the reported adverse reactions in the past few years. Consequently it sees no reason to propose any change in the National Immunization Programme.

Chapter 1

Introduction

1.1 Background

Under the National Immunization Programme (NIP) hundreds of thousands of children a year are vaccinated against diseases such as pertussis and measles. There are usually no adverse reactions, but sometimes medical problems arise as a result of vaccination. To establish precisely which problems are due to vaccination, we have an elaborate multi-stage system in the Netherlands for recording and assessing notifications of these problems.

The present report by the Health Council has a function within that system: it reassesses some of the 2002 and 2003 notifications of possible adverse reactions of vaccinations which took place mostly in 2001 and 2002.

Notifications of suspected adverse reactions of vaccinations carried out under the NIP are recorded and assessed by the RIVM (the NIP Safety Monitoring and Child Health Care, which has been the responsibility of the Centre for Infectious Disease Control since 2005).

Until 1995 the Health Council's Committee on Adverse reactions to vaccination in the National Immunization Programme (referred to below as 'the Committee') reassessed all notifications dealt with by the RIVM in writing, and reported on them annually. This changed as a result of two developments.

First, since 1994 the RIVM has reported annually on the assessed notifications itself.[1] In fact, the committee's reassessment of the vast majority of cases

added little, because of the routine nature of the process: since 1996 the Committee has therefore only reassessed a selection of notifications of serious or complicated adverse reactions. The cases to be reassessed are selected by the RIVM using criteria drawn up by the Committee. The Committee keeps an eye on the total number of notifications to the RIVM by reviewing the RIVM's annual report. The Committee's remit is set out in Annex A and its composition in Annex B.

Meanwhile an even more important change has taken place, which means that this report by the Committee will be the last of its kind: vaccine production was transferred from the RIVM to the new Netherlands Vaccine Institute in 2003, hence the RIVM is no longer a vaccine manufacturer. In 2004 the RIVM set up a focus group of experts to carry out the reassessment of unusual cases.

With the publication of this report, this part of the Health Council Committee's remit has therefore come to an end.

1.2 Procedures

Recording of notifications by the RIVM

The RIVM records suspected adverse reactions of vaccinations administered under the NIP. It uses a low-threshold system whereby every notification is accepted, irrespective of (a) the likelihood of there being a connection between the symptoms and prior vaccination(s), and (b) the time that elapsed between the vaccination and the medical problem. The notifications are not only of serious syndromes but also of unusual or unexpected events and events that cause concern to parents, health professionals or the Dutch public. The majority of the notifications are made by doctors working at child health centres.

The RIVM allocates a diagnosis to each notification, if necessary after obtaining additional information. It then passes a judgment on the causality of each notification, i.e. the likelihood of there being a causal connection between the symptoms and the prior vaccination(s). Here the RIVM takes into account the diagnosis, the likelihood of a biological explanation for the symptoms, the duration of the symptoms and the time since the last vaccination, and any other possible causes of the symptoms. It then draws up a written report of the serious or more complex cases, setting out the data, the diagnosis, the assessment of causality and a recommendation for subsequent vaccinations.

The selection of notifications for the Committee

The Committee reviews a selection of the notifications received by the RIVM, which in turn has selected these based on criteria drawn up by the Committee.

The RIVM sends the Committee all notifications of deaths, but also of acute encephalopathy, diabetes, encephalitis, meningitis, sepsis and thrombocytopaenia, among others (for a glossary see Annex C). Notifications of unusual symptoms and symptoms with lasting effects are also submitted. Cases of merely high and/or protracted fever, convulsions with fever, convulsions without fever, prolonged shrieking, collapse or abcesses are not selected, unless the case presents special features that warrant inclusion. The RIVM can however submit notifications to the Committee that fall outside the selection criteria, when it considers a review to be prudent.

As a result of this selection process the total number of notifications reassessed by the Committee is much smaller than the number originally assessed by the RIVM and included in the latter's annual reports.

The committee's procedure

In the case of each selected notification, the Committee gives its opinion on the diagnosis and the likelihood of there being a connection between the symptoms or death and the prior vaccination (the assessment of causality). The Committee set out the criteria it uses for this in its 1997 report.[2] First the Committee checks whether the information is sufficient: if not, it notes that it has not been able to make an assessment of causality.

The Committee then classifies each case in one of the following six causality categories:

1 there is highly likely to be a connection
2 there is likely to be a connection
3 it is possible that there is a connection
4 there is unlikely to be a connection
5 whether there is a connection cannot be assessed
6 there is no connection.

These causality categories have been based on the international standards.[3,4] The sixth category, ('There is no connection'), however, has been added by the Committee, to distinguish between cases where it is convinced there is no link between the symptoms and the vaccination, and cases where it considers a link unlikely. In order to abide by the international standards – also used by the RIVM

– as far as possible, the Committee has decided to retain the order of the first five categories. There are differences in the wordings of the various categories, however: the RIVM refers to the connection between the vaccination and symptoms in the causality category with the highest probability as ‘certain’, for instance, whereas the Committee prefers the term ‘highly likely’.

1.3 The organisation of this report

In Chapter 2 the Committee discusses the results of its reassessment of the selected notifications for the years 2002 and 2003. As this report represents the committee’s last review, it concludes in Chapter 3 with a consideration of some topics that in its opinion still call for particular attention in the future.

Chapter 2

Review of selected notifications

2.1 The source of the notifications

In this final report the Committee discusses the 74 notifications it reassessed since the publication of the previous report, up to the point when it ceased carrying out this task (Table 1). Sixty-two notifications are of symptoms and 12 of deaths.

Sixty-nine of the notifications reassessed by the Committee were made to the RIVM in 2001 and 2002; five notifications discussed in this report go back to 2000. In 2001 and 2002 the RIVM assessed a total of 2,663 notifications of possible adverse reactions of vaccinations.[5,6]

In line with its assignment the Committee has reviewed reports of adverse reactions of vaccinations carried out under the NIP. In the period covered by this report there were two notifications to the RIVM of deaths following vaccinations outside the NIP. In view of the seriousness of these cases the Committee decided to review these as well, and discuss them in its report; they are not included in the tables, however, as they relate to vaccinations outside the NIP.

Table 1 Notifications reassessed in the report on 2002 and 2003.

Year of notification	Total number	Symptoms	Deaths
2000	5	5	-
2001	39	35	4
2002	30	22	8
Total	*74*	*62*	*12*

2.2 Verdict on the RIVM reports

The Committee assessed the RIVM reports on the years 2001[5] and 2002[6] to check whether it received all the relevant notifications. The Committee commends the thorough reporting and the clear presentation of the results. It concludes from the data that it has received all the relevant reports from the RIVM. It notes that the RIVM has also succeeded in reducing the time between the end of the reporting year and the publication of the annual report still further.

2.3 Reassessment of individual notifications of symptoms

The Committee assessed 62 notifications of symptoms, with a causality ranging from '2' (There is likely to be a connection) to '6' (There is no connection) (Table 2). The Committee considers a connection with a prior vaccination to be unlikely or non-existent in 42 cases. In 20 cases the Committee adjudged the existence of a connection to be possible (15 notifications) or likely (5 notifications).

Table 2 Notifications of symptoms grouped by causality category.

Year of notification	Total number	Causality category					
		1	2	3	4	5	6
2000	5			2	1		2
2001	35		3	10	5		17
2002	22		2	3	3		14
Total	*62*	-	*5*	*15*	*9*		*33*

Table 3 Notifications of symptoms grouped by diagnosis.

Diagnosis	Number
Collapse and atypical seizures	4
Convulsion and epilepsy	20
Encephalitis and encephalopathy	3
Other neurological problems	9
Skin symptoms	2
Serious infections	5
Shaken baby syndrome	2
Metabolic diseases	3
Diabetes	3
Thrombocytopaenia	4
Other notifications	7
Total	*62*

The Committee has grouped the notifications by diagnosis (Table 3), giving comments on each category. It only comments on individual notifications if the case histories in a category differ so much that it is not possible to discuss them as a group.

Medical terminology is used where necessary when describing the histories: the meanings of the terms are explained in the glossary (Annex C).

2.3.1 *Collapse and atypical seizure*

Description

The Committee assessed four notifications of collapse (seizure with limpness, pallor and unconsciousness) or atypical seizure. The Committee defines a case as an atypical seizure when the description does not meet the criteria for collapse, but is suggestive of it. The symptoms occurred in otherwise healthy children, and there were no residual complaints. These cases were submitted to the Committee by the RIVM, even though they are outside the agreed selection criteria.

Assessment of causality

The Committee considers that there is likely to be a connection with a vaccination in two cases; it considers this unlikely in two other cases. The Committee would note here that collapse is a known but rare side effect of vaccination,[7] and the outcome is almost always good – as in the cases described here. Research has shown that collapse is not a contraindication for future vaccinations.[8]

2.3.2 *Convulsion and epilepsy*

Description

The Committee assessed 20 notifications of convulsions, i.e. seizures with rhythmic muscle spasms, of epileptic origin or otherwise. Twelve notifications were of children with epilepsy, including nine with West's syndrome, a condition where epileptic seizures are one of the manifestations. Epilepsy is diagnosed once two or more unprovoked epileptic seizures have occurred. Two cases were of children with isolated status epilepticus, a protracted epileptic seizure (lasting more than 30 minutes). Six notifications – four of febrile convulsions and two of convulsions without fever – were submitted to the Committee by the RIVM, even though they are outside the agreed selection criteria.

Assessment of causality

The committee's verdict is that there is no connection between vaccination and the development of epilepsy, although it does envisage the possibility of vaccination occasionally causing an epileptic process that is already latent to manifest clinically.

In one of the four cases of febrile convulsions the Committee considers that there is likely to be a connection with the prior vaccination; in two of them a connection is possible, and in the fourth the Committee considers that there is no connection. Febrile convulsions occur following a fever that has developed as a result of illness or vaccination, but are not specific to that illness or vaccination.

The Committee considers that there is a possible connection with the vaccination in both cases of single convulsions without fever. The first case was of an isolated epileptic seizure, the second was of the first manifestation of epilepsy (which was already latent). The Committee will return to this second case later on (see 2.6). Epidemiological research shows that a convulsion following vaccination is no more likely to result in epilepsy or neurological developmental disorders than a convulsion not connected with a prior vaccination.[9]

2.3.3 Encephalitis and encephalopathy

Description

The Committee assessed three notifications of encephalitis or encephalopathy. Encephalopathy is an acute or chronic acquired abnormality, injury or functional disorder of the brain. Encephalitis is inflammation of the brain and can result in encephalopathy. In two of the three cases there were residual neurological symptoms; in the third case the information is insufficient:

- A 14-month-old child became feverish and listless a week after its MMR vaccination. Ear inflammation also developed a week later, and gait disorders and increasing drowsiness more than three weeks after the injection. The picture was consistent with acute encephalitis in the form of acute disseminated encephalomyelitis (ADEM). Based on the information supplied, the Committee concludes that the child improved, but whether it recovered fully is not clear.
- The night after its MMR vaccination a 14-month-old child developed fever and protracted convulsions, with abnormalities on the EEG consistent with epilepsy. This recurred three days later, along with unconsciousness lasting four days. After that, the convulsions ceased, and there was some gradual

improvement. The Committee diagnoses acute encephalopathy, possibly caused by status epilepticus.

- Two days after being vaccinated against meningitis C a sixteen month-old child developed fever and had a convulsion. During the next few days a picture emerged that suggests, to the Committee, encephalopathy. A temporary improvement was again followed by a period when the child had to be admitted to a paediatric intensive care unit. The child was left with severe residual symptoms.

Assessment of causality

Possible adverse reactions of a live vaccine such as MMR do not manifest until at least five days after vaccination, so the Committee considers it possible that there is a connection between the vaccination and the symptoms in the first case. In the second case, also after an MMR vaccination, the first symptoms developed in the night following the vaccination, so the Committee concludes that the syndrome is not connected. In the case of the meningitis C vaccination, which uses a dead vaccine, the period between the vaccination and the symptoms was relatively long, so the Committee considers that there is unlikely to be a connection.

2.3.4 Other neurological problems

Description

The Committee assessed nine notifications of neurological problems that do not fit into any of the previous categories:

- Three days after being vaccinated against meningitis C, a sixteen-year-old girl had a cerebral infarction and was left with severe residual symptoms. She had started taking the contraceptive pill two weeks previously.
- A three-year-old child with a developmental disorder had a severe brain contusion as a result of falling down the stairs on the day of its DTP vaccination (DTP = diphtheria/tetanus/polio in the Netherlands).
- A 15-month-old child who by mistake was given its fourth DPTP/Hib vaccination (DPTP = diphtheria/pertussis/tetanus/polio) twice, developed speech and language retardation in the following months.
- In the weeks following her third DPTP/Hib vaccination, a child manifested symptoms which were probably related to Aicardi-Goutières syndrome, a severe hereditary neurological condition. Her case was reported at the age of three years, because of concern about the vaccination of a younger sibling.

- On the day after its MMR vaccination an eighteen month-old child displayed symptoms of acute (possibly post-infectious) ataxia.
- During the months following its third DPTP/Hib vaccination, a four-month-old child's head size increased too rapidly.
- Three children aged eighteen months to four years displayed autistic behaviour that developed in the period following their MMR vaccination.

Assessment of causality

The Committee considers that there is unlikely to be a connection between the meningitis C vaccination and the cerebral infarction; it sees this syndrome as being a possible side effect of the contraceptive pill.

In the other eight cases the Committee considers that there is no connection between the symptoms and the vaccination. The brain contusion due to falling down the stairs and the development of speech and language retardation are not connected with the vaccination; this is also the case with the Aicardi-Goutières syndrome. The acute, possibly post-infectious, ataxia developed so soon after the MMR vaccination that this cannot have been the cause. The Committee considers that the increase in head size is also unconnected with the vaccination; indeed, the possibility cannot be ruled out that the increase is consistent with normal development.

Wakefield and colleagues first reported on a possible link between vaccination and the development of autism in 1998.[10] This finding has not been confirmed in any of the large amount of research carried out in response.[11-13] The Committee therefore considers the development of autism to be unconnected with vaccination. It intends to return to this point in a special report devoted to this topic.

2.3.5 Skin symptoms

Description

The Committee assessed two cases of unusual skin symptoms:

- Following its third DPTP/Hib vaccination, combined with a hepatitis B vaccination, a four-month-old child developed a protracted discolouration of the thigh.
- Seventeen days after its MMR vaccination, a 15-month-old child developed urticarial exanthema.

Assessment of causality

The Committee considers that the thigh discolouration is likely to be due to the vaccination. No discolouration took place following subsequent vaccinations. Given the long time that elapsed between the vaccination and the urticarial exanthema, the Committee considers that there is unlikely to be a connection between the vaccination and the symptoms. Urticarial exanthema is occasionally seen following vaccination with a live vaccine such as MMR, especially during the period of viraemia due to the vaccine (five to twelve days after vaccination).

2.3.6 Serious infections

Description

The Committee assessed five notifications of serious or unusual infections. There is no regular pattern in them that could be attributed to one or more vaccinations. In two cases it was not possible to isolate the pathogen responsible for the infection using laboratory tests, in the other three it was:

- Four weeks after its MMR vaccination a thirteen-month-old child was found to have discitis of a lumbar vertebra. The child healed, following treatment with antibiotics. A week after the vaccination the child had been feverish and listless.
- Starting a week after its first MMR vaccination a fifteen-month-old child with von Willebrand's disease developed fever and a painful swelling in the wrist. The symptoms disappeared spontaneously.
- Starting three days after its MMR vaccination a fifteen-month-old child developed high fever and was admitted to hospital with suspected meningitis. Streptococcus pneumoniae was isolated from the cerebrospinal fluid and blood. The inflammation caused complications and the child was left with severe residual symptoms.
- Three days after its fourth DPTP vaccination, a nine-month-old child developed a respiratory infection with fever. In view of its deteriorating condition, with indications of meningitis, the child was admitted to hospital, where Streptococcus pneumoniae was isolated from the blood. The bacterium was also found in the cerebrospinal fluid. The child had previously had epileptic seizures, before its third DPTP/Hib vaccination. The sepsis and meningitis following the DPTP vaccination were complicated by the occurrence of several epileptic seizures and eventually status epilepticus.

- Two days after being vaccinated against meningitis C, a child aged two years and four months was admitted to hospital, where it was diagnosed with meningitis. Neisseria meningitidis group B was isolated from the cerebrospinal fluid.

Assessment of causality

The Committee considers it unlikely that the discitis was caused by the vaccination, as the period between the vaccination and the symptoms was too long. The symptoms in the first week, however, could have been caused by the vaccination.

In the other cases of infections, the Committee considers that there is no connection with the vaccination. In the three cases of serious infections where a pathogen was isolated, this was not a microorganism targeted by the vaccine, so the Committee concludes that the infections occurred independently.

2.3.7 Shaken baby syndrome

Description

The Committee assessed two notifications of 'shaken baby syndrome'. This can occur if children are held by the trunk or shoulders and shaken back and forth, causing various types of bleeding in the brain and retina, with no outward signs of trauma.

Assessment of causality

There is no connection between the vaccinations and shaken baby syndrome.

2.3.8 Metabolic diseases

Description

The Committee assessed three cases of children with congenital metabolic disease:

- Following its DTP5/aP vaccination, a child aged three years and ten months with adrenal cortex insufficiency underwent an Addisonian crisis.
- Four days after its first DPTP/Hib vaccination, a child just under two months old was admitted to hospital with an epileptic seizure. Investigation showed that the child had Menkes disease.

- A one-year-old child with a clearly defined metabolic disorder of the mitochondria, manifesting as encephalopathy, was reported some time after the DPTP/Hib vaccinations, because the parents wondered whether the symptoms might be connected with the vaccination after all.

Assessment of causality

The Committee considers that the stress that vaccination can cause might have contributed to the Addisonian crisis in the child with adrenal cortex insufficiency. The insufficiency is otherwise unconnected with the vaccination, as is Menkes disease and the mitochondrial metabolic disorder in the other two cases.

2.3.9 Diabetes

Description

The Committee assessed three cases of children with diabetes.

Assessment of causality

The Committee considers that there is no connection between the vaccination and the development of diabetes in these three cases, and it is supported in this by recent international publications on scientific studies.[14-17] Dutch research also shows that there is no indication of a connection of this kind.[18]

2.3.10 Thrombocytopaenia

Description

The Committee assessed four notifications of thrombocytopaenia, a shortage of platelets. This condition occurred in all the children following MMR vaccination, one, three and five weeks and over six months later respectively.

Assessment of causality

The Committee considers it possible that the MMR vaccination caused the thrombocytopaenia in three of the four children. In the fourth child, whose symptoms manifested six months after vaccination, the Committee considers that there is no connection.

(Temporary) thrombocytopaenia is a known but rare side effect of MMR vaccination in particular.[7] The condition is in fact more common following natural infection by mumps, measles or German measles virus than following vaccination for these viruses.[19] Recovery is usually spontaneous.[20] In all the cases discussed here, the number of platelets returned to normal after a while.

2.3.11 *Other notifications*

Description and assessment of causality

The Committee assessed seven notifications that it was unable to fit into a particular category: these are discussed here on a case-by-case basis.

In one case the Committee considers it likely that the problems were caused by the vaccination:

- After its fourth DPTP/Hib vaccination a child aged just under one year became almost immobile and unable to stand up for several days. Recovery was spontaneous and there were no problems with the meningitis C vaccination. To the Committee this picture suggests avoidance behaviour in young children, probably based not so much on an inability to move as a desire to avoid pain. Although patients recover from the condition spontaneously, as was the case here, the Committee can well imagine that it is very worrying for the parents.

In five cases the Committee considers that there is a possible connection between the vaccination and the symptoms:

- Five days after its MMR vaccination a fifteen-month-old child's hands and ears swelled up. The child had had chickenpox five days before the vaccination. During the days following the swelling of the hands and ears, the child's feet also became swollen, and it later developed fever. The symptoms disappeared spontaneously. The Committee considers it possible that the symptoms were due to the vaccination, but it cannot rule out the possibility that the earlier chickenpox played a role.
- During the days following her fourth DPTP/Hib vaccination, a ten-month-old child had high fever and leg problems. No satisfactory explanation was found for the symptoms: laboratory tests did not indicate a bacterial infection. The child recovered spontaneously after a few days.
- During the days after its MMR vaccination, a fifteen-month-old child developed red eyes, followed by a rash and fluctuating fever. Two weeks after the vaccination the child was admitted to hospital with anaemia, where labora-

tory tests showed that the anaemia was caused by antibodies to red blood cells. These antibodies can be induced by German measles, but the syndrome developed relatively soon after the vaccination, and no German measles antibodies were found yet. The red eyes soon after vaccination could point to another viral infection. The problems did not recur.

- During the hours following its second MMR vaccination, a nine-year-old child tired quickly and felt so shaky and weak that it stopped walking. Laboratory tests did not indicate any abnormalities. Following initial deterioration, the child recovered with the aid of physiotherapy.
- Two days after its first DPTP/Hib vaccination a 10-week-old child took on a marked preferred posture, with its head turned to the right and the body arched. Clinical investigation and imaging did not reveal the cause. The situation improved with physiotherapy. The same thing happened after the second DPTP/Hib vaccination, but this time with the preferred posture of the head turned to the left. No preferred posture developed after the third DPTP vaccination, but one did after the third Hib vaccination, this time to the right. To the Committee this pattern suggests spasmodic torticollis. This has not previously been described following vaccination, and how it developed is not clear.

In one case the Committee considers that there is no connection between the vaccination and the symptoms:

- During the days after its second DPTP/Hib vaccination, a three-month-old child was admitted to hospital with generalised oedema. Investigation there revealed nephrotic syndrome and terminal renal insufficiency due to DMS (diffuse mesangial sclerosis). This syndrome is unconnected with the vaccination.

2.4 Reassessment of notifications of deaths

The Committee reassessed twelve notifications of deaths following vaccinations under the NIP during the period under review (Table 4). As in the previous report the cases are classified by diagnosis (Table 5) and the Committee gives a description of each category. It also discusses two notifications of deaths following vaccinations outside the NIP.

Table 4 Notifications of deaths grouped by causality category.

Year of notification	Total number	Causality category 1	2	3	4	5	6
2000	-						
2001	4					1	3
2002	8				5		3
Total	*12*				*5*	*1*	*6*

Table 5 Notifications of deaths grouped by diagnosis.

Patient	Committee's diagnosis	Age (months)	Vaccination	Death after (days)	Post-mortem findings	Causal connection
A	Cot death	16	MMR	40	Autopsy: no cause of death	No connection
B	Death of child with congenital abnormalities	2	DPTP/Hib 2	0	Unexplained anaemia with pre-existing blood breakdown	No connection
C	Death of child with mitochondrial metabolic disorder and brain tumour	14	MMR	74	No autopsy	No connection
D	Death of child with peroxisomal disorder	6	DPTP/Hib 3	1	No autopsy	Unlikely
E	Death of child with severe congenital heart abnormality	5	DPTP/Hib 3	0	No autopsy	Unlikely
F	Death of child with Kawasaki disease	4	DPTP/Hib 1	74	No autopsy	Unlikely
G	Undiagnosed, endocarditis?	16	MMR	32	Endocarditis (septic?) and possible metabolic disorder	No connection
H	Undiagnosed, bacterial respiratory infection?	15	MMR	48	High glucose level	No connection
I	Undiagnosed, shaken baby syndrome?	4	DPTP/Hib 3	4	Autopsy: no conclusive diagnosis	No connection
J	Death of child following metabolic disturbance	7	MMR	42	Autopsy: no cause of death	Unlikely
K	Undiagnosed	4	DPTP/Hib 3	3	No autopsy	Unlikely
L	Undiagnosed	5	DPTP/Hib 2	0	No autopsy	Impossible to assess

In one case (patient A), the Committee concludes from the findings of the post-mortem that this was a cot death. The committee's verdict is that there is no connection between the vaccination and the death, based on publications on epidemiological research.[21-23]

Four children who died were known to have severe congenital abnormalities (patients B, C, D and E). In two of them, the Committee considers that the death was unconnected with the vaccination. An autopsy on patient B revealed that the child had pre-existing severe anaemia, which had resulted in pronounced haematopoiesis, also outside the bone marrow. Patient C had a mitochondrial metabolic disorder manifested in several organs, as well as a brain tumour.

The hereditary peroxisomal disorder in patient D and the severe congenital heart abnormality in patient E were not caused by vaccinations. There is unlikely to be a connection between vaccination and death in these patients, though it cannot be ruled out entirely, as the vaccination might have contributed indirectly, for example as a result of the ensuing stress.

Two cases were of patients who did not have hereditary abnormalities, but there were clear indications as to the cause of death. Patient F suffered from Kawasaki disease, a syndrome characterised by inflammation of the blood vessels and swelling of the skin and lymph glands. The cause of the syndrome is not known, and there are no data that suggest a link with vaccinations.[24,25] The Committee therefore considers a connection between the vaccination and the syndrome to be unlikely. In patient G there were clear indications of endocarditis, most probably caused by a viral infection. The Committee therefore considers the endocarditis to be unconnected with the vaccination.

In five cases the Committee did not reach a conclusive diagnosis, despite the fact that post-mortems were carried out in some of them. In two of these patients, the Committee considers the deaths to be unconnected with the vaccination. In patient H the post-mortem found indications of a bacterial respiratory infection. In patient I it was impossible to reach a conclusive diagnosis, in spite of the post-mortem. Based on the findings, the Committee cannot rule out the possibility of shaken baby syndrome in this patient.

Soon after vaccination patient J suffered a metabolic disturbance, characterised by acidosis and hyperglycaemia. The situation returned to normal, but a few weeks later there was a second disturbance that eventually led to the child's

death. The Committee cannot rule out the possibility that the first episode of disturbance was attributable to stress following the vaccination, but it considers it unlikely that this was also the cause of the second episode, six weeks after the vaccination.

In the cases of patients K and L the absence of a post-mortem made it impossible to reach a conclusive diagnosis. Where patient K is concerned, the Committee considers that a connection is unlikely, however, given the three-day interval between vaccination and death. Case L cannot be fully assessed by the Committee, because of lack of data: it would note, however, that the data it *was* able to study do not point to a connection between the death and prior vaccination or vaccinations.

2.4.2 *Notifications outside the NIP*

The Committee also discusses two notifications of deaths following vaccinations outside the NIP. The first case is of a patient who was vaccinated against meningitis C at the age of seven months, before the official vaccination campaign against this microorganism was launched. Three days after the vaccination, the child was found dead. A thorough post-mortem did not provide any clear indications of the cause of death. The Committee diagnoses cot death.

What verdict does the Committee give on a possible causal connection in this case? When vaccines have been administered for many years and have long been included in the NIP, the Committee considers cot death to be unconnected to vaccination, given the available knowledge. With this relatively new vaccine, of which we have less knowledge, the Committee is more cautious: here it considers that there is unlikely to be a connection between the vaccination and the cot death. There are in fact no indications of adverse reactions that give cause for concern, given our current experience of vaccination against meningitis C, either in the Netherlands or elsewhere.[26-28]

The second case outside the NIP is of a Dutch child who was vaccinated abroad, with a vaccine not used in the Netherlands. The patient died at the age of 15 months, seven days after the MMR vaccination. Cot death has been suggested as a possible cause of death, but no post-mortem was carried out on the brain, so this diagnosis can neither be made nor rejected. The patient suffered from asthma and was taking salbutamol syrup as medication for this. Given the three possible causes of death (cot death, asthma or excessive use of salbutamol), all the Committee can do is describe this as a death with no clearly demonstrable cause. The Committee considers that the death is unlikely to be connected with the vaccination.

2.5 Comparison with the RIVM reports

In the period covered by this report, the Committee reassessed a total of fourteen notifications of fatalities, twelve following vaccinations under the NIP and two following vaccinations outside the NIP. These fourteen notifications are also discussed in the two RIVM reports. In its report on 2001 the RIVM also mentions a death already described by the Committee in its report on the 1997-2001 period.[24]

In eleven of the twelve cases of death following vaccinations under the NIP both the Committee and the RIVM conclude that a connection between vaccination and death is unlikely or non-existent. In one case both the Committee and the RIVM consider that the information is too inadequate to make an assessment.

In the two cases of death following vaccinations outside the NIP both the Committee and the RIVM conclude that a connection between vaccination and death is unlikely or non-existent.

2.6 Conclusion

In the period covered by this report, the Committee has reviewed a selection of 74 notifications of serious or complicated symptoms or death. In fifteen cases it considers that there is no connection between the symptoms and the vaccination. In five cases it thinks that there is likely to be an indirect connection.

These twenty cases do not include fatalities. In one case, where a connection was assessed as being possible, the symptoms were the first indication of a severe neurological condition. This related to a child with impaired development who had a convulsion without fever on the day of the vaccination, which turned out to be the first manifestation of epilepsy. The Committee would point out here that its assessment of causality as ‘possible’ is based on the relationship between the vaccination and the convulsion. The epilepsy that manifested later is unconnected with the vaccination.

From the RIVM reports and its own findings, the Committee concludes that there were no significant shifts, during the period under review, in the numbers, nature or seriousness of the reported adverse reactions. It therefore sees no reason to suggest that any changes be made to the National Immunization Programme.

Chapter 3

Concluding remarks

This report is the last in the series. In some of its previous reports, the Committee considered topics that it deemed important to the exercise of its duties. The Committee returns to some of these topics here, because they touch upon the work of the RIVM's new focus group.

3.1 The importance of post-mortems

The Committee reassessed twelve cases of fatalities during the period under review. In six of these cases no autopsy was carried out, with the result that data that could have made it easier to decide whether there was a link between the vaccination and the death may have been missing. The Committee finds it unsatisfactory that it was not able to assess such a large proportion of the fatalities properly, for one thing because this could reduce trust in the NIP.

As in the previous report, the Committee would again strongly stress the importance of a thorough post-mortem, including an autopsy, when a child dies unexpectedly.[24] Research in the United Kingdom shows that in 50 of the 209 deaths studied there, an autopsy provided information that would not have been obtained without it.[29]

3.2 The importance of vaccinating children with serious health problems

Five deaths occurred in children with serious conditions or congenital abnormalities. The notifications of symptoms also included children with underlying problems, e.g. those with metabolic diseases.

In its previous report, the Committee considered the sometimes serious dilemma that arises when it comes to vaccinating children with serious underlying health problems.[24] It would again urge that children with serious conditions or congenital abnormalities be vaccinated. This must not be done, however, without very careful consideration of the risks, and only with proper supervision and monitoring if necessary.[30] The Committee realises that vaccination in these cases sometimes confronts doctors with a very difficult decision: on the one hand, the consequences of vaccination, e.g. stress and fever, can place a severe strain on these children. on the other hand, the illness these children are protected from by vaccination can be particularly dangerous for them.

3.3 The importance of watching out for symptoms in recently vaccinated children

When children have just been vaccinated, there can be a tendency to attribute certain symptoms to the vaccination that are not adverse reactions, but symptoms of a separate health problem. This can delay diagnosis and possibly treatment. In the case of a serious syndrome, such as meningitis, this is highly detrimental. There are no indications in the cases discussed in this report, however, that any such delay did take place.

3.4 The importance of vaccination

The importance of vaccination to health has been confirmed in recent years, unfortunately above all by the occurrence of epidemics in people who have not been vaccinated. In its previous report the Committee described a measles epidemic in unvaccinated people in the Netherlands in 1999 and 2000.[24,31] There was an epidemic of German measles in this country in 2004 and 2005.[32] German measles is usually fairly harmless in childhood, but an infection during pregnancy can cause congenital abnormalities or miscarriage.[33] All 166 patients in the epidemic were unvaccinated, and the cases included at least twelve of infection during pregnancy.[32] The proportion of children vaccinated against German

measles nationwide was over 95 percent on 1 January 2003,[34] though there was considerable variation from one municipality to another.

3.5 The importance of the NIP

In recent years, the Committee has reassessed 74 notifications of serious or complicated suspected adverse reactions of vaccinations. The Committee regrets the tragic events and sometimes very traumatic and stressful effects for all concerned that emerge from the case histories in these notifications.

The number of cases where a connection between the vaccination and the symptoms is possible or even likely is relatively small: of the notifications reviewed during the period under review, there are a total of 20 where it is conceivable that there could be a link between the vaccinations and the severe symptoms that occurred. In one of them the symptoms were the first indication – but not the cause – of a persistent severe condition; in the other cases the symptoms disappeared after a shorter or longer period.

The Committee considers that these 20 cases far from outweigh the benefits of the NIP, i.e. preventing serious illness and complications on a large scale. During the period under review, over 2.8 million vaccinations protected an estimated 1.6 million children against serious child diseases.

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Annexes

Annex **A**

The committee's remit

The committee's remit is:

- to assess notifications of deaths and serious or unusual symptoms submitted to it by the RIVM
- to evaluate reported possible adverse reactions in the light of the aims of the NIP
- to identify new adverse reactions (and possible adverse reactions) of the NIP based on its own assessment of the unusual notifications submitted by the RIVM and the scientific literature, and to gain an impression of current scientific knowledge on the subject
- to assess the RIVM's annual reports on possible adverse reactions of the NIP, including reviewing the RIVM's methodology and quality assurance
- to identify and interpret trends in the frequencies of suspected adverse reactions of the NIP, based on the RIVM's annual reports, and against the background of the scientific literature
- to report its findings at least once a year, making recommendations, if necessary, on such things as the need to make changes to the NIP.

Annex **B**

The Committee

- Dr A.C.B. Peters, *chair*
  Emeritus professor of child neurology, Oegstgeest
- A. Ambler, *adviser until 1 December 2005*
  Inspectie voor de Gezondheidszorg (Health Care Inspectorate)
- Dr S.G. van Duinen
  neuropathologist, Leiden University Medical Centre
- Dr E.J.P. Lommen
  paediatrician; Waalre
- Dr R.H.B. Meyboom
  physician, Dutch Pharmacovigilance Centre (Lareb),'s-Hertogenbosch; Uppsala Monitoring Centre, Uppsala, Sweden
- Dr H.C. Rümke
  clinical trials director, Vaxinostics, Vaccine Centre of Erasmus University Rotterdam
- Dr H.P. Verbrugge
  youth health care physician, Santpoort
- P.E. Vermeer-de Bondt, *adviser*
  youth health care physician, National Institute for Public Health and the Environment (RIVM), Bilthoven
- Dr P.M.E. Wertheim-van Dillen
  clinical virologist, Nigtevecht

- Dr K. Groeneveld, *secretary*
  Health Council, The Hague

The Health Council and interests

Members of Health Council Committees are appointed in a personal capacity because of their special expertise in the matters to be addressed. Nonetheless, it is precisely because of this expertise that they may also have interests. This in itself does not necessarily present an obstacle for membership of a Health Council Committee. Transparency regarding possible conflicts of interest is nonetheless important, both for the chairperson and members of a Committee and for the President of the Health Council. On being invited to join a Committee, members are asked to submit a form detailing the functions they hold and any other material and immaterial interests which could be relevant for the Committee's work. It is the responsibility of the President of the Health Council to assess whether the interests indicated constitute grounds for non-appointment. An advisorship will then sometimes make it possible to exploit the expertise of the specialist involved. During the inaugural meeting the declarations issued are discussed, so that all members of the Committee are aware of each other's possible interests.

Annex

C
Glossary

acidosis
: highly elevated blood acidity

addisonian crisis
: severe disturbance of water and salt management due to adrenal cortex insufficiency

ADEM
: acute disseminated encephalomyelitis

adrenal cortex insufficiency
: inadequate production of adrenocortical hormones

anaemia
: shortage of red blood cells due to inadequate production in the bone marrow, loss or augmented breakdown

ataxia
: impaired coordination of voluntary muscle movement due to a functional impairment of the brain

collapse
: seizure with limpness and pallor and unconsciousness

convulsion
: seizure with muscle spasms, of epileptic origin or otherwise

discitis
: inflammation of an intervertebral disc

DMS
: diffuse mesangial sclerosis, a particular form of nephrotic syndrome

encephalitis
: inflammation of the brain that can result in encephalopathy

encephalomyelitis
: inflammation of the brain and spinal cord

encephalopathy
: acute or chronic abnormality, injury or functional disorder of the brain

endocarditis
: inflammation of the endocardium, the inner lining of the heart.

epilepsy
: two or more unprovoked epileptic seizures

epileptic seizure
: sudden abnormal and transitory symptoms caused by abnormal and excessive discharge of a nerve cell population from the cerebral cortex

febrile convulsion
: convulsion occurring in fever due to illness or following

hyperglycaemia
: excessive blood glucose level vaccination, but not specific to that illness or vaccination

Menkes disease
: hereditary disorder of copper metabolism with structural abnormalities of the blood vessels (in the brain), skin and hair

mitochondrion
: part of a body cell that supplies energy

nephrotic syndrome
: renal failure with loss of protein into urine and oedema

oedema
: accumulation of fluid in the skin and underlying tissues

peroxisomal disorder
: impairment of the quality, structure or quantity of the peroxisomes, accompanied by congenital shape abnormalities and various malfunctions of fatty acid metabolism

seizure
: sudden change in behaviour, consciousness or motor function, with or without rhythmic muscle contractions

sepsis
: bacterial Infection of the blood

shaken baby syndrome
: syndrome that can occur if children are held by the trunk or shoulders and shaken back and forth, causing bleeding in or around the brain and retina

spasmodic torticollis
: sudden lopsided position of the head

status epilepticus
: protracted complicated epileptic seizure (lasting more than 30 minutes)

syndrome of Aicardi-Goutières
: hereditary disorder with calcification of certain parts of the brain, encephalopathy and an increased number of white blood cells in the cerebrospinal fluid

syndrome of Kawasaki
: syndrome characterised by inflammation of the blood vessels (especially in the heart) and swelling of the skin and lymph glands

thrombocytopaenia
: shortage of platelets

urticarial exanthema
: hives

viraemia
: presence of virus particles in the blood

von Willebrand's disease
: coagulation disorder due to shortage of Factor VIII

West's syndrome
: syndrome consisting of epileptic seizures, specific abnormalities on the electroencephalogram and halted mental development