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N.A.T. van der Maas et al.

Adverse events following immunization under the National Vaccination Programme of the Netherlands

Number XVI-Reports in 2009

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Abstract

Adverse events following immunization under the National Vaccination Programme of the Netherlands

Number XVI- Reports in 2009

In 2009 the safety surveillance of the National Immunisation Programme of the Netherlands (RVP) received 1647 reports on adverse events following immunisation (AEFI). This is an increase of 28% compared with 2008, caused by more reports on local reactions and fever following the DTP-IPV booster dose at four years of age. In 81% (1322) of the classifiable events a possible causal relation with vaccination was established. These concerned major adverse reactions in 38% and minor adverse reactions in 62% of the reports. Of the reported adverse events 19% (318) were considered chance occurrences.

This is the main conclusion of the report on the safety of the RVP in 2009. Reported severe infections, reports on epilepsy and encephalitis had no causal relation with the vaccination. Furthermore, nine reports on death were not caused or hastened by the vaccination.

Each year 1.4 million vaccinations are administered through the RVP. Although the reported adverse reactions can be very frightening, they reveal without sequelae. The benefit of the programme outweighs the reported adverse events.

AEFI in the RVP have been monitored through an enhanced passive surveillance system by the National Institute for Public Health and the Environment (RIVM) since 1962. Signal detection of the system is good and the reporting rate is high, due to many reports, received mainly from Child Health Care professionals. There is only minor underreporting of rare, severe events. Name based reports enable follow up studies.

Key words:
adverse events following immunization, AEFI, vaccination programme, safety surveillance, childhood vaccines

Rapport in het kort

Postvaccinale gebeurtenissen binnen het Rijksvaccinatieprogramma
Deel XVI- Meldingen in 2009

In 2009 heeft de bijwerkingenbewaking van het Rijksvaccinatieprogramma (RVP) 1647 meldingen ontvangen, een toename van 28 procent ten opzicht van 2008. De oorzaak van de toename is een groter aantal meldingen van lokale reacties en koorts na de herhalingsvaccinatie die kinderen op vier jarige leeftijd krijgen. Van alle meldingen werd 81 procent beoordeeld als bijwerking van een vaccinatie. Hiervan ging het in 38 procent om heftige verschijnselen, vooral zeer hoge koorts, langdurig huilen, 'collapsreacties', verkleurde benen, koortsstuipen en atypische aanvallen met rillerigheid, schrikschokken en gespannenheid of juist een heel slappe houding. Bij het overige deel van de meldingen (19 procent) waren de verschijnselen geen gevolg van een vaccinatie maar van een toevallige samenloop van gebeurtenissen.

Dit blijkt uit de jaarlijkse rapportage van de bijwerkingenbewaking van het RVP in 2009. De ernstige infecties die zijn gerapporteerd hadden geen relatie met de vaccinaties, net als de meldingen van epilepsie en hersenontsteking. Bij de negen meldingen van overleden kinderen zijn de vaccinaties daar niet de oorzaak van geweest.

Elk jaar worden voor het RVP bijna 7 miljoen vaccincomponenten toegediend in de vorm van 1,4 miljoen prikken. Hoewel de bijwerkingen omstanders erg kunnen laten schrikken, zijn ze medisch gezien niet gevaarlijk. Ze zijn van voorbijgaande aard en leiden niet tot blijvende gevolgen. De grote gezondheidswinst die het RVP oplevert, weegt op tegen de bijwerkingen.

Het RVP bestaat sinds 1957 en wordt sinds 1962 intensief bewaakt. Dat gebeurt in de vorm van een zogeheten spontaan meldsysteem, aangevuld met andere vormen van onderzoek naar bijwerkingen. Dit meldsysteem is een goed instrument om signalen over mogelijke bijwerkingen op te pikken. Het systeem is bovendien zodanig ingericht dat gegevens te achterhalen zijn, wat vervolgonderzoek mogelijk maakt. In Nederland is de meldgraad van vermoede bijwerkingen hoog, onder andere doordat consultatiebureaus in hoge mate bereid zijn om bijwerkingen door te geven. Heftige en zeldzame reacties worden in bijna alle gevallen gemeld.

Trefwoorden:
Bijwerking, Rijksvaccinatieprogramma, veiligheidsbewaking, vaccinaties, RVP

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Preface

Thanks to N. Moorer, E. Pieper-van Delft, K. Vellheuer, S. de Jong, S. Schotman, S. David and I.F. Zonnenberg-Hoff, who also contributed to the contents of this report.

Contents

List of abbreviations

AE	Adverse Event
AEFI	Adverse Event Following Immunization
AR	Adverse Reaction
BCG	Bacille Calmette Guérin vaccine
BHS	Breath Holding Spell
CB	Child Health Clinic (consultatiebureau)
CBG	Medical Evaluation Board of the Netherlands
CBS	Statistics Netherlands
CIb	Centre for Infectious Disease Control (of RIVM)
DM	Diabetes Mellitus
DT-IPV	Diphtheria Tetanus Inactivated Polio (vaccine)
DTP-IPV	Diphtheria Tetanus Pertussis Inactivated Polio (vaccine)
DTP-IPV-Hib	Diphtheria Tetanus Pertussis Inactivated Polio *Haemophilus influenza* type B (vaccine)
DTP-IPV-Hib-HepB	Diphtheria Tetanus Pertussis Inactivated Polio *Haemophilus influenza* type B Hepatitis B (vaccine)
EPI	Expanded Programme on Immunization
EMEA	European Medicines Agency
GGD	Municipal Public Health Department
GP	General Practitioner
GR	Health Council
HepB	Hepatitis B (vaccine)
HBIg	Hepatitis B Immunoglobulin
HBsAg	Hepatitis B surface antigen
HHE	Hypotonic Hyporesponsive Episode (collapse)
IGZ	Inspectorate of Health Care
ICH	International Conference on Harmonisation
ITP	Idiopathic Thrombocytopenic Purpura
JGZ	Child Health Care
LAREB	Netherlands Pharmacovigilance Foundation
MAE	Medical Consultant of PEA
MCADD	Medium Chain ACYL-CoA Dehydrogenase Deficiency
MenC	Meningococcal C infection (vaccine)
MMR	Measles Mumps Rubella (vaccine)
NSCK	Netherlands Paediatrics Surveillance Unit
NVI	Netherlands Vaccine Institute
PCV7	7-valent conjugated pneumococcal (vaccine)
PMS	Post Marketing Surveillance
RCP	Regional Coordination Programmes
RIVM	National Institute for Public Health and the Environment
RVP	National Immunization Programme
SAE	Serious Adverse Event
SIDS	Sudden Infant Death Syndrome
SMEI	Severe myoclonic epilepsy in infancy
TBC	Tuberculosis
WHO	World Health Organisation

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Summary

Adverse Events Following Immunization (AEFI) under the National Immunization Programme (RVP) of the Netherlands has been monitored by the National Institute for Public Health and the Environment (RIVM) since 1962. From 1984 until 2003 evaluation has been done in close collaboration with the Health Council (GR). An RIVM expert panel continued the reassessment of selected adverse events from 2004 onwards. The telephone service for reporting and consultation is an important tool for this enhanced passive surveillance system. The RIVM reports fully, on all incoming reports in a calendar year, irrespective of causal relation, since 1994. This report on 2009 is the sixteenth annual report.
The majority of reports (87%) came in by telephone. Child Health Care professionals are the main reporters (82%). Parents, GPs and/or hospital provided additional data on request (79%). The RIVM made a (working) diagnosis and assessed causality after supplementation and verification of data.
In 2009, on a total of over 1.4 million vaccination dates, 1647 AEFI were submitted, concerning 1522 children. Of these only six were not classifiable because of missing information. Of the classifiable events 1322 (81%) were judged to be possibly, probably or definitely causally related with the vaccination (adverse reactions) and 318 (19%) were considered coincidental events.
So-called “minor” local, skin or systemic events were assessed in 1005 cases with 817 reports (82%) classified as possible adverse reactions. The so-called “major” adverse events, grouped under fits, faints, discoloured legs, persistent, screaming, major-illness, encephalopathy and death (with inclusion of severe local reactions) occurred in 642 cases. In 79% (505) these were considered possible adverse reactions. Discoloured legs were reported 76 times with possible causal relation in all but four. Collapse occurred 89 times, in only 16 cases without causal relation. 18 Breath holding spells were reported, all but two with inferred causality and 43 times fainting in older children. Convulsions were diagnosed in 45 cases, in all but six with fever. Of the convulsions 31 were considered causally related. Atypical attacks (32) had possible causal relation in 18 cases. Epilepsy (6) was considered chance occurrence in all instances. Of persistent screaming 39 out of 42 reports were considered adverse reactions. Fever of ≥ 40.5 °C was the working diagnosis in 53 reports of the major-illness category, in all but 11 with inferred causality. Of the other 68 major-illness cases 13 had a possible causal relation. There were seven abscesses. One case of encephalopathy/-itis was reported in 2009, not induced by the vaccination but considered coincidental.
In 2009 all nine reported deaths were considered chance occurrences after thorough assessment. Six children were examined post mortem. Five children had SIDS, one child died due to post anoxic encephalopathy following near SIDS, one child had sepsis and necrotising pneumonia, one child may have had a misbalance in neurotransmitter in relation to a inborn error of metabolism and in one child the cause of death is unknown.
Most frequently (757) reports involved simultaneous vaccination against diphtheria, pertussis, tetanus, polio, *Haemophilus influenzae* type b infections (DTP-IPV-Hib) and seven valent conjugated pneumococcal vaccine (PCV7). DTP-IPV-Hib is sometimes combined with Hepatitis B vaccine. Measles, mumps and rubella (MMR) was involved 280 times, 258 times with simultaneous other vaccines, most often DT-IPV or conjugated meningococcal C vaccine (MenC).
In 2009 the number of reports increased compared to 2008, explained by an increase of reported local reactions and fever following DTP-IPV at four years of age.
The total of 1647 reports should be weighted against the large number of vaccines administered, with over 1.4 million vaccination dates and nearly 7 million vaccine components. The risk balance greatly favours the continuation of the vaccination programme.

1. Introduction

Identification, registration and assessment of adverse events following drug-use are important aspects of post marketing surveillance (PMS). Safety surveillance is even more important in the programmatic use of preventive interventions, especially when children are involved. In the Netherlands the National Institute for Public Health and the Environment (RIVM) has the task to monitor adverse event following immunization (AEFI) under the National Immunization Programme (RVP). This programme started in 1957 with adoption of a passive safety surveillance system in 1962.
Since 1994 the RIVM reports annually on adverse events, based on the year of notification. The present report contains a description of the procedures for soliciting notifications, verification of symptoms, diagnosis according to case definitions, and causality assessment for 2009. It also includes a description of the major characteristics of the National Vaccination Programme and the embedding in the Child Health Care System (JGZ).
In the present report we will go into the number of reports and the different aspects of the nature of the reported adverse events in 2009 and compare them with previous years. In 2009 the programme was similar to 2008, although some vaccines were supplied by different manufacturers. Reports have been carefully monitored for unexpected, unknown, new severe or particular adverse events and to changes in trend and severity. The headlines of this fourteenth RIVM report on adverse events are also issued in Dutch. The summary and aggregated tables will be posted on the RVP website, www.rvp.nl.

2 The National Immunization Programme of the Netherlands

2.1 Vaccines, schedule and registration

In the Netherlands mass vaccination of children was undertaken since 1952, with institution of the RVP in 1957. For the current schedule see Box 1. From the start all vaccinations were free of charge and have never been mandatory.

Box 1. Schedule of the National Vaccination Programme of the Netherlands in 2009

At birth	HepB0[a]		
2 months	DTP-IPV-Hib1(+HepB1)	+	PCV7 1
3 months	DTP-IPV-Hib2(+HepB2)	+	PCV7 2
4 months	DTP-IPV-Hib3(+HepB3)	+	PCV7 3
11 months	DTP-IPV-Hib4(+HepB4)	+	PCV7 4
14 months	MMR1	+	MenC
4 years[c]	DTP-IPV5		
9 years	DT-IPV6	+	MMR2

[a] = for children born from HepB carrier mothers

HepB-vaccination is only offered to children with a parent born in a country with moderate and high prevalence of hepatitis B carriage and to children of HBsAg positive mothers.[1] For this last group an additional neonatal HepB vaccination was introduced. At 2, 3, 4 and 11 months of age these children receive DTP-IPV-Hib-HepB. Children of refugees and those awaiting political asylum have an accelerated schedule for MMR and catch up doses up till the age of 19 years.[2] For the RVP the age limit is 13 years.
Vaccines for the RVP are supplied by the Netherlands Vaccine Institute (NVI) and are kept in depot at a regional level of the Regional Coordination of Programmes (RCP).[2,3] The PEA is responsible for further distribution to the providers and also has the task to implement and monitor cold chain procedures. The District Consultant of the RCP promotes and guards programme adherence.
The national vaccination register contains name, sex, address and birth date of all children up till 13 years of age. The database is linked with the municipal population register and is updated regularly or on line, for birth, death and migration. All administered vaccinations are entered in the database on individual level.
Summarised product characteristics of all used vaccines in 2009 are listed in the Appendix and full documents at www.cbg-meb.nl.

2.2 Child Health Care system

The Child Health Care system (JGZ) aims to enrol all children living in the Netherlands. Child Health Care in the Netherlands is programmatic, following national guidelines with emphasis on age-specific items and uniform registration on the patient charts, up till the age of 18 years.[4]
Up till four years of age (pre school) children attend the Child Health Clinic (CB) regularly. At school entry the Municipal Health Service (GGD) takes over. The RVP is fully embedded in the Child Health Care system and vaccinations are given during the routine visits. Good professional standards include asking explicitly after adverse events following vaccination at the next visit and before administration of the next dose. The four-year booster DTP-IPV is usually given at the last CB visit, before school entrance. Booster vaccination with DT-IPV and MMR at nine years of age is organised in mass vaccination settings.
Attendance of Child Health Clinics is very high, up to 99% and vaccination coverage for the primary series DTP-IPV-Hib is over 97% and slightly lower for MMR.[5] (Accurate numbers on birth cohort 2007-2009 have not been released as yet).

2.3 Safety surveillance

The safety surveillance of the RVP is an acknowledged task of the National Institute for Public Health and the Environment (RIVM) and is performed by Centre for Infectious Disease Control[6], independently from vaccine manufacturers.
Requirements for Post Marketing Surveillance of adverse events have been stipulated in Dutch and European guidelines and legislation.[7,8] The World Health Organisation (WHO) advises on monitoring of adverse events following immunizations (AEFI) against the target diseases of the Expanded Programme on Immunization (EPI) and on implementation of safety surveillance in the monitoring of immunization programmes.[9] The WHO keeps a register of adverse reactions as part of the global drug-monitoring programme.[10] Currently there are several international projects to achieve increased quality of safety surveillance and to establish a register specifically for vaccines and vaccination programmes.[11,12]
Close evaluation of the safety of vaccines is of special importance for maintaining public confidence in the vaccination programme as well as maintaining motivation and confidence of the health care providers. With the successful prevention of the target diseases, the perceived side effects of vaccines gain in importance.[13,14] Not only true side effects but also events with only temporal association with vaccination may jeopardise uptake of the vaccination programme.[15] This has been exemplified in Sweden, in the United Kingdom and in Japan in the seventies and eighties of the last century. Commotion about assumed neurological side effects caused a steep decline in vaccination coverage of pertussis vaccine and resulted in a subsequent rise of pertussis incidence with dozens of deaths and hundreds of children with severe and lasting sequela of pertussis infection.[16] But also recently concerns about safety rather than actual causal associations caused cessation of the hepatitis B programme in France.[17] Even at this moment the uptake of MMR in the United Kingdom and the Republic of Ireland is very much under pressure because of unfounded allegations about association of the vaccine with autism and inflammatory bowel disease.[13,18,19,20,21] Subsequent (local) measles epidemics have occurred.[22,23]
In the Netherlands the basis for the safety surveillance is an enhanced passive reporting system. Professionals ask for consultation and advice on vaccination matters like schedules, contra-indications, precautions and adverse events. Reporting can be done by telephone, regular mail, fax or e-mail. See

for detailed description on procedures chapter 3. The annually distributed vaccination programme (Appendix) encourages health care providers to report adverse events to the RIVM.

RIVM promotes reporting through information, education and publications. Feedback to the reporter of AE and other involved professionals has been an important tool in keeping the reporting rate at high levels.

Aggregated analysis of all reported adverse events is published annually by RIVM. Signals may lead to specific follow up and systematic study of selected adverse events.[24,25,26,27,28,29] These reports support a better understanding of pathogenesis and risk factors of specific adverse reactions. In turn, this may lead to changes in the vaccine or vaccination procedures or schedules and adjustment of precautions and contra-indications and improved management of adverse events. The annual reports may also serve for the purpose of public accountability for the safety of the programme.[30]

3 Materials and methods

3.1 Post vaccination events

Events following immunizations do not necessarily have causal relation with vaccination. Some have temporal association only and are in fact merely coincidental.[13,14] Therefore the neutral term adverse event is used to describe potential side effects. In this report the word "notification" designates all adverse events reported to us. We accept and record all notified events; generally only events within 28 days of vaccination are regarded as potential side effects for killed or inactivated vaccines and for live vaccines this risk window is six weeks. For some disease entities a longer risk period seems reasonable.
Following are some definitions used in this report:
Vaccine: immuno-biologic product meant for active immunization against one or more diseases.
Vaccination: all activities necessary for vaccine administration.
Post vaccination event or Adverse Events Following Immunization (AEFI): neutral term for unwanted, undesirable, unfavourable or adverse symptoms within certain time limits after vaccination irrespective of causal relation.
Side effects or adverse reaction (AR): adverse event with presumed, supposed or assessed causal relation with vaccination.
Adverse events are thus divided in coincidental events and genuine side effects. Side effects are further subdivided in vaccine or vaccination intrinsic reactions, vaccine or vaccination potentiated events, and side effects through programmatic errors (see Box 2).[2,31,32]

Box 2. Origin / subdivision of adverse events by mechanism

a- Vaccine or vaccination intrinsic reactions	are caused by vaccine constituents or by vaccination procedures;Examples are fever, local inflammation and crying.
b- Vaccine or vaccination potentiated events	are brought about in children with a special predisposition or risk factor. For instance, febrile convulsions.
c- Programmatic errors	are due to faulty procedures; for example the use of non-sterile materials. Loss of effectiveness due to faulty procedures may also be seen as adverse event.
d- Chance occurrences or coincidental events	have temporal relationship with the vaccination but no causal relation. These events are of course most variable and tend to be age-specific common events.

3.2 Reporting criteria

Any severe event, irrespective of assumed causality and medical intervention, is to be reported. Furthermore peculiar, uncommon or unexpected events and events that give rise to apprehension in parents and providers or lead to adverse publicity are also reportable. Events resulting in deferral or cessation of further vaccinations are considered as serious and therefore should be reported as well (see Box 3). Vaccine failures may result from programmatic errors and professionals are therefore invited to report these also.

Box 3. Reporting criteria for AEFI under the National Immunization Programme

- serious events
- uncommon events
- symptoms affecting subsequent vaccinations
- symptoms leading to public anxiety or concern

3.3 Notifications

All incoming information on AEFI under the RVP, whether intended reports or requests for consultation about cases, are regarded as notifications. In this sense also events that come from medical journals or lay press may be taken in if the reporting criteria apply (Box 3). The same applies for events from active studies. All notifications are recorded on individual level.
Notifications are subdivided in *single, multiple* and *compound* reports (Box 4). Most notifications concern events following just one vaccination date. These are filed as *single* reports.
If the notification concerns more than one distinct event with severe or peculiar symptoms, classification occurs for each event separately. These reports are termed *compound*. If the notification is about severe or peculiar symptoms following different dates of vaccinations then the report is *multiple* and each date is booked separately in the relevant categories. If however the reported events consist of only minor local or systemic symptoms, the report is classified as single under the most appropriate vaccination date. If notifications on different vaccinations of the same child are reported at different moments, the events are treated as distinct reports irrespective of nature and severity of symptoms. This is also a multiple report. Notifications concern just one person with very few exceptions. In case of *cluster* notifications special procedures are followed because of the potential of signal/hazard detection. If assessed as non-important, minor symptoms or unrelated minor events, cluster notifications are booked as one single report. In case of severe events the original cluster notification will, after follow-up, be booked as separate reports and are thus booked as several single, multiple or compound reports.

Box 4. Subdivision of notifications of adverse events following vaccinations

single reports	concern one vaccination date have only minor symptoms and/or one distinct severe event
compound reports	concern one vaccination date have more than one distinct severe event
multiple reports	concern more than one vaccination date have one or more distinct severe event following each date or are notified separately for each date
cluster reports single, multiple or compound	group of notifications on one vaccination date and/or one set of vaccines or badges or one age group or one provider or area

3.4 Reporters and information sources

The first person to notify the RIVM about an adverse event is considered to be the reporter. All others contacted are “informers”.

3.5 Additional information

In the first notifying telephone call with the reporter we try to obtain all necessary data on vaccines, symptoms, circumstances and medical history. Thereafter physicians review the incoming notifications. The data are verified and the need for additional information is determined. As is often the case, apprehension, conflicting or missing data, makes it necessary to take a full history from the parents with a detailed description of the adverse event and circumstances.
Furthermore the involved general practitioner (GP) or hospital is contacted to verify or complete symptoms in case of severe and complex events.

3.6 Working diagnosis and event categories

After verification and completion of data a diagnosis is made. If symptoms do not fulfil the criteria for a specific diagnosis, a working diagnosis is made based on the most important symptoms. Also the severity of the event, the duration of the symptoms and the time interval with the vaccination are determined as precisely as possible. Case definitions are used for the most common adverse events and for other diagnoses current medical standards are used.
For the annual report the (working) diagnoses are classified under one of ten different categories clarified below. Some categories are subdivided in minor and major according to the severity of symptoms. Major is not the same as medically serious or severe, but this group does contain the severe events. Definitions for Serious Adverse Events (SAE) by EMEA and ICH differ from the criteria for major in this report.

Local (inflammatory) symptoms

Events are booked here if accompanying systemic symptoms do not prevail. Events are booked as minor in case of (atypical) symptoms, limited in size and/or duration. Major events are extensive and/or prolonged and include abscess or erysipelas.

General illness

This category includes all events that cannot be categorised elsewhere. Fever associated with convulsions or as part of another specific event is not listed here separately. Crying as part of discoloured legs syndrome is not booked here separately. Symptoms like crying < 3 hours, fever < 40.5 °C, irritability, pallor, feeding and sleeping problems, mild infections, etceteras are booked as minor events. Major events include fever ≥ 40.5 ºC, autism, diabetes, ITP, severe infections, et cetera.

Persistent screaming

This major event is defined as (sudden) screaming, non-consolable and lasting for three hours or more. Persistent screaming as part of discoloured legs syndrome is not booked here separately.

General skin symptoms

Symptoms booked here are not part of general (rash) illness and not restricted to the reaction site. The subdivision in minor and major is made according to severity

Discoloured legs
Events in this category are classified as major and defined as even or patchy discoloration of the leg(s) and/or leg petechiae, with or without swelling. Extensive local reactions are not included
Faints
Symptoms listed here are not explicable as post-ictal state or part of another disease entity. Three different diagnoses are included, all considered major.
* Collapse: sudden pallor, loss of muscle tone and consciousness.
* Breath holding spell: fierce crying, followed by breath holding and accompanied with no or just a short period of pallor/cyanosis.
* Fainting: sudden onset of pallor, sometimes with limpness and accompanied by vasomotor symptoms, occurring in older children.
Fits
Three different diagnoses are included in this category, all considered major.
* Convulsions: are discriminated in non-febrile and febrile convulsions and include all episodes with tonic and/or clonic muscle spasms and loss of consciousness. Simple febrile seizures last ≤ 15 minutes. Complex febrile seizures last > 15 minutes recur within 24 hours or have asymmetrical spasms.
* Epilepsy: definite epileptic fits or epilepsy.
* Atypical attack: paroxysmal occurrence, not fully meeting criteria for collapse or convulsion.
Encephalitis /encephalopathy
Events booked here are considered major. A child < 24 months with encephalopathy has loss of consciousness for ≥ 24 hours. Children > 24 months have at least two out of three criteria: change in mental state, decrease in consciousness, seizures. In case of encephalitis symptoms are accompanied by inflammatory signs. Symptoms are not explained as post-ictal state or intoxication.
Anaphylactic shock
These major events must be in close temporal relation with intake of an allergen, type I allergic mechanism is involved. In case of anaphylactic shock there is circulatory insufficiency with hypotension and life threatening hypoperfusion of vital organs with or without laryngeal oedema or bronchospasm.
Death:
This category contains any death following immunization. Preceding diseases or underlying disorders are not booked separately. All events are considered major (Box 5).

Box 5. Main event categories with subdivision according to severity

local reaction	minor	mild or moderate injection site inflammation or other local symptoms
	major	severe or prolonged local symptoms or abscess
general illness	minor	mild or moderate general illness not included in the other specific categories
	major	severe general illness, not included in the listed specific categories
persistent screaming	major	inconsolable crying for 3 or more hours on end
general skin symptoms	minor	skin symptoms not attributable to systemic disease or local reaction
	major	severe skin symptoms or skin disease
discoloured legs	major	disease entity with diffuse or patchy discoloration of legs not restricted to injection site and/or leg petechiae
faints	major	collapse with pallor or cyanosis, limpness and loss of consciousness; included are also fainting and breath holding spells.
fits	major	seizures with or without fever, epilepsy or atypical attacks that could have been seizures
encephalitis/encephalopathy	major	stupor, coma or abnormal mental status for more than 24 hours not attributable to drugs, intoxication or post-ictal state, with or without markers for cerebral inflammation (age dependent)
anaphylactic shock	major	life threatening circulatory insufficiency in close connection with intake of allergen, with or without laryngeal oedema or bronchospasm.
death	major	any death following vaccination irrespective of cause

3.7 Causality assessment

Once it is clear what exactly happened and when, and predisposing factors and underlying disease and circumstances have been established, causality will be assessed. This requires adequate knowledge of epidemiology, child health, immunology, vaccinology, aetiology and differential diagnoses in paediatrics.

Box 6. Points of consideration in appraisals of causality of AEFI

- diagnosis with severity and duration
- time interval
- biologic plausibility
- specificity of symptoms
- indications of other causes
- proof of vaccine causation
- underlying illness or concomitant health problems

The nature of the vaccine and its constituents determine which side effects it may have and after how much time they occur. For different (nature of) side effects different time limits/risk windows may be applied. Causal relation will then be appraised on the basis of a checklist, resulting in an indication of

the probability/likelihood that the vaccine is indeed the cause of the event. This list is not (to be) used as an algorithm although there are rules and limits for each point of consideration (Box 6). Causality is classified under one of five different categories. See for details of criteria Box 7.

Box 7. Criteria for causality categorisation of AEFI

1-Certain	involvement of vaccine vaccination is conclusive through laboratory proof or mono-specificity of the symptoms and a proper time interval
2-Probable	involvement of the vaccine is acceptable with high biologic plausibility and fitting interval without indication of other causes
3-Possible	involvement of the vaccine is conceivable, because of the interval and the biologic plausibility but other cause are as well plausible/possible
4-Improbable	other causes are established or plausible with the given interval and diagnosis
5-Unclassifiable	the data are insufficient for diagnosis and/or causality assessment

If a certain, probable or possible causal relation is established, the event is classified as adverse reaction or side effect. If causal relation is considered (highly) *improbable*, the event is considered coincidental or chance occurence. This category also includes events without any causal relation with the vaccination.
By design of the RVP most vaccinations contain multiple antigens and single mono-vaccines are rarely administered. Therefore, even in case of assumed causality, attribution of the adverse events to a specific vaccine component or antigen may be difficult if not impossible.
Sometimes, with simultaneous administration of a dead and a live vaccine, attribution may be possible because of the different time intervals involved.

3.8 Recording, filing and feedback

Symptoms, (working) diagnosis, event category and assessed causal relation are recorded in the notification file together with all other information about the child, as medical history or discharge letters. All notifications are, after completion of assessment and feedback, coded on a structured form. If there is new follow-up information or scientific knowledge changes, the case is reassessed and depending on the information, the original categorisation may be adapted.
Mostly information on the probability of a causal relation is communicated during the first contact with the reporter. Severe and otherwise important adverse events as peculiarity or public unrest may be put down in a formal written assessment and sent as feedback to the notifying physician and other involved medical professionals. This assures that everyone involved gets the same information and makes the assessment (procedure) transparent. This document is filed together with the other information on the case.

3.9 Annual reports and aggregated analysis

The coded forms are used as data sheets for the annual reports. Coding is performed according to strict criteria for case definitions and causality assessment. Grouped events were checked for maximum consistency. Yearly we report on all incoming notifications.

3.10 Expert panel

An expert panel re-evaluates the formal written assessments by the RIVM. The group consists of specialists on paediatrics, neurology, immunology, pharmacovigilance, microbiology and epidemiology and is set up by RIVM to promote broad scientific discussion on reported adverse events.

3.11 Quality assurance

Assessment of adverse events is directed by standard operating procedure.
On regular basis internal inspections are done. Severe, complex, controversial and otherwise interesting events are discussed regularly in clinical conferences of the physicians of the RIVM.

3.12 Medical control agency and pharmacovigilance

The RIVM and the Netherlands Pharmacovigilance Centre (LAREB) exchange all reported adverse events on the RVP, thus allowing the Medical Evaluation Board of the Netherlands (CBG) to fulfil its obligations towards WHO and EMEA.

4 Results

4.1 Number of reports

In 2009 RIVM received 1647 notifications of adverse events (Table 1). This is a statistically significant increase compared with 2008. Since 2005 the number of reports has decreased following the introduction of DTaP-IPV-Hib.[27] In 2006 we gradually switched to an infant vaccine formulation with five instead of three pertussis components and we added the seven valent pneumococcal conjugate vaccine (PCV7) to the programme for children born from April onwards.[28] In the year under report the RVP schedule did not change. Besides the normal RVP, in 2009 a Human Papiloma Virus (HPV) vaccination catch-up campaign was organised for all 13 to 16 year old girls. Furthermore, vaccination against Influenza A(H1N1) took place but was not included in the RVP. For the period 1994 up to 2004 inclusive, with use of DTwcP-IPV, there was a gradual increase in number of reported adverse events due to reduced underreporting, introduction of new vaccines, changes of the schedule and increased media attention. Information on birth cohort size is retrieved from www.statline.nl. Vaccination coverage was always above 94% since 1994.[5]

Table 1. Number of reported AEFI per year (statistically significant changes in red)

year of notification	total	birth cohort
1994	**712**	195,611
1995	800	190,513
1996	732	189,521
1997	822	192,443
1998	**1100**	199,408
1999	1197	200,445
2000	1142	206,619
2001	**1331**	202,603
2002	1332	202,083
2003	1374	200,297
2004	**2141**	194,007
2005	**1036**	187,910
2006	**1159**	185,057
2007	**995**	181,336
2008	**1290**	184,634
2009	**1647**	184,824

The 1647 notifications of 2009 concerned 1524 children. 75 Notifications were multiple, resulting in 151 reports. 43 Notifications were compound. Two notifications were compound and multiple, resulting in six reports (Table 2). Multiple and compound reports are listed under the respective event categories. See section 3.3 for definitions.

Table 2. Number and type of reports of notified AEFI in 2004-2009

notifications	children 2009	reports 2009	reports 2008	reports 2007	reports 2006	reports 2005	reports 2004
single	1404[a]	1404	1161	837	967	890	1756
multiple	75[b]	151	60	107	116	99	280
compound	43	86	50	44	66	44	80
compound and multiple	2	6	19	7	10	3	25
Total 2009	1524	1647	1290	995	1159	1036	2141

[a] 17 children had also reports in previous (7) or following (10) years; these are not included
[b] 3 children with triple reports
[c] all children had double reports

The reports per month showed variation, similar to previous years. In general, the number of montly reports is higher compared with previous five years, with exception of 2004 (Figure 1).

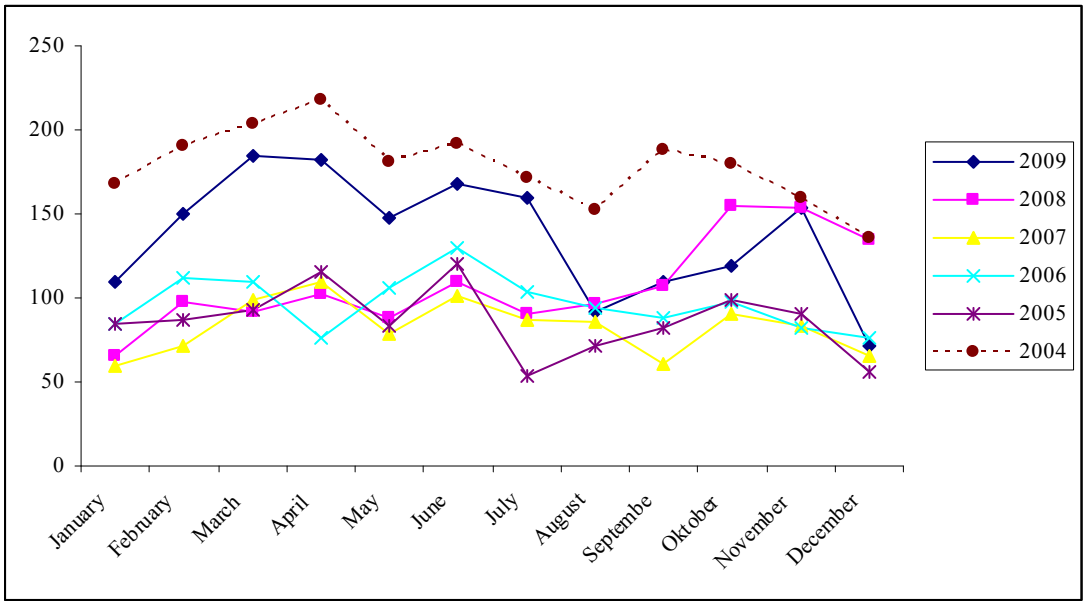

Figure 1. Absolute numbers of reports per month in 2004-2009; reports during use of whole cell DTP-IPV-Hib are dashed lines

4.2 Reporters, source and route of information

Child Health Care professionals accounted for 1350 reports (82%). In 2004-2008 this varied between 77% and 85%. In 206 reports (12.5%), parents were the reporters (range 9.7%-12.6% in 2004-2008). The share of other report sources also was more or less stable (detailed information in Figure 2 and Table 3).

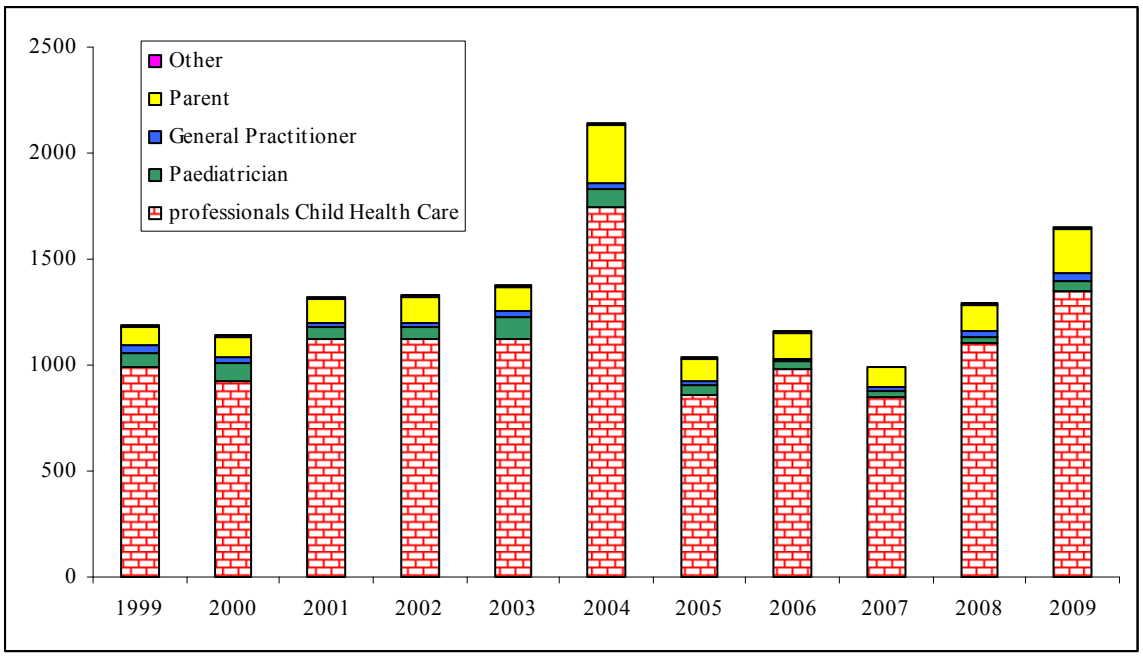

Figure 2. Reporters of adverse events following vaccinations under the RVP 1999-2009

As in previous years the vast majority of reports (1430; 86.8%) reached us by telephone. We received 217 (13.2%; range 7.8%-12.9% for 2004-2008) written reports, including 67 electronic/digital reports, 88 reports by e-mail and six reports by fax.

Table 3. Source of AEFI in 2004-2009

		2009	2008	2007	2006	2005	2004
Child Health Care	Child health clinic	1271	1010	777	894	775	1685
	Municipal health service	51	81	50	80	76	44
	District Consultant	28	9	18	8	12	21
Paediatrician		46	35	33	35	48	84
General Practitioner		35	23	15	11	13	24
Parent		206	125	98	121	102	271
Other		10	7	4	10	10	12
Unknown		-	-	-	-	-	-
total		1647	1290	995	1159	1036	2141
(% written)		(13.2)	(8.1)	(7.8)	(9.6)	(11.3)	(12.9)

In 2009 the reporter was the sole informer in 21% (348 reports). 41% (144) of these reports concerned local reactions. Additional information was received in 79%, both spontaneously and requested (range 87-94% for 2004-2008). The increase in reports with only one information source is statistically significant in reports on local reactions and minor general illness (Figure 3).

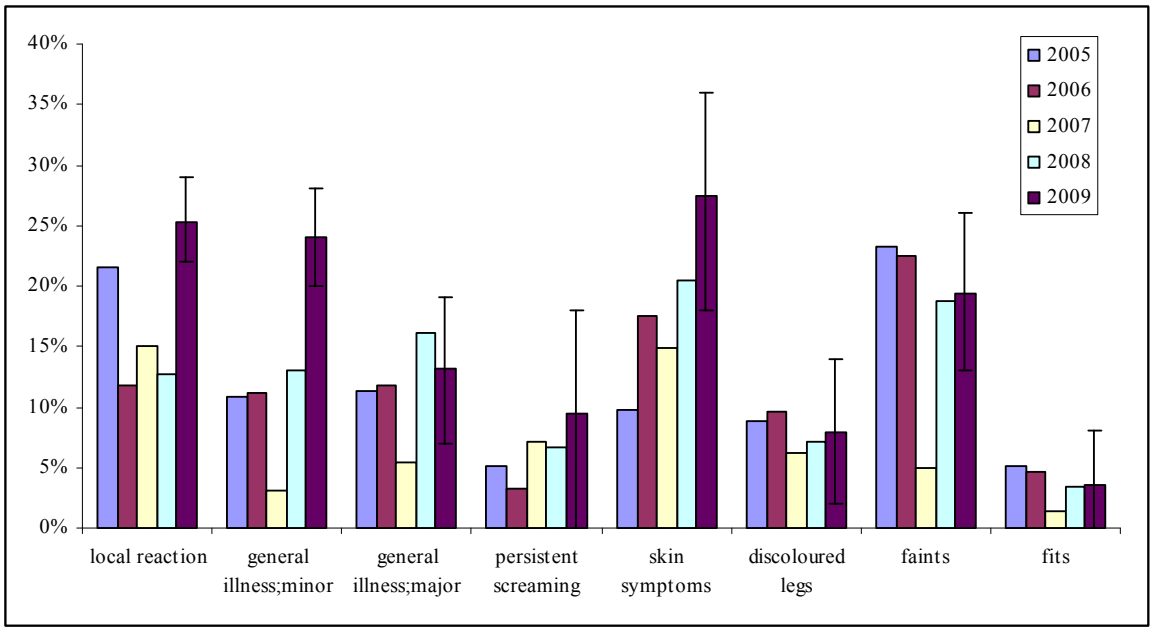

Figure 3. percentage of reports with one information source per category for 2005-2009

Professionals of Child Health Care supplied information in 84%, compared to 88-95% in the five previous years. Parents were contacted in 87%, (range 89%-97% for 2004-2008). Reports in which the parents were the sole informers (151) are included. Hospital specialists supplied information in 13% of the reports (range 13%-18% for 2004-2008). See for details Table 4.

Table 4. Information source and type of events in reported AEFI in 2009

																					Total	(%)
info ⇒	clinic*	+	+	+	+	+	+	+	+	+	-	-	-	-	-	-	-	-	-	1383	(84)
	parent	-	+	+	+	+	+	-	-	-	+	+	+	+	+	+	-	-	-	1432	(87)
	gen.pract.	-	-	-	+	+	-	-	+	+	+	-	-	-	-	+	+	-	-	46	(3)
	hospital	-	-	+	-	+	+	+	-	+	-	+	+	-	-	+	-	+	-	217	(13)
event ⇓	other	-	-	-	-	-	+	-	-	-	-	+	-	+	-	-	-	-	+	37	(2)
local reaction		90	399	5	7	-	-	1	-	-	3	-	9	3	48	-	4	-	2	571	
general illness	minor	50	310	31	3	-	-	5	-	1	7	1	13	7	62	-	3	1	4	498	
	major	2	57	27	1	-	1	3	-	-	1	2	10	2	11	1	2	1	-	121	
persistent screaming		1	35	2	-	-	-	-	-	-	-	-	-	1	3	-	-	-	-	42	
skin symptoms		12	56	6	1	1	-	-	1	-	-	-	3	1	12	-	1	-	1	95	
discoloured legs		2	63	4	-	1	-	-	-	-	-	-	1	1	4	-	-	-	-	76	
faints		18	90	17	-	1	-	1	-	-	1	1	9	2	9	-	1	1	-	150	
fits		-	35	24	2	1	2	3	-	-	-	-	8	3	2	1	-	1	-	83	
anaphylactic shock		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	0	
encephalopathy/-itis		-	-	1	-	-	-	1	-	-	-	-	-	-	-	-	-	-	-	2	
death		-	-	3	-	1	3	2	-	-	-	-	-	-	-	-	-	-	-	9	
total 2009		175	1045	120	14	5	6	16	1	1	12	4	53	20	151	2	11	4	7	1647	

* = professionals of child health clinic or municipal health service

4.3 Sex distribution

In the current year 53% of the reported cases were male, in line with the national sex distribution. For the years 2004-2008 this ranged between 51-54% (Table 5). Of five children the sex is not known.

Table 5. Events and sex of reported AEFI in 2004-2009 (total number of children and percentage males)

event ⇓	sex⇒	m%	2009 total	m%	2008 total	m%	2007 total	m%	2006 total	m%	2005 total	m%	2004 total
local reaction		54	571	54	313	54	93	51	102	46	93	48	129
general illness	minor	52	498	52	414	56	390	52	403	55	389	56	704
	major	63	121	49	87	62	73	47	111	52	97	53	194
persistent screaming		60	42	53	60	55	42	54	61	47	58	50	133
skin symptoms		53	95	57	88	55	101	54	97	49	82	53	106
discoloured legs		42	76	43	70	51	81	50	124	51	57	53	279
faints		51	150	53	165	53	141	50	169	51	75	54	318
fits		39	83	47	88	48	69	47	85	53	71	56	98
anaphylactic shock		-	-	100	1	-	-	-	-	-	-	-	-
encephalopathy/-itis		50	2	0	1	0	1	100	1	100	1	0	3
death		44	9	0	3	75	4	83	6	38	8	25	4
total		53	1647	52	1290	54	995	51	1159	52	1036	54	2141

4.4 Vaccines and schedule to the programme

In the current year 96% of the notifications concerned recent vaccinations. Some of the 61 late reports arose from concerns about planned boosters or vaccination of younger siblings. AEFI described here, do not exclusively concern the RVP schedule of the year under report (Table 6). Children may receive different vaccines because of immigration or medical reasons. Some children, born in a calendar year, are not eligible to follow the specified programme, because introduction of new vaccines or changes in the programme not always start at January first. Furthermore 4% of the reports concern vaccinations, administered more than one year before reporting.
In Table 6 scheduled and actually administered vaccines are listed. For the second year in a row, reports following DTP-IPV at four years of age are the most prevalent. Distribution of reports following other doses, were more or less stable.

Table 6. Schedule and vaccines of reported AEFI in 2009

vaccine given⇒ / scheduled ⇓	dtp-ipv-hib	dtp-ipv-hib+hepb	pneu	dtp-ipv-hib+pneu	dtp-ipv-hib+hepb+pneu	mmr	mmr men c	dt-ipv	dtp-ipv	dt-ipv mmr	other	total 2009	2008	2007	2006	2005	2004
at birth	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	2
dose 1[j]	8	-	1[a]	244	33	-	-	-	1[g]	-	-	287	278	296	285	205	725
dose 2[j]	-	1	1	150	34	-	-	-	-	-	-	186	190	145	195	153	379
dose 3[j]	5	-	4[a]	101	18	-	-	-	-	-	-	128	97	118	99	111	289
dose 4[j]	7	-	3[b]	119[c]	17	-	-	1	1[g]	-	-	148	118	112	154	119	340
dose?[j]	-	-	-	-	-	-	-	-	-	-	-	-	-	1	1	3	3
mmr0	-	-	-	-	-	8	-	-	-	-	-	8	5	4	7	10	1
mmr1+menC	-	-	1[d]	-	-	15	168[e]	-	-	-	-	184	193	174	226	246	225
dtp-ipv5	8	-	-	-	-	-	4[f]	1[d]	582[h]	-	9	604	312	80	98	114	90
dtp6+mmr2	-	-	-	-	-	2	1[f]	4	-	88[d]	-	95	94	62	88	62	62
menc	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	5	19
other	-	-	-	-	-	-	-	1	-	-	6	7	3	3	6	8	6
total 2009	28	1	10	614	102	25	173	7	584	88	15[i]	1647	1290	995	1159	1036	2141

[a] = once with DTP-IPV
[b] = once with HepB, once with Hib and HepB
[c] = twice with MMR
[d] = once with Hib
[e] = once with DTP-IPV-Hib-HepB, three times only MenC
[f] = MenC only
[g] = once with PCV7
[h] = once with HepB
[i] = four times Influenza, three times HepA+B, twice HepA, twice BCG, once typhoid fever, once HepA+B and typhoid fever, once BCG, yellow fever and typhoid fever
[j] = DTP-IPV-Hib(HepB) + PCV7

The relative frequencies of involved vaccinations changed a little since 2005. After the introduction of DTP-IPV-Hib with acellular pertussis components, the number of reported adverse events after DTP-IPV-Hib doses fluctuates at a lower level compared to the period of whole cell pertussis. In the year under report the continuing increase in reports following DTP-IPV at four years of age influenced the relative frequencies of the other doses considerably. See for information on reporting rates per dose section 4.5. Further details in Table 6 and Figure 4.

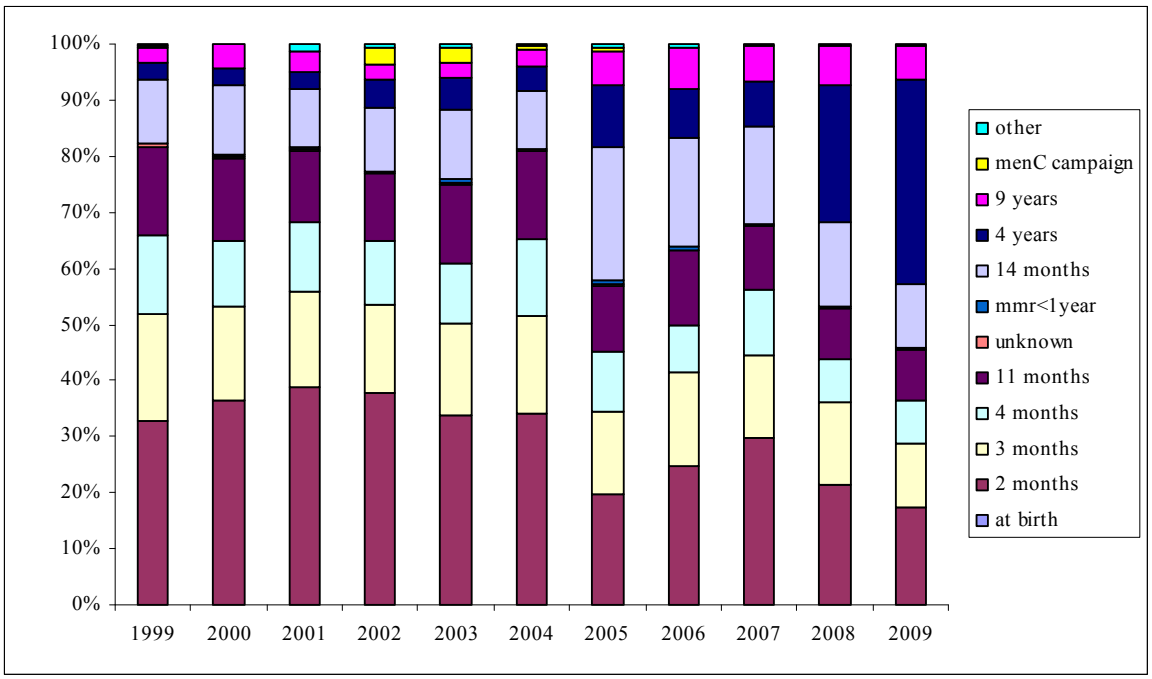

Figure 4. Relative frequencies of vaccine doses in reported AEFI in 1999-2009

Reporting rates

Reports were not evenly spread over region and dose. Standardisation of these rates per 1000 vaccinated infants is done according to coverage data from the RCP. Rates were calculated with vaccination coverage data from Praeventis, the centralised web based vaccination register. Since the regular summarised reports of coverage data do not contain information on timing of the vaccination there will remain inevitably some inaccuracy in estimated rates per region.

The birth cohort increased from a little below 190,000 in 1996 to 206,619 in 2000. Subsequently the birth cohort decreased to 181,336 in 2007. Then again an increase occurred to 184,634 and 184,824 in 2008 and 2009, respectively (www.statline.nl). The overall reporting rate was 9.2 per 1000 vaccinated infants (DTP-IPV-Hib3) in 2009. Range for 2005-2008 is 5.6-7.2 (DTP-IPV-Hib3), with an exceptional high reporting rate of 11.5 in 2004, due to intensive adverse publicity. In 2009, there was less dispersion of the reporting rates over the different regions, compared to 2008.

Table 7. Regional distribution of reported AEFI in 2004-2009, per 1000 vaccinated children[a] with proportionate confidence interval for 2009 (major adverse events). Figures not containing overall reporting rate in red

	2009 (major)	95% CI 2009 (major)	2008 (major)	2007 (major)	2006 (major)	2005 (major)	2004 (major)
Groningen	8.6 (4.3)	6.2-11.1 (2.6-6.0)	6.3 (3.4)	5.0 (2.3)	7.4 (3.8)	6.7 (2.5)	16.4 (9.8)
Friesland	8.4 (2.4)	6.3-10.5 (1.2-3.5)	6.9 (3.4)	4.2 (2.4)	5.9 (3.1)	5.1 (3.0)	13.1 (7.7)
Drenthe	8.7 (4.1)	6.2-11.3 (2.3-5.8)	3.3 (1.6)	2.5 (1.4)	5.4 (2.7)	5.3 (2.7)	12.6 (10.1)
Overijssel	11.6 (4.4)	9.7-13.4 (3.2-5.5)	8.3 (3.7)	6.2 (2.9)	7.0 (3.5)	4.2 (1.6)	11.2 (5.8)
Flevoland	10.2 (4.1)	7.4-12.9 (2.3-5.9)	7.6 (2.5)	4.9 (1.4)	6.1 (2.5)	8.7 (3.7)	16.3 (9.1)
Gelderland	9.6 (3.6)	8.3-10.9 (2.8-4.4)	6.6 (2.5)	5.7 (2.4)	6.0 (2.9)	5.8 (2.4)	10.8 (5.8)
Utrecht	11.1 (4.9)	9.4-12.8 (3.7-6.0)	9.9 (5.7)	7.3 (3.2)	8.6 (5.5)	8.1 (4.6)	8.1 (4.9)
Noord-Holland[b]	8.8 (3.2)	7.5-10.1 (2.4-4.0)	6.5 (2.4)	4.9 (1.9)	5.8 (3.2)	5.0 (2.5)	9.3 (5.2)
Amsterdam	6.6 (2.4)	4.9-8.4 (1.4-3.5)	9.5 (4.3)	4.7 (1.8)	6.9 (3.6)	5.4 (2.1)	9.8 (4.1)
Zuid-Holland[b]	9.9 (3.6)	8.7-11.1 (2.8-4.3)	7.2 (3.7)	5.7 (2.4)	6.6 (2.9)	5.2 (2.5)	11.8 (6.4)
Rotterdam	3.6 (1.4)	2.1-5.1 (0,5-2.3)	5.0 (2.3)	3.1 (1.4)	4.5 (2.0)	3.7 (1.9)	6.6 (4.7)
Den Haag	8.6 (3.4)	6.2-10.9 (1.9-4.9)	6.5 (3.3)	6.9 (3.6)	4.1 (1.5)	5.8 (1.9)	9.5 (5.8)
Zeeland	10.2 (5.1)	6.9-13.5 (2.7-7.5)	4.8 (2.8)	6.0 (2.6)	5.4 (2.8)	4.1 (1.6)	14.1 (10.7)
Noord-Brabant	8.8 (3.3)	7.6-9.9 (2.6-4.0)	7.9 (3.9)	6.8 (3.2)	7.1 (3.6)	6.8 (3.3)	14.5 (8.5)
Limburg	8.6 (4.1)	6.8-10.5 (2.8-5.3)	5.4 (2.7)	4.1 (2.3)	6.3 (2.7)	5.2 (2.9)	12.0 (6.8)
Netherlands	9.2 (3.6)	8.8-9.7 (3.3-3.9)	7.2 (3.4)	5.6 (2.5)	6.5 (3.3)	5.7 (2.7)	11.5 (6.6)

a for 2004 until 2006 included coverage data of the corresponding year from Praeventis have been used; data of 2006 have been applied to 2007, 2008 and 2009 as well, because definite numbers were not available yet.

b provinces without the three big cities (Amsterdam, Rotterdam, Den Haag)

The 95% confidence intervals for the reporting rates in the different regions contained the country's overall reporting rate in 11 of the 15 regions. The country's average reporting rate for major events is 3.6/1000. Range for 2005-2008 is 2.5-3.4, with an outlier of 6.6 in 2004. One region had a higher reporting rate for major events only and three regions a lower. We will present and compare differences in numbers of specific events in the respective sections under 4.8. For more information see Table 7.

For 2007-2009 rates mentioned above are an estimate of the true reporting rates, due to unknown actual vaccination coverage and changes in birth cohort. However, vaccination coverage is very stable.[5] For reporting rates per dose and per category we therefore used data of the actual birth cohort.

Event categories are not equally distributed over the (scheduled) vaccinations. As shown in Table 6 reports on infant vaccinations are the most prevalent. However, absolute numbers are influenced by changes in birth cohort and vaccination coverage. Figure 5 shows the reporting rate per dose for the last five years. For the year under report, the reporting rate for reports following booster DTP-IPV at four years is significantly higher compared to the four previous years. Rates for the other doses show normal (non significant) variation.

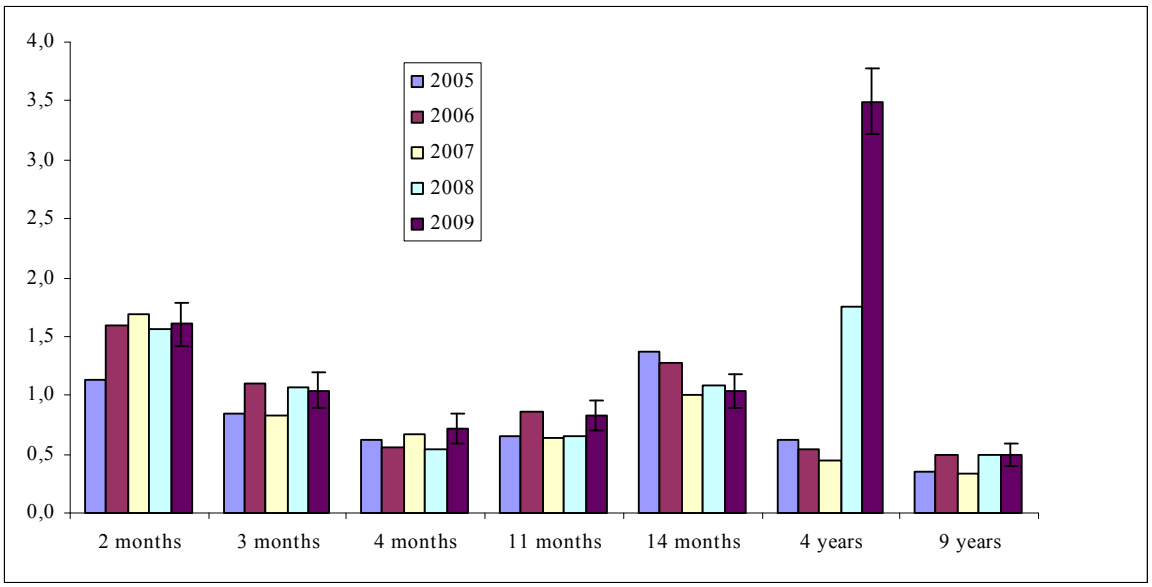

Figure 5. Reporting rate per dose per 1000 vaccinated children for 2005-2009

4.5 Severity of reported events and medical intervention

The severity of reported adverse events is historically categorised in minor and major events. See for information on this subject section 3.6. The number of the so-called major events was 642 of 1647 (39.0%). Ranges for 2005-2008 and 1999-2004 were 44.3% - 50.5% and 51.5% - 57.3% respectively. (Figure 6).

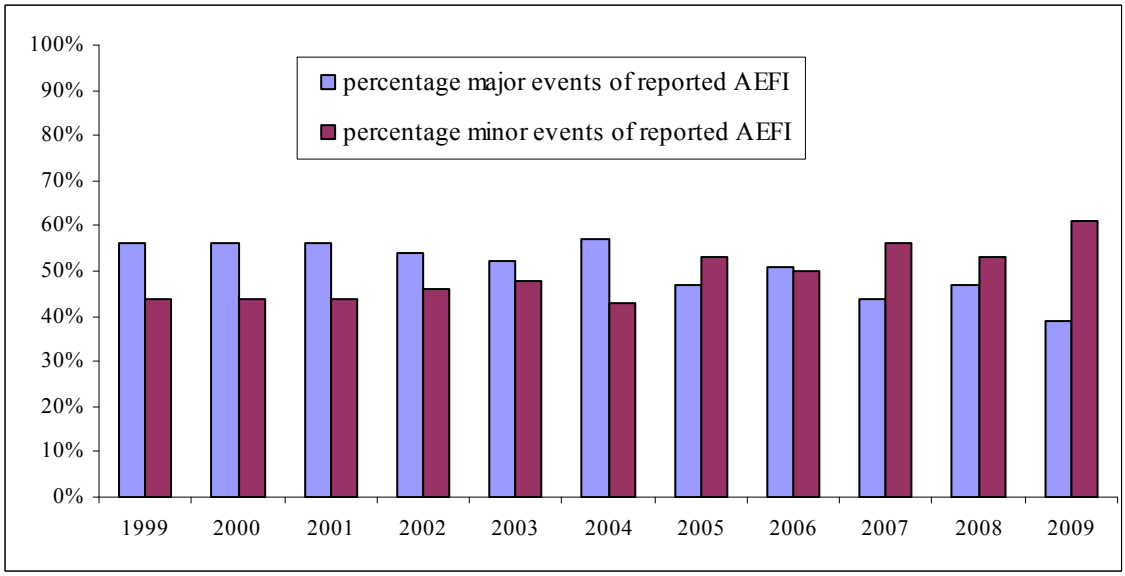

Figure 6. Percentage of reported minor and major AEFI in 1999-2009

The level of medical intervention may also illustrate the impact of adverse events. In 13.7% (225) of reports no medical help was sought or was not reported or recorded by us (range 15-18% for 2004-2008). Parents administered paracetamol suppositories, diazepam by rectiole or other home medication 140 times (9%; range 12-27% for 2004-2008). In Table 8 and Figure 7 intervention is shown according to highest level. In 77%, parents contacted the clinic or GP, called the ambulance or went to hospital. For the five previous years these percentages varied from 57-70%. In 8% of the cases children were hospitalized (range 8%-11% for 2004-2008).

Table 8. Intervention and events of reported AEFI in 2009 (irrespective of causality)

intervention⇒ / event⇓		?	none	Supp[a]	Clinic[b]	GPtel[c]	GP[d]	Ambu[e]	Out-patient	Emer-gency	Admis-sion	Auto-psy	Other[f]	Grand Total
Local reaction		15	55	24	273	47	128	-	10	13	4	-	2	571
General illness	major	4	3	6	1	11	40	-	11	3	42	-	-	121
	minor	25	65	73	71	41	139	2	18	20	33	-	11	498
Persistent screaming		1	5	12	4	4	9	-	3	1	2	-	1	42
Skin symptoms		6	12	8	11	6	34	-	15	1	-	-	2	95
Discoloured legs		-	14	10	11	8	24	-	3	3	2	-	1	76
Faints		3	15	2	47	9	30	10	9	7	18	-	-	150
Fits		1	1	5	-	3	18	7	9	13	26	-	-	83
Anaphylactic shock		-	-	-	-	-	-	-	-	-	-	-	-	-
Encephalopathy/-itis		-	-	-	-	-	-	-	-	-	2	-	-	2
Death		-	-	-	-	-	-	-	-	-	3	6	-	9
Total 2009		55	170	140	418	129	422	19	78	61	132	6	17	1647

[a] paracetamol suppositories, stesolid rectioles and other prescribed or over the counter drugs are included

[b] telephone call or special visit to the clinic

[c] consultation of general practitioner by telephone

[d] examination by general practitioner

[e] ambulance call and home visit without subsequent transport to hospital

[f] mainly homeopaths

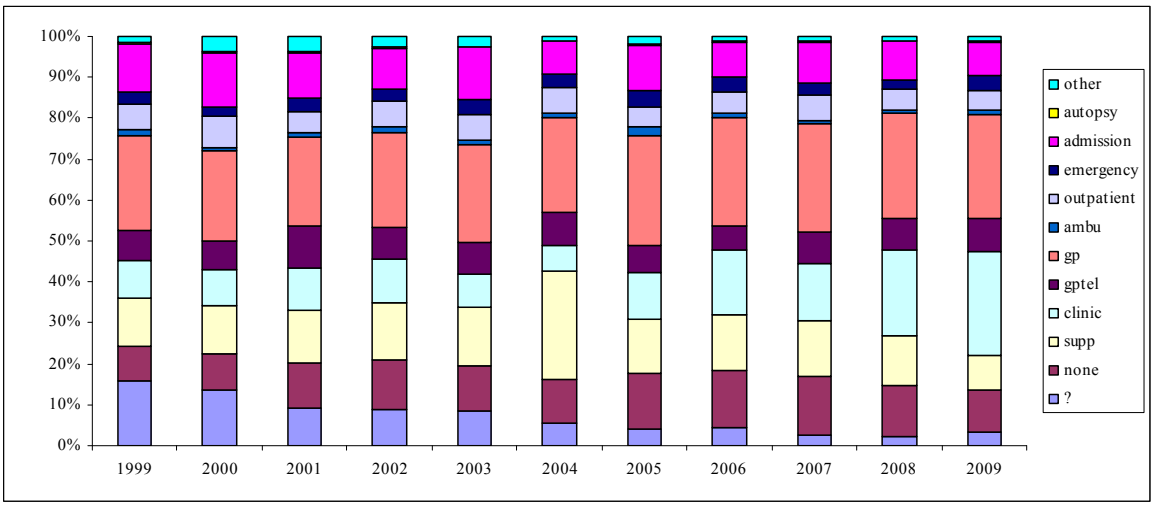

Figure 7. Highest level of medical intervention for AEFI 1998-2009

4.6 Causal relation

Events with (likelihood of) causality assessed as certain, probable or possible are considered adverse reactions (AR). See chapter 3.7 for explanation on this subject. In 2009, 81% of reports were adverse reactions, with exclusion of six non-classifiable events. Range for 2004-2008 is 72%-83%. For the first time, causality for minor events is higher compared with causality of major events. (Figure 8)

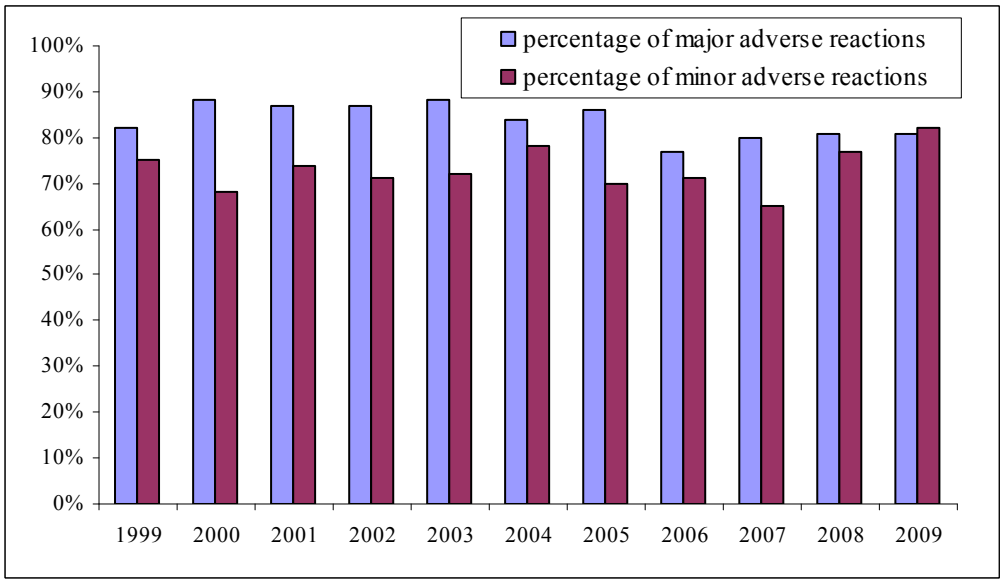

Figure 8. Percentage minor and major AEFI with positive causality for 1999-2009

There are great differences in causality between the different event categories (Table 9), but over the years causality within each category is very consistent. See for description and more detail the specific sections under 4.9 and discussion in chapter 5.

Table 9. Causality and events of reported AEFI in 2009 (% adverse reaction)

event ⇓ causality⇒	certain-probable-possible	improbable	non classifiable	total	(% AR*)
local reaction	571	-	-	571	(100)
general illness minor	344	151	3	498	(69)
major	55	66	-	121	(45)
persistent screaming	39	3	-	42	(93)
skin symptoms	61	33	1	95	(65)
discoloured legs	72	4	-	76	(95)
faints	131	18	1	150	(88)
fits	49	33	1	83	(60)
anaphylactic shock	-	-	-	-	-
encephalopathy/-itis	-	2	-	2	(0)
death	-	9	-	9	(0)
total 2009	1322	319	6	1647	(81)

* = percentage of reports considered adverse reactions (causality certain, probable, possible) excluding non-classifiable events

Positive causality per dose ranged between 65% for MMR and MenC vaccinations at fourteen months of age and 96% for DTP-IPV at four years of age (Figure 9). Of course, this percentage is dependant on the reported events. At four years of age, mainly local reactions are reported, with an acknowledged causal relation with vaccination.

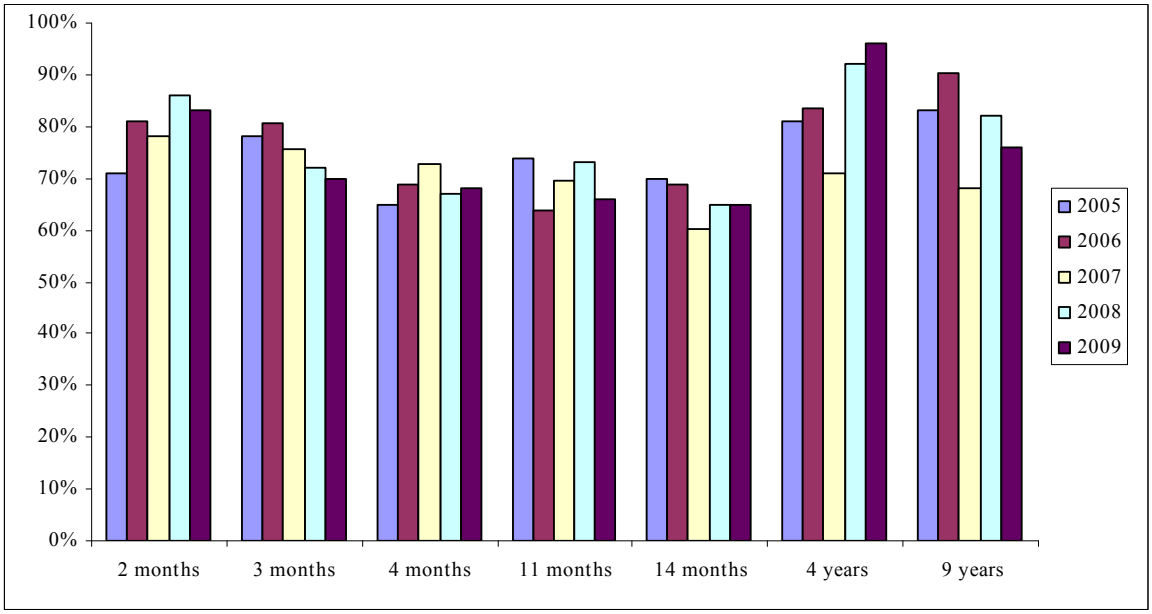

Figure 9. Percentage of reports with assessed causality per dose for 2005-2009

4.7 Expert panel

RIVM very much values a broad scientific discussion on particular or severe reported events. Until 2004 GR re-evaluated a selection of severe and/or rare events. From 2004 onwards RIVM has set up an expert panel. Currently this group includes specialists on paediatrics, neurology, immunology, pharmacovigilance, microbiology, vaccinology and epidemiology. Written assessments are reassessed on diagnosis and causality.
In 2009 the expert panel has focussed on 70 cases (Table 10).

Table 10.total numbers of reports per category and numbers of reports (percentage) reassessed by the expert panel

event ⇓		expert panel	total	(% *)
local reaction		2	571	(<1%)
general illness	minor		498	(<1%)
	major	37	121	(10%)
persistent screaming		-	42	-
skin symptoms		2	95	(2%)
discoloured legs		-	76	-
faints		2	150	(1%)
fits		16	83	(19%)
anaphylactic shock		-	-	-
encephalopathy/-itis		2	2	(100%)
death		9	9	(100%)
total 2009		70	1647	(4.3%)

* = % reassessments

The expert panel agreed in 100% of the reports with (working) diagnosis and causality assessment, determined by RIVM.

4.8 Categories of adverse events

Classification into disease groups or event categories is done after full assessment of the reported event. The relative frequency of the different event categories has changed since the introduction of acellular DTP-IPV-Hib vaccine (Figure 10). General illness (minor and major) remains the largest category, with a relative frequency of around 40%. There is an increase in reports on local reactions, compared with previous years.

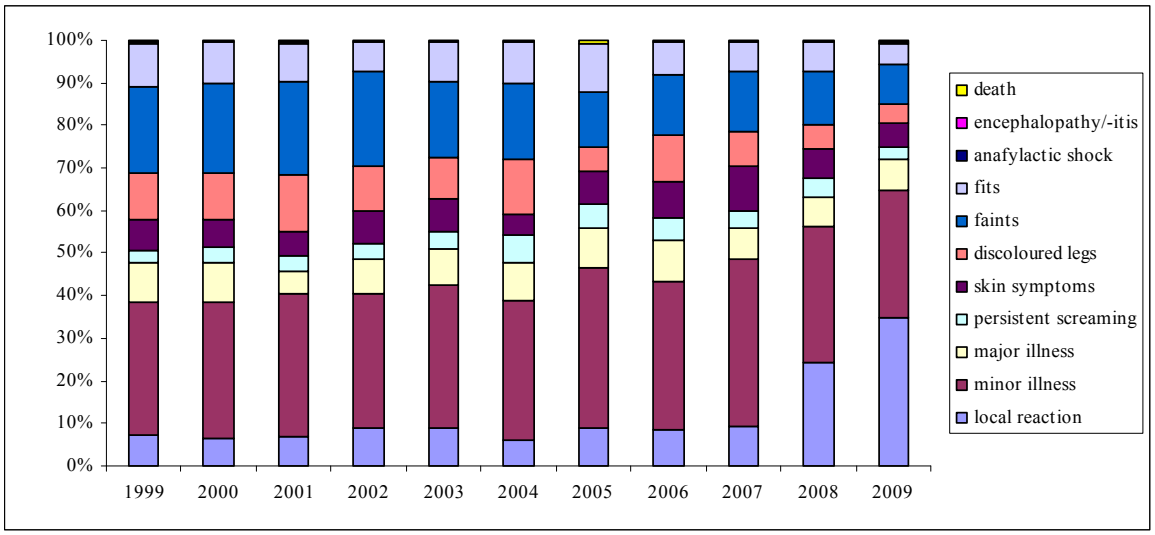

Figure 10. Relative frequencies of categories in reported AEFI 1999-2009

4.8.1 Local reactions

In 2009, local reactions were the main or only feature in 571 reports, mostly following the booster DTP-IPV at four years of age. Over the last four years reporting rates per dose fluctuate. Only for the booster DTP-IPV at four years this change is statistically significant, due to 486 reports, compared to 19-40 in 2005-2007 and 247 in 2008. (Figure 11) However, absolute numbers per dose are small and therefore 95% confidence intervals are large.

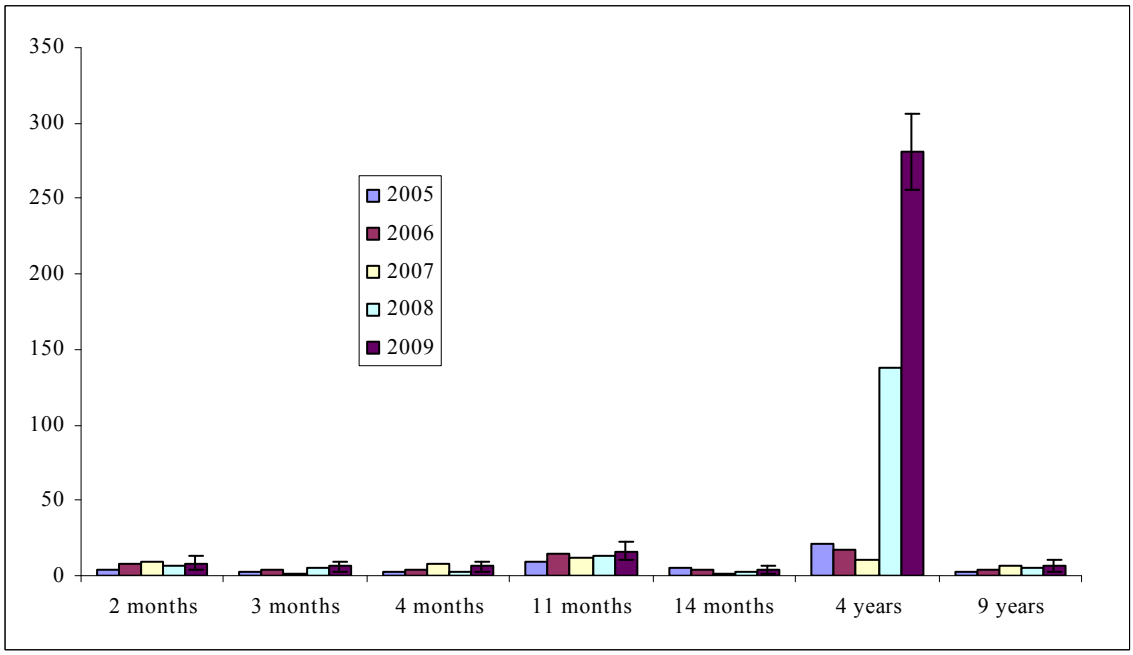

Figure 11. Reporting rate of local reactions per dose per 100,000 vaccinated children for 2005-2009

The majority of reported local events (414; 73%) were classified as minor reactions. 157 Reports (27%) were considered major local events because of size, severity, intensity or duration. There was no difference in distribution of 'major' local reactions among the separate doses. Inflammation was the most prevalent aspect in 535 reports (150 considered major). 15 Reports concerned atypical local reactions with local rash or discoloration, possible infection, (de)pigmentation, haematoma, swelling, itch or pain, atypical time interval or combination of atypical symptoms. Four children had marked reduction in the use of the limb with mild or no signs of inflammation. This is booked separately as "avoidance behaviour" (Table 11).

Table 11. Local events of reported AEFI in 2003-2009 (with major events and number of adverse reaction)

event	2009 (major)	AR[8]	2008 (major)	2007 (major)	2006 (major)	2005 (major)	2004 (major)
inflammation	535 (150)	535	286 (125)	65 (25)	78 (20)	55 (7)	60 (10)
abscess/ cellulitis	7 (7)	7	6 (6)	5 (5)	6 (6)	13 (13)	14 (14)
pustule	-	-	-	-	-	1 (0)	1 (0)
atypical reaction	15 (0)	15	10 (0)	11 (0)	14 (2)	18 (0)	29 (0)
haematoma	-	-	3 (0)	1 (0)	-	-	2 (0)
nodule	10 (0)	10	7 (0)	5 (0)	1 (0)	4 (0)	6 (0)
avoidance	4 (0)	4	1 (0)	3 (0)	3 (0)	2 (0)	17 (1)
total (major)	571 (157)	571	313 (131)	93 (30)	102 (28)	93 (20)	129 (25)

In 2009 all reported local events were considered causally related with the vaccination. The lowest percentage for causality in 2004-2008 was 98%, with some atypical local skin symptoms considered coincidental.

4.8.2 Minor general illness

Events that are not classifiable in any of the specific event categories are listed under general illness, depending on severity subdivided in minor or major (see section 3.5).
In 498 children the event was considered to be minor illness. Of the reported events 59% concerned the scheduled DTP-IPV-Hib vaccinations (range 2005-2008 is 60-67%). In the last four years of whole cell DTP-IPV-Hib this ranged between 75 and 81%.

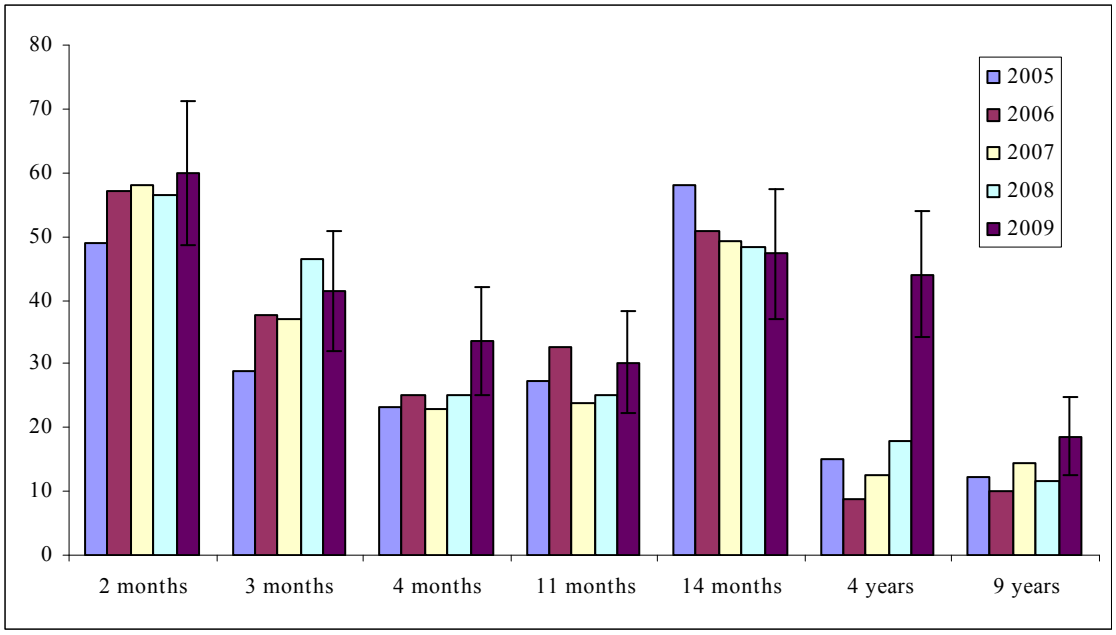

Figure 12. Reporting rate of minor general illness per dose per 100,000 vaccinated children for 2005-2009

As shown in Figure 12 the reporting rate of the booster dose at four year of age increased significantly. Reporting rates of the other vaccination moments show minor variation compared with previous years. Only very few times a definite diagnosis was possible; mostly working diagnoses were used. Fever is the most prominent symptom in 258 reports, 225 times considered possibly causally related. Of these reports on fever, 20% concerned the booster DTP-IPV dose at four years of age, compared with 13% and 6% in 2008 and 2007, respectively. Crying was the main feature in 33 reports, predominantly following the first two vaccinations. Since the introduction of acellular pertussis vaccine for infants, pallor and/or cyanosis (10) and chills/myoclonics (15) are less frequently reported. For the other working diagnoses numbers remained more or less the same over the last years (Table 12).

Table 12. Main (working) diagnosis or symptom in category of minor illness of reported AEFI in 2004-2009 (with number of adverse reactions)

Symptom or diagnosis	2009	AR*	2008	2007	2006	2005	2004
fever	258	225	159	128	135	120	212
crying	33	27	64	56	61	57	157
pallor and/or cyanosis	10	10	19	11	16	20	83
myoclonics and chills	15	11	5	14	9	7	46
prolonged/deep sleep/sleeping problems	10	10	14	10	14	7	10
rash(illness)	26	0	37	33	52	38	34
vaccinitis	37	37	33	23	24	39	31
airway and lung disorders	25	5	18	36	21	22	28
gastro-intestinal tract disorders	36	4	30	31	39	17	28
arthralgia/arthritis/coxitix/limping/disbalance/pain in limbs	6	3	5	3	5	18	6
behavioural problems/-illness	10	2	8	7	5	1	12
other	32	10	22	38	22	43	57
	498	344	414	390	403	389	704

* number of adverse reactions

In this minor general illness category 31% of the reports (151) were considered to have improbable causal relation with the vaccination. For 2004-2008 this range was 21-40%. The percentage of adverse reactions decreased a little since the introduction of acellular DTP-IPV-Hib in 2005 (Table 12 and Figure 13).

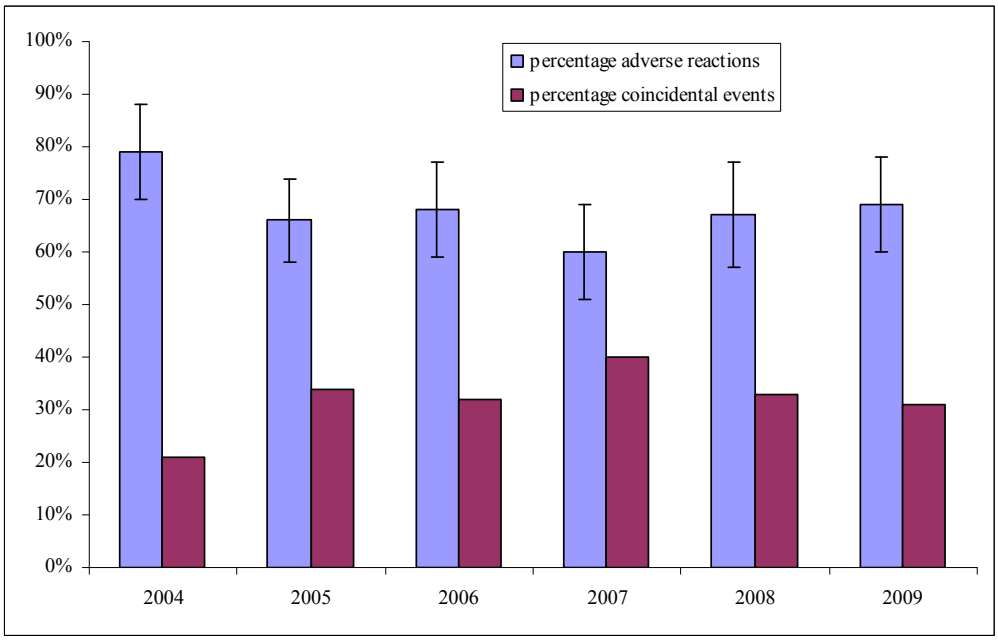

Figure 13. Percentage of adverse reactions and coincidental reports in minor general illness for 2004-2009

For 2009 the percentage of adverse reactions varies between 82% for the first DTP-IPV-Hib and PCV7 vaccination at two months of age and 53% for the fourth dose of DTP-IPV-Hib and PCV7, scheduled at eleven months (Figure 14). Over the years there is some fluctuation in these percentages. Only the increase at four years of age is statistically significant compared with 2005-2007

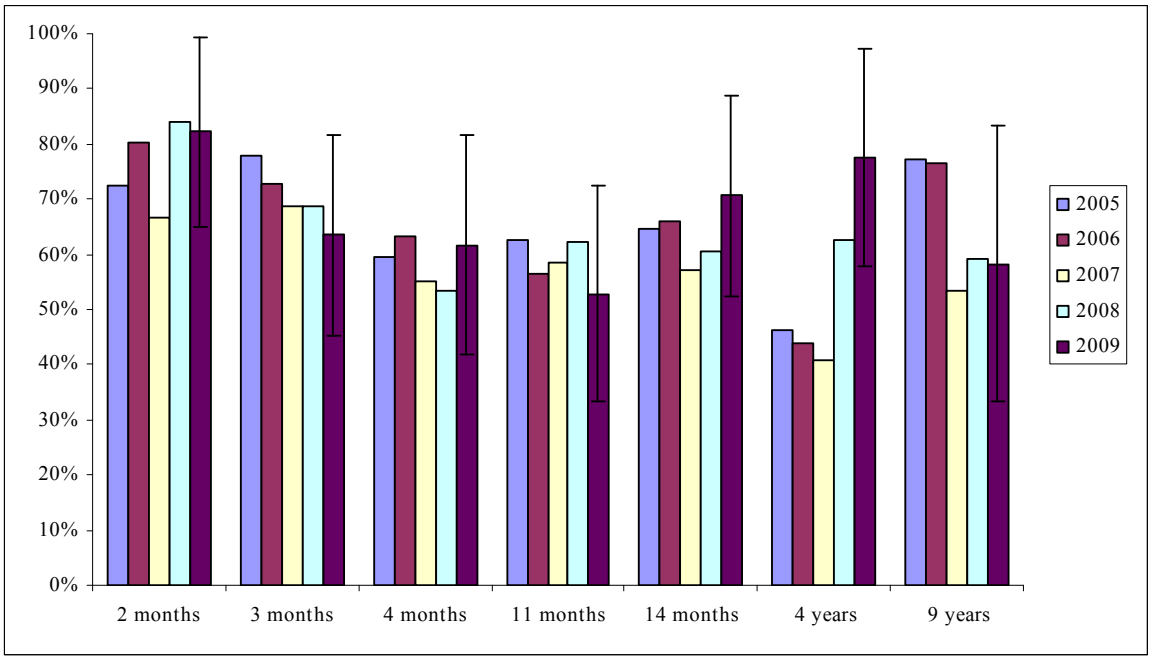

Figure 14. Percentage of reports on minor general illness with assessed causality per dose for 2005-2009

4.8.3 Major general illness

Major general illness was recorded 121 times, an increase compared with 2008. Reporting rate per dose fluctuates with large confidence intervals, due to small numbers. Only the change at 11 months is statistically significant compared with both 2007 and 2008 (Figure 15).

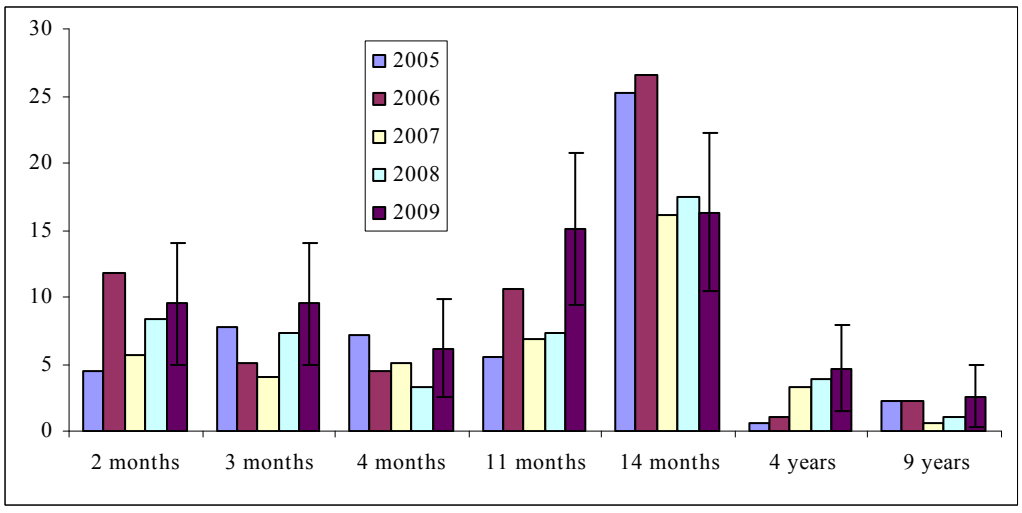

Figure 15. Reporting rate of major general illness per dose per 100,000 vaccinated children for 2005-2009

Very high fever (≥ 40.5 °C) was the working diagnosis in 53 cases, compared with 36-123 in 2004-2008. In 79% of these cases the fever was considered causally related to the vaccination (Table 13).

Table 13. (Working) diagnosis in category of major illness of reported AEFI in 2003-2009 (with number of adverse reactions)

symptom or diagnosis	2009	AR*	2008	2007	2006	2005	2004
very high fever (≥ 40.5 °C)	53	42	36	41	53	37	123
chills/myoclonics, accompanied with very high fever	1	0	-	-	2	1	5
gastro-intestinal tract disorder	4	1	3	1	4	2	7
respiratory tract disorder, apneu, respiratory insufficience	13	1	8	6	11	7	6
meningitis	3	0	3	7	4	5	3
vaccinitis/rash illness, accompanied with very high fever	6	6	15	2	17	13	6
infection	10	2	3	2	2	-	-
arthritis/osteomyelitis/JIA/myopathie	6	2	5	2	1	4	4
cardiomyopathy/myocarditis/arrhythmia/vasculitis	3	0	-	-	2	1	1
ITP	1	1	2	4	1	7	15
cerebellar ataxia	-	-	-	-	1	-	-
endocrinological disorders	4	0	-	-	1	1	2
kawasaki	1	0	-	1	-	2	2
neurological disorders	5	0	-	-	-	-	2
optic neuritis/atrophy/visus disorder	-	-	-	-	1	-	-
intussusception	-	-	-	-	-	-	2
facial paralysis	-	-	-	-	-	2	-
urogenital tract disorder/henoch schonlein	1	0	1	1	-	1	5
ahoi	-	-	-	1	-	-	-
retardation/autism/pervasive-behavioral disorder	4	0	3	3	2	7	5
lymphadenitis colli/abcess/cellulitis	-	-	1	-	3	1	-
ALTE	2	0	2	-	-	-	2
shaken baby syndrome	-	-	-	-	-	-	1
other	4	0	5	2	6	3	2
total	121	55	87	73	111	97	194

* number of adverse reactions

In the category major illness 45% (55) of the reports were considered adverse reactions. For the first time, the percentage of coincidental reports exceeds the percentage of causal related reports. However, there has always been some fluctuation in this percentage and confidence intervals are large due to small numbers. (Figure 16).

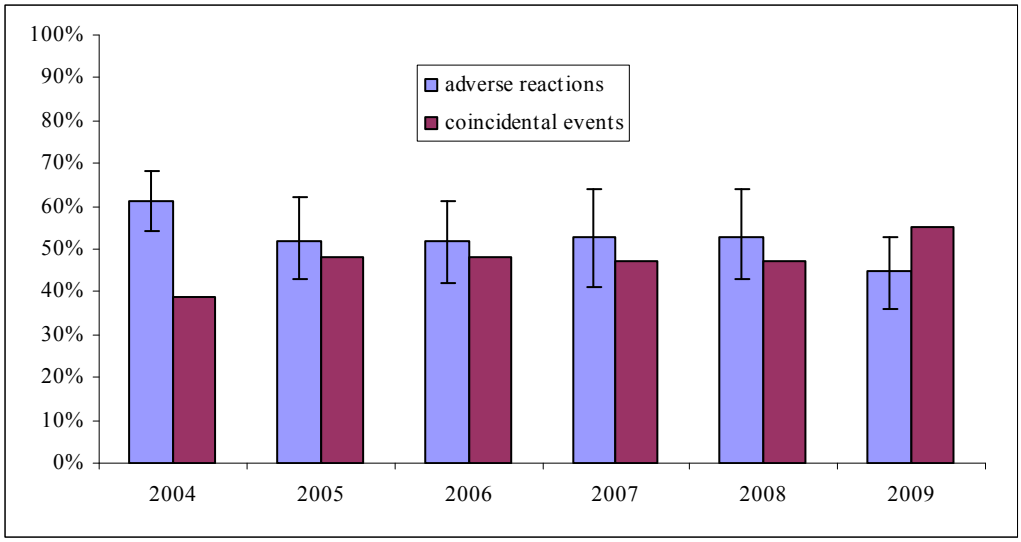

Figure 16. Percentage of adverse reactions and coincidental events in major general illness for 2004-2009

For 2009 the percentage of adverse reactions in the category major illness varies between 35% for the second dose of DTP-IPV-Hib and PCV7 vaccination at two months of age and 63% for the booster dose of DTP-IPV, scheduled at four years. However, absolute numbers are very small in this category, varying between five and 29 reports per dose for 2009 (Figure 17).

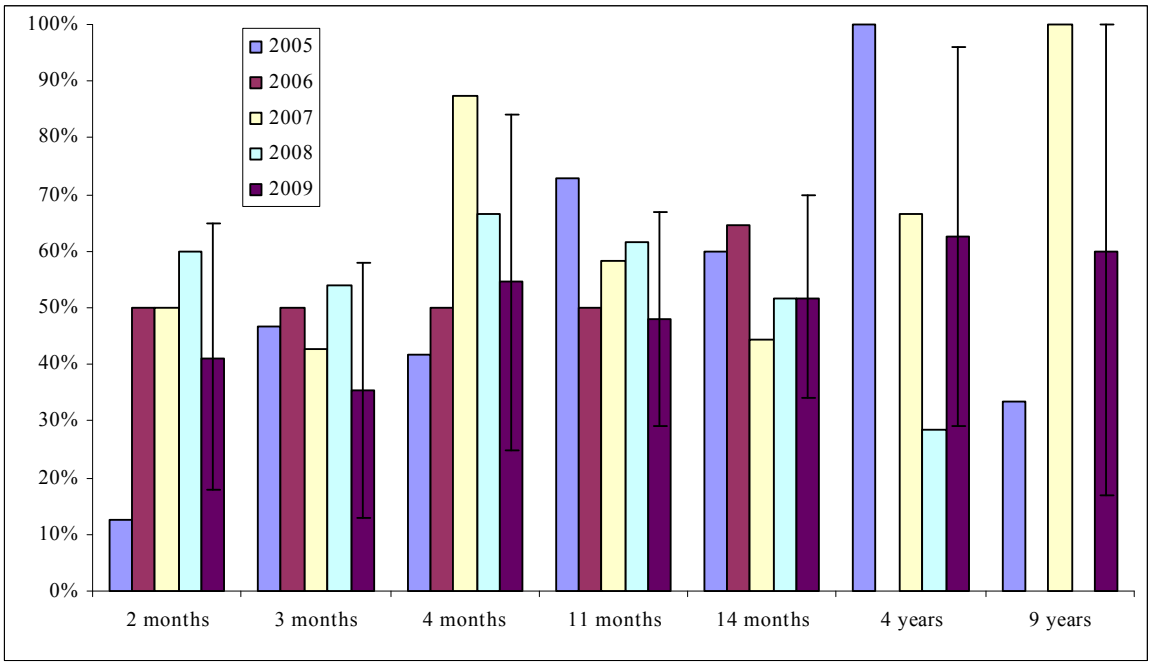

Figure 17. Percentage of adverse reactions in major general illness per dose for 2005-2009

4.8.4 Persistent screaming

In 2009 42 cases meeting the case definition of persistent screaming, were reported, mostly following vaccination of young infants. No cases above the age of one year were reported (Figure 18).

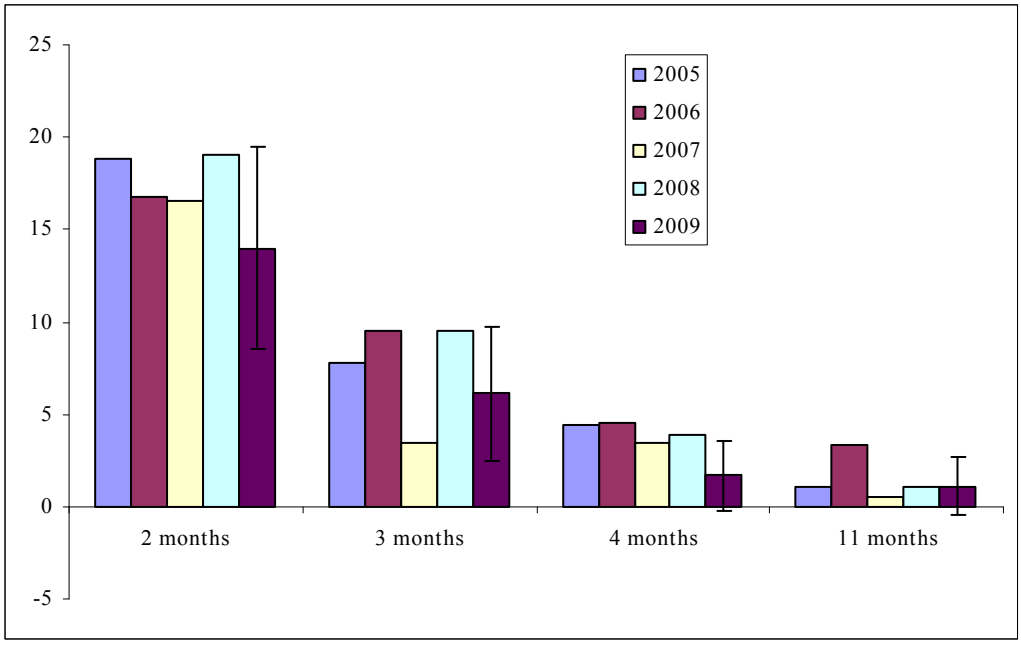

Figure 18. Reporting rate of persistent screaming per dose per 100,000 vaccinated infants for 2005-2009

Additional symptoms were pain and swelling at the injection site, restlessness, pallor, myoclonic jerks and fever. 12 Parents gave suppositories, 13 contacted the GP and six children were seen in the hospital (Table 8).

The overall causality for this category is high and constant over the last years, range for 2004-2008 is 91-98% (Figure 19). The percentage of reports with assessed causality per dose approaches 100%is over 90% for all doses.

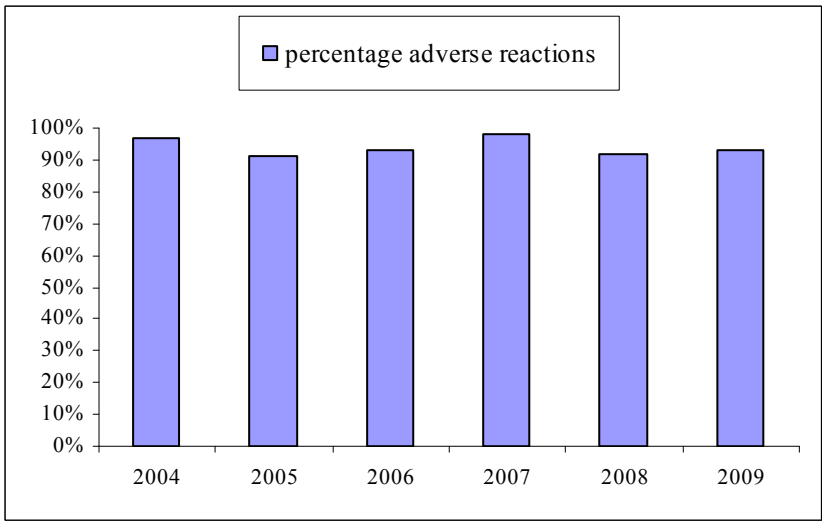

Figure 19. Percentage of reports on persistent screaming with assessed causality for 2004-2009

4.8.5 General skin symptoms

In 2009, skin symptoms were the main or only feature in 95 reports, two of them classified as major. In 2004-2008 this ranged from 82-101. Reporting rates per dose fluctuate over the last five years (Figure 20).

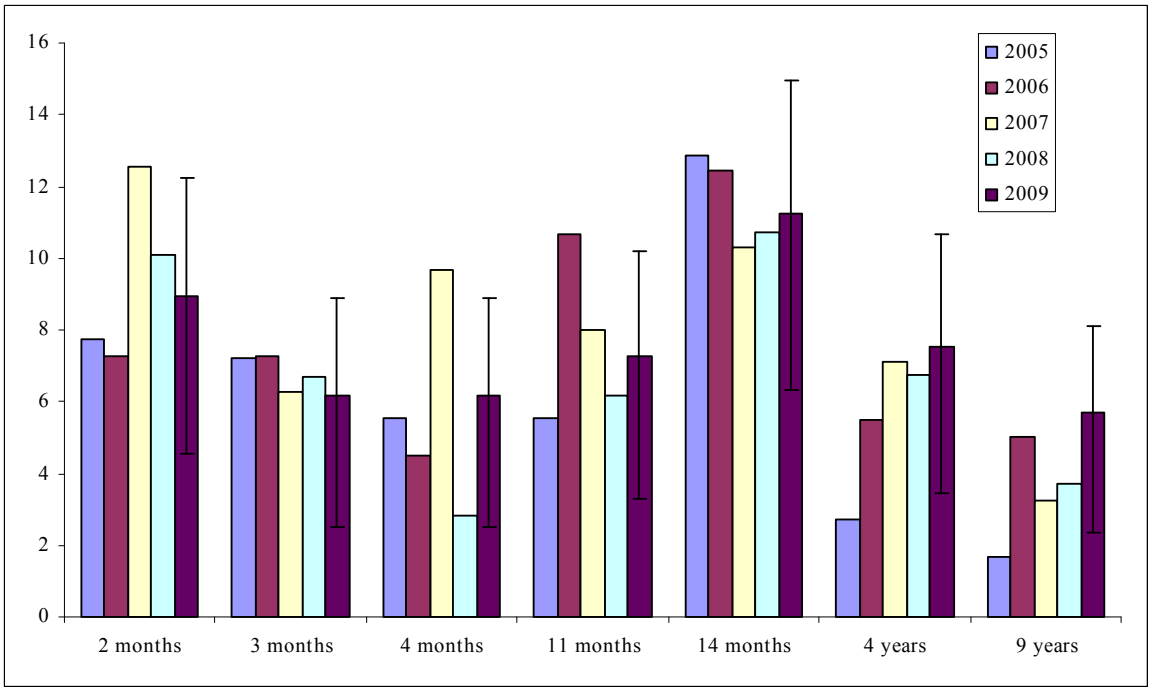

Figure 20. Reporting rate of general skin symptoms per dose per 100,000 vaccinated children for 2005-2009

Exanthema, (increased) eczema and urticaria were the most frequent reported events (83%). Six times swelling/angiooedema were reported. Two reported children had petechial rash on upper body and/or face. Children with petechiae on the legs only are categorised under discoloured legs (Table 14).

Table 14. Diagnosis in category of general skin symptoms of reported AEFI in 2004-2009 with number of adverse reactions

diagnosis	2009	AR*	2008	2007	2006	2005	2004
angio-oedema/swelling	6	5	9	11	5	10	10
exanthema/erythema	46	26	48	55	52	46	60
urticaria	10	4	16	9	18	7	8
eczema (increase)	23	19	7	13	16	16	13
petechiae/purpura	2	2	1	4	3	2	5
other	8	5	7	9	3	1	10
total	95	61	88	101	97	82	106

* number of adverse reactions

Of the reports, 65% (61) were considered adverse reactions (range 2004-2008 is 50-65%, Figure 21).

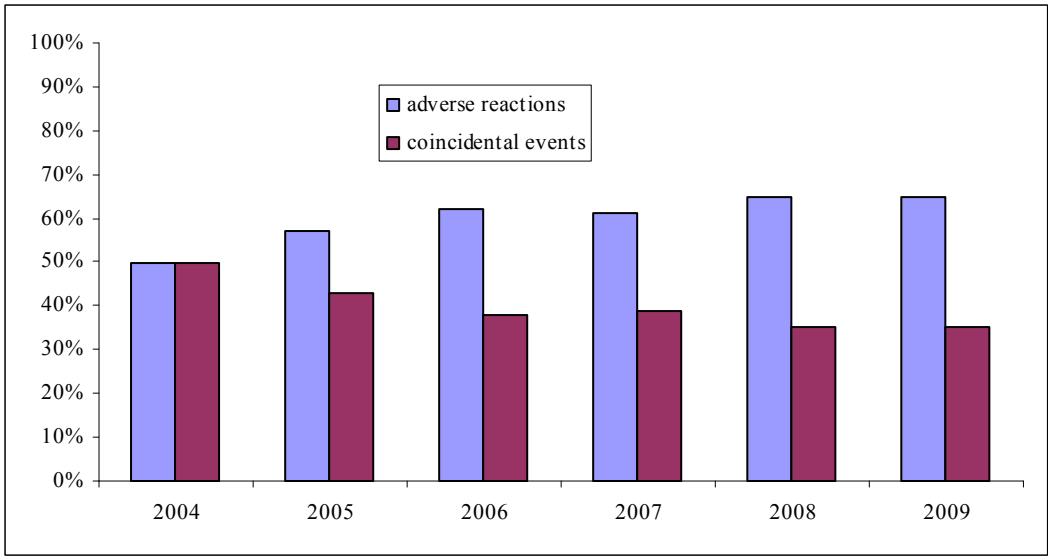

Figure 21. Percentage of adverse reactions and coincidental events in skin symptoms for 2004-2009

Causality per dose peaks at 11 months of age with 85% assessed causality and is lowest at 14 months (50%). However, absolute numbers per dose are small (range 11-20) Figure 22.

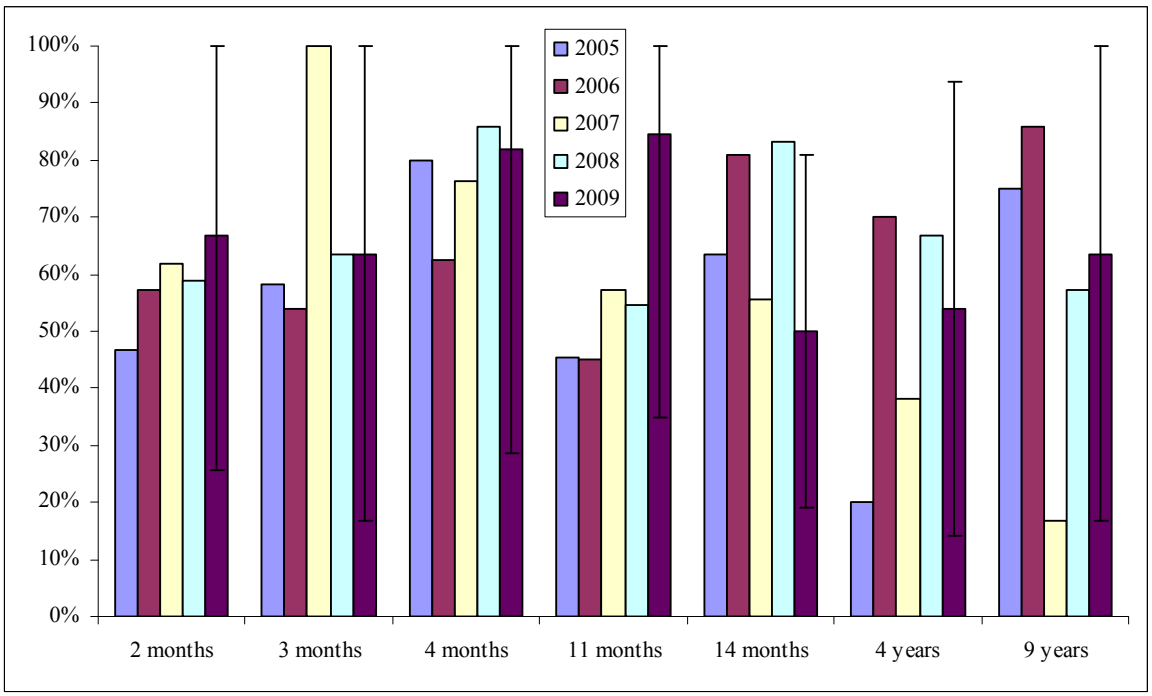

Figure 22. Percentage of reports on skin symptoms with assessed causality per dose for 2005-2009

4.8.6 Discoloured legs

Starting in 1995, discoloured legs are listed as a separate event category, subdivided in blue, red or purple legs with even or patchy discoloration, with or without petechial rash. Petechiae on legs without noted discoloration are also grouped in this category. The same applies for swollen limbs without noted discoloration.
In 2009 we received 76 reports of discoloured legs, mostly following the first two doses of DTP-IPV-Hib and PCV7. In the last five years the reporting rate fluctuates between 24 and 66 per 100,000 vaccinated infants under one year of age (Figure 23).

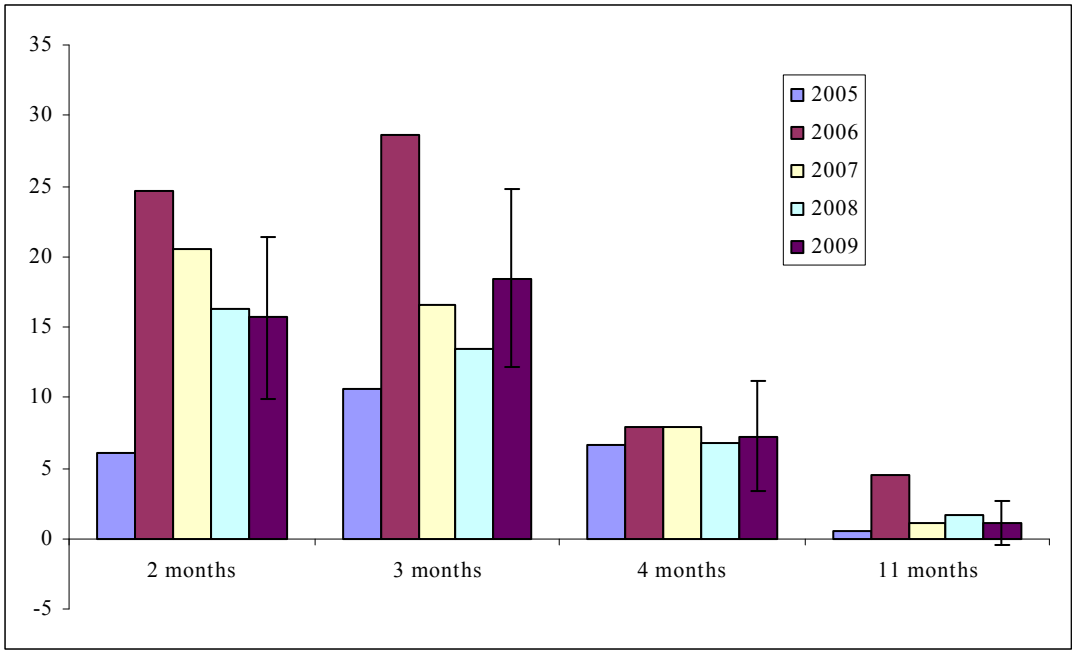

Figure 23. Reporting rate of discoloured legs per dose per 100,000 vaccinated infants for 2005-2009

10 Reports were categorised as blue legs (seven times double-sided), 38 as red legs (21 double sided) and 17 (16 double sided) as purple legs. In two cases legs were only swollen without noted discoloration (both double sided). In nine cases (six double-sided) leg petechiae only, without noted prior discoloration were reported (Table 15).

Table 15. Discoloured legs of reported AEFI in 2004-2009 with number of adverse reactions

diagnosis	2009	AR*	2008	2007	2006	2005	2004
blue legs	10	10	6	6	12	5	36
red legs	38	35	35	49	60	26	130
purple legs	17	16	15	12	30	8	69
petechiae only	9	9	14	11	19	15	40
swollen limb	2	2	-	1	3	3	4
total	76	72	70	79	124	57	279

* number of adverse reactions

Causal relation with the vaccines was inferred in all but four cases (95%). In the previous five years the rate of positive causality has always been ≥ 94%.

Numbers of double-sided discoloured legs fluctuate over the last nine years. Until March 2003 whole cell DTP-IPV and Hib were administered simultaneously, but in different legs. From April 2006 onwards infants received PCV7 at the same time as acellular DTP-IPV-Hib. Therefore, the period in between, infants received one vaccination instead of two. In Figure 24 the percentage of double-sided discoloured legs is shown for 2000-2009.

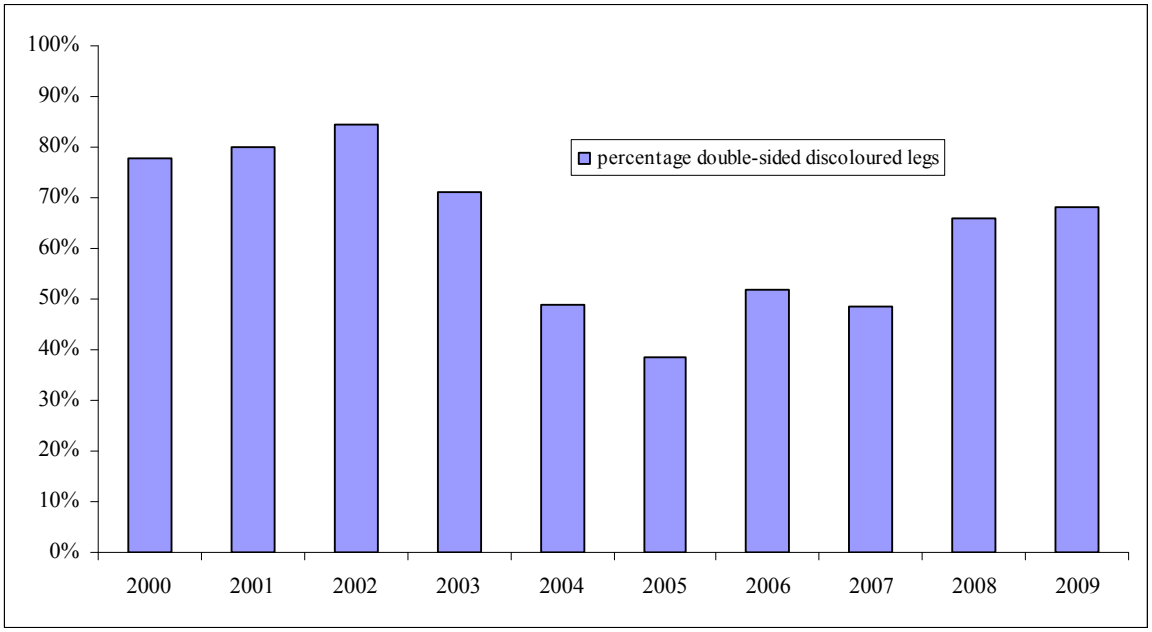

Figure 24. Percentage of double-sided discoloured legs for 2000-2009.

4.8.7 Faints

In this event category, collapse (hypotonic-hyporesponsive episode, HHE), syncope (fainting) and breath holding spells (BHS) are listed (Table 16).
In 2009 collapse was reported in 89 cases. This is similar to 2008-2007, an increase compared with 2005-2006, but a sharp decrease in numbers compared with 2001-2004, the period of use of whole cell DTP-IPV-Hib. In 63% of cases collapse occurred after the first DTP-IPV-Hib and PCV7 vaccination. In 2005-2008 this ranged between 37%- 75%. Numbers diminished with dose number and age, similar to 2001-2004.[33] See for reporting rates per dose Figure 25.

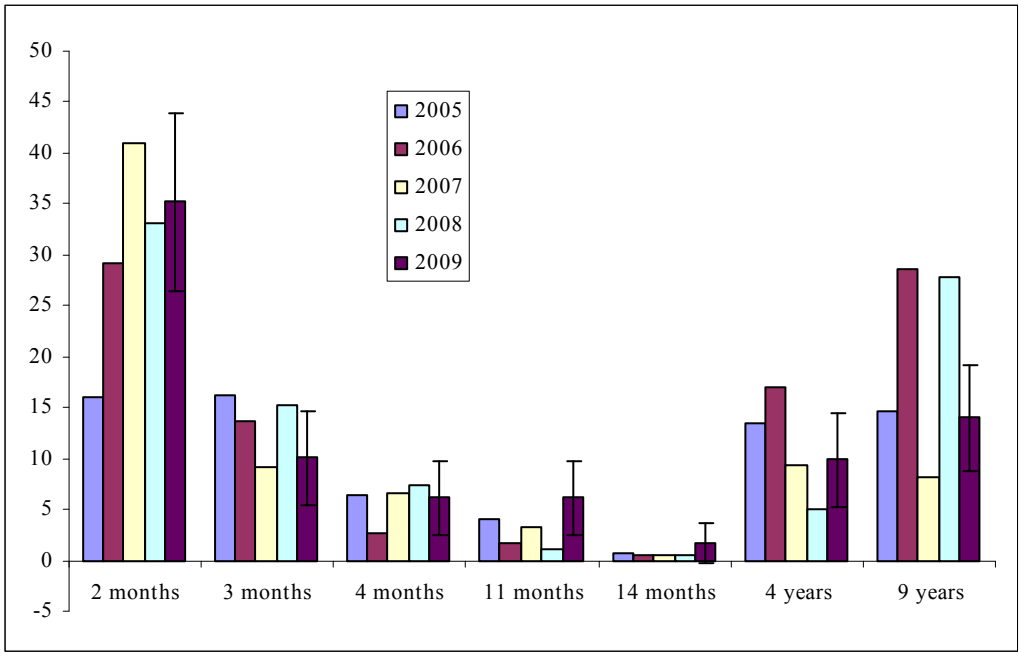

Figure 25. Reporting rate of faints per dose per 100,000 vaccinated children for 2005-2009

BHS occurred 18 times; the children turned blue, after stopping to breathe in expiration when crying vehemently or after other stimuli, with a very short phase of diminished responsiveness and no limpness or pallor. Fainting in older children was reported 43 times and fluctuates in previous five years.

Table 16. Diagnosis in category of faints of reported AEFI in 2003-2009 (with number of adverse reactions)

diagnosis	2009	AR*	2008	2007	2006	2005	2004
collapse	89	73	95	96	76	75	318
breath holding spell	18	16	9	14	11	6	23
fainting	43	42	61	31	82	52	37
total	150	131	165	141	169	133	378

* number of adverse reactions

Events in this category are acknowledged adverse reactions following vaccination. The percentage of causally related events for 2009 was 88% (range 84%-95% for 2004-2008).

4.8.8 Fits

Convulsion (febrile or non-febrile) and epileptic seizures are categorised here. In the subcategory of "atypical attacks" paroxysmal events are listed in case no definite diagnosis could be made and convulsion could not be fully excluded either. See also section 3.5 for case definitions.
Most reported convulsions were febrile (39 out of 45), occurring predominantly after the fourth DTP-IPV-Hib + PCV7 (7) and MMR1 + MenC (28) vaccinations (Figure 26).

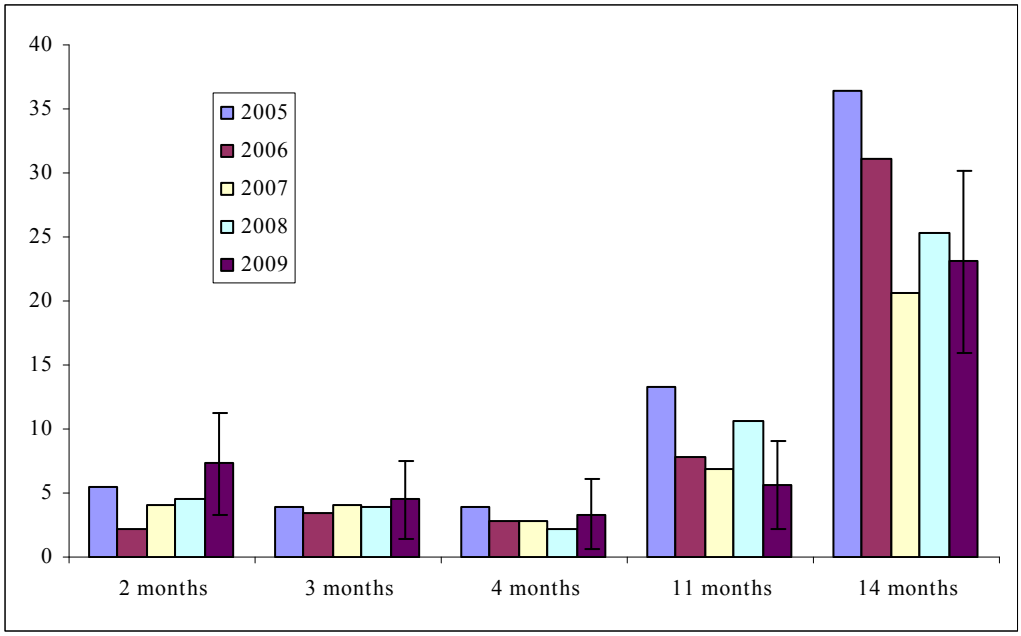

Figure 26. Reporting rate of fits per dose per 100,000 vaccinated children for 2005-2009

Six non-febrile convulsions were reported.
Furthermore, six children with epilepsy were reported. In none of these children (fever caused by) the vaccine was regarded as trigger.
In 2009 atypical attacks were recorded 32 times, slightly higher than the two previous years and lower than 2004-2005. Of these atypical attacks, 17 were accompanied by fever. None of these children fulfilled the case definitions for collapse or convulsion (Table 17).

Table 17. Diagnosis in category of fits of reported AEFI in 2003-2009 (with number of adverse reactions)

diagnosis		2009	AR*	2008	2007	2006	2005	2004
febrile convulsion	simplex	18	12	23	25	30	34	45
	complex	17	11	27	13	24	24	32
	atypical	4	4	6	4	3	7	13
non febrile convulsion		6	4	4	3	6	6	8
epilepsy		6	0	4	6	3	4	9
atypical attack		32	18	24	18	19	43	104
total		83	49	88	69	85	118	211

* number of adverse reactions

Causality was assessed in 69% of the febrile convulsions (range 2004-2008 74%-85%). For atypical attacks this percentage was 56%, varying between 53% and 74% in the previous five years (Figure 27).

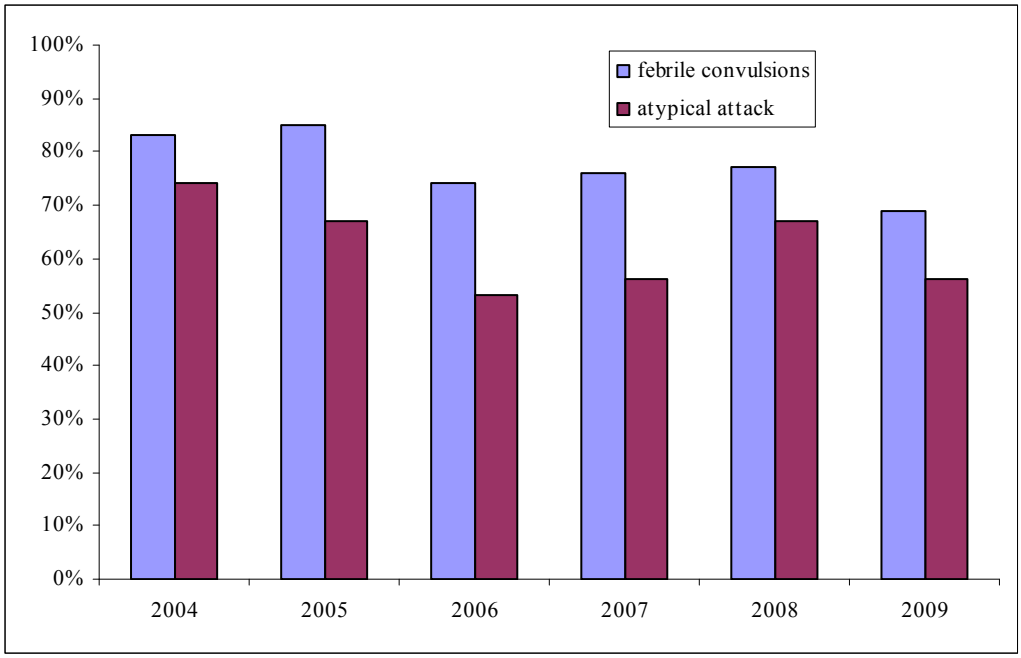

Figure 27. Percentage of febrile convulsions and atypical attacks with assessed causality for 2004-2009

The percentage of febrile convulsions with assessed causality for the booster DTP-IPV-Hib and PCV7 vaccination was 50%, compared to 79% for MMR and MenC at 14 months (Figure 28). For atypical attacks the percentages per dose ranged between 50% and 100%. However absolute numbers are small for this event.

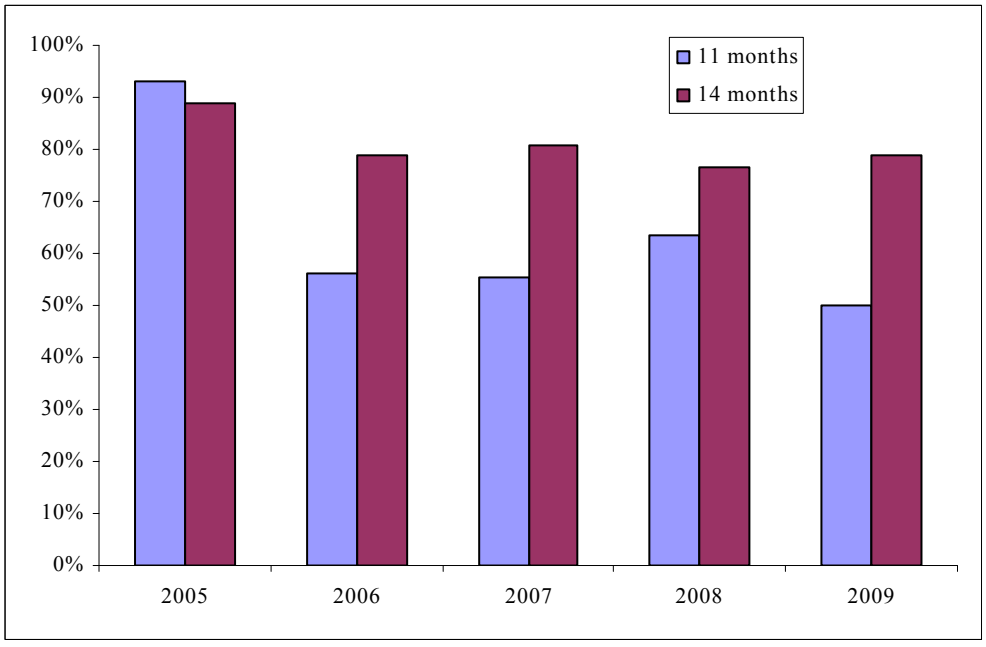

Figure 28. Percentage of reports on febrile convulsions with assessed causality per dose for 2005-2009

4.8.9 Encephalopathy/encephalitis

The two events reported in 2009 listed in this category were considered a chance occurrence and not induced or aggravated by the vaccination (Table 18)

Table 18. Encephalopathy/encephalitis and vaccines of reported AEFI in 2009

child	sex	age[a]	vaccines	interval	symptoms/diagnosis	causality
A	f	4 years	DTaP-IPV	6 weeks	Vomiting, sleepiness, afebrile seizure, viral encephalitis	no
B	m	16 months	MMR + MenC	1 day	Vomiting, diarrhoea, drowsiness, neurological deterioration, acute hemorrhagic encephalomyelitis with unknown cause	no

[a] age at vaccination

4.8.10 Anaphylactic shock

There were no reports on anaphylactic shock in 2009. As a matter of fact, we have never received notification of anaphylactic shock with inferred causality and/or appropriate time interval since the surveillance system was installed.

4.8.11 Death

In 2009, nine children were reported, who died following vaccination (Table 19). The reports concerned four boys and five girls. Autopsy was performed six times. Without full post-mortem investigation a definite diagnosis is often impossible. In all nine cases death was judged not to be caused or hastened by the vaccination. In three cases, reported in a short period of time, an identical batch of PCV7 was used. Administration of this batch was suspended until additional information, requested by the European Medicines Agency (EMA), was available. This additional information revealed no batch of vaccine-related problems and EMA cancelled the suspension.

Table 19. Death and vaccines of reported AEFI in 2009

child	sex	age[a]	vaccines	time interval		symptoms/diagnosis	causality	autopsy
				illness	death			
A	m	8y	dtp +MMR	2 d	3.5d	fever, drowsiness, shortness of breath, necrotising pneumonia and sepsis caused by group A haemolytic streptococci and staphylococci following Influenza B infection	no	yes
B	f	2m	dtp-ipv-hib-hepB 1 + pcv7 1	< 24 h	< 24h	Sudden Infant Death Syndrome (SIDS)	no	yes
C	m	1y	dtp-ipv-hib-hepB 4 + pcv7 4	1d	3d	hydrocephalus due to congenital malformation with well functioning drain, surgically corrected congenital heart malformation, loss of appetite,	no	no

						vomiting, no fever, upper respiratory tract infection, SIDS		
D	f	11m	dtp-ipv-hib-hepB 1 + pcv7 1	25h	25h	dihydropteridine reductase deficiency, no fever, unknown cause of death, possible disbalance in neurotransmittors	no	no
E	m	6m	dtp-ipv-hib 3 + pcv7 3	1.5h	3d	premature, post anoxic encephalopathy following near SIDS, abstinence policy	no	yes
F	f	4m	dtp-ipv-hib-hepB 3 + pcv7 3	0d	11d	sleepiness, vomiting, followed by a symptom free interval, death of unknown cause	no	no
G	f	3m	dtp-ipv-hib-hepB 2 + pcv7 2	1.5d	1.5d	Turner-like syndrome, SIDS	no	yes
H	f	5m	dtp-ipv-hib 3 + pcv7 3	10d	10d	SIDS	no	yes
I	m	3m	dtp-ipv-hib-hepB 2 + pcv7 2	4d	4d	SIDS	no	yes

[a] age at vaccination

5 Discussion

The success of the vaccination programme, having brought the target diseases under control, increases the relative importance of adverse events.[13,14] This enhances the demands on the safety surveillance system likewise. Mere registration and reporting of possible adverse reactions is not enough to sustain confidence in the safety of the programme.[34,35,36] Intensified awareness of public and professionals with regard to safety of vaccines may have adverse consequences for the willingness to participate in the programme. This in turn, may also influence the number and type of AEFI reported to the safety surveillance system.
We will discuss the characteristics of the current enhanced passive surveillance system with its strength and weaknesses and we will go into the changes in number and the different aspects of the nature of the reported adverse events in 2009.
In 2009 there have been no changes in the programme. Besides the normal RVP, in 2009 a Human Papilloma Virus (HPV) vaccination catch-up campaign was organised for all 13 to 16 year old girls. Regularly administration of HPV to 12 year old girls will be implemented in 2010. Furthermore, vaccination against Influenza A(H1N1) took place but was not included in the RVP. On the safety of these campaigns will be reported elsewhere. Reports of the current year have been carefully monitored for unexpected, unknown, new severe or particular adverse events and for changes in trends and severity.

5.1 Discussion related to data on 2009

5.1.1 Number of reports, vaccines and dose, information sources

In 2005-2007 the number of reports fluctuates at a lower level, compared with the period of whole cell DTP-IPV-Hib vaccine, which ended after 2004. This was to be expected, since acellular pertussis vaccines are known to have a more favourable safety profile both for common and severe adverse events.[37,38,39] In 2008 the number of reports increased with 30% compared with 2007, followed by another increase of 28% in 2009 compared with 2008. The involved birth cohorts, eligible for RVP vaccinations in 2008 and 2009 of 2000-2009 do not differ much compared to the cohorts, eligible for vaccination in the years 2005-2007 (www.statline.nl). Furthermore, vaccination coverage is very stable over the years. Therefore, a change in birth cohort can not explain this ongoing increase in reporting rate.
Reports following DTP-IPV at four years of age have increased significantly in 2008 and 2009, as shown in Figure 4. This is probably due to the introduction of acellular DTP-IPV-Hib since January 2005. Infants, born from September 2004 onwards, reached the age of four years during the second half of 2008. At that moment they received an acellular DTP-IPV booster dose. Furthermore, due to intense adverse publicity in 2004 some parents asked their GP to administer acellular DTP-IPV-Hib prior to the introduction in the RVP. From October 2008 onwards, nearly all children receiving the booster dose at four years of age, had a full series of acellular DTP-IPV-Hib at infancy.[40] An increased risk on local reactions following booster doses of acellular pertussis containing vaccines is described in literature and is higher for children with a complete acellular primary series.[46,47,48] This explains the ongoing increase in reports following this booster DTP-IPV in 2008 and 2009.
Verification and validation of reported adverse events were under stress, due to increased workload because of the HPV catch-up campaign and vaccination against Influenza A(H1N1). Decreased

validation was most obvious in the categories 'local reactions' and 'minor general illness'. For all reports following booster DTP-IPV at four years, we send a questionnaire to parents for validation and supplementation of reported symptoms instead of a case history by telephone. Perhaps, a low response to this questionnaire can explain this decreased validation. Furthermore, in 43% of the reports with only one information source, parents were the reporter. After a parental eye witness account, further validation and supplementation is only necessary when medical assistance was sought. This occurs seldom after local reactions.

5.1.2 Severity and causality

Since 2005 the absolute number as well as the relative share of so called major adverse events decreased, compared to the period of whole cell DTP-IPV-Hib. This is consistent with the better safety profile of a DTP-IPV-Hib vaccine with an acellular pertussis component.[37,38,39] In 2009 the share of minor adverse events was higher compared with the four previous years. Furthermore, the percentage of minor events with assessed causality has increased. Both changes are probably explained by the increase in reports following booster DTP-IPV at four years of age. These reports concerned mostly local reactions and/or fever, both acknowledged side effect of immunization. Most of these reports are considered to be 'minor' adverse events, according to the criteria described in section 3.6.
In the year under report the highest level of medical intervention has increased compared with the five previous years. This increase is most prominent in the consultation of health care professionals.
Up till four years of age (pre school) children attend the Child Health Clinic regularly. Booster DTP-IPV at four year of age is given during the last visit and thereafter Municipal Health Service takes over. Therefore, follow up of adverse events after the four-year-old-booster is not regularly embedded. However, the increase in reports following this vaccination was communicated with all health care professionals in September 2008 and probably resulted in ongoing increased awareness and a strong advice to parents to report adverse events to the health care clinic or directly to RIVM.

5.1.3 Specific events

The increase in numbers can almost exclusively be attributed to the increase in adverse events following booster doses of DTP-IPV at four years of age, mainly due to reports on local reactions and/or fever, categorised in minor general illness. The other events categories show no significant changes. See for additional information the subsections below.

5.1.3.1 Local reactions

Not only the absolute number of reported local reactions, but also the reporting rate of these reactions at four years of age has increased significantly. The percentage of major events within this category was 27%, compared with 22%-42% in 2005-2008. This higher risk of extensive local reactions is described in literature.[41,42,43] In the Netherlands, estimated incidence rate is 3:1000 vaccinated four years olds, based on reports to the passive surveillance system. However, these systems are prone to (selective) underreporting. Therefore, in 2008 we performed a questionnaire study on adverse events after DTP-IPV in 4 year olds, primed with whole cell pertussis vaccine. In 2009 we repeated this study in children, who received only acellular DTP-IPV-Hib as an infant. Results will be published in 2011 and reveal more precise incidence rates. Pathogenesis of this local reaction is complex and not yet elucidated. Perhaps immune complexes play a part.[40] No signals of systemic involvement have been detected yet.

5.1.3.2 Minor general illness

The overall reporting rate in this category does not differ significantly from 2005-2008. However, the reporting rate of the booster DTP-IPV at four years of age increased statistically significant, mostly due to increased reports on fever.
The reports of acknowledged side effects like fever, crying, pallor/cyanosis and myoclonics have fluctuated at a lower level compared with the years before 2004. The introduction of PVC7 to the programme from April 2006 onwards led to an increase in these numbers (OR 1.5; 95%CI 1.4-1.6).[51] This also led to an increase in use of therapeutic medication, for instance paracetamol[44]. In a large questionnaire survey on adverse events following infant vaccinations from 2003 till 2007, we found a significant decrease in incidence rates of fever, crying and pallor between whole cell- and acellular DTP-IPV-Hib. In our study, the contribution of PCV7 to the incidence rates of the acellular vaccine was negligible. Schmitt et al. evaluated the safety of DTP-IPV-Hib compared to DTP-IPV-Hib+PCV7 and found only minor differences in fever and drowsiness between these groups. [45] However, several studies on the reactogenicity of DTP-IPV-Hib-HepB compared to concurrently administered DTP-IPV-Hib-HepB and PCV7 showed a significant increase of fever < 39 °C for the group, receiving two vaccines. [46,47,48] Comparing these results is hampered by different schedules, vaccine combinations, methods and levels of assessment and lack of uniform case definitions. [38,39,49] In 2012, universal infant DTP-IPV-Hib-HepB will be included in the NIP. To assess changes in reactogenicity on infant vaccinations, we will perform a questionnaire study on frequent adverse events following DTP-IPV-Hib and PCV7 in 2011 and compare these results with a questionnaire study in 2012 among parents of infants receiving DTP-IPV-Hib-HepB and conjugated pneumococcal vaccine. More precise frequencies of fever, pallor, crying and other solicited adverse events will be available afterwards.

5.1.3.3 Major general illness

Overall reporting rate of major general illness (17:100,000; 95%CI 14-20) has increased compared with 2005-2008; only for 2006 this increase is not statistically significant. There is always some fluctuation in reports, included in this category, due to the reporting on coincidental events, manifesting itself during infancy. However, since 2005, there is a sharp decrease on reports of Idiopathic Thrombocytopenic Purpura (ITP). This disease is a known AEFI following MMR vaccine, with an estimated incidence rate of 1:19,000 and an attributable risk (AR) of 1:22,000 in the Netherlands (article in preparation)[50].Therefore, the small number of ITP-reports since 2006 is probably due to underreporting.
64% of the cases with very high fever were reported after DTP-IPV-Hib and PCV7, compared with 59%-62% in 2005-2008. In 2009, the share of reports on very high fever following the fourth dose was 50%, compared with 29%-62% in 2005-2008.
In the literature difference in height of fever between DTP-IPV-Hib(+HepB) vaccine with or without PCV7 are described, but variable cut off points of very high fever hamper a good comparison [49,53,55,56.]
The questionnaire study on more severe adverse reactions, mentioned earlier, found no statistically significant difference for the two groups[51]. This is probably due to small numbers.
Vaccinitis is defined as rash and fever possibly caused by vaccine virus 5-12 days after MMR. Depending on the height of the temperature this is categorised in minor general illness (fever < 40.5 °C) or major general illness (fever ≥ 40.5 °C). Both the number of cases in minor and major general illness show random fluctuation in the last four years. Reactogenicity of the different MMR-vaccines, used in 2005-2009, are comparable.[42,43,45] Therefore, the use of different MMR vaccines can not explain these fluctuations.

5.1.3.4 Discoloured legs

The number of reports in this category has fluctuated during the last five years. In 2006 numbers have more than doubled compared to 2005, with a relative large share of concomitant administered PCV7 (42% compared to 30% for all reports on average). As shown in Figure 23, the percentage of double-sided discoloured legs is partly associated with vaccination in one or two legs. Kemmeren et al. suggested that this disease-entity is based on a vasomotor pathway. Ongoing surveillance is necessary to gather more accurate information on this subject[52].

5.1.3.5 Faints; collapse

In the category "Faints" the number of reports decreased, due to fewer aggregated reports on fainting in older children, almost entirely vaccinated during mass vaccination sessions. There has always been fluctuation in reports on fainting, caused by known underreporting. For the last five years the number of reports on collapse ranges between 75 and 96. After the introduction of acellular DTP-IPV-Hib the number of reported collapse decreased, due to the better safety profile of acellular vaccines compared to whole cell vaccines.[37,38,39] In 2005 one quarter of the reports concerned whole cell DTP-IPV-Hib, due to a normal reporting delay. In 2006 the number of collapse was equal to 2005, possibly due to the introduction of PCV7 from April 2006 onwards. Ongoing surveillance is necessary to gain insight in incidence rates for collapse following DTP-IPV-Hib combined with PCV7. Our questionnaire study on rare severe adverse events following whole cell and acellular DTP-IPV-Hib underpinned the good performance with no significant underreporting of the enhanced passive surveillance system for more complex events like collapse.[51,53] Therefore reduced underreporting is probably a less significant factor in the explanation of this fluctuation.

5.1.3.6 Fits; febrile convulsions

The number of febrile convulsions, mostly occurring in the one-year-olds, has decreased since 2005. This is partly caused by the introduction of acellular DTP-IPV-Hib, with a lower frequency of fever compared with whole cell vaccines.[37,38,39] The introduction of PCV7 had no great influence on the reporting rate at these age groups, as shown in Figure 24.

5.1.3.7 Encephalopathy/encephalitis

Press allegations about possible causal relation between MMR vaccination and autism dented the confidence of parents in the vaccination programme. [32] Despite the fact that based on scientific evidence renowned (groups of) scientists have refuted these alleged associations, the vaccination coverage dropped considerably, especially in the United Kingdom and the Republic of Ireland. [32] In the current year we have received very few reports on behavioural problems in the autistic spectrum or other specific problems in mental retardation. Some parents have no real suspicion but have been made insecure; others simply clutch the last straw. In none of the reported cases a causal relation was found, and in some the event preceded the vaccination.

It is to be expected that the number of reports of events that have attracted public attention will increase. A passive surveillance system, even an enhanced one, is not the proper tool for a refutation of false hypotheses, or for substantiating true ones for that matter. Recently a few systematic studies have been published showing no causal relation of disturbances in the autistic spectrum with MMR vaccination or thiomersal containing pertussis vaccine. [32] Studies refuting the causal relation of

encephalopathy or retardation with pertussis vaccinations have been published earlier and confirmed lately. [32]

In fact, in Australia 11 of 14 children with alleged vaccine encephalopathy appeared to have a SCN1A mutation. [54] This mutation is associated with Severe Myoclonic epilepsy in infancy (SMEI). Most mutations are 'de novo' and not inherited. In collaboration with the section for genetic counseling of the UMC Utrecht, we will investigate all reported complex febrile convulsions, epilepsy or pervasive disorders of the years 1997-2006 to see if this mutation plays a role.

5.1.3.8 Death

This year nine deceased children were reported who died some time after immunization. The number of reports in this category is in line with expectations considering background rate. After thorough evaluation causality with the vaccinations was assessed in none of these children. Systematic studies and evaluation of the Institute of Medicine have shown infant death to be unrelated to childhood vaccinations. In an individual case, this may not be demonstrated easily. It should be emphasised that death in close time relationship, i.e. for inactivated and live vaccines within one month and six weeks respectively, should be reported in all instances, regardless of cause. Structural thorough evaluation of deceased children in temporal relation with a vaccination is important for the parents in order to be able to deal with such a stressful event. Furthermore, it will prevent emerging rumours, even if on first sight causal relation seems to be remote. Both the reports on the 8 year old boy, who died 3.5 days following vaccination and the cluster of three reported children, all vaccinated with an identical PCV7 batch created a lot of media attention. These issues emphasized the need to develop mutual agreements between professionals on extensiveness of postmortal investigation and the timeliness of outcomes of these investigations. Furthermore, clear communication to parents, public and health care professionals, again appeared to be very important in these delicate situations. Guidelines on these topics are being developed.

5.2 Safety surveillance; general discussion

5.2.1 Enhanced passive safety surveillance in the Netherlands

Safety surveillance of the vaccination programme seems to be of increasing importance.[13,14,55,56,57] The Dutch system has several strong points. All administered vaccines are recorded on an individual level, so precise denominators are known.[3,4,5] The RVP is embedded in the regular Child Health Care with its near total coverage and programme delivery by a relatively small group of specifically trained professionals. Good professional standards include asking after adverse events at the next clinic visit and before administering the next dose. The RIVM's central information and consultation service for professionals is an important and efficient tool in adverse event reporting.[58] It also allows a close watch on risk perception and programme adherence. Reporting in low-level terms with signs and symptoms and not only (assumed) diagnoses allows application of standardised case definitions and stratified analysis if necessary. Validation and supplementation of reporting data from medical records and eye-witness case histories is an important aspect of the system, resulting in homogeneous event categorisation. The wide reporting criteria allow sensitive signal detection of new adverse events or interactions. Trend analysis is possible. The name based reports facilitate follow up and some other systematic studies, like nested case-control studies.[59] The strength of the current enhanced passive surveillance system outweighs the inherent weaknesses. Additional active surveillance should supplement the passive system.

5.2.2 Causality assessment and case definitions

Assessing causal relation is essential in monitoring the safety of the vaccination programme.[60,61,62,63] Of course, after vaccination does not mean caused by vaccination. The RIVM requests an expert panel to reassess selected cases with up till now complete agreement on diagnosis and causality. Some other countries, like Canada, USA and Australia have followed suit.[64,65,66] Five different categories are used for causal relation for the purpose of international comparison. However, different design and criteria for surveillance systems, diagnostic procedures, causality assessment and inconsistent case definitions and case ascertainment hamper international comparison.[67] Furthermore, different schedules and/or vaccines and combinations do preclude direct analysis or pooling of data and require cautious interpretation. The Brighton Collaboration, in which RIVM also participates, aims to arrive at defined standardised case definitions for specific AEFI.[68] (www.brightoncollaboration.org)

5.2.3 Trend analysis

Our passive surveillance system has several strong points. Due to the use of standardized case definitions, well known reporting criteria, a high reporting rate, a limited underreporting for severe AEFI and the availability of denominators, trend analysis is possible. However, frequent changes in vaccine formulations hamper a good comparison over the years, with less possibility to monitor the influence on the overall safety of the programme properly, when new vaccines are introduced.

5.2.4 Passive versus active surveillance

Although the current enhanced passive surveillance system is the backbone of our safety surveillance, supplementation by more active monitoring and systematic studies is important to test generated signals and hypotheses. For the more common adverse events questionnaire survey should be done on a regular basis to test the safety profile of the (new) vaccines or schedules in the programme. Data linkage studies are important to monitor vaccine safety in relation to medical consumption. Hereby, linking databases is most suitable to study more severe, well defined diagnoses. Problems arising from privacy legislation should be addressed and the introduction of a unique personal identifier should facilitate this kind of surveillance. With the possible uptake of new vaccines at different age-groups, there is a growing need for monitoring specific adverse events, especially immune-mediated disorders.[69] Background incidences are an essential part of such a monitoring system, in order to detect a possibly causal related rise in adverse events after introduction of a new vaccine.

6 Conclusions and recommendations

In 2005 the number of reported adverse events decreased significantly due to adoption of an acellular DTP-IPV-Hib vaccine with a more favourable safety profile. In 2006 an increase of reports on AEFI was seen, not fully explained by the introduction of conjugated pneumococcal vaccine.[28] In 2007, results of a full year use of PVC7 showed no great influence of this introduction on the safety profile of the RVP. In 2008, there was an increase in number of reported adverse events, mainly caused by more reports on local reactions following booster DTP-IPV at four years of age. In the year under report, a further increase in reported adverse events was seen, again due to an increase in local reactions and/or fever following the DTP-IPV booster dose at four years of age. This increased risk is described in literature. [41,42,43]

Continuous monitoring of safety is an essential and integral part of the surveillance of a vaccination programme. Especially now that introduction in the RVP of more (novel) vaccines is expected in the forthcoming years, (foreseeable) safety concerns should be included in the discussion about introducing the vaccines in the programme.[69,70,71,72] Introduction of new vaccines should be organised in a manner that allow safety studies on both short and long term, for frequent and more rare, severe AEFI.

Only then it will be possible to study new suspected adverse reactions properly and to adequately refute allegations. A problem is that one can not know what the next signal will be. National and international collaboration should be expanded, in order to move towards a comprehensive safety surveillance network of childhood vaccination programmes. This may also help to perform specific studies and increase scientific knowledge about AEFI. Eventually this will boost public confidence in the programmes.

For the coming year are recommended:

- further implementation of database applications and mutual adjustment with LAREB;
- annual report on 2010;
- maintenance and evaluation of the current passive surveillance system;
- further increasing reporting compliance and promoting safety surveillance of child health care providers, general practitioners and paediatricians;
- exploration of possibilities of data linkage or sentinel studies, to test generated hypotheses;
- case control study on risk factors and follow up of collapse reactions;
- background incidence rates for auto-immune disorders;
- study on vaccinations and SIDS;
- study on epilepsy/retardation and SMEI;
- study on adverse events following DTP-IPV-Hib and PCV7 vaccinations of preterm infants;

The total of 1647 reports must be seen in relation to a total of over 1.4 million vaccination dates administered with nearly 7 million components. We showed that the vaccination programme is safe with the potential side effects far less in weight than the apparent achievements/prevented illness and complications. We plan to keep up a thorough high quality safety-surveillance-system and to stimulate reporting in the coming year.

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Appendix 1: Resumé product information

Vaccines in RVP	Producer	constituents	
DTP-IPV-Hib vaccine Diphtheria, acellular Pertussis, Tetanus and inactivated Poliomyelitis vaccine mixed with conjugated Hib-vaccine 0.5 ml	Aventis Pasteur RVG 32118	Diphtheria toxoid Tetanus toxoid Pertussis toxoid (PT) Filamenteuze hemagglutinine (FHA) Fimbriae agglutinogenen 2 and 3 (FIM) Pertactin (PRN) Inactivated poliovirus type 1 (Mahoney) Inactivated poliovirus type 2 (MEF-1) Inactivated poliovirus type 3 (Saukett) Haemophilus influenzae type b polysaccharide Conjugated to tetanus toxoid (PRP-T)	≥ 30 IE ≥ 40 IE 20 µg 20 µg 5 µg 3 µg 40 DE 8 DE 32 DE 10 µg 20 µg
DTP-IPV-Hib vaccine Diphtheria, acellular Pertussis, Tetanus and inactivated Poliomyelitis vaccine mixed with conjugated Hib-vaccine 0.5 ml	GSK RVG 22123	Diphtheria toxoid* Tetanus toxoid* Pertussis toxoid (PT)* Filamenteuze hemagglutinine (FHA)* Pertactin* Inactivated poliovirus type 1 Inactivated poliovirus type 2 Inactivated poliovirus type 3 Haemophilus influenzae type b polysaccharide** *adsorbed to aluminiumhydroxide **conjugated to tetanus toxoid and absorbed to aluminium phosphate	≥ 30 IE ≥ 40 IE 25 µg 25 µg 8 µg 40 DE 8 DE 32 DE 10 µg 0.95 mg 1.45 mg

DTP-IPV-Hib-HepB vaccine Diphtheria, acellular Pertussis, Tetanus, inactivated Poliomyelitis and Hepatitis B vaccine mixed with conjugated Hib-vaccine 0.5 ml	GSK EU/1/00/152/001 EU/1/00/152/002 EU/1/00/152/003 EU/1/00/152/004 EU/1/00/152/005 EU/1/00/152/006 EU/1/00/152/007 EU/1/00/152/008	Diphtheria toxoid* Tetanus toxoid* Pertussis toxoid* (PT) Filamenteuze hemagglutinine* (FHA) Pertactin* (PRN) Hepatitis-B**,*** Inactivated poliovirus type 1 (Mahoney) Inactivated poliovirus type 2 (MEF-1) Inactivated poliovirus type 3 (Saukett) Haemophilus influenzae type b polysaccharide*** Conjugated to tetanus toxoid (PRP-T) *adsorbed to aluminiumhydroxide **produced in yeast (Saccharomyces cerevisiae) by recombinant DNA techniques ***adsorbed to aluminium phosphate	≥ 30 IE ≥ 40 IE 25 µg 25 µg 8 µg 10 µg 40 DE 8 DE 32 DE 10 µg 20-40 µg 0.95 mg 1.45 mg
DTP-IPV vaccine Diphtheria, Acellular Pertussis, Tetanus and inactivated Poliomyelitis vaccine 0.5 ml	Sanofi Pasteur RVG 27569	Diphtheria toxoid Tetanus toxoid Pertussis toxoid (PT) Filamentous hemagglutinin (FHA) Fimbriae 2 and 3 (FIM) Pertactin (PRN) Inactivated poliovirus type 1 Inactivated poliovirus type 2 Inactivated poliovirus type 3 adsorbed to aluminium phosphate	≥ 2 IE ≥ 20 IE 2.5 µg 5 µg 5 µg 3 µg 40 DE 8 DE 32 DE 0.33 mg Al
DTP-IPV vaccine Diphtheria, acellular Pertussis, Tetanus and inactivated Poliomyelitis vaccine 0.5 ml	GSK RVG 28912	Diphtheria toxoid* Tetanus toxoid* Pertussis toxoid (PT)* Filamenteuze hemagglutinine (FHA)* Pertactin* Inactivated poliovirus type 1 Inactivated poliovirus type 2 Inactivated poliovirus type 3 *adsorbed to aluminiumhydroxide	≥ 30 IE ≥ 40 IE 25 µg 25 µg 8 µg 40 DE 8 DE 32 DE 0.95 mg

DT-IPV vaccine Diphtheria, Tetanus and inactivated Poliomyelitis vaccine 1 ml	NVI RVG 17641	Diphtheria toxoid * Tetanus toxoid* Inactivated poliovirus type 1 Inactivated poliovirus type 2 Inactivated poliovirus type 3 *adsorbed to aluminium phosphate	≥ 5 IE ≥ 20 IE ≥ 20 DE ≥ 2 DE ≥ 3.5 DE 1.5 mg
Pneumococcal vaccine Pneumococcal conjugated vaccine absorbed with aluminiumfosfate 0.5 ml	Wyeth EU/1/00/167/001	Pneumococcal polysaccharide Serotype 4 Pneumococcal polysaccharide Serotype 6B Pneumococcal polysaccharide Serotype 9V Pneumococcal polysaccharide Serotype 14 Pneumococcal polysaccharide Serotype 18C Pneumococcal polysaccharide Serotype 19F Pneumococcal polysaccharide Serotype 23F Conjugated CRM_{197} and absorbed to aluminium phosphate	2 μg 4 μg 2 μg 2 μg 2 μg 2 μg 2 μg 0.5 mg
MMR vaccine Mumps, measles and rubella vaccine 0.5 ml	Sanofi Pasteur RVG 17672	Mumps virus Measles virus Rubella virus	≥ 12.500 p.f.u. ≥ 1000 p.f.u. ≥ 1000 p.f.u.
MMR vaccine Mumps, measles and rubella vaccine 0.5 ml	GSK RVG 22052	Mumps virus Measles virus Rubella virus	≥ 7500 p.f.u. ≥ 1000 p.f.u. ≥ 1000 p.f.u.
Meningococcal C vaccine Conjugated menC vaccine 0.5 ml	Baxter RVG 26343	Neisseria meningitidis (C!!-strain) Polysaccharide ()-deacetylated Conjugated to Tetanus toxoid Adsorbed to aluminium hydroxide	 10 μg 10-20 mg 0.5 mg Al^{3+}
Hepatitis B vaccine Hepatitis B vaccine for children 0.5 ml	GSK RVG 24290	Hepatitis B-virus surface antigen, recombinant* (HBsAg)	10 μg

Rijksvaccinatieprogramma 2009

Richtlijnen voor de uitvoering van vaccinaties tegen difterie, kinkhoest, tetanus, poliomyelitis, Hib-ziekte (ziekte veroorzaakt door Haemophilus influenzae type b), hepatitis B, bof, mazelen, rodehond, meningokokken C-ziekten, pneumokokken-ziekten en baarmoederhalskanker.

Informatie over de implementatie van deze RVP-richtlijnen vindt u in de Uitvoeringsregels RVP en de VaccInformatiemap (www.rivm.nl/cib/rvp).

Opmerkelijke wijzigingen ten opzichte van 2008:

- Per 1 september 2009 wordt de HPV-vaccinatie tegen baarmoederhalskanker in het RVP opgenomen voor 12-jarige meisjes. Vanaf maart 2009 wordt een inhaalcampagne voor de meisjes geboren in 1993 tot en met 1996 georganiseerd.
- Per 1 januari 2009 wordt de preventieve zorg voor asielzoekerskinderen overgedragen aan de GGD'en. De MOA-stichtingen worden opgeheven.

Overzicht van vaccinaties in 2009

Geboortejaar	Vaccinaties
2009	HepB-0* DKTP-Hib** en Pneu
2008	DKTP-Hib** en Pneu BMR en MenC
2005	DKTP
2000	DTP en BMR
1997 (1 jan-1 sept)***	HPV

* Alleen voor kinderen van HBsAg-positieve moeders

** De vaccinatie wordt vervangen door DKTP-Hib-HepB voor kinderen die in aanmerking komen voor een HepB-vaccinatie
Voor asielzoekerskinderen gelden aparte regels (zie pagina 3)

*** alleen voor meisjes

1 Algemeen

1.1 Organisatie

De minister van VWS bepaalt de inhoud van het Rijksvaccinatieprogramma (RVP). In opdracht van de minister is het RIVM/Centrum Infectieziektebestrijding (CIb) verantwoordelijk voor de regie van het programma. De uitvoering van het RVP wordt verzorgd door thuiszorgorganisaties, GGD'en, en verloskundig hulpverleners, onder verantwoordelijkheid en medisch toezicht van RIVM-Regionale Coördinatie Programma's (RIVM-RCP's). Naast de controle, veiligheidsbewaking en evaluatie van het vaccinatieprogramma, coördineert het RIVM de communicatie over het RVP.

1.2 Vaccinatieschema per kind in 2009

Zie het schema bovenaan pagina 2.

1.3 Algemene regels voor toedienen van vaccins

Het toedienen van RVP-vaccins is een medische handeling. Hiervoor dient altijd een indicatie door een arts te zijn gesteld.
Alle vaccins in het RVP moeten in beginsel volgens het in deze RVP-richtlijnen aangegeven

rijksvaccinatieprogramma

Vaccinatieschema per kind in 2009

Leeftijd	Vaccinaties (regulier)	Vaccinaties (doelgroep HepB)
0 maanden (< 48 uur)		HepB-0[1]
2 maanden	DKTP-Hib-1 + Pneu-1	DKTP-Hib-HepB-1[2] + Pneu-1
3 maanden	DKTP-Hib-2 + Pneu-2	DKTP-Hib-HepB-2[2] + Pneu-2
4 maanden	DKTP-Hib-3 + Pneu-3	DKTP-Hib-HepB-3[2] + Pneu-3
11 maanden	DKTP-Hib-4 + Pneu-4	DKTP-Hib-HepB-4[2] + Pneu-4
14 maanden	BMR-1 + MenC	BMR-1 + MenC
4 jaar	DKTP-5	DKTP-5
9 jaar	DTP-6 + BMR-2	DTP-6 + BMR-2
12 jaar (alleen meisjes)	HPV-1 + HPV-2 + HPV-3	HPV-1 + HPV-2 + HPV-3

[1] Alleen voor kinderen van HBsAg-positieve moeders.
[2] Alleen voor die in paragraaf 2 van deze richtlijnen omschreven doelgroepen.

schema worden toegediend. Afwijkingen van het schema vereisen de goedkeuring van de medisch adviseur van RIVM-RCP. Het is niet toegestaan de dosering van het vaccin te halveren. Het effect hiervan op de werkzaamheid is onbekend en leidt tevens niet tot minder bijwerkingen. Ook toedienen van andere afwijkende doseringen of verdunningen en mengen van de vaccins is niet toegestaan.

1.4 Onvolledig gevaccineerde kinderen

Kinderen die niet of niet volledig zijn gevaccineerd, kunnen tot 13 jaar de nog noodzakelijke vaccinaties, kosteloos ontvangen in het kader van het RVP. Asielzoekerskinderen ontvangen de noodzakelijke vaccinaties tot 19 jaar. Voor het afmaken van onvolledige schema's gelden de volgende regels: zie schema hiernaast. Informatie over recente inhaalschema's kunt u bij de medisch adviseur van RIVM-RCP in uw werkgebied verkrijgen.

1.5 Registratie en verantwoording

De vaccinaties worden bij het RIVM-RCP door de uitvoerende organisatie verantwoord door inzending van de ingevulde oproepkaart. RIVM-RCP registreert en beoordeelt de toegediende vaccinaties. Het is voor de uitvoerenden mogelijk de vaccinaties digitaal te registreren (RVP-Online). Hierover kan de uitvoerende organisatie contact opnemen met RIVM-RCP.

Schema voor onvolledig gevaccineerde kinderen

Vaccinatie	Alleen voor :
MenC	kinderen geboren op of na 1 juni 2001
BMR-0	asielzoekerskinderen op de leeftijd van 9 maanden als extra BMR
HepB	kinderen geboren op of na 1 januari 2003, op voorwaarde dat: • tenminste één ouder afkomstig is uit een land waar hepatitis B middel- of hoogendemisch is, • het een asielzoekerskind is, • de moeder HBsAg-positief is.
	kinderen met het syndroom van Down en geboren op of na 1 januari 2008
Pneu	kinderen geboren op of na 1 april 2006 en tot de 2e verjaardag
DKTP 4 jaar	kinderen die de volledige basisimmunisatie DKTP-(Hib) voor de tweede verjaardag hebben afgerond

1.6 Financiële regels

De kosten van de uitvoering van het RVP komen ten laste van de AWBZ. De RIVM-RCP's ontvangen een bedrag per toegediende vaccinatie. De RIVM-RCP's dragen zorg voor de doorbetaling van de ter beschikking gestelde gelden aan de uitvoerende organisaties volgens landelijke richtlijnen.
Voor vaccinaties die in het kader van het RVP zijn

uitgevoerd door de thuiszorg, GGD, verloskundig hulpverlener en ziekenhuizen betalen de ouders geen bijdrage. Als ouders kiezen voor een ander vaccin dan het vaccin dat door RIVM-RCP ter beschikking is gesteld, vervalt het recht op kosteloze verstrekking. Zij kunnen zich met hun wensen tot de huisarts wenden.
Ook voor vaccinaties gegeven overeenkomstig het RVP maar zonder tussenkomst van de RIVM-RCP's, worden geen gratis vaccins ter beschikking gesteld, noch enige vergoeding gegeven.

1.7 Tijdigheid vaccinaties

Het is van groot belang de vaccinaties volgens het geldende schema te geven. De in deze richtlijnen vermelde vaccinatieleeftijden in maanden of jaren zijn geen minimale leeftijden maar optimale leeftijden. De 1e vaccinatie krijgt een kind als het 6, 7, 8 of 9 weken oud is. In geval van de HepB-0-vaccinatie is tijdigheid (binnen 48 uur ná de geboorte) een noodzaak, omdat het hier postexpositieprofylaxe betreft en geen preventie.

1.8 Vaccindistributie

RCP's houden toezicht op de distributie en het gebruik van de vaccins. De uitvoerende instellingen krijgen alleen vaccins na aanvraag bij de RIVM-RCP's. Vaccins worden verstrekt onder voorwaarde dat deze uitsluitend worden gebruikt voor de uitvoering van het RVP of, in bijzondere omstandigheden, volgens richtlijnen gegeven door of namens de minister van Volksgezondheid, Welzijn en Sport.

1.9 Vaccinbeheer

De RIVM-RCP's leveren de vaccins aan de uitvoerende instellingen. Vaccins worden opgeslagen en beheerd conform de vigerende Cold-Chainrichtlijnen van het RIVM-RCP. Bij vaccinincidenten dient men altijd contact op te nemen met de RIVM-RCP's.

1.10 Asielzoekerskinderen

Asielzoekerskinderen kunnen de noodzakelijke vaccinaties ontvangen tot zij 19 jaar worden. Voor deze kinderen gelden aparte regels, vooral met betrekking tot HepB en BMR-0. Inhaalschema's zijn vinden in de Uitvoeringsregels RVP.
Asielzoekers hebben aanspraak op voorzieningen krachtens de AWBZ. Kosten voor vaccinaties van deze doelgroep worden vergoed door de ziektekostenregeling asielzoekers (ZRA).

2 Zuigelingen

Toelichting op vaccins en vaccinaties

DKTP (tegen difterie – kinkhoest - tetanus - poliomyelitis) – **Hib** (tegen ziekte veroorzaakt door *Haemophilus influenzae* type b)
Zuigelingen krijgen de DKTP-Hib-vaccinatie op de leeftijd van respectievelijk **2, 3** en **4** maanden. Tussen de eerste drie vaccinaties dient een periode van 4 weken te zitten. De vierde DKTP-Hib-vaccinatie krijgen kinderen volgens schema op de leeftijd van **11** maanden.
In het RVP wordt in principe het DKTP-Hib-combinatievaccin gebruikt. Voor reeds DKTP-gevaccineerde kinderen, geboren op of na 1 april 1993, die formeel aanspraak hebben op Hib-vaccinatie maar op latere leeftijd Nederland zijn binnengekomen, is separaat Hib-vaccin beschikbaar. Vanaf de leeftijd van 1 jaar volstaat één dosis. Als zij ook aanvullend tegen DKTP moeten worden gevaccineerd, is hiervoor na een eerste dosis met DKTP-Hib, DKTP-vaccin beschikbaar.

HepB-0 (tegen hepatitis B)
Voor deze vaccinatie komen kinderen van HBsAg-positieve moeders (draagsters van het hepatitis B-virus) in aanmerking. De verloskundig hulpverlener dient het hepatitis B-vaccin **binnen**

rijksVaccinatieprogramma

rijksVaccinatieprogramma

48 uur na de geboorte toe, bij voorkeur direct na het toedienen van de hepatitis B-immunoglobuline, maar in een ander ledemaat. Deze tijdigheid is noodzakelijk, omdat het hier postexpositieprofylaxe betreft en geen preventie. Het RIVM-RCP verstrekt het vaccin.
Kinderen van HBsAg-positieve moeders krijgen vervolgens op de leeftijd van **2, 3, 4** en **11** maanden een hepatitis B-vaccinatie in de vorm van DKTP-Hib-HepB-vaccin; zie volgende paragraaf.

DKTP (tegen difterie – kinkhoest - tetanus - poliomyelitis) - **Hib** (tegen ziekte veroorzaakt door *Haemophilus influenzae* type b) – **HepB** (tegen hepatitis B)
Voor deze vaccinatie komen vier groepen kinderen in aanmerking:
1. kinderen waarvan tenminste één van de ouders afkomstig is uit een land waar hepatitis B middel- of hoog-endemisch is (prevalentie van dragerschap ≥2%)[3],
2. kinderen van HBsAg-positieve moeders,
3. kinderen met het syndroom van Down, geboren op of na 1 januari 2008,
4. asielzoekerskinderen.

Ad 1) Deze kinderen krijgen de hepatitis B-vaccinatie op de leeftijd van **2, 3** en **4** maanden in de vorm van het combinatievaccin DKTP-Hib-HepB. Tussen deze eerste drie vaccinaties dient een periode van 4 weken te zitten. De vierde DKTP-Hib-HepB-vaccinatie krijgen ze volgens schema op de leeftijd van **11** maanden.
Ad 2) Bij deze kinderen wordt de serie HepB-vaccinaties waarmee direct na de geboorte is begonnen (zie HepB-0), afgemaakt volgens het schema en de richtlijnen zoals hierboven vermeld onder ad 1. Omdat het hier postexpositieprofylaxe betreft en geen preventie, dient het schema van 0, 2, 3, 4 en 11 maanden bij deze kinderen strikt gevolgd te worden. Om te voorkomen dat het kind besmet raakt en zelf ook drager wordt, is uitstel van de HepB-vaccinatie niet toegestaan.
Ad 3) Idem als de categorie hierboven genoemd onder ad 1.

Voor alle kinderen met een indicatie voor HepB-vaccinatie is zowel los HepB-vaccin als het combinatievaccin DKTP-Hib-HepB beschikbaar.

Pneu (tegen pneumokokkenziekte)
Op de leeftijd van **2, 3, 4,** en **11** maanden krijgen kinderen een pneumokokkenvaccinatie. De Pneu-vaccinatie wordt simultaan (op dezelfde dag) met de DKTP-Hib of DKTP-Hib-HepB-vaccinatie gegeven, maar in een ander ledemaat.

BMR (tegen bof - mazelen - rodehond)
Op de leeftijd van **14** maanden krijgen kinderen de eerste BMR-vaccinatie.
Deze vaccinatie wordt simultaan (op dezelfde dag) met de MenC-vaccinatie toegediend, maar in een ander ledemaat.
Een asielzoekerskind krijgt de eerste (extra) vaccinatie op de leeftijd van **9** maanden (BMR-0).

MenC (tegen meningokokken C-ziekte)
Op de leeftijd van **14** maanden krijgen kinderen de MenC-vaccinatie.
Deze vaccinatie wordt simultaan (op dezelfde dag) met de BMR-vaccinatie toegediend, maar in een ander ledemaat.

[3] Wat betreft de prevalentie van dragerschap gaf de WHO een lijst uit van landen waar hepatitis B laag-endemisch is, de zogenoemde 'negatieve landenlijst': Andorra, Australië, Bahamas, Barbados, België, Bermuda, Canada, Chili, Colombia, Costa Rica, Cuba, Cyprus, Denemarken, Duitsland, El Salvador, Estland, Finland, Frankrijk, Hongarije, Ierland, Luxemburg, Mexico, Monaco, Nederland, Nicaragua, Nieuw-Zeeland, Noorwegen, Oostenrijk, Paraguay, Peru, San Marino, Sri Lanka, Slowakije, Tsjechië, Uruguay, IJsland, Verenigd Koninkrijk, Verenigde Staten, Zweden en Zwitserland. Hoewel de epidemiologische situatie door het hepatitis B-vaccinatiebeleid in veel landen veranderd is en de WHO geen actualisering van de landenlijst meer publiceert, blijft de 'oude' landenlijst een goede indicatie geven voor bepaling van de doelgroep voor hepatitis B-vaccinatie.

3 Kleuters

Toelichting op vaccins en vaccinaties

DKTP (Difterie - Kinkhoest - Tetanus - Poliomyelitis)
De in 2005 geboren kinderen worden in 2009 gerevaccineerd met DKTP-vaccin voor 4-jarigen.

4 Schoolkinderen

Toelichting op vaccins en vaccinaties

DTP (tegen difterie - tetanus - poliomyelitis)
Kinderen geboren in 2000 krijgen in 2009 een revaccinatie met DTP-vaccin.
Toediening van de DTP-vaccinatie gebeurt simultaan (op dezelfde dag) met de BMR-vaccinatie, maar in een ander ledemaat.

BMR (tegen bof - mazelen - rodehond)
Kinderen geboren in 2000 krijgen in 2009 de tweede BMR-vaccinatie.

Toediening van de BMR-vaccinatie gebeurt simultaan (op dezelfde dag) met de DTP-vaccinatie, maar in een ander ledemaat.

5 Adolescente meisjes

Toelichting op vaccins en vaccinaties

HPV tegen humaan papillomavirus ter preventie van baarmoederhalskanker
In 2009 komen meisjes geboren op of na 1 januari 1997 en voor 1 september 1997 in aanmerking voor HPV-vaccinatie. Daarnaast wordt een inhaal-campagne georganiseerd voor meisjes geboren op of na 1 januari 1993 tot en met 31 december 1996. De vaccinatie bestaat uit een serie van drie doses met een schema 0, 1 en 6 maanden. Tussen de 1e en 2e vaccinatie zit een interval van 1 maand. De derde vaccinatie wordt 6 maanden na de eerste inenting gegeven. Als men al eerder op eigen initiatief buiten het RVP één of twee doses HPV-vaccin heeft gehad, kan de serie alleen binnen het RVP worden afgemaakt als met het vaccin Cervarix® (GSK) is gevaccineerd. De HPV-vaccins zijn namelijk niet onderling uitwisselbaar.
Het vaccin wordt intramusculair toegediend.

6 Simultane vaccinaties en registratie van partijnummers

Simultane vaccinaties zijn vaccinaties die op dezelfde dag worden toegediend, meestal gelijktijdig, maar in principe binnen 24 uur na elkaar. Deze toediening dient altijd in verschillende ledematen plaats te vinden.

Van elke gevaccineerde zuigeling, kleuter en schoolkind moet bekend zijn welk vaccin in welke ledemaat is toegediend. Dit is nodig voor de herkenning en duiding van (mogelijke) lokale bijwerkingen. Daarnaast dienen ook de partijnummers van toegediende vaccins geregistreerd te worden, zodat deze zo nodig te herleiden zijn naar individuele kinderen.

7 Bijwerkingen

Na vaccinaties kunnen bijwerkingen optreden. Meestal gaat het om niet ernstige, voorbijgaande verschijnselen. Voor een goede veiligheidsbewaking is melding van bijwerkingen van groot belang. Er wordt dan ook dringend verzocht elke ernstige of onverwachte (mogelijke) bijwerking te melden aan het RIVM/Centrum Infectieziektebestrijding te Bilthoven, onder vermelding van het partijnummer van het betreffende vaccin (tel. 030 274 24 24; fax 030 274 44 30; e-mail: libris@rivm.nl).

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RIVM-RCP

Voor informatie over het Rijksvaccinatieprogramma, over de wijze van uitvoering en voor consultatie over individuele kinderen kunt u zich wenden tot het RIVM-RCP in uw werkgebied.

RIVM-RCP Noord	**Groningen / Friesland / Drenthe**	050-368 6350	rcpnoord@rivm.nl
RIVM-RCP Oost	**Overijssel / Gelderland**	0570-661 520	rcpoost@rivm.nl
RIVM-RCP Midden-West	**Utrecht / Noord-Holland / Flevoland**	0346-550 040	rcpmiddenwest@rivm.nl
RIVM-RCP Zuid-West	**Zuid-Holland**	079-341 8238	rcpzuidwest@rivm.nl
RIVM-RCP Zuid	**Zeeland / Noord-Brabant / Limburg**	*	rcpzuid.nbr@rivm.nl

Algemene informatie over het RVP kunt u verkrijgen bij **RIVM/Centrum Infectieziektebestrijding**, tel. 030-274 3433 of **RIVM/RCP Centraal**, tel. 030-274 8699.

Voor achtergrondinformatie over het Rijksvaccinatieprogramma verwijs ik u naar de Uitvoeringsregels RVP en de VaccInformatiemap die te vinden zijn op **www.rivm.nl/cib/rvp**
Vragen over de VaccInformatiemap kunt u mailen aan rvpcommunicatie@rivm.nl

Exemplaren van deze richtlijnen kunt u downloaden van de website **www.rivm.nl/cib/rvp** of aanvragen bij het RIVM-RCP in uw werkgebied.

Dr. M.A.E. Conyn-van Spaendonck, arts-epidemioloog
RVP Programmamanager
Centrum Infectieziektebestrijding

Bilthoven, december 2008

rijksVaccinatieprogramma

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